DOI: 10.7860/JCDR/2025/78942.21355

Original Article

Oncology Section

Pathological Response Assessment following Long Course Neoadjuvant Chemoradiation in Locally Advanced Rectal Cancer: A Single Institutional Cohort Study

MARIA BABY[1], JOMON RAPHAEL[2], B RAJKRISHNA[3], MATHEW VARGHESE[4], FEBIN ANTONY[5]

BY-NC-ND

ABSTRACT

Introduction: Neoadjuvant chemoradiation and Total Mesorectal Excision (TME) have shown pathological Complete Response (pCR) rates of 15-27%. The pCR is a significant predictor of survival. The Mandard Tumour Regression Grading (TRG) system is used to report pathological response.

Aim: To evaluate the pathological response in patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation and to investigate Disease-Free Survival (DFS).

Materials and Methods: This single-centre cohort ambispective study was conducted from January 2019 to July 2023 at the Amala Institute of Medical Sciences, Thrissur, Kerala, India. It included patients aged 18-75 years with T3, T4, any NM0, and any T, N1, N2M0 rectal cancer, with an Eastern Cooperative Oncology Group (ECOG) performance status of 1-2. Patients who did not undergo surgery or chemotherapy at our centre, those who refused surgery, and those planned for Total Neoadjuvant Therapy (TNT) or short-course radiation therapy were excluded. Thirty-nine patients meeting the criteria were included in the study. All patients underwent neoadjuvant chemoradiation using Intensity Modulated Radiation Therapy (IMRT) to a dose of 50.4 Gy in 28 fractions over five and a half weeks, combined with concurrent chemotherapy using Capecitabine 825 mg/m² twice daily. All operable patients subsequently underwent TME, followed by adjuvant chemotherapy. Pathological response was assessed using Mandard TRG.

Results: Thirty-nine patients were enrolled. The most common tumour location was found to be between 6-10 cm from the anal verge (22, 56.41%). The most frequent radiological T stage was T3, constituting 26 patients (66.67%), and 16 patients (41.03%) presented with N2 disease. TRG 1 was observed in seven patients (17.95%), TRG 2 in six patients (15.38%), TRG 3 in 21 patients (53.85%), TRG 4 in four patients (10.26%), and TRG 5 in one patient (2.56%). The median follow-up time was 24 months (range: 3-60 months). The two-year DFS was 86%.

Conclusion: Neoadjuvant chemoradiation in locally advanced rectal cancer demonstrated meaningful pathological tumour regression and encouraging DFS outcomes.

Keywords: Disease-free survival, Total mesorectal excision, Tumour regression grading

INTRODUCTION

According to GLOBOCAN 2022, rectal cancer ranks eighth in incidence, with 729,833 new cases and 343,817 deaths [1]. From several randomised controlled trials, the standard approach to treating locally advanced rectal cancer involves neoadjuvant chemoradiation (NACT RT) followed by TME. NACT RT provides superior local control with tolerable toxicity and a higher likelihood of sphincter-sparing surgery [2]. High-resolution Magnetic Resonance Imaging (MRI) is necessary for staging and predicting prognosis in rectal cancers. It aids in assessing the extent of the tumour, mesorectal fascia involvement, and the Circumferential Resection Margin (CRM) [3]. After NACT RT, high-resolution MRI will help to assess downstaging of both the primary disease and the lymph nodes. Following NACT RT and TME, 15-27% may show pCR. The pCR is a significant predictor of survival [4]. Complete Response (CR) to NACT RT can be accurately assessed only by histopathological examination [5,6]. There are several grading systems to evaluate the pathological response to neoadjuvant therapy. One such system is the Mandard TRG system, which evaluates the ratio of residual tumour cells to fibrosis in the resected specimen. [Table/Fig-1] shows the different TRG scores based on the Mandard system [7]. No imaging methods can accurately predict a CR [8-10].

Hence, the aim of the study was to assess the pathological response in rectal cancer patients following neoadjuvant chemoradiation using the Mandard TRG system and secondary objectives were to determine the rate of pCR and to estimate the DFS.

TRG	Characterisation
TRG 1	Complete regression with absence of residual cancer and fibrosis extending through the wall
TRG 2	Rare residual tumour cells scattered throughout the fibrosis
TRG 3	Predominant fibrosis but increase in the number of cancer cells
TRG 4	Residual cancer cells outgrowing the fibrosis
TRG 5	Absence of regressive changes

[Table/Fig-1]: Mandard Tumour Regression Grading (TRG) [7].

MATERIALS AND METHODS

This ambispective cohort study was performed at the Amala Institute of Medical Sciences in Thrissur, Kerala, India, in the Department of Radiation Oncology, with support from the Departments of Radiodiagnosis, Surgical Oncology, Medical Oncology and Pathology, spanning January 2019 to July 2023. Retrospective data were collected from January 2019 to October 2022, and prospective data were collected from November 2022 to July 2023.

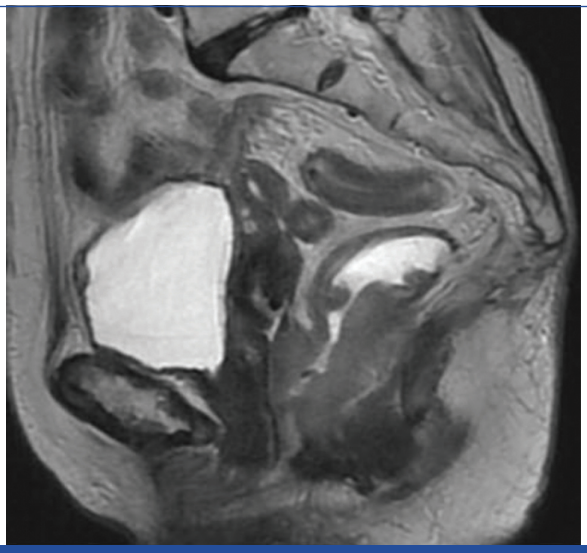
Inclusion criteria: Patients aged 18-75 years with T3, T4, any NM0, and any T, N1, N2M0 rectal cancer, with an ECOG performance status of 1-2 were included in the study.

Exclusion criteria: Patients who did not undergo surgery and/or chemotherapy at our centre, who refused surgery, those planned for TNT or short-course radiation therapy, synchronous primary malignancy, patients with prior pelvic malignancies, prior radiation to the abdomen and pelvis were excluded from the study.

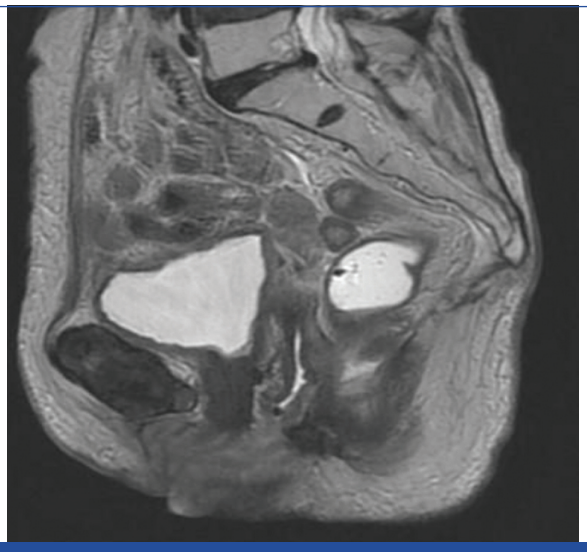
Study Procedure

Among the 211 patients screened, 39 met the criteria and were included in the study. A complete medical history and clinical assessment, including a digital rectal examination, were performed for all patients. Complete blood counts, liver and renal function tests, and baseline Carcinoembryonic Antigen (CEA) levels, as well as colonoscopy and biopsy, were carried out for all the patients. Local disease staging workup was performed using MRI of the pelvis. The metastatic workup included Positron Emission Tomography Computed Tomography (PET CT) or chest radiograph/Computed Tomography (CT) of the thorax and Ultrasound (USG)/CT of the abdomen. All patients were staged based on the American Joint Committee on Cancer (AJCC) eighth edition [11].

External beam radiation therapy was administered using the Intensity-Modulated Radiation Therapy (IMRT) technique for all patients. A total dose of 50.4 Gy in 28 fractions was delivered in two phases (Phase 1: 45 Gy in 25 fractions and Phase 2: 5.4 Gy in 3 fractions), along with concurrent chemotherapy using Capecitabine at 825 mg/m^2 twice daily for a duration of five and a half weeks. A follow-up MRI of the pelvis was performed 6–8 weeks after NACT RT for reassessment. In the reassessment MRI, the following characteristics were examined: the residual tumour, fibrosis and response to chemoradiotherapy. [Table/Fig-2,3] presents the MRI findings at diagnosis and post-neoadjuvant chemoradiation reassessment. All patients deemed operable underwent TME followed by adjuvant chemotherapy. The patients were staged pathologically using the AJCC eighth edition [11]. Pathological response was assessed using the Mandard TRG system.



[Table/Fig-2]: High-resolution T2 MRI sagittal view at diagnosis.



[Table/Fig-3]: High-resolution T2 MRI sagittal view post neoadjuvant chemoradiation.

STATISTICAL ANALYSIS

The data were entered into an Excel worksheet, and analysis was performed using R version 4.3.2. Categorical variables were summarised using frequencies and percentages, while quantitative variables were expressed as either means or medians with interquartile ranges, depending on the distribution. DFS was calculated from the date of diagnosis to the date of local or distant progression. Kaplan-Meier curves were used to evaluate the DFS.

RESULTS

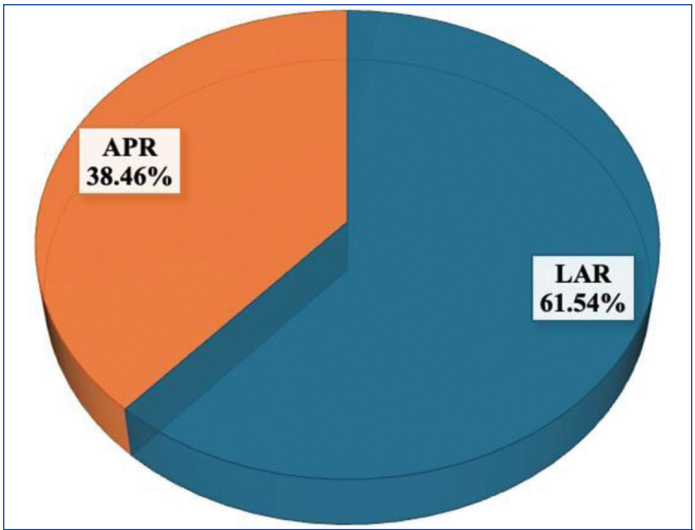
This study included 39 patients who fitted the inclusion criteria. The median age was 60 years, ranging from 33 to 75 years. Twenty (51.28%) were male and 19 (48.72%) were female. All patients had an ECOG performance status of 1.

In 22 patients (56.41%), the tumour was located between 6-10 cm from the anal verge, while in 15 patients (38.46%), the tumour was between 0–5 cm, and in 2 patients (5.13%), the tumour was between 11–15 cm from the anal verge. Among the radiological T stage, 26 patients (66.67%) were T3, 6 (15.38%) were T4a, 5 (12.82%) were T4b, and 2 (5.13%) were T2. Regarding the N stage, 10 patients (25.64%) were N0, 13 (33.33%) were N1, 11 (28.21%) were N2a, and 5 (12.82%) were N2b. Involvement of the CRM was observed in 22 patients (56.41%). The majority of patients were negative for extramural vascular invasion (29, 74.36%). [Table/Fig-4] shows the patient and disease characteristics.

Parameters	n (%)
Age (years)	Median: 60 years (33-75 years)
Gender	
Male	20 (51.28)
Female	19 (48.72)
Distance from anal verge (cm)	
0-5	15 (38.46)
6-10	22 (56.41)
11-15	2 (5.13)
T stage	
T2	2 (5.13)
T3	26 (66.67)
T4a	6 (15.38)
T4b	5 (12.82)
N stage	
N0	10 (25.64)
N1	13 (33.33)
N2a	11 (28.21)
N2b	5 (12.82)
EMVI	
Positive	10 (25.64)
Negative	29 (74.36)
CRM	
Involved	22 (56.41)
Uninvolved	17 (43.59)

[Table/Fig-4]: Patient and tumour characteristics.
EMVI: Extramural vascular invasion; CRM: Circumferential resection margin

TME was performed in all patients, with 24 patients (61.54%) undergoing Low Anterior Resection (LAR) and 15 patients (38.46%) Undergoing Abdominoperineal Resection (APR) [Table/Fig-5]. The pathological Complete Response (pCR; TRG 1) was observed in seven patients (17.95%), near complete response (TRG 2) in six patients (15.38%), moderate response (TRG 3) in 21 patients (53.85%), minimal response (TRG 4) in four patients (10.26%), and no response (TRG 5) in one patient (2.56%). [Table/Fig-6] shows the pathological TRG.

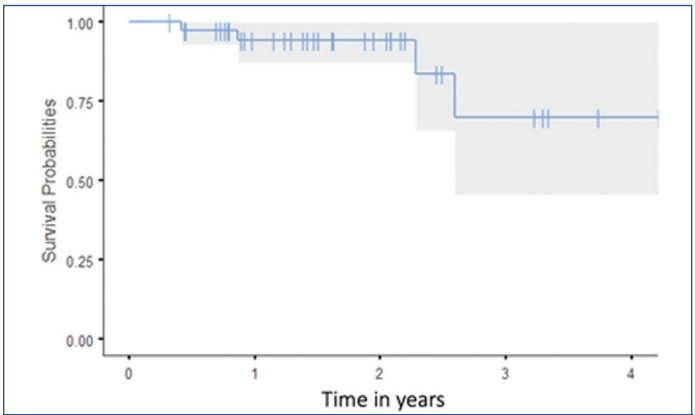


[Table/Fig-5]: Details of surgery.

Pathological TRG (Mandard)	n (%)
TRG 1 (complete response)	7 (17.95)
TRG 2 (near complete response)	6 (15.38)
TRG 3 (moderate response)	21 (53.85)
TRG 4 (minimal response)	4 (10.26)
TRG 5 (no response)	1 (2.56)

[Table/Fig-6]: Pathological tumour regression grade (Mandard TRG).

The median follow-up duration was 24 months, ranging from 3 to 60 months. The two-year DFS rate was 86% [Table/Fig-7]. Three patients developed distant metastases, while local relapse was observed in two patients. Among those who had local relapse, one occurred after 28 months and the other after 17 months post-NACT RT.



[Table/Fig-7]: Disease Free Survival (DFS).

DISCUSSION

NACT RT and TME have been shown to reduce local relapse rates to below 10% with manageable toxicity in patients with LARC [2,12-15]. Multiple studies have demonstrated that NACT RT can achieve pCR ranging from 15-27% [Table/Fig-8] [2,4,6,16]. In a meta-analysis of 14 studies by Maas M et al., which included 3,105 patients who received NACT RT for rectal cancer, a pCR rate of 16% was reported, along with a 5-year Disease-Free Survival (DFS) rate of 83.8% for those with pCR, compared to 65.6% for those without pCR [4].

The German rectal cancer study, a randomised controlled trial involving 823 patients with locally advanced rectal cancer, demonstrated a pCR rate of 9% and a 10-year DFS of 68.5% with NACT RT [2]. A systematic review and meta-analysis by Martin ST et al., which included 16 studies and 3,363 patients who received NACT RT for rectal cancer, reported a mean pCR rate of 24.4% and a 5-year DFS of 87% for those who achieved pCR [6]. Sinukumar S et al., assessed the outcomes of NACT RT in LARC within the Indian context, which included 430 patients, and observed pCR rates of 14.8%, with a 3-year DFS of 88.5% for those with pCR and 52% for those without pCR [16]. It is evident from the literature that pCR may be a predictor of better DFS and Overall Survival (OS) [17-20].

Study	n	Radiation dose and concurrent chemotherapy	pCR	DFS
Maas M et al., [4] (2010)	3105	50.4 Gy+5-fluorouracil (5 FU)	16%	5 y DFS: 83.8% for pCR and 65.6% for those without pCR
Sauer et.al., [2] (2012)	823	50.4 Gy+5 FU	9%	10 y DFS: 68.5%
Martin ST et al., [6] (2012)	3363	45-50.4 Gy+5 FU	24.4%	5 y DFS: 87% for those with pCR
Sinukumar S et al., [16] (2014)	430	40-50 Gy+Capecitabine	14.8%	3 y DFS: 88.5%
Present study (2025)	39	50.4 Gy+Capecitabine	18%	2 y DFS: 86%

[Table/Fig-8]: Studies showing pCR rates and DFS after NACT RT [2,4,6,16].

Present study observed a pCR of 18% and a near complete response (near CR) of 15%. Two-year DFS of 86%. These findings are in accordance with the existing literature, affirming NACT RT as a reliable and effective strategy for enhancing local control and surgical outcomes in LARC.

Limitation(s)

The major limitation of present study was the lack of centralised reporting of pathological specimens. Additionally, the sample size was small, and only those patients who had completed treatment at the centre were included, and the follow-up period was shorter.

CONCLUSION(S)

Neoadjuvant chemoradiation is an essential component in the management of locally advanced rectal cancer, facilitating significant tumour regression and sustained disease control. Notably, over one-third of patients exhibited a near complete response (near CR). These results support its continued use as a standard treatment strategy.

Acknowledgement

Authors are immensely thankful for the contributions made by our data analyst, Mrs. Donna Liza Thampan.

REFERENCES

[1] 9-rectum-fact-sheet.pdf [Internet]. [cited 2024 Jun 17]. Available from: https://gco.iarc.who.int/media/globocan/factsheets/cancers/9-rectum-fact-sheet.pdf.
[2] Sauer R, Liersch T, Merkel S, Fietkau R, Hohenberger W, Hess C, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(16):1926-33.
[3] Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: A systematic review and meta-analysis. Ann Surg Oncol. 2012;19(7):2212-23.
[4] Maas M, Nelemans PJ, Valentini V, Das P, Rödel C, Kuo LJ, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: A pooled analysis of individual patient data. Lancet Oncol. 2010;11(9):835-44.
[5] Capirci C, Valentini V, Cionini L, De Paoli A, Rodel C, Glynne-Jones R, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: Long-term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys. 2008;72(1):99-107.
[6] Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg. 2012;99(7):918-28.
[7] Mandard AM, Dalibard F, Mandard JC, Marnay J, Henry-Amar M, Petiot JF, et al. Pathologic assessment of tumour regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. Cancer. 1994;73(11):2680-86.

[8] Lambregts DMJ, van Heeswijk MM, Delli Pizzi A, van Elderen SGC, Andrade L, Peters NHGM, et al. Diffusion-weighted MRI to assess response to chemoradiotherapy in rectal cancer: Main interpretation pitfalls and their use for teaching. EurRadiol. 2017;27(10):4445-54.
[9] Lambregts DMJ, Boellaard TN, Beets-Tan RGH. Response evaluation after neoadjuvant treatment for rectal cancer using modern MR imaging: A pictorial review. Insights Imaging. 2019;10(1):15.
[10] Foti PV, Privitera G, Piana S, Palmucci S, Spatola C, Bevilacqua R, et al. Locally advanced rectal cancer: Qualitative and quantitative evaluation of diffusion-weighted MR imaging in the response assessment after neoadjuvant chemo-radiotherapy. Eur J Radiol Open. 2016;3:145-52.
[11] Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-99.
[12] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731-40.
[13] Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006;355(11):1114-23.
[14] Gérard JP, Azria D, Gourgou-Bourgade S, Martel-Lafay I, Hennequin C, Etienne PL, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol Off J Am Soc Clin Oncol. 2012;30(36):4558-65.
[15] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with t3 rectal cancer: Trans-tasman radiation oncology group trial 01.04. J Clin Oncol. 2012;30(31):3827-33.
[16] Sinukumar S, Patil P, Engineer R, Desouza A, Saklani A. Clinical outcome of patients with complete pathological response to neoadjuvant chemoradiotherapy for locally advanced rectal cancers: The Indian scenario. Gastroenterol Res Pract. 2014;2014(1):867841.
[17] Hoendervangers S, Burbach JPM, Lacle MM, Koopman M, van Grevenstein WMU, Intven MPW, et al. Pathological complete response following different neoadjuvant treatment strategies for locally advanced rectal cancer: A systematic review and meta-analysis. Ann Surg Oncol. 2020;(27):4319-36. Available from: https://doi.org/10.1245/s10434-020-08615-2.
[18] Fokas E, Glynne-Jones R, Appelt A, Beets-Tan R, Beets G, Haustermans K, et al. Outcome measures in multimodal rectal cancer trials. Lancet Oncol. 2020;21(5):e252-64. Doi: 10.1016/S1470-2045(20)30024-3.
[19] Bujko K, Kolodziejczyk M, Nasierowska-Guttmejer A, Michalski W, Kepka L, Chmielik E, et al. Tumour regression grading in patients with residual rectal cancer after preoperative chemoradiation. Radiother Oncol J Eur Soc Ther Radiol Oncol. 2010;95(3):298-302.
[20] Topova L, Hellmich G, Puffer E, Schubert C, Christen N, Boldt T, et al. Prognostic value of tumour response to neoadjuvant therapy in rectal carcinoma. Dis Colon Rectum. 2011;54(4):401-11.

PARTICULARS OF CONTRIBUTORS:
1. Junior Resident, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
2. Professor, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
3. Associate Professor, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
4. Associate Professor, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.
5. Assistant Professor, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur, Kerala, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. B Rajkrishna,
Associate Professor, Department of Radiation Oncology, Amala Institute of Medical Sciences, Thrissur-680555, Kerala, India.
E-mail: rajkb111@yahoo.co.in

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Mar 26, 2025
- Manual Googling: Jul 17, 2025
- iThenticate Software: Jul 19, 2025 (10%)

ETYMOLOGY: Author Origin

EMENDATIONS: 8

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? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Mar 04, 2025**
Date of Peer Review: **May 31, 2025**
Date of Acceptance: **Jul 21, 2025**
Date of Publishing: **Aug 01, 2025**