

Clinicopathological Study of Neoadjuvant Therapy in Carcinoma Rectum with Assessment of Pathologic Response: A Cross-sectional Study

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ABSTRACT

Introduction: Rectal carcinoma is a major public health problem. It is the third most common carcinoma of the large intestine and the third most common carcinoma in men and women worldwide. Nowadays, there is an increase in the use of chemoradiation, creating uncertain challenges for Surgical Pathologists in observing and evaluating gross, microscopic, and tumour response. Also, it creates difficulties in the assessment and prognostic relevance of pathologic features.

Aim: To study histopathologic changes that occurs after Neoadjuvant Chemoradiation Therapy (NACRT) in carcinoma rectum.

Materials and Methods: The present cross-sectional study was conducted in the Department of Pathology, Chhatrapati Sambhajnagar (Aurangabad), Maharashtra, India from January 2019 to December 2024. Patients whose post-NACRT carcinoma rectum specimen was received in the department were included. This study emphasises histopathologic changes and response after NACRT in patients with carcinoma rectum. The specimen was adequately sampled and then embedded in paraffin wax. Multiple sections were taken from the tumour area. Sections of 3-5 µm thickness were cut and stained with Haematoxylin and Eosin (H&E) for microscopic examination, all according to standard procedures. Statistical software Statistical Package for Social Sciences (SPSS) version 25 was used to enter and

analyse the data. Descriptive statistics such as frequencies and percentages were used to summarise categorical variables like histopathological types, Tumour Regression Grades (TRG), and the presence of features such as lymphovascular invasion, acellular mucin pools.

Results: A total of 34 post-NACRT cases were studied. Out of this, the maximum number of patients was found in the age group 41-50 years, with 12 (35.3%) cases. The youngest case was 25 years, and the oldest case was 76 years, with a mean age of 50.5 years. A maximum number of cases were male, 22 (64.7%), M: F-1.83:1. Acellular pools of mucin were present in five cases (14.7%), and 10 (29.4%) cases had no residual tumour. Moderately differentiated mucinous adenocarcinoma was found in a maximum of 5 (14.7%) cases. Fibrosis (12 cases) and dense lymphoplasmacytic infiltrates (13 cases) were observed. In most cases, 17 (50%) have TRG-3 and have a poor response. Complete response (TRG-0) was seen in 7 (20.5%) cases.

Conclusion: Preoperative chemoradiation induces changes in the gross appearance of the surgical specimen and its pathologic features, which could impact patient management and outcome. Tumour and fibrosis are very difficult to demonstrate on gross examination and, hence, require maximum sampling. The presence of acellular mucin pools represents a completely eradicated tumour. Tumour regression score is a useful method of scoring tumour response after NACRT.

Keywords: Chemoradiation, Rectal carcinoma, Tumour regression score

INTRODUCTION

Rectal cancer is the third most common cancer of the large intestine, also known as colorectal or bowel cancer, and it is one of the major public health problems [1]. Although its geographical incidence varies worldwide, its pattern is similar among men and women. According to GLOBOCAN 2020, an estimated 19.3 million new cancer cases and 10.0 million cancer-related deaths occurred worldwide in 2020. For both sexes combined, newly diagnosed colorectal cancer cases are 10.0% [2]. Colorectal cancer is the third most commonly diagnosed cancer and the third most common cause of cancer-related death in both men and women in the United States [3]. Lung cancer is the leading cause of cancer death (18.0% of the total cancer deaths), followed by colorectal (9.4%). It is the second most common cause of death worldwide. Regarding its prevalence, it is more common in developed regions of the world than in developing countries [3]. According to the latest data (Globocan 2020), in India, new colorectal cancer cases account for 65358 (4.9%). Out of these, males correspond to 40408 (6.3%) and females to 24950 (3.7%) cases. The 5-year prevalence of all ages

includes about 62827 cases [2,4]. Due to the different embryonic origins of the colon and rectum, the cancers arising from them have several other distinctive features [5].

Rectal carcinoma incidence has been steadily increasing worldwide, especially in developing countries that are adopting the "Western" way of life. A sedentary lifestyle, red meat consumption, obesity, alcohol, and tobacco are considered the driving factors behind the growth of rectal carcinoma [6].

The first known concept of the mesorectum was by Romanian Surgeon and Anatomist Jonnes Coin, who called it "la gainefibreuse du rectum" [7]. The technique of TME is based on the sharp dissection of the endopelvic fascia with scissors or cautery along the areolar plane between the visceral fascia of the mesorectum and the parietal fascia of the pelvic wall (through the avascular embryologic plane). A big Non Peritonealised Surface (NPS) is created by this dissection and a tumour with all associated lymph nodes [8]. Since the late '70s, Total Mesorectal Excision (TME) has become the standard surgical approach to rectal carcinomas [9].

Many confounding factors (i.e., obesity, previous surgery) in the patients' anatomy make it difficult to dissect a complete TME [10]. TME can play a major role in decreasing the risk of local recurrence of rectal cancer. Short-term preoperative radiotherapy reduces the risk of local recurrence in patients with rectal cancer who undergo a standardised TME [11].

There is a high-risk of local recurrence in conventional surgery. To avoid local recurrence and increase survival, postoperative chemoradiation is given. NACRT followed by radical surgery is still the "gold standard" approach for locally advanced rectal carcinoma. However, pathological Complete Response (pCR) could be achieved in up to 30% of patients after NACRT [9]. NACRT reduces the risk of local recurrence in patients with rectal carcinoma who undergo a standardised TME. Preoperative chemoradiation alters the macroscopic and microscopic features; therefore, it becomes difficult for Surgical Pathologists when it comes to observing and evaluating gross, difficult microscopic and tumour regression [12].

The primary objective was to study the response after NACRT in patients with carcinoma rectum.

MATERIALS AND METHODS

The present cross-sectional study was conducted from January 2019 to April 2024, as approved by Chhatrapati Sambhajnagar IEC-GMCA/Approval/249/2023. A total of 34 cases of rectal carcinoma treated with NACRT followed by surgery (abdominoperineal resection or anterior resection) were included. Specimens received in the Department of Pathology at the Tertiary Care Center. As per the standard protocol, most patients received capecitabine (825 mg/m² PO Bid) with radiation (45 Gy/20 fractions) followed by surgery (abdominoperineal resection or anterior resection). The history of neoadjuvant therapy should always be sought in instances to complete the response to neoadjuvant treatment. It's important to know the preoperative biopsy diagnosis and the exact site of the tumour for selecting the area for sampling.

Inclusion criteria: Post- NACRT carcinoma rectum specimen.

Exclusion criteria: Slides received for review or a second opinion; Rectal biopsies; Autolysed specimen.

Study Procedure

The anterior and posterior aspects of the mesorectum were photographed to document their smoothness/irregularity. Then, the mesorectal fat (CRM/NPS) was inked; the peritonealised surfaces were not inked. Then, the specimen was measured and cut open from the anterior aspect, starting from either end of the tumour, till 1 cm above and below the tumour. Except in the case of the absence of a tumour following neoadjuvant treatment, the specimen should be completely opened and then fixed. Then, loose, formalin-soaked gauze wicks were inserted into the intact segment of the rectum. All specimens were fixed in 10% neutral-buffered formalin for 24 hours.

After fixation segment was sliced transversely, not more than 5 mm thick, to identify the area of deepest invasion. The cut-section was photographed again to keep a record of the quality of the excised mesorectum, location, and distance to all surgical margins, and size of the tumour measured in two dimensions. The specimen was adequately sampled and then embedded in paraffin wax. Multiple sections were taken from the tumour area, including proximal and distal (longitudinal mucosal resection margins) and circumferential resected margins at all sites (rectum and colon), as well as adjacent mucosa. Lymph nodes were sampled from the perirectal fat. Mesorectum and perirectal fat were sampled to confirm the presence or absence of extramural venous invasion. Sections of 3-5 µm thickness were cut and stained with Haematoxylin and Eosin (H&E) for microscopic examination, all according to standard procedures.

Relevant preop and postop radiology findings were noted whenever available. Pathologic changes were studied, including stromal fibrosis, lymphoplasmacytic infiltrates, Circumferential Resection Margins (CRM), the extent of the tumour in the muscle layer and perirectal fat, extramural involvement, Lymphovascular Invasion (LVI), Perineural Invasion (PNI), and acellular pools of mucin. The lymph node was evaluated for the presence of metastasis.

Also, the Tumour Regression Grade (TRG) or pathologic response (pCR) was evaluated according to the modified RYAN scheme {College of American Pathologists (CAP) Protocol}, needed for prognostication and further management [Table/Fig-1] [13].

S. no.	Tumour Regression Grade (TRG)	Tumour response
1	0	No viable cancer cells (complete response).
2	1	Minimal residual cancer with single cells or small groups of cancer cells (near-complete response).
3	2	Residual cancer with evident tumour regression, which is more than single cells or small groups of cancer cells (partial response)
4	3	Extensive residual cancer with no evident tumour regression (poor or no response)

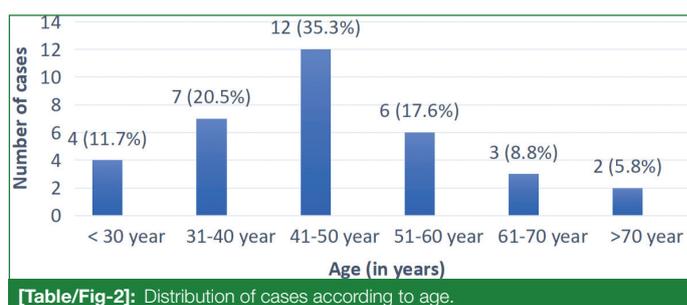
[Table/Fig-1]: Tumour Regression score according to Modified RYAN Scheme (College of American Pathologists).

STATISTICAL ANALYSIS

Statistical software SPSS version 25 was used to enter and analyse the data. Descriptive statistics such as frequencies and percentages were used to summarise categorical variables like histopathological types, TRG, and the presence of features such as LVI, acellular mucin pools. Age was expressed as mean and range, and grouped frequencies.

RESULTS

In the present study, males were affected more than females, with 22 males (64.7%) and 12 females (35.2%), resulting in an M:F ratio of 1.83:1. The peak incidence was seen in the age group 41-50 years with 12 cases (35.3%). The youngest case is of 25 years and the oldest case is of 76 years, with a mean age of 50.5 years [Table/Fig-2].



In the present study, the most common presentation is moderately differentiated adenocarcinoma in 12 cases (35.3%), with signet ring cell carcinoma in 2.94%. Acellular pools of mucin present in 5 (14.7%) and 10 cases (29.4%) were of no residual tumour, i.e., complete response [Table/Fig-3].

S. no.	Microscopic diagnosis	No. of cases	%
1	Moderately differentiated adenocarcinoma	12	35.3
2	Moderately differentiated mucinous adenocarcinoma	5	14.7
3	Mucinous Adenocarcinoma with signet ring cells	6	17.6
4	Signet ring cell carcinoma	1	2.94
5	No residual tumour	10	29.4
6	Acellular mucin pools	5	14.7

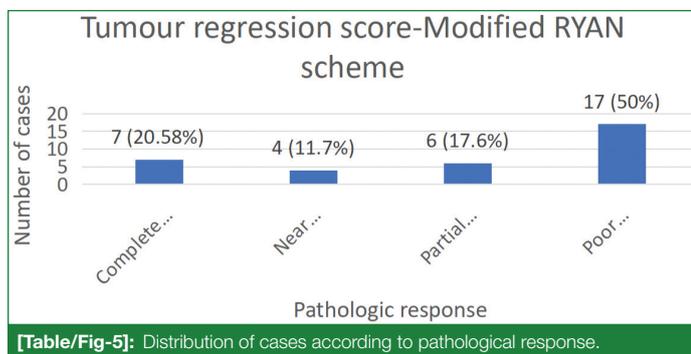
[Table/Fig-3]: Distribution of cases according to histopathologic findings.

In the present study, fibrosis was seen in 12 cases (35.3%) and lymphoplasmacytic inflammatory infiltrates (L-P Infiltrates) were seen in 13 cases (38.2%). Tumour is extending up to the CRM in five cases (14.7%) [Table/Fig-4].

S. no.	Histopathological changes	No. of cases	Percentage
1	Fibrosis	12	35.3%
2	Lymphoplasmacytic infiltrates	13	38.2%
3	Lymphovascular invasion	4	11.7%
4	Perineural Invasion (PNI)	3	8.8%
5	Up to the muscularis propria	25	73.5%
6	Up to perirectal fat	8	23.5%
7	Up to CRM	5	14.7%
8	Lymph node involvement	9	26.5%

[Table/Fig-4]: Distribution of cases according to histopathological changes.

In the present case, in most cases, 17 (50%) have TRG-3 and have a poor response. Complete response (TRG-0) was seen in seven cases (20.5%) [Table/Fig-5].



[Table/Fig-5]: Distribution of cases according to pathologic response.

DISCUSSION

The incidence of colorectal carcinoma has been rising in younger people [14]. Previously, males were affected more than females, but now the incidence is the same for both genders [1]. Like the present study, in a study by Rajagopal R et al., males were affected more. (M: F ratio was 1.2:1) [15]. According to Chen H et al., and Asthana S et al., the incidence of rectal cancer was observed to be higher in males than in females [13,16]. In this study, peak incidence was seen in the age group of 41-50 years with 12 cases (35.3%). In a study by Rajagopal R et al., the most common age group affected was 61-70 years [15]. According to Asthana S et al., maximum colorectal cancer cases were found in the more than 50 years age group in both sexes [16]. The most common presentation is moderately differentiated adenocarcinoma. Like the present study, in a study by Rajagopal R et al., moderately differentiated adenocarcinoma was found mostly (86.6%) [15]. Increasing the use of preoperative chemoradiation has led to an increasing duration of disease-free survival [17] and satisfactory tumour regression [18]. Many pathological changes occur after chemoradiation, including tumour regression, node shrinkage, radiation-induced fibrosis, etc., Tumours and fibrosis are very difficult to demonstrate on gross examination. This study emphasises macroscopic and microscopic assessment and response after preoperative chemoradiation.

Macroscopic Assessment

In the present study, mainly abdominoperineal resection specimens were received that have a non-peritonealised inked surface (NPS & CRM), lateral surface [Table/Fig-6a], and anterior surface [Table/Fig-6b]. The specimen should be cut open to inspect the tumour [Table/Fig-6c]. Mesorectum quality assessment is necessary because the incompleteness of mesorectum excision is associated with disease recurrence [19].

Hassan T et al., Careful microscopic and macroscopic assessment of the distance of the tumour to CRM is the most significant predictor



[Table/Fig-6]: An abdominoperineal resection specimen, a) Lateral surface, b) Anterior surface (arrow indicates anterior peritoneal reflection), c) a cut-open abdominoperineal resection specimen showing greyish white tumour.

of local recurrence [20]. Distal resection margin was involved in about 3.7% of cases ($p < 0.05$). Preoperative RCT could reduce the lymph node yield by approximately 33%. A study by Bernstein TE et al., examined the prognostic impact of the CRM in patients with rectal cancer treated by TME with or without radiotherapy [21]. A CRM of 2 mm less confers a poorer prognosis, and patients should be considered for neoadjuvant treatment.

Microscopic Assessment

Assessment of Circumferential Resection Margin (CRM) and lymph node positivity: In a study conducted by Rajagopal R et al., [15], Hassan T et al., 2018 [20], Wang Y et al., 2019 [22], CRM was involved in 4.4%, 13.2%, and 99.4% cases, respectively. In the present study, the tumour extends up to the CRM in 14.7% ($n=5$) cases [Table/Fig-7a], In a study conducted by Rajagopal R et al., [15], Hassan T et al., 2018 [20], Wang Y et al., 2019 [22], lymph node positivity is 27%, 54.7%, 29.9% respectively and in the present study it was 26.4% [Table/Fig-8].

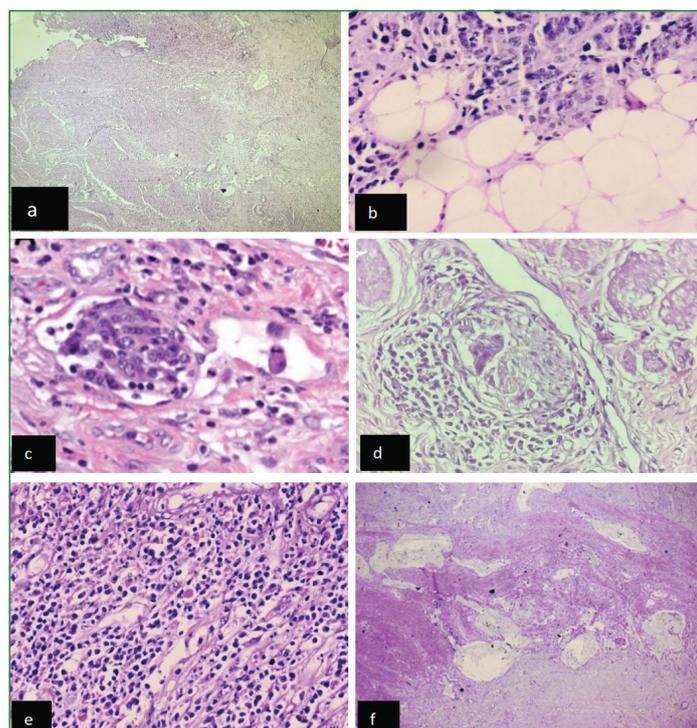
Assessment of Tumour Deposits (TD): In the study case, the TDs in the perirectal fat were seen in eight cases (23.5%) [Table/Fig-7b]. In the study by Rajagopal R et al., TDs occurred in up to 5.6% of cases, and their presence was associated with reduced disease-free survival [15]. In a study conducted by Agger E et al., TDs have a negative impact on the prognosis of rectal cancer [23].

Assessment of LVI and PNI: In a study conducted by Rajagopal R et al., [15], cases of LVI were 24.4% and PNI were 12.2%. In the present study, LVI was seen in 3 cases (11.11%), and PNI was seen in 1 case (3.70%) [Table/Fig-7c,d].

Assessment of fibroinflammatory changes: In the present study, the local inflammatory response is seen in almost all cases. Nagtegaal ID et al., extensive fibro-inflammatory infiltrates have a lower recurrence rate [24]. After NACRT, rectal carcinoma undergoes tumour regression (replacement by fibroinflammatory tissue). Rajagopal R et al., the predominant type of stromal response was the fibroinflammatory type (53.3% of cases) [Table/Fig-7e] [15].

Assessment of acellular mucin pools (aMUC): In the present study, acellular pools of mucin were seen in 5 cases (14.7%). The presence of "acellular" mucin, i.e., mucin pools lacking neoplastic epithelium [25]. Mian Chen H et al., de Campos Lobato LF et al., studied that the acellular mucin pools may be a sign of invasive tumour biology, which indicates a negative prognosis [26,27]. In contrast to this study, CAP PROTOCOL [28] put forward a very interesting fact that acellular mucin pools are considered to represent completely eradicated tumours and are not used to assign the pathological (pT) stage, and also their presence does not count as positive lymph nodes. Also, de Campos Lobato LF et al., a study suggests that a MUC (Mucin) did not affect local recurrence [27].

According to Bhatti ABH et al., in rectal cancer patients with pCR, no definite prognostic role of acellular pools of mucin was found [29]. The present study also believed in the fact that the presence of mucin pools after NACRT represents the eradication of tumours [Table/Fig-7f].



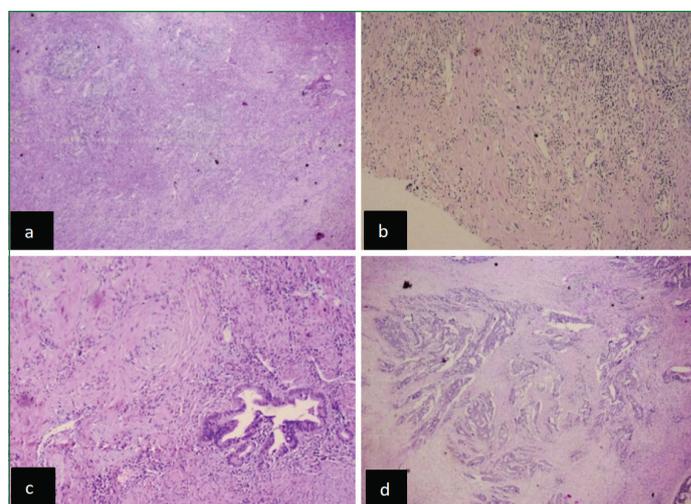
[Table/Fig-7]: a) H&E-(4x), Tumour extending up to the Circumferential Resection Margin (CRM); b) H&E- A (40x), Tumour extending to perirectal fat (Tumor arranged in a glandular pattern having round to oval cells with round to oval vesicular to hyperchromatic nuclei having prominent nucleoli, stroma shows infiltrates of lymphocytes); c) H&E-(40x), Lymphovascular invasion (Blood vessel shows round to oval cells having pleomorphic round to oval vesicular nuclei with prominent nucleoli); d) H&E-(40x) Perineural Invasion (PNI) (Few tumour cells seen around the nerve). e) H&E -B (40x), Fibroinflammatory changes (fibrocollagenous tissue showing dense infiltrates of lymphocytes and plasma cells with areas of fibrosis); f) H&E - (40x), Acellular pools of mucin, (Pools of acellular mucin in muscle layer).

S. no.	Studies	CRM	Lymph nodes positivity
1	Present study 2025	14.7%	26.4%
2	Hassan T et al., 2018 [20]	13.2%	54.7%
3	Rajagopal R et al., 2021 [15]	4.4%	27%
4	Wang Y et al., 2019 [22]	99.4%	29.9%

[Table/Fig-8]: Comparison of Circumferential Resection Margin (CRM) and lymph node positivity in different studies [15,20,22].

Assessment of tumour regression score according to the modified RYAN scheme: The tumour regression score is given according to the modified RYAN scheme (CAP protocol) [28]. In this study case, in most cases, 17 (50 %) have a tumour regression score of 3 (TRG-3), which means most cases have a poor response. This might be due to differences in the treating regimen, patients' non-compliance, late presentation etc., Tumour regression scoring holds a great place in knowing patients' response to chemoradiation, which helps in further management and prognosis. In a study by Rajagopal R et al., the maximum cases fall under TRG [Table/Fig-1] [Table/Fig-9a-d]. It is recommended that complete total mesorectal excision with good mesorectal bulk and an intact mesorectal fascia should be done, as this is associated with lower local recurrence rates and improved oncologic outcomes [Table/Fig-10].

In a study by Chen H et al., [13] and Wang Y et al., 2019 [23], no residual tumour (TRG 0) found in 21.3% and 21.2% cases respectively. Rajagopal R et al., 2021 [15] have maximum cases of TRG-2, hence non-concordant with present study. In this study, the incidence of TRG 3 was maximum, like in a study by Yang Y et al., TRG 3- 61.2% cases [30], hence concordant with present study [Table/Fig-11].



[Table/Fig-9]: a) H&E-(4X), (a) TRG-0 (No viable cancer cells, only fibro inflammatory response seen (complete response); b) H&E-(4x), (b) TRG-1 (Minimal residual cancer with single cells or small groups of cancer cells (near-complete response); c) H&E-(4x), (c) TRG-2 (Residual cancer with evident tumour regression, which is more than single cells or small groups of cancer cells (partial response); d) H&E-(4x), (d) TRG-3 (Extensive residual cancer with no evident tumour regression (poor or no response).

Sr. no.	Mesorectum	Bulk removed
1	Complete	Good bulk
2	Near complete	Moderate bulk
3	Incomplete	Little bulk

[Table/Fig-10]: Evaluation of the mesorectum [19].

S. no.	Study	TRG 0	TRG 1	TRG 2	TRG 3
1	Present study 2025	20.5%	11.7%	17.6%	50%
2	Chen H et al., 2021 [13]	21.3%	25.7%	40.6%	12.3%
3	Rajagopal R et al., 2021 [15]	12%	32%	34%	22%
4	Yang Y et al., 2022 [30]	4%	5.4%	29.3%	61.2%
5	Wang Y et al., 2019 [22]	21.2%	26.9%	44.8%	7.1%

[Table/Fig-11]: This table demonstrates a comparison of Tumour Regression Grade (TRG) after NACRT in rectal carcinoma. (TRG: Tumour regression grade) [13,15,22,30].

Limitation(s)

As this is a hospital-based study, it may not apply to the general population. Chemoradiation therapy response may vary depending on the treatment options available.

CONCLUSION(S)

Preoperative chemoradiation induces numerous histomorphological changes. Therefore, proper examination of gross specimens is necessary. Tumour and fibrosis are very difficult to demonstrate on gross examination and, hence, require maximum sampling. The presence of acellular mucin pools represents a completely eradicated tumour. The presence of acellular mucin pools in lymph nodes is not counted as positive. Tumour regression score is a useful method of scoring tumour response after NACRT.

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AUTHOR DECLARATION:

- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. NA

PLAGIARISM CHECKING METHODS: [Jain H et al.]

- Plagiarism X-checker: Apr 04, 2025
- Manual Googling: Jul 03, 2025
- iThenticate Software: Jul 23, 2025 (16%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

Date of Submission: **Mar 18, 2025**

Date of Peer Review: **Jun 11, 2025**

Date of Acceptance: **Jul 24, 2025**

Date of Publishing: **Apr 01, 2026**