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# RESEARCH ARTICLE

## RELATIONSHIP BETWEEN MAXIMUM SIZE OF THE PRIMARY TUMOR AND SERUM CEA WITH PREOPERATIVE CLINICAL STAGING IN RECTAL CANCER PATIENTS

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**ABSTRACT**

**Background:** Patients in resource limited setup have limited access to preoperative Magnetic Resonance Imaging (MRI). The study aims to assess the relationship between maximum size of the primary tumor and baseline serum CEA with AJCC primary tumor stage (T) and nodal staging (N). **Methods:** A retrospective analysis of 67 rectal cancer patients, treated at a tertiary care centre was undertaken. Patients were evaluated for clinical profile and treatment details. Ordinal regression was employed to assess relationship between maximum size of the primary tumor, serum CEA and AJCC 'T' and 'N' staging. **Results:** Nearly 49% (n=33) patients presented in stage III, 66% (n=44) patients underwent abdominal perineal resection (APR), 46% (n=31) patients received neoadjuvant chemoradiotherapy while 21% (n=14) received neoadjuvant chemotherapy. The mean size of primary tumor (cm) and serum CEA (ng/ml) for the study participants was 5.47 (2-9) and 16.98 (0-112) respectively. For every one unit increase in maximum size of the primary tumor, there is a 0.437 times increase in the odds of the tumor upstaging (p=0.003). If the serum CEA increases by one unit, there is 0.011 times increase in the odds of number of positive nodes (p=0.049). **Conclusions:** Maximum size of the primary tumor and serum CEA were significant predictor of 'T' stage and 'N' stage respectively. In resource limited settings where affordability and accessibility to MRI limits accurate preoperative rectal cancer staging, maximum size of the primary tumor and serum CEA can complement CT findings for clinical staging and neoadjuvant treatment decisions.



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# INTRODUCTION

More than 1.9 million new colorectal cancer cases and 935,000 deaths were estimated to occur in 2020, representing about one in 10 cancer cases and deaths, globally.[1] Overall, colorectal cancer ranks third in terms of incidence, but second in terms of mortality. Incidence rates are approximately 4-fold higher in transitioned countries compared with transitioning countries, but there is less variation in the mortality rates because of higher fatality in transitioning countries.[1] Time trend report for 1982-2010 of population-based cancer registry (PBCR) in India shows that colon and rectum both sites are having a significantly increasing trend in all major cancer registries with annual percentage change (APC) ranged from 0.9% to 5.8% for colon cancer and 2.7% to 9.8% for the rectal cancer. Among Indian men, the annual incidence rates for colon and rectal cancer are at 4.4 and 4.1 per 100,000 population. [1]

Rectal cancer staging includes assessment of local and distant extent of disease. Accurate assessment of local T (tumor), N (lymph node involvement), and M (distant metastases) is crucially important for determining the best stage-specific treatment.[2] Current assessment techniques include physical examination, CECT scan (contrast enhanced computed tomography), EUS (endoscopic ultrasonography), MRI (magnetic resonance imaging) and PET (positron emission tomography) scan.[3] Patients with preoperative evidence of locally advanced disease with T3 -T4 tumors and node positive disease usually receive neoadjuvant therapy including chemoradiotherapy, chemotherapy or both.[4] However, the pathological stage is not known with certainty in this situation and often patients may be over treated. It is therefore in the best interest of the patient and the treating team to choose diagnostic tests that can estimate the preoperative stage as accurately as possible.[5]

The gold standard for preoperative rectal cancer staging remains MRI pelvis[6] due to its accuracy in determining the primary rectal tumor stage, location and morphology of primary tumor, predicting circumferential resection margin, detecting extramural vascular invasion, involvement of sphincter complex, lymph nodes and adjacent organs. However, MRI is not commonly available at all treating institutes in low- and middle-income countries (LMICs).[7] In such a situation, CECT pelvis is the most commonly used investigation.[8] While conventional CECT is accurate in identifying invasion of neighbouring structures, it is not able to demonstrate the layers of the rectal wall accurately. This drawback limits the role of conventional CECT in the determination of local rectal cancer stage.[9] Decisions about use of neoadjuvant treatment or upfront surgery become difficult with CECT alone. Use of additional information like the maximum size of the primary tumor (in centimetres) on CECT scan may give supplementary information about bulk of tumor and may further help in correlation with staging. Many studies have also suggested the incorporation of CEA in the staging of rectal cancer. [10,11]

Studies have been carried to see the co relation between the rectal segment involved as a measure of its distance from the anal verge and its association with outcomes, with lower rectal lesions doing poorly as compared to middle or upper one third of the lesions.[12] Depth of tumor infiltration within the rectal wall, mesorectum and adjacent organ infiltration, lymph node involvement and lymphovascular involvement (LVI) are considered to be important prognostic factors.[13] However, none of the studies have evaluated the relationship of the maximum size of the primary tumor (in cms) with the primary rectal tumor staging (T). This maximum size of the primary tumor involved irrespective of its location in the rectum is an indicative of bulk of the disease and hence should be co-related to the stage. Various studies have shown that higher values of serum CEA at presentation are associated with adverse prognosis.[14,15] Raised serum CEA values are indicator of aggressive disease with potential for systemic spread.[16] However, preoperative serum CEA levels have not been correlated with tumor stage or lymph node involvement.

In our study we have tried to analyse this relationship between the maximum size of the primary tumor (in cms), as determined radiologically with the primary tumor staging and nodal involvement on MRI. Similarly, we have also tried to analyze the relationship of serum CEA levels with the primary tumor and lymph node involvement at presentation.

# MATERIALS AND METHODS

This was a retrospective analysis, where rectal cancer patients, reporting to the Department of Radiation Oncology at a tertiary care centre during the years from 2009 to 2019 were evaluated. Only patients of biopsy proven adenocarcinoma rectum were included. Patients with histopathology from outside the institute were included only if the histopathology report had been re-evaluated by the institutional pathology department. Only patients with pre-operative MRI available were included for the analysis. Patients with inadequate hospital record or who did not complete treatment were excluded from the analysis. Patients (n= 67) were evaluated for the demographic characteristics and clinical profile including biopsy, grade of tumor, baseline serum CEA (ng/ml), maximum size of primary tumor on radiology (cm), stage of the disease, type of surgery performed, details of neoadjuvant or adjuvant treatment received, postoperative histopathology details like number of lymph nodes dissected, number of lymph nodes positive, margin status, LVI, perineural invasion (PNI), etc. Survival outcomes could not be evaluated in view of poor follow up and inability to contact the patients. Neoadjuvant treatment consisted of a combination of radiation with concomitant chemotherapy (NACTRT) or neoadjuvant chemotherapy alone. Patients receiving surgical intervention were classified as either undergoing abdominoperineal resection (APR), low anterior resection (LAR) or others (exploratory laparotomy for unresectable disease, palliative colostomy). Adjuvant treatment was indicated for patients with stage II and stage III disease on postoperative histopathology. Adjuvant treatment consisted of 6 months of chemotherapy and a combination of chemotherapy and radiation for patients who did not receive radiation in the neoadjuvant setting. Radiotherapy was delivered using conventional planning. A dose of 45 Gy/25 fractions over 5 weeks was delivered to the whole pelvis using bony landmarks. Superior border was taken at L5 – S1 interface and inferior border was taken 2.5 cm beyond the lowermost extent of the growth. Radio-opaque marker was placed at the lower end of the growth. Lateral borders were taken 1.5 cm beyond the bony pelvis. This was followed by a boost of 5.4 Gy in 3 fractions delivered using three field, two lateral and one direct posterior, using 45 degree wedges. For patients with anterio posterior separartion of more than 18cm, whole pelvis was treated by four fields. Concomitant chemotherapy with radiation consisted of Tab capecitabine 825mg/$m^2$ BD given per orally on days of radiation.[17] For adjuvant chemotherapy most commonly used regimen was modified FOLFOX-6 at doses of Injection oxaliplatin 85mg/$m^2$ D1, Injection leucovorin 400mg/$m^2$ D1, Injection 5FU bolus 400mg/$m^2$ D1 and continuous infusion 5FU 1200mg/$m^2$ D1, D2 delivered over 22hours and repeated 2 weekly. FOLFOX was delivered in indoor setting while other chemotherapy regimen CAPEOX (Inj oxaliplatin 130mg/$m^2$ D1, Tab Capecitabine 1000mg/$m^2$ PO twice daily for 14 days, repeated 3 weekly) was delivered in Day Care setting.[17,18]

### STATISTICS

The data was analyzed using the SPSS software and R programming. Descriptive statistics were used for analysis of clinical variables. Variable collinearity was checked to ensure no strong correlation existed between the predictors. Ordinal regression was employed to assess relationship between the size of primary tumor and AJCC tumor and nodal staging on MRI while multi-linear regression was used to assess the relationship of serum CEA at presentation and AJCC tumor and nodal staging on MRI.

# RESULTS

The mean age of patients was 51.3 years, wherein 30% (n=20) patients were in the age-group of above 60 years (Table-1). T2 tumors were seen in 45% (n=30) patients. Most common stage at presentation was stage III, seen in 49% (n=33) patients. The mean serum carcinoembryonic antigen (CEA) value of rectal patients was 16.98 ng/ml (0-112). The mean size of the primary tumor of rectal cancer patients was 5.47cm (2cm-9cm) (Table 2). The detailed sample characteristics of the patients is presented in Table-1.

**Table 1. Sample characteristics of the study participants**

| Category | | Patient number (n=67) |
|---|---|---|
| Age Group | Below 31 | 8 (11.9%) |
| | 31-40 | 9 (13.4%) |
| | 41-50 | 12 (17.9%) |
| | 51-60 | 18 (26.9%) |
| | Above 60 | 20 (29.9%) |
| Tumor | T1 | 2 (3.0%) |
| | T2 | 30 (44.8%) |
| | T3 | 26 (38.8%) |
| | T4 | 9 (13.4%) |
| Stage | I | 11 (16.4%) |
| | II | 10 (14.9%) |
| | III | 33 (49.3%) |
| | IV | 13 (19.4%) |
| Mean serum CEA (ng/ml) | 16.98 | Range (0-112) |
| Maximum size (mean) of the primary tumor (cm) | 5.47 | Range (2 -9) |

CEA- Carcino embryonic antigen

Sixty seven percent (n=45) patients received some form of neoadjuvant treatment of which 46% (n=31) patients received neoadjuvant chemoradiotherapy and 21% (n=14) received neoadjuvant chemotherapy alone. APR was the most common surgical procedure done in 66% (n=44) patients while LAR was done in 9% (n=6) patients. A group of patients constituting 12% (n=8) was found to be unresectable on exploration and could be undertaken for palliative procedures like colostomy only. Adjuvant chemotherapy based on postoperative histopathology was received by 56% (n=33) patients while both adjuvant chemotherapy and radiation were received by 31% (n=18) patients. Table 2 shows the treatment details of the patients.

**Table 2. Treatment Details and Outcomes**

| | | |
|---|---|---|
| Type of Surgery | No Surgery | 9 (13.4%) |
| | LAR | 6 (9%) |
| | APR | 44 (65.7%) |
| | Other | 8 (11.9%) |
| Neoadjuvant Treatment | None | 22 (32.8%) |
| | Chemoradiotherapy | 31 (46.3%) |
| | Chemotherapy Only | 14 (20.9%) |
| Adjuvant Treatment | None | 8 (13.6%) |
| | Radiotherapy and Chemotherapy | 18 (30.5%) |
| | Chemotherapy Only | 33 (55.9%) |
| Recurrence | Systemic metastases (with or without local recurrence) | 28 (48.3%) |
| | Local recurrence | 17 (29.3%) |

LAR-Low anterior resection, APR-Abdomino perineal resection

Postoperative histopathology details are shown in Table 3 and revealed a margin positive resection in 18% (n=11) patients. LVI and PNI was seen in 20% (n=12) and 15% (n=9) of patients respectively. Mean number of lymph nodes dissected and mean number of lymph nodes positive on histopathology were 9 (6-22) and 3 (0-8) respectively.

**Table 3. Pathological characteristics of the study participants**

| | | |
|---|---|---|
| Mean Lymph Nodes Dissected | 9 | Range (6-22) |
| Mean Lymph Node Positivity | 3 | Range (0-8) |
| Grade | Well Diff | 10 (14.9%) |
| | Mod Diff | 51 (76.1%) |
| | Poorly Diff | 6 (9%) |
| Margin | Negative | 49 (81.7%) |
| | Positive | 11 (18.3%) |
| LVI | Negative | 48 (80%) |
| | Positive | 12 (20%) |
| PNI | Negative | 51 (85%) |
| | Positive | 9 (15%) |

LVI-Lymphovascular invasion, PNI-Perineural invasion

To evaluate the relationship between maximum size of the primary tumor and serum CEA levels with the T staging in AJCC, ordinal regression using stage of tumor as dependent variable, maximum size of the primary tumor and serum CEA as independent variables was done (Table 4). The ordinal regression for maximum size of the primary tumor (0.44), suggests that as the size of the primary tumor increases by 1 unit, there is 0.44 increase in the odds of upstaging of the tumor stage after controlling effect of other covariates. This relatioship is statistically significant (p= 0.003). Thus, the maximum size of the primary tumor was a significant positive predictor of interest. However no significant relationship is seen between serum CEA at presentation and T staging of the primary tumor. When ordinal regression was carried out to see the relationship between maximum size of the primary tumor and serum CEA with the lymph node involvement as dependent variable, it was seen that increased CEA in the rectal cancer patient positively influenced the number of positive nodes. If the serum CEA increases by one unit, there is 0.011 increase in the odds of increase in the number of positive nodes, after controlling effect of other covariates. This relationship is statistically significant (p=0.049). However, no significant association is seen with maximum size of the primary tumor and involved lymph nodes (Table 5).

# DISCUSSION

There has been emphasis on rectal cancer staging based on the depth of involvement, lymph node involvement and presence or absence of metastatic disease. Many studies also suggest incorporation of serum CEA in the staging based on the prognostic significance.[19] However, there has not been much discussion on the maximum size of the primary tumor of the rectum as an indicator for primary tumor bulk (T stage) or overall stage (AJCC TNM). Staging of the colon cancer is based on depth of infiltration of primary tumor while that of anal canal cancer is based on the maximum size of the primary tumor.[2] Rectal cancer which extends to the sigmoid colon is labelled as rectosigmoid cancer, similarly rectal cancer which extend to the anal canal is labelled as anorectal cancer. Most of the systemic management protocols for adjuvant chemotherapy for rectal cancers[20] are extrapolated from colon cancer while local management protocols involve chemoradiation like anal cancer.[21] Hence maximum size of the primary tumor as representative of bulk of the primary tumor, on lines of anal canal cancer should be investigated for rectal cancer patients. Management of rectal cancers involves a multidisciplinary approach involving radiation, chemotherapy, surgery used in combination with the aim to improve locoregional control, overall survival and most importantly sphincter preservation.[22] Rectal cancer is staged surgically, however accurate assessment of preoperative stage for this tumor is most important for management decisions, with advanced tumors (T3 and T4) requiring preoperative radiotherapy, chemotherapy or both while patients with limited disease (T1, T2) are expected to have clear circumferential resection margins and are taken for upfront surgery.[23] Conventional CECT detects local invasion of neighbouring structures and distant metastases.[24] High-resolution MRI images obtained in multiple planes with high soft tissue contrast resolution provides detailed information concerning the relation of the tumor to the circumferential resection margin and adjacent structures, extramural venous invasion, lateral pelvic lymphadenopathy, and peritoneal surface involvement by tumor.[3,4] In LMICs like

**Table 4. Determinants of Primary tumor stage (T) among rectal cancer patients**

| Parameter Estimates | Estimate | Std. Error | Significance (p) | Exp (β) | 95% Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound |
| CEA | 0.002 | 0.012 | 0.832 | 1.002 | -.020 | 0.025 |
| Maximum size of Primary Tumor | 0.437 | 0.145 | 0.003 | 1.548 | 0.152 | 0.722 |

**Table 5. Determinants of node positivity (N) among rectal cancer patients**

| Parameter Estimates | Estimate | Std. Error | Significance (p) | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| CEA | 0.011 | 0.006 | 0.049 | 0.000 | 0.023 |
| LSI | 0.084 | 0.091 | 0.351 | -0.093 | 0.262 |

India, access to MRI is limited and decisions are based on CECT scan.[7] CECT scan, cannot reliably predict the depth of tumor infiltration, however it can reliably predict the maximum size of the primary tumor.[24] The results of our study show that the ordinal regression for maximum size of the primary tumor (0.44), suggests that as the maximum size increases the T stage also increases and this is statistically significant (p= 0.003). For every one unit increase in the maximum size of the primary tumor, there is 0.437 times increase in the odds of the upstaging of the primary tumor.

The significant positive prediction of maximum size of the primary tumor with T stage in our study on ordinal regression, shows that maximum size of the primary tumor can be used to supplement information for T staging of rectal cancers. This can facilitate clinical decision making for management when in dilemma about T staging on endoscopy and/or CECT radiology. To the best of our knowledge, we could not find similar studies evaluating the relationship of maximum size of the primary tumor with primary 'T' or TNM staging. Serum CEA is a non-invasive and cheap tumor marker, over expressed in more than 90% of colorectal cancers.[25] Several studies[25,26] have confirmed its prognostic significance in colorectal cancers. Previous large studies have shown that elevated preoperative serum CEA levels are associated with worse prognosis in all stages. [27] In 2000, the Colorectal Working Group of the AJCC proposed the inclusion of serum level of serum CEA into the conventional AJCC TNM staging system of colorectal cancer. American Society of Clinical Oncology and the European Group on Tumor Markers have both supported the inclusion of preoperative serum CEA level as a prognostic tool in colorectal cancer.[10] A study reported that in stage T1N0M0 disease, elevated level of serum CEA was associated with 227.6% increased risk of mortality compared to normal level of serum CEA in rectal cancer patients.[27] Preoperative serum CEA elevation, even in very early stage rectal cancer could be a marker of biologically aggressive disease and correlate with unfavourable oncologic outcomes. Serum CEA is associated with cancer cell adhesion and facilitates attachment of colorectal cancer cells to sites of metastasis and supports tumor progression.[28] Node positive patients are candidates for adjuvant chemotherapy. Patients with node-negative early-stage rectal cancer regardless of serum CEA level would generally not be offered adjuvant chemotherapy.[20] Studies have identified however that patients with elevated preoperative serum CEA may be candidates for adjuvant chemotherapy after curative resection in stage II colorectal cancer.[29,30] Furthermore, patients with node-negative, early-stage colon cancer but with elevated preoperative serum 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.[14] Both lymph node involvement and serum CEA elevation are deemed as the acquisition of metastatic ability.[11] In our study when we analysed the relationship between maximum size of the primary tumor and serum CEA with the lymph node involvement as dependent variable, it was seen on ordinal regression that increased CEA in the rectal cancer patients positively influenced the number of positive nodes. If the serum CEA value increases by one unit, there is 0.011 times increase in the odds of increase in the number of positive nodes, after controlling effect of other covariates. This relationship is statistically significant (p=0.049). However, no such association is seen with maximum size of the primary tumor. Serum CEA is known to be a marker of systemic disease as reported by its prognostic significance by multiple studies .[27,28] Similarly in our study serum CEA shows statistically significant relation only with the number of positive lymph nodes and not with primary tumor stage corroborating the same. Although this study is limited by retrospective nature and small sample size, it shows that the maximum size of the primary tumor in rectal cancer is significantly related to primary 'T' stage and may be used to complement CECT scan findings in patients not undergoing MRI for management decisions involving use of neoadjuvant treatment. The significant association of serum CEA with node involvement suggests that both serum CEA and node positivity are regarded as markers of systemic spread and biological aggressiveness of the tumor for a matched T stage. Prospective studies with large number of patients are required to further confirm these findings.

# CONCLUSION

Majority of patients in LMICs present with locally advanced rectal cancer, decisions for neoadjuvant treatment are predominantly based on MRI pelvis findings. Access to MRI is limited in such setup and use of additional information like maximum size of the primary tumor and serum CEA may help to complement the CECT scan findings and guide treatment decisions. Our study shows that maximum size of the primary tumor is significantly related to the primary tumor stage while serum CEA significantly co relates with the nodal stage for rectal cancer patients.

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**Conflicts of Interest:** None

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