Section: Radiation Oncology

Original Research Article

EVALUATION OF PATHOLOGICAL COMPLETE RESPONSE FOLLOWING NEOADJUVANT CHEMORADIATION AND ITS PREDICTORS IN LOCALLY ADVANCED CARCINOMA RECTUM

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Abstract

Background: Colorectal cancer is the third most common cancer in incidence and the second most common cancer in terms of mortality globally, with increasing incidence in India. The study aims to evaluate the incidence of pathological complete response post-NACRT in our population's locally advanced carcinoma rectum and determine the predisposing factors. **Materials and Methods:** Retrospective analysis of Pathological Complete Response achieved in Locally Advanced Carcinoma Rectum patients treated with neoadjuvant chemoradiotherapy followed by surgery in a government tertiary care institution was done from January 2019 to April 2022. Parameters including the age of presentation, sexual preponderance, comorbidities, tobacco usage, tumour length, and location; histological variants, primary tumour (T) and regional nodal (N) categories and the interval between NACRT and surgery were studied in this group of population to assess their correlation to PCR. **Result:** A total of 113 carcinoma rectum patients received radiotherapy. Of them, 80 patients were started on neoadjuvant chemoradiotherapy for their locally advanced disease. Twenty-four of them completed the protocol treatment. Pathological complete response was observed in 7 (29%) of 24 patients. Patients below 60 years of age, with no comorbidities, no tobacco history, length of tumor < 4cm, with non-mucinous adenocarcinoma variants occurring in the middle 1/3rd of the rectum, with primary tumor (T) categories T1-2 & regional nodal (N) categories N0-1 and with long intervals between NACRT and surgery (>12 weeks) have good chances of achieving pCR following NACRT. **Conclusion:** NACRT is the preferred approach for locally advanced carcinoma rectum patients because of the high chance of tumor downstaging and associated pCR response.

INTRODUCTION

According to the global cancer statistics 2022, colorectal cancer is the third most common cancer in incidence and the second most common cancer in mortality.[1] Surgery is the standard treatment for patients with clinically resectable rectal cancer. Postoperative radio chemotherapy was initially recommended for locally advanced disease (pT3/4 or pN+). Many studies then established preoperative chemoradiotherapy over postoperative chemoradiotherapy as the preferred treatment in addition to surgery for locally advanced rectal cancer because of better local control.[2,3] Recent studies have focused on decreasing distant metastases without compromising locoregional control, thus improving survival outcomes, using techniques like short-course radiotherapy and total neoadjuvant therapy.[4]

Preoperative neoadjuvant chemoradiotherapy can reduce tumor volume and stage, thus increasing resectability and sphincter preservation. It can also

result in a pathological complete response (PCR) in 7 to 30% of carcinoma rectum patients, according to various studies worldwide.[1] Pathologic complete response in carcinoma rectum is defined as the absence of viable tumor cells in the rectal wall and any resected lymph node. Many studies have also reported lower rates of recurrences and favorable survival outcomes in these patients achieving PCR compared to their non-PCR counterparts.[5]

Also, according to some literature, in case of complete clinical response after neoadjuvant chemoradiotherapy (NACRT), surgery does not lead to improved outcomes but can cause unnecessary morbidity. They emphasize the need to identify that subgroup of patients who would more likely attain this complete response post-NACRT so that they may be planned for a wait-and-watch approach instead of a planned surgery.[6]

Unfortunately, the incidence of colorectal cancers is on the rise in India due to changing lifestyles adding to the cancer morbidity of our country. This makes it important to evaluate the predictors of complete response post-NACRT, which could predict better oncological outcomes in our patients. It may facilitate the wait-and-watch approach with careful patient selection and follow-up.

Our study aims to evaluate the incidence of pathological complete response post-NACRT in our population's locally advanced carcinoma rectum and determine the factors predisposing to PCR and better survival outcomes.

MATERIALS AND METHODS

This retrospective observational study was done in a government tertiary care institution (regional cancer centre). Patients who presented to our OPD, evaluated and diagnosed with locally advanced adenocarcinoma of the rectum and planned for neoadjuvant chemoradiotherapy in tumor board were included in the study after applying exclusion criteria. We analyzed patients treated with NACRT between January 2019 and April 2022.

Inclusion Criteria

Histologically confirmed adenocarcinomas of the rectum, planned for neoadjuvant chemoradiotherapy in tumor board, and cT3-4 or N+ disease before NACRT were included.

Exclusion Criteria

Patients with any prior anti-cancer therapy, history of pelvic radiation treatment, distant metastases at presentation, and synchronous malignant tumors were excluded.

Radiotherapy was administered as External Beam Radiotherapy to the pelvic locoregional site with a total dose of 50 Gy in 1.8 – 2 Gy fractions, five consecutive days per week, for 5-6 weeks by 3-Dimensional Conformal Radiotherapy method in a Linear Accelerator along with concurrent chemotherapy with Tab. Capecitabine 825 mg/m2 BD during RT.

Patients were assessed for response and resectability six weeks post-NACRT with physical examination, MRI imaging and endoscopy. Clinical characteristics evaluated to determine the feasibility and nature of surgery include the size of the tumor, distance from the anal verge and anorectal ring, location within the rectal lumen, circumferential involvement, the extent of obstruction, invasion and fixation to the rectal wall, sphincter involvement and sphincter tone. Low Anterior Resection and Abdomino Perineal Resection were the surgeries performed. Total mesorectal excision was performed in both surgeries.

College of American Pathologists (CAP) guidelines were applied to examine specimens of the rectum for neoadjuvant treatment effect if present or not, in which a complete response (0) denotes no remaining viable cancer cells with only fibrotic masses or acellular mucin pools.

The following parameters were analysed for their correlation to pathological complete response: mean age of presentation, sexual preponderance, comorbidities, tobacco usage, tumour length, location, histological variants, primary tumour (T) and regional nodal (N) categories and the interval between NACRT and surgery.

RESULTS

One hundred thirteen carcinoma rectum patients received radiotherapy between January 2019 and April 2022. Of them, 23 (20%) were postoperative patients who underwent adjuvant radiotherapy, 10 (9%) were with metastatic disease and received palliative RT. The remaining 80 (71%) patients were the ones who were started on neoadjuvant chemoradiotherapy for their locally advanced disease.

Of the 80 locally advanced rectal adenocarcinoma patients, 73 completed neoadjuvant chemoradiotherapy. Out of whom, 24 (33%) patients underwent surgery.

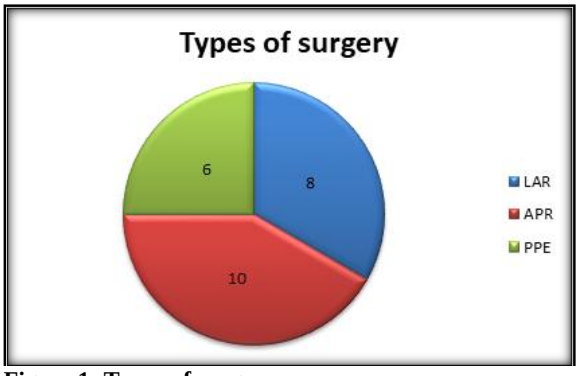

Figure 1: Types of surgery

7 (29%) of 24 patients have achieved a pathologic complete response.

The median interval from completion of chemoradiotherapy to surgery was 72 days (45 – 127 days).

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Our study associated interval to surgery after NACRT of > 84 days (12 weeks) with more PCR responses.

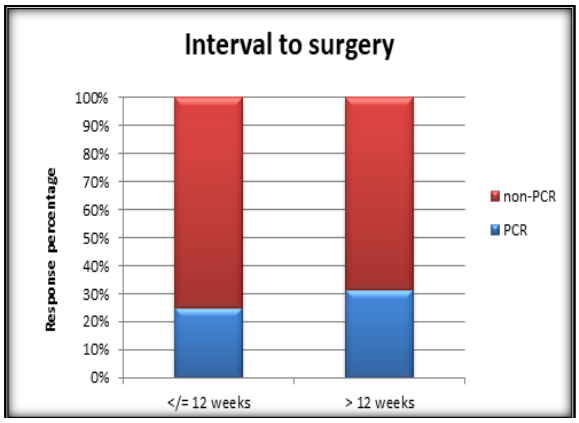

Figure 2: Interval to surgery and PCR

On stratifying the responses to surgery based on demographic and tumor characteristics, we obtained the following results:
PCR response was more when the age of presentation was below 60 years.

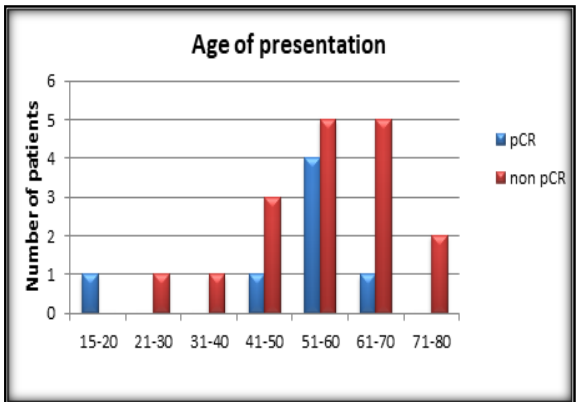

Figure 3: Age of presentation and PCR

The mean age of presentation in the PCR group was 48 years (17-68 years).
There was not much difference between the responses when stratified by gender in our study.

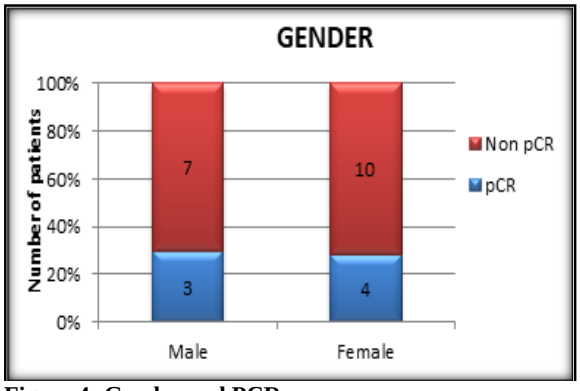

Figure 4: Gender and PCR

PCR response was more pronounced when the tumor was in the middle 1/3 of the rectum.

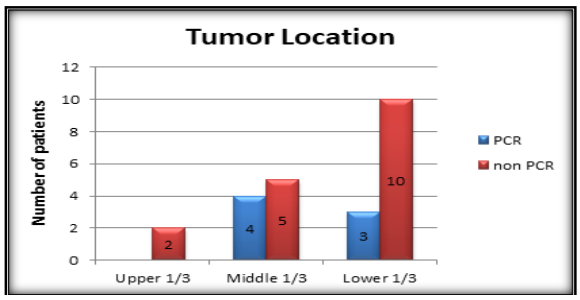

Figure 5: Tumor location and PCR

The presence of comorbidities also negatively influenced the tumor response to NACRT.

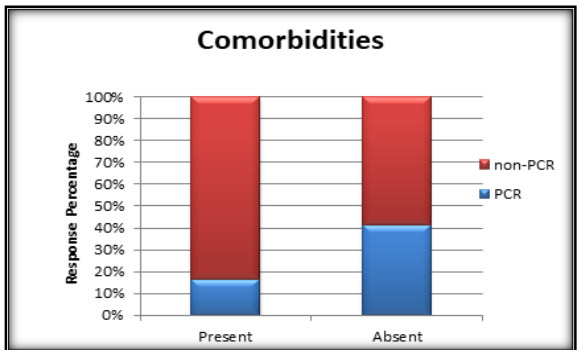

Figure 6: Comorbidities and PCR

Stratifying the tumor responses based on tobacco usage yielded the following results.

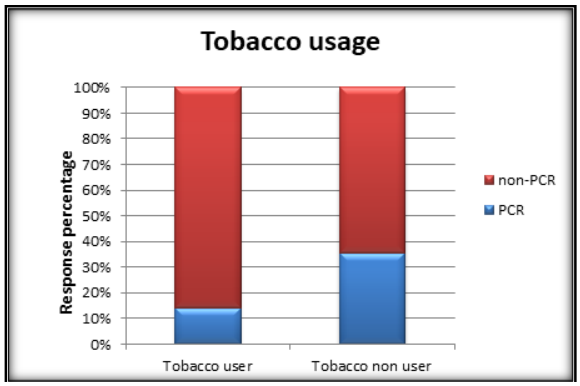

Figure 7: Tobacco usage and PCR

On assessment based on histological types, the non-mucinous adenocarcinoma variant has more preference for a pathological complete response.

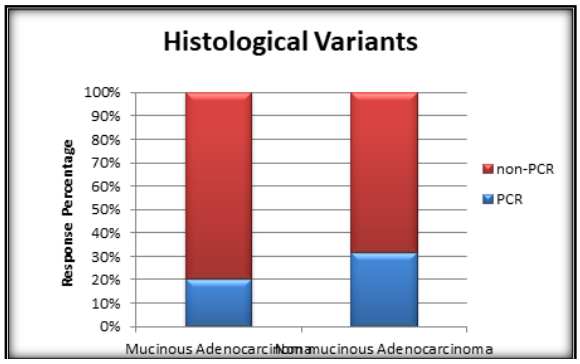

Figure 8: Histological variants and PCR

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More PCR responses were seen when the tumor invasion was limited to the pericolorectal tissues (T2, T3) and when the number of regional nodes was less than or equal to 3 (N1)).

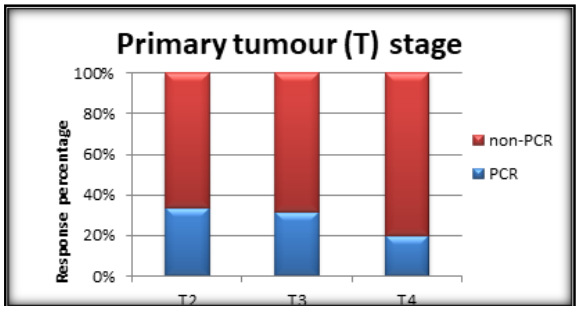

Figure 9: T stage and PCR

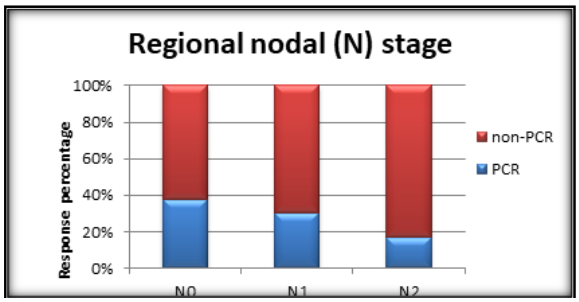

Figure 10: N stage and PCR

Also, a tumor length of <4cm resulted in more PCR responses.

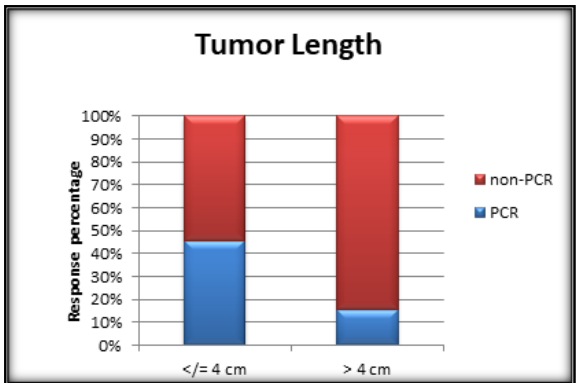

Figure 11: Tumor length and PCR

DISCUSSION

In our study, 91.2% of the patients planned for NACRT completed the treatment, with the remaining defaulting midway due to covid-19 pandemic and personal reasons. But the proportion falls when assessing the number of patients who underwent surgery following NACRT. Only 33% of the patients who completed NACRT underwent the planned surgery. Though the covid-19 pandemic had its role to play in this decline, other factors such as patients not willing for a permanent colostomy and thus not willing for surgery, patients not fit to undergo surgery, tumor progressing and becoming unresectable or throwing distant meets while on treatment are also important attributable reasons.

The pathological complete response found in our study (24%) was similar to those in the literature. Most studies report PCR in the range of about 10 – 30%.[5-8] Previous studies have also found that prolonging the interval between NACRT and surgery was associated with better PCR responses,[7,9] as was the finding in our study.

A study by Wang K et al. on the predictors of pathological response found age to be an independent risk factor affecting outcomes, and the same was true in our study. This can be attributed to the strong immune response seen in the younger population.[1] Peng H et al in 2018,[10] analyzed the clinical characteristics predicting PCR and found that gender does not have a significant role to play in this setting. Our study shows that males and females have almost equal chances of obtaining PCR when matched for other factors affecting outcomes.

Tumors located in the middle 1/3 of the rectum have more chance of obtaining PCR, which was the finding in our study and in the study by Nawaz S et al.[11] They state that the mid and lower rectal tumors show better responses (complete and near complete) to NACRT than the upper rectal tumors (54% vs 20 %). Our study's PCR responses in mid, lower and upper rectal tumors are 44%, 30% and 0%, respectively. The presence of comorbidities is found to impact the treatment outcomes negatively. Comorbidities are known to decrease the tolerability and increase the toxicity of cancer treatments, thus reducing patient compliance and affecting responses to NACRT.

Tobacco usage is another negative factor associated with poor responses in our study. This finding aligns with the study by Wallin et al. in 2013,[12] in which they analyzed the predictors for PCR in carcinoma rectum. They found smoking to be a negative factor impacting response to chemoradiation. In the study by Wallin et al,[12] tumors were also stratified based on their pre-treatment differentiation. The mucinous variant of adenocarcinoma has been shown to have poorer outcomes when compared to non-mucinous variants. The same translated to PCR outcomes in our study.

Zhang et al,[13] 2019 found that the clinical T stage plays an important role in determining response to NACRT, with T2, T3 and T4 tumors showing PCR responses of 33%, 17%, and 15%, respectively. In our study, these proportions were 33%, 31% and 20%. The clinical N category also plays a similar role in determining PCR, with N1 and N2 diseases achieving PCR responses of 21% and 14% in their study and 30% and 17% in our study. Zhang et al,[13] assessed pre-therapeutic parameters predicting PCR and found that the tumor length had an independent association with PCR following neoadjuvant treatment. The median tumor length in their study was 4 cm, and the tumors with length </= 4 cm were found to have more PCR responses than those > 4cm (25% vs 9%). The same was true in our study (45% vs 15%).

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In locally advanced rectal cancer, NACRT followed by surgery is the gold standard approach. In patients achieving PCR after NACRT, the oncological outcomes are better than their non – PCR counterparts. But since the evaluation of PCR is challenging as the clinical complete response (cCR) does not always translate into a pathological complete response, assessing factors that predict PCR becomes paramount. Caution should be exercised before implementing the wait-and-watch approach in patients with cCR. This is now recommended only in elderly patients with limited life expectancy.[14,15] In the circumstances like a patient refusing surgery or in clinical trials with strict selection criteria and follow-up, where wait and watch approach may be employed,[15,16] the above-found factors predicting PCR can be used during the selection of the patients.

Limitations

This study is limited by the fact that it is a retrospective study and also by its low sample size. Large prospective studies are needed to more precisely identify this population subgroup that would benefit more from NACRT and thus have better disease-free and overall survival outcomes.

CONCLUSION

NACRT is the preferred approach for locally advanced carcinoma rectum because of a high chance of tumor downstaging and pCR response. Patients below 60yrs of age, with no comorbidities, no tobacco history, length of tumor < 4cm, with non-mucinous adenocarcinoma variants, occurring in the middle 1/3rd of the rectum, with primary tumor (T) categories T1-2 & regional nodal (N) categories N0-1 and with long intervals between NACRT and surgery have good chances of achieving pCR following NACRT. These clinical factors can be used as predictors of PCR post-NACRT and better oncological outcomes in these patients.

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