



Original Research

The role of preoperative CEA in the management of colorectal cancer: A cohort study from two cancer centres



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ABSTRACT

Background: The primary aim of this study was to investigate whether a preoperative elevation in serum CEA is an independent prognostic factor for both 5-year overall and disease-free survival within an Australian patient cohort.

Materials and methods: A retrospective study of a prospectively maintained colorectal neoplasia database for patients between January 2010 and June 2016 was performed. Patients were categorized into two groups according to the preoperative serum CEA level: low (< 2.5), high CEA (≥ 2.5), and elevated (≥ 5 ng/ml); and further stratified by disease stage. Inclusion criteria were patients having had a resection for either a colonic or upper third rectal adenocarcinoma and with a preoperative CEA value. Data on patient demographics, mortality, and morbidity and survival were compiled. Five-year estimates of overall (OS) and disease-free survival (DFS) were assessed.

Results: 623 patients met the inclusion criteria. The median patient age was 73 (range 22–97) and 55% female (n = 340). There were 572 colonic cancers and 51 rectal cancers. The median follow-up time was 25 months (range 1–71). Eight patients (1%) had a local recurrence and 62 patients (10%) had evidence of metastatic disease after the initial curative resection. The 5-year OS and DFS rates for patients with CEA level < 2.5 ng/ml were 85% and 86% respectively, which were higher than those with CEA level ≥ 2.5 ng/ml (73% and 79% respectively). Independent predictors of recurrence were a CEA ≥ 5 ng/ml (HR 1.8; 95% CI 1.09–3.00; p = 0.002) and stage II (HR 5.33; 95% CI 1.59–17.90; p = 0.007) and stage III (HR 10.91; 95% CI 3.34–35.60; p = < 0.001). A CEA ≥ 5 ng/ml was associated with a higher risk of death (HR 1.79; 95% CI 1.00–3.19; p = 0.046).

Conclusion: Preoperative CEA levels were associated with age, BMI, ASA and tumour stage. Overall, CEA remains a reliable predictor of recurrence and survival after curative surgery in patients with colorectal cancer.

1. Introduction

Colorectal cancer (CRC) is an important global health issue which can impact on patient morbidity and mortality [1]. It is estimated to be the third most commonly diagnosed type of cancer in Australia and the second leading cause of cancer death. In 2018, it is estimated that 12.3% of all new cancers diagnosed and 8.5% of all cancer deaths within Australia will be secondary to CRC [2].

Carcinoembryonic antigen (CEA) is a readily available tumour marker to assist in the management of colorectal cancer. CEA has been used postoperatively to guide cancer surveillance and higher

preoperative CEA levels have been identified as an independent predictor of both overall and disease-free survival rates [3–5]. Furthermore, patients with node-negative early-stage colon cancer but with elevated preoperative CEA levels may have a poor prognosis similar to those with node-positive disease, possibly due to disease upstaging and may therefore be candidates for adjuvant chemotherapy [6].

Traditionally, the TNM classification system has been used for tumour staging and can project a stage-derived survival estimate, however it likely oversimplifies assessment of the biological potential of the tumour and the overall risk of recurrence and death [7,8]. The timing of CEA measurement is important as it can either reflect remaining disease

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if measured early postoperatively or reflect cancer recurrence later during the surveillance period [9]. Accordingly, the primary aim of this study was to investigate whether a preoperative elevation in serum CEA is an independent prognostic factor for both 5-year overall and disease-free survival within an Australian patient cohort.

2. Materials and methods

2.1. Patients and inclusion criteria

A retrospective study of patients on the prospectively maintained Cabrini Monash University colorectal neoplasia database, incorporating data from Cabrini Hospital (private patients), and The Alfred Hospital (public patients) in Melbourne Australia, identified patients entered between January 2010 and June 2016. All data entered into the database were collected prospectively with near 100% complete data entry for surgeries performed at the two centres [10]. Ethics approval for this study was granted by the Cabrini Human Research Ethics Committee (HREC reference #06-02-05-16). Inclusion criteria were patients having had a resection for either a colonic or upper third rectal adenocarcinoma and with a documented preoperative CEA value. Data on patient demographics, mortality, and morbidity and survival were compiled. The primary outcome was assessing 5-year estimates of overall (OS) and disease-free survival (DFS).

2.2. Follow up

Typically, in general practice, patients had regular follow-up every 3–6 months for the first 2 years' post-surgery. Serial measurements of CEA were performed in addition to clinical, colonoscopic and radiological examinations (CT of the chest, abdomen and pelvis) for the first year. For patients in this study, after 2 years, follow-up was usually annual, with CT, CEA and colonoscopy for detecting local recurrence and metachronous disease performed at the discretion of the treating surgeon and in line with national guidelines [11]. For data analyses, follow-up was defined as the time from the date of primary surgery to a patient event, such as disease recurrence or death. There was no minimum duration of follow-up. Follow-up information was derived from the colorectal neoplasia database and patient hospital records. After surgery for the primary tumour, patients who developed local recurrence or metastases were no longer considered disease-free for statistical analysis. Patients who died at any time, for any reason, after surgery were counted as deaths in overall survival analysis.

2.3. CEA measurement and definitions

Serum CEA levels were measured preoperatively using the Cobas CEA Electro-chemiluminescence immunoassay on a Roche Cobas E601 system (Roche Diagnostics GmbH) in which the reference level was 2.5 ng/ml. Patients were categorized into two CEA tiers of low CEA (< 2.5 ng/ml) and high CEA (\geq 2.5 ng/ml) based on results from the National Surgical Adjuvant Breast and Bowel Project (NSABP) published data [12]. Analysis for local recurrence and survival outcomes were further divided by elevated CEA levels (\geq 5 ng/ml) in line with other published literature. Colonic tumours were those arising anywhere between the caecum and rectosigmoid junction. Upper rectal cancers were defined as tumours arising 10–15 cm from the anal verge.

2.4. Statistical analysis

Data were analysed with Fisher exact tests and χ^2 tests. Associations with preoperative CEA (level as a continuous variable) were assessed using linear regression. Explanatory variables included age, sex, BMI, smoking status, tumour location, tumour type, tumour grade, ASA score, T stage, N stage, overall American Joint Committee on Cancer (AJCC) stage and presence of lymphovascular invasion. DFS and OS

were assessed using survival analysis techniques (Cox regression, Kaplan–Meier survival analysis and log rank tests) with study entry set at the date of surgery and follow-up date at the earlier of 1) most recent follow-up and 2) date of recurrence for DFS or death date for OS. Significance was set as a p-value < 0.05. To account for lack of independence between episodes within patients with multiple treatment episodes, all regression standard errors were calculated using the Huber–White Sandwich Estimator as implemented in Stata 14 (StataCorp LP, College Station, Texas, USA).

This study has been reported in line with STROCSS criteria [13]. The research registry unique identifying number for this study is #4539 (www.researchregistry.com).

3. Results

3.1. Patient and tumour characteristics

A total of 656 patients were identified from the database. 33 patients were excluded from this study because preoperative serum CEA data were not available, resulting in 623 cases eligible for analysis. The median patient age for the eligible 623 patients was 73 (range 22–97 years) and 54.6% of patients were female (n = 340). There were 574 colonic cancers and 51 rectal cancers. The majority of patients (60.8%) had an ASA score of I or II. A higher proportion of patients had AJCC stage II disease (39.5%) than stages I and III. Patient clinical and pathological characteristics are shown in Table 1.

3.2. Factors associated with preoperative CEA levels

Table 2 shows the results of the univariate linear regression analysis to identify factors associated with preoperative CEA levels. CEA levels were lower for patients with higher BMI. CEA levels were higher for ASA IV and higher T stages. Tumour characteristics associated with

Table 1
Patient clinical and pathological characteristics.

Feature	Data (N = 623)	%
Patient characteristics		
<i>Sex</i>		
Male	283	45
Female	340	55
Mean age (years)	71.4	
Tumour characteristics		
<i>Tumour location</i>		
Colon	574	92
Upper Rectum	51	8
<i>ASA score</i>		
1	141	23
2	238	38
3	210	34
4	31	5
<i>AJCC Stage</i>		
I	180	29
II	246	40
III	197	31
<i>T stage</i>		
1	94	15
2	114	18
3	357	57
4	58	9
<i>N stage</i>		
0	426	68
1	142	23
2	55	9
<i>Tumour grade</i>		
Undifferentiated	5	1
Poorly differentiated	139	24
Moderate differentiation	414	71
Well differentiated	27	4

Table 2
Univariate analysis of factors affecting preoperative CEA.

Variable	β coefficient	95% CI	P value
Age	0.019	0.012 to 0.026	< 0.001
Sex			
Male	0.038	-0.134 to 0.210	0.666
Female			
BMI	-0.027	-0.044 to -0.010	0.002
Current Smoker			
No	Reference group		
Yes	-0.009	-0.284 to 0.266	0.947
Previous smoker			
No	Reference group		
Yes	0.048	-0.124 to 0.221	0.582
Rectal Cancer			
No	Reference group		
Yes	-0.256	-0.529 to 0.016	0.065
Tumour site			
Caecum	Reference group		
Ascending colon	0.114	-0.236 to 0.463	0.524
Hepatic flexure	0.004	-0.407 to 0.415	0.986
Transverse colon	-0.010	-0.334 to 0.313	0.950
Splenic flexure	-0.232	-0.623 to 0.159	0.243
Descending colon	0.011	-0.519 to 0.541	0.968
Sigmoid colon	-0.170	-0.458 to 0.118	0.247
Rectosigmoid	0.052	-0.366 to 0.470	0.808
Rectum upper	-0.281	-0.639 to 0.077	0.123
Tumour type			
Adenocarcinoma	Reference group		
Adeno mucinous	0.345	-0.002 to 0.692	0.051
Adeno signet	1.745	0.946 to 2.545	< 0.001
No residual	-0.713	-0.957 to -0.469	< 0.001
ASA			
1	Reference group		
2	0.330	0.117 to 0.544	0.002
3	0.558	0.328 to 0.787	< 0.001
4	0.896	0.488 to 1.304	< 0.001
T stage			
1	Reference group		
2	0.339	0.141 to 0.538	0.001
3	0.814	0.632 to 0.995	< 0.001
4	1.201	0.851 to 1.550	< 0.001
N stage			
0	Reference group		
1	0.307	0.082 to 0.533	0.008
2	0.184	-0.139 to 0.508	0.264
AJCC			
1			
2	0.630	0.451 to 0.809	< 0.001
3	0.638	0.432 to 0.843	< 0.001
LVI			
No			
Yes	0.306	0.113 to 0.500	0.002
Tumour grade			
Well differentiated			
Undifferentiated	-0.927	-1.501 to -0.353	0.002
Poor differentiation	0.551	0.183 to 0.919	0.003
Moderate differentiation	0.174	-0.139 to 0.487	0.275

higher CEA levels were higher AJCC stage, signet cell subtype, and both undifferentiated and poorly differentiated tumours. Neither smoking status (either current or previous) nor tumour site had an effect on preoperative CEA levels. Node positivity influenced CEA levels. Specifically, only N1 disease impacted on the levels, however N2 disease did not. Table 3 shows results of the multivariable regression. Elevated CEA levels correlated with increasing age and higher T stages. CEA levels were also higher for ASA scores 3 and 4 compared to ASA 1. An increasing BMI was associated with lower preoperative CEA levels.

3.3. Oncological outcomes

The median follow-up time was 25 months (range 1–71). Eight patients (1%) had a local recurrence and 62 patients (10%) had evidence of metastatic disease after the initial curative resection. The 5-

Table 3
Multivariable analysis of factors affecting preoperative CEA^a.

Variable	β coefficient	95% CI	P-value
Age	0.009	0.001 to -0.016	0.030
BMI	-0.022	-0.038 to -0.006	0.007
ASA			
1	Reference group		
2	0.195	-0.047 to 0.437	0.114
3	0.358	0.093 to 0.623	0.008
4	0.616	0.204 to 1.028	0.003
T stage			
1	Reference group		
2	0.318	0.112 to 0.525	0.003
3	0.744	0.560 to 0.927	< 0.001
4	1.088	0.738 to 1.438	< 0.001

^a Linear regression using CEA (< 2.5 ng/ml or ≥ 2.5 ng/ml) as a dichotomous variable.

year OS and DFS rates for patients with CEA level < 2.5 ng/ml were 85% and 86% respectively, which were higher than the rates for those with CEA level ≥ 2.5 ng/ml (73% and 79% respectively).

Univariate Cox regression indicated a higher risk of death for those with CEA ≥ 2.5 ng/ml (Hazard ratio (HR) 2.7, 95% CI 1.5–5.1) and for those with AJCC stage II tumours (HR 2.7, 95% CI 1.2–6.3) or stage III tumours (HR 2.8, 95% CI 1.2–6.4). Multivariable analysis revealed that a preoperative CEA level ≥ 2.5 ng/ml was a significant independent prognostic factor for OS after adjusting for stage (HR 2.4, 95% CI 1.3–4.5). Univariate Cox regression for DFS indicated a higher risk of disease progression for those in the high CEA group (HR 2.1; 95% CI 1.2, 3.5) and for those with AJCC stage II (HR 6.3, 95% CI 1.9–21.1) or AJCC stage III (HR 12.3, 95% CI 3.8–39.8). After adjusting for stage in a multivariable analysis, the high CEA group was no longer significantly associated with risk of disease progression (HR 2, 95% CI 0.98–2.8). Figs. 1 and 2 depict the Kaplan-Meier 5-year OS and DFS curves stratified by preoperative CEA level. A high pre-operative CEA level corresponds with a worse survival.

Table 4 shows a subgroup analysis of survival outcomes between AJCC stages II (node negative) and AJCC stages III (node positive) stratified by different CEA levels. There was a lower risk of death for patients in the AJCC III and CEA < 2.5 ng/ml group. No differences in disease-free survival were identified between the other various subgroups.

In addition, a CEA between 2.5 and 5 ng/ml (HR 3.05; 95% CI 1.27–7.32; p = 0.012) and an elevated CEA ≥ 5 ng/ml (HR 3.3; 95% CI 1.39–8.00; p = 0.007) were independent predictors of overall survival. Only an elevated CEA level ≥ 5 ng/ml (HR 2.4; 95% CI 1.10–5.24; p = 0.027) was a predictor for disease-free survival. Independent predictors of recurrence were a CEA ≥ 5 ng/ml (HR 1.8; 95% CI 1.09–3.00; p = 0.002) and AJCC stage II (HR 5.33; 95% CI 1.59–17.90; p = 0.007) and stage III (HR 10.91; 95% CI 3.34–35.60; p < 0.001). CEA ≥ 5 ng/ml was associated with a higher risk of death (HR 1.79; 95% CI 1.00–3.19; p = 0.046), however when only colonic cases were examined this association was no longer statistically significant.

4. Discussion

This study demonstrates that the serum CEA level was likely to rise with higher age, ASA scores and increasing T stages. There was also an inverse relationship between BMI and CEA. The possible explanation for the association between high BMI and low CEA could be due to the haemodilutional effect from increased plasma volume observed in patients with higher BMI [14,15]. In this study, smoking status did not affect CEA levels which is in contrast to other studies [16,17].

CEA was an independent predictor of survival which is consistent with other studies [18,19]. A population study by Thirunavukarasu et al., assessed over 16,000 patients with colorectal cancer from the

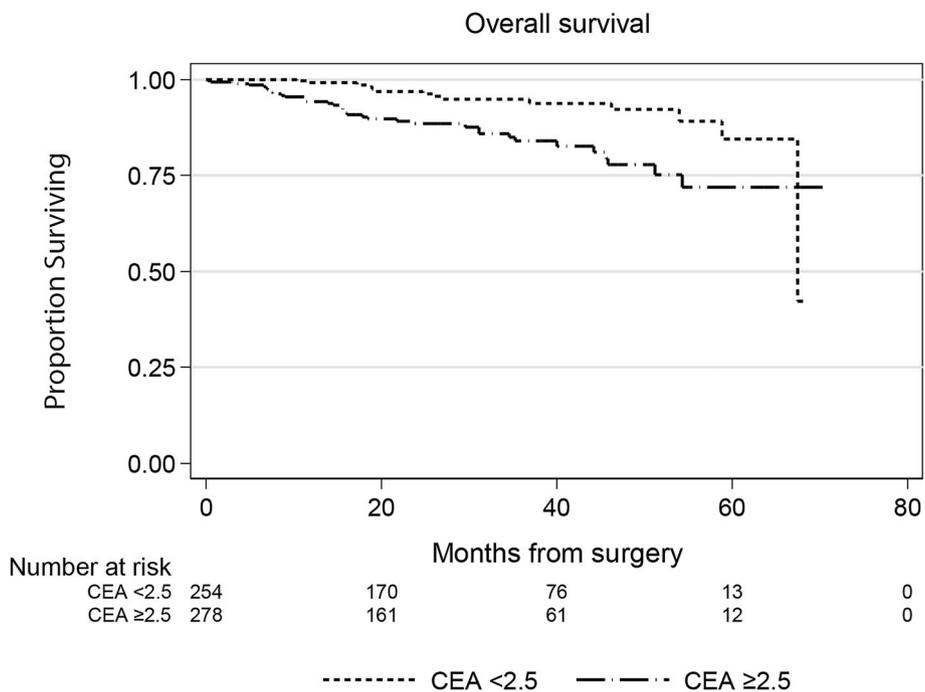


Fig. 1.

Surveillance, Epidemiology and End Results database to analyse the survival outcomes after inclusion of pre-treatment CEA levels into the AJCC staging [6]. The authors found that a serum level CEA ≥ 5 ng/ml was found to have a 60% increased risk of overall mortality; however, the authors were not able to adjust for potentially important covariates like comorbidities and BMI [6]. Thirunavukarasu et al., found that inclusion of varying CEA levels into the TNM system could prognostically cause stage migration [6]. Specifically, patients who had lower AJCC stages (e.g. I/II) but higher CEA levels had a similar or worse prognosis compared to corresponding higher AJCC stages (III) but with normal CEA levels [6]. In the current study, AJCC stages II and III were independent predictors for both overall and disease-free survival rates.

Patients had a better overall survival both with a low CEA (< 2.5 ng/ml) and AJCC stage III but there was no difference in survival (either OS or DFS) for patients with higher CEA levels (≥ 5 ng/ml) and stages II and III. This conflicting result is likely explained by the cohort size for these specific AJCC stages in this study.

Currently, patients with stage I/II (node-negative) disease are treated with surgery alone, and patients with stage III (node-positive) disease are treated with multimodal therapy (surgery, systemic chemotherapy). The major decisive factor for adjuvant chemotherapy is node positivity. Patients with node-negative early-stage colon cancer regardless of CEA level would generally not be offered adjuvant chemotherapy [20]. Studies have identified however that patients with an

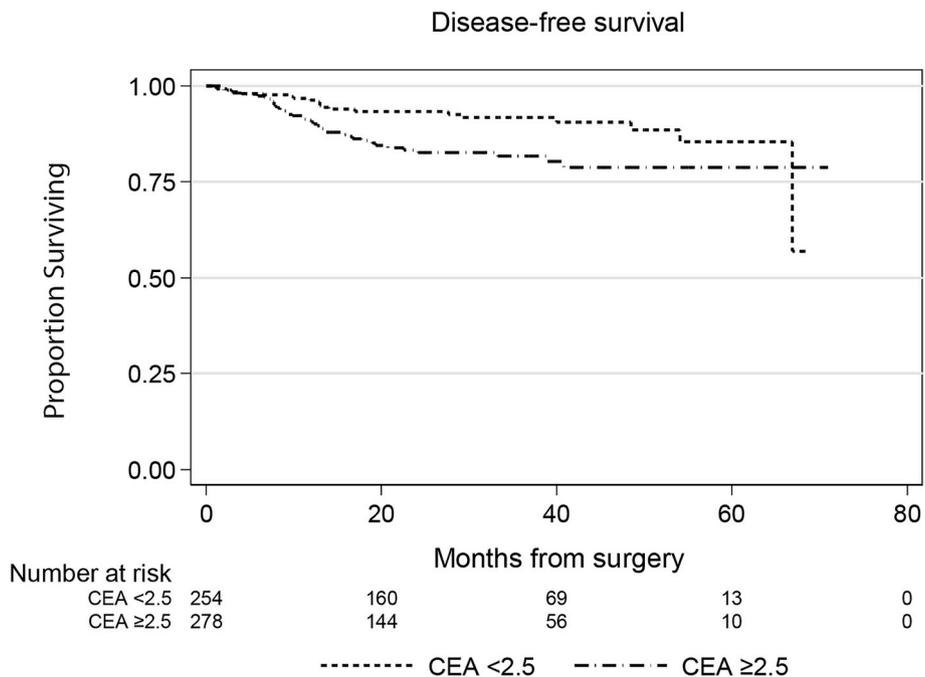


Fig. 2.

Table 4
Comparison of survival outcomes between AJCC stages II and III stratified by CEA level.

	AJCC II + CEA \geq 5 vs. AJCC III + CEA < 5		AJCC II + CEA \geq 2.5 vs. AJCC III + CEA < 2.5	
	HR (95% CI)	P value	HR (95% CI)	P value
Overall Survival				
Stage II (Reference Group)	–	–	–	–
Stage III	0.73 (0.283–1.89)	0.518	0.32 (0.11–0.95)	0.040
Disease Free Survival				
Stage II (Reference Group)	–	–	–	–
Stage III	1.103 (0.519–2.343)	0.799	1.19 (0.58–2.44)	0.630

elevated preoperative CEA may be candidates for adjuvant chemotherapy after curative resection in stage II colon cancer [6,21].

In this study, a preoperative elevated CEA \geq 5 ng/ml was an independent predictor of overall survival, disease-free survival and recurrence and was associated with a higher risk of death for the entire cohort, a finding which mirrors other studies. Destri et al., who studied 395 patients with colorectal cancer found that a preoperative CEA \geq 5 ng/ml was associated with a significantly increased risk of recurrence (OR 1.02, $p = 0.004$) [22]. Although the conventional cut-off value of CEA (\geq 5 ng/ml) is usually an independent prognostic factor on the whole, individualised or stage adjusted CEA cut-off levels may be a more practical prognostic marker. Jeon et al., found that the optimal cut-off values were 7.4, 5.5, and 4.5 ng/ml for TNM stage I, II, and III, respectively [23]. This study used 2.5 ng/ml as a cut-off in some analyses as published data from the NSABP has demonstrated that the distribution of tumour stage is markedly different for CEA levels of < 2.5 and > 10 ng/ml respectively [12].

This study had the usual limitations of being a retrospective analysis of patients however, the data are derived from a prospectively maintained database with almost 100% complete data entry. The sample size may have limited the ability to detect further predictors of survival and recurrence. The cut-off value or reference level for CEA elevation was set based on NSABP data and this may have impacted upon the prognostic function of serum CEA levels. Despite these limitations, we found that pre-operative CEA retained its prognostic ability.

5. Conclusions

In this study, a preoperative elevated CEA \geq 5 ng/ml was an independent predictor of overall survival, disease-free survival and recurrence and was associated with a higher risk of death for the entire cohort, a finding which mirrors other studies. Further large-scale studies are necessary to determine a specific valid cutoff point for serum CEA level to achieve prognostic stratification and to assess the role of incorporating CEA into existing staging systems.

Ethical approval

This study was approved. Cabrini Hospital HREC #06-02-05-16.

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Conflicts of interest

None.

Author contribution

- 1-Study Design.
- 2-Prospective data collection.
- 3-Retrospective data collection.
- 4-Data analysis.
- 5-Manuscript preparation.

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Guarantor

Mr Ali Riaz Baqar.
Dr Simon Wilkins.
A/Prof Paul McMurrick.

Data statement

Study participants were assured raw data would remain confidential and not be shared.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijso.2019.02.014>.

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