

Acute Toxicity and Tumor Response in Rectal Cancer after Shortened Chemoradiation

Suresh Kumar Rout¹, Sunita Sethy^{2*}, Sanjukta Padhi³

¹Assistant Professor, Dept. of Radiation Oncology, VIMSAR, Burla, Sambalpur, Odisha, India

²Assistant Professor, Dept. of Medicine, SCB Medical College & Hospital, Cuttack, Odisha, India

³Professor and HOD, Dept. of Radiation Oncology, AHPGIC, Cuttack, Odisha, India

***Address for Correspondence:** Dr Sunita Sethy, Assistant Professor, Dept. of Medicine, SCB Medical College & Hospital, Cuttack, Odisha, India

E-mail: sunitasethy100@gmail.com

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ABSTRACT

Background: Colorectal cancer (CRC) remains a major global health burden. In India, colon cancer ranks ninth and rectal cancer tenth among men, whereas in women, colon cancer ranks ninth and rectal cancer is not among the top ten cancers. Approximately 1.2 million new CRC cases occur annually, with nearly 60% reported from developed countries. Intensity Modulated Radiotherapy (IMRT) allows escalation of the radiation dose to the primary rectal tumor while sparing surrounding normal tissues, potentially reducing acute and late toxicities. However, clinical data on dose-escalated IMRT in rectal cancer are limited.

Methods: This prospective study was conducted among patients with histologically confirmed locally advanced rectal adenocarcinoma (T3–T4 or node-positive, non-metastatic) treated at Acharya Harihar Regional Cancer Center and SCB Medical College, Cuttack, from September 2015 to December 2017. Eligible patients received pre-operative chemoradiation using the IMRT-SIB (Simultaneous Integrated Boost) technique with concurrent capecitabine.

Results: Patients ranged in age from 21–68 years, with most below 50 years and an ECOG performance status of 0. Six patients had lower rectal tumors. Most toxicities were Grade 1–2; Grade 3 diarrhea occurred in one patient, and seven developed Grade 2 perianal dermatitis. No Grade 4 skin toxicity was observed. Six patients achieved complete response, five partial responses, and one had disease progression. Seven patients became operable after chemoradiation, while five remained inoperable.

Conclusion: Pre-operative chemoradiation with IMRT-SIB and capecitabine was well tolerated, with acceptable toxicity, reduced treatment time, and favorable tumor response, making it a promising approach for locally advanced rectal cancer.

Key-words: Colorectal Cancer, CTCAE Criteria, Neoadjuvant chemoradiotherapy, IMRT-SIB

INTRODUCTION

Colorectal cancer (CRC) is a major global health problem. It is the third most common cancer in men (663,000 cases; 10.0% of all cancer cases) and the second most common in women (571,000 cases; 9.4% of all cancer cases) ^[1]. Worldwide, CRC accounts for approximately 1.2 million new cases annually, with nearly 60% occurring in developed countries.

It causes about 608,000 deaths each year, representing 8% of all cancer-related deaths and ranking as the fourth leading cause of cancer mortality ^[2]. In India, colon cancer ranks ninth and rectal cancer tenth among men. For women, colon cancer ranks ninth, while rectal cancer does not appear among the top ten malignancies ^[2]. The annual incidence rate for colon cancer in Indian men is 4.4 per 100,000 and for rectal cancer 4.1 per 100,000, while in women the rate for colon cancer is 3.9 per 100,000 ^[2]. Most patients present with nonspecific symptoms such as anemia, asthenia, intermittent abdominal pain, or vomiting. These vague presentations often delay diagnosis, emphasizing the need for effective screening strategies for early detection.

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Surgery is considered the mainstay of treatment for rectal cancer. However, despite curative resections, 20–50% of patients develop local recurrence. Local tumor recurrence is closely associated with the depth of tumor invasion and lymph node involvement ^[1]. Achieving a clear circumferential resection margin (CRM) is often difficult, even with optimal total mesorectal excision (TME). Therefore, neoadjuvant therapy using radiotherapy alone or in combination with chemotherapy is used to downstage the tumor, making it more amenable to surgical resection.

Unlike colonic cancers, rectal cancers are more suitable for radiotherapy due to their fixed anatomical position and predictable lymphatic drainage involving the perirectal, presacral, and internal iliac regions. Neoadjuvant chemoradiation has become the preferred treatment modality ^[3]. It offers tumor downstaging, improved resectability, better tolerance, and increased chances of sphincter preservation for distal rectal tumors.

Chemoradiotherapy using 5-fluorouracil (5-FU) has shown significant benefits in terms of local control. Continuous infusion of 5-FU provides superior tumor response and fewer hematological and non-hematological toxicities compared with bolus administration ^[4]. However, continuous infusion requires hospitalization and central venous access, posing additional risks.

Capecitabine, an oral fluoropyrimidine carbamate, is designed to preferentially generate 5-FU within tumor cells due to higher thymidine phosphorylase activity. Radiation upregulates this enzyme, enhancing the synergistic effect of capecitabine with radiotherapy. Thus, oral capecitabine administered daily mimics continuous 5-FU infusion while improving patient compliance ^[4].

Pre-operative chemoradiotherapy is now the standard of care for locally advanced rectal cancer. A complete pathological response (pCR) after neoadjuvant therapy is associated with improved local control and overall survival ^[5]. Strategies to increase pCR include concurrent chemoradiation using 5-FU/oxaliplatin combinations or the addition of biologic agents such as bevacizumab. Dose escalation of radiotherapy has also been explored to enhance tumor regression. Studies show that higher radiation doses improve pCR rates and downstaging from cT3–T4 or node-positive disease to ypT0–T2N0 ^[6].

However, increasing the radiation dose also increases exposure to surrounding critical structures, leading to greater acute and late toxicities. Organs at risk, including the small bowel, bladder, and femoral heads, must be protected during treatment. Intensity Modulated Radiotherapy (IMRT) enables conformal dose distribution, allowing escalation to the tumor while minimizing exposure to normal tissues. Dosimetric studies demonstrate that IMRT provides superior small bowel sparing compared with three-dimensional conformal radiotherapy (3DCRT) ^[7–10]. Despite these advantages, there is still limited clinical data, and prospective studies are required to evaluate the clinical outcomes of dose-escalated IMRT in rectal cancer.

MATERIALS AND METHODS

Patient Selection and Study Period- Our study was conducted among all new patients of carcinoma rectum at AHRCC and S.C.B. Medical College, Cuttack, from September 2015 to December 2017. Patients who fulfilled the eligibility criteria and who were treated with pre-operative chemoradiation by the IMRT-SIB technique were included in the study.

Inclusion criteria

- ❖ Patients with histologically confirmed adenocarcinoma of the rectum were included. The lesion was required to be located within the rectum and clinically staged as locally advanced (T3–T4 with regional lymph node involvement, N1–N2) based on physical examination or pelvic MRI.
- ❖ Eligible patients were ≥18 years of age with ECOG performance status 0–1 and adequate organ function (TLC >3000/μL, platelet count >100,000/μL, serum creatinine <2 mg/dl, and serum bilirubin <2 mg/dl). All participants provided written informed consent and were able to comply with study requirements.

Exclusion criteria

- ❖ Patients with distant metastasis, prior pelvic irradiation, or chemotherapy within the previous six months were excluded. Those with serious medical or psychiatric illnesses that could interfere with treatment or consent were not eligible. Pregnant or lactating women, patients with a second primary malignancy, or a history of inflammatory bowel

disease or malabsorption disorders were also excluded from the study.

Pretreatment Evaluation

- ❖ Complete history, physical examination, and surgical evaluation.
- ❖ Complete routine laboratory tests i.e. CBC, LFT, Serum Urea and creatinine, serum CEA level.
- ❖ Colonoscopy.
- ❖ Colonoscopy-guided biopsy of the lesion.
- ❖ USG of Abdomen and Pelvis.
- ❖ CECT Scan of Abdomen and Pelvis and pelvic MRI.

Study protocol- Patients who fulfilled the eligibility criteria were treated with pre-operative chemoradiation by IMRT-SIB technique (Fig. 1).

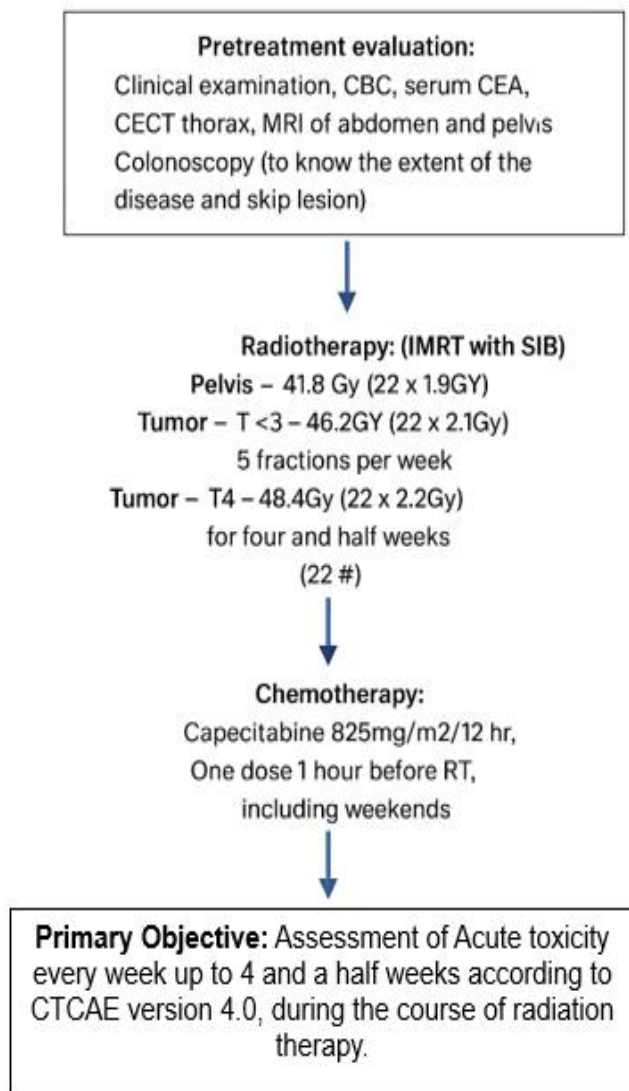


Fig. 1: Treatment Protocol (IMRT-SIB with Concurrent Capecitabine)

Table 1: Equivalent dose for the IMRT SIB fractionation schedule

IMRT-SIB	Gy	Pelvis	Tumor (T<=3)	Tumor (T>4)
	TD/d	41.8/1.9	46.2/2.1	48.4/2.2
	EQD2	43.25	51.38	55.2
	BED	35.9	42.1	45.2

Chemotherapy- Tablet capecitabine was administered orally at a dose of 825 mg per m² twice a day throughout the radiation course, including Saturday and Sunday. The first dose was administered approximately 2 hours before radiotherapy, and the second dose 12 hours after. During treatment, patients were evaluated weekly to assess acute toxicity and compliance with the treatment schedule. Clinical examination and complete blood count were performed. Toxic side effects were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

RESULTS

The study was conducted in the department of Radiation Oncology, Acharya Harihar Regional Cancer Centre, and SCB Medical College, Cuttack. Twenty patients of locally advanced Adenocarcinoma Rectal cancer were eligible for the study, out of which four patients did not give consent for this study, and family members of four patients did not agree to treatment due to some personal reasons. Twelve patients were included in the study during this period, from 2015 to 2017. Patients were treated by external beam radiation using the IMRT SIB technique and oral Capecitabine (Table 2).

Table 2: Age and Sex Distribution

Age Group (years)	No. of Patients
21-30	3
31-40	5
41-50	1
51-60	1
61-70	2
Sex	
Female	5
Male	7
Total	12

The above table shows the age distribution of the patients enrolled in the study. The age range of the study

group was 21 to 68 years. The majority of the patients in the present study were in the age group 21 -50 years. The mean age was 40 years. The majority of the 7 patients were males and 5 patients were female. The above table shows that the majority (50%) of the cases, tumor was located at the lower one third of the rectum where as in 4 cases (33%) it was in the upper one third of the rectum, in 2 patients (17%) the tumor was located at the middle one third of the rectum (Table 3).

Table 3: Distribution of patients according to location of tumour

Location of tumor	No. of patients	Percentages (%)
Lower 1/3rd of Rectum	6	50
Middle 1/3rd of Rectum	2	17
Upper 1/3rd of Rectum	4	33

Fig. 2a shows that most of the patients were in good general condition. Ten patients had an ECOG performance score of 0, ECOG score of 1 was found in two patients. Out of twelve patients, no patient developed grade 3 or grade 4 toxicity. The majority of the patients developed grade 2 toxicity. Grade 1 toxicity was seen in five patients (Fig. 2b). Grade 1 toxicity was observed in four patients, whereas the majority of the patients developed grade 2 mucositis. None of the patients developed grade 3 or 4 mucositis (Fig. 2c). The majority of the patients developed grade 2 toxicity. Grade 2 toxicity was observed in six patients; only one patient developed grade 3 toxicity. None of the patients developed grade 4 toxicity (Fig. 2d). The Majority of the patients developed grade 1 toxicity, grade 2 vomiting was observed in 4 patients, and none of the patients developed grade 3 or 4 toxicity (Fig. 2e). Grade 1 anaemia developed in seven patients. Five patients developed grade 2 anaemia. No grade 3 or 4 toxicity was seen (Fig. 2f). Most of the patients developed Hand Foot Syndrome during the treatment. In ten patients, it was low grade (grade 1). Grade 2 hand-foot syndrome was observed in two cases. No grade 3 or 4 toxicity was observed during the study (Fig. 2g).

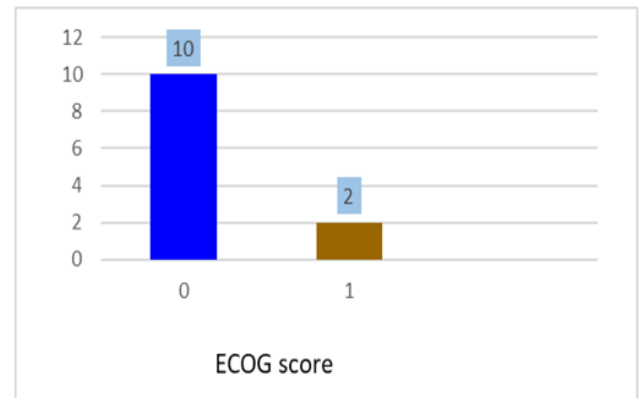


Fig. 2a: ECOG performance score

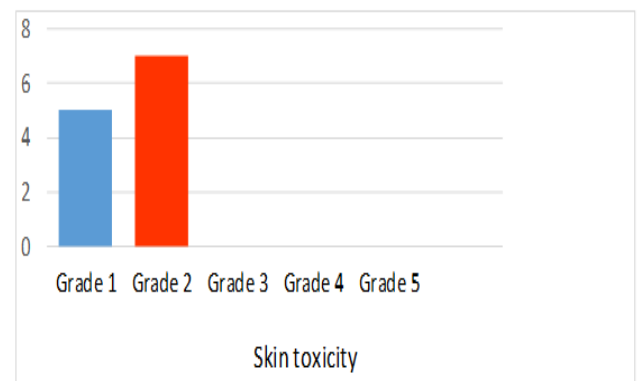


Fig. 2b: Acute toxicities during treatment

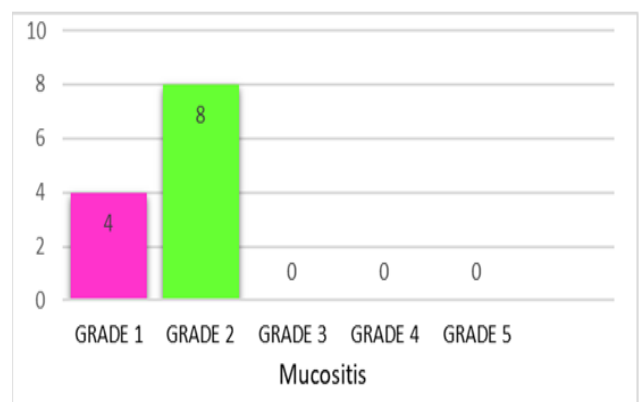


Fig. 2c: Mucositis toxicity

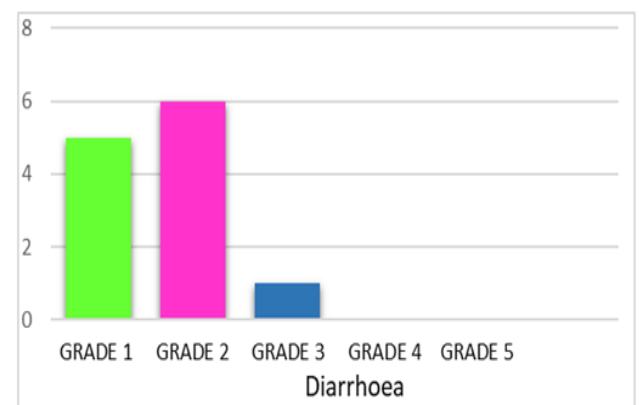


Fig. 2d: Toxicity distribution

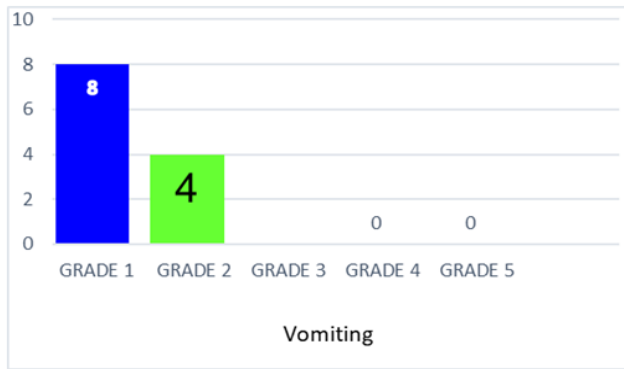


Fig. 2e: Vomiting toxicity

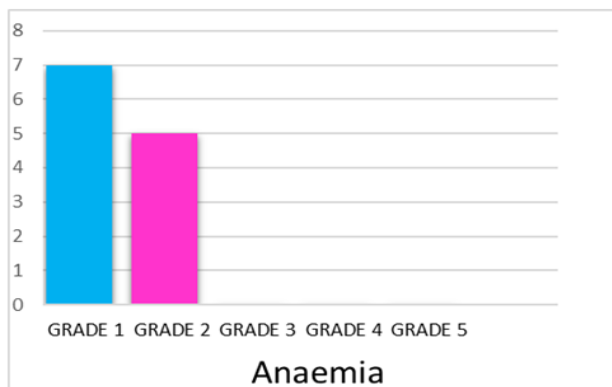


Fig. 2f: Anaemia toxicity

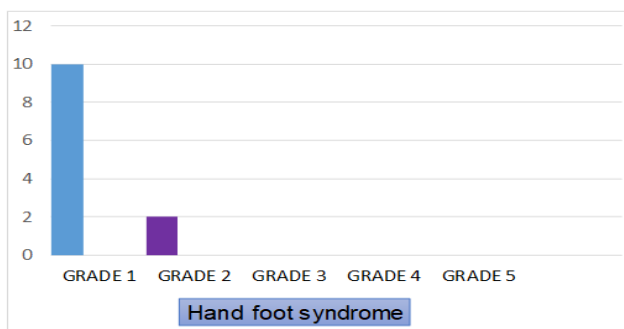


Fig. 2g: Hand-foot syndrome

Most of the patients 83% completed treatment without interruption. However, in two patients, treatment was delayed due to the development of toxicities during the treatment course. Complete response was achieved in six patients (50%), whereas partial response was achieved in five patients (42%). One patient showed progression of the disease. None of the patients was lost for follow-up after the chemoradiation course. One evaluation, after the completion of the chemoradiation course, showed that patients (58%) were operable. The disease was inoperable in five patients (42%) (Table 4).

Table 4: Treatment completion, response outcome, and surgical status

Parameter	Category	No. of Patients	Percentage (%)
Treatment Duration	< 5 weeks	10	83
	> 5 weeks	2	17
Response Outcome	Complete Response (CR)	6	50
	Partial Response (PR)	5	42
	Progressive Disease	1	8
	Lost for follow-up	0	0
	Death	0	0
Surgical Status	Operable	7	58
	Inoperable	5	42

DISCUSSION

The present study was conducted on twenty patients with adenocarcinoma of the rectum. Of these, four patients did not provide consent for participation, and the family members of another four patients declined treatment for personal reasons. Thus, twelve patients were finally enrolled in the study at the Acharya Harihar Regional Cancer Centre, Cuttack. All were treated with pre-operative concurrent chemoradiation using the IMRT-SIB technique along with capecitabine at a dose of 825 mg/m² twice daily throughout the course of treatment. The results were compared with those reported in the published literature.

In our study, both the mean and median age of the patients were 40 years. Western literature reports that rectal carcinoma is more prevalent in individuals above 50 years of age. However, in our study, most patients were between 30 and 50 years old.

Among the twelve patients, there were seven males and five females, giving a male-to-female ratio of 1.4:1, which is comparable with the German trial ^[3], where it was 2.4:1. Similar findings were reported by De Bruin *et al.* (2.1:1) ^[11] and Lay *et al.* (2.8:1) ^[12]. These data are consistent with our results.

In our study, seven patients developed Grade 2 skin toxicity, and five patients developed Grade 1 skin toxicity. No Grade 3 or Grade 4 skin toxicity was observed. The lower incidence of severe skin reactions

contributed to better treatment compliance and fewer interruptions. Eight patients developed Grade 2 mucositis, while four patients had Grade 1 mucositis; none experienced Grade 3 or 4 mucositis. In the German trial, skin and mucosal toxicity occurred in 11% of patients [3]. De Bruin *et al.* [11] reported radiation dermatitis in 3% of cases.

Gastrointestinal toxicity in the form of diarrhea was the most common side effect. Six patients developed Grade 2 diarrhea, five had Grade 1, and one patient developed Grade 3 diarrhea. No Grade 4 toxicity was observed. All patients were advised to follow a bland diet throughout radiotherapy. Diarrhea was managed with anti-motility and anti-secretory agents, along with ORS. One patient required intravenous fluids and antibiotics. In the German trial [3], acute diarrhea was observed in 12% of patients, while De Bruin *et al.* [11] reported Grade 3 diarrhea in 3% of cases. The slightly higher incidence in our study may be attributed to the higher daily radiation dose and the concomitant use of capecitabine during the four-and-a-half-week course, consistent with the findings from the NSABP R-04 trial [13].

Grade 1 hand-foot syndrome was observed in ten patients, and Grade 2 in two patients. No Grade 3 or 4 toxicity was noted. The high incidence of this side effect was likely related to the continuous use of capecitabine during radiotherapy. The condition was managed with oral analgesics, pyridoxine tablets, and local application of moisturizing agents containing urea.

The most common hematological toxicity was anemia: seven patients had Grade 1 and five had Grade 2 anemia. No Grade 3 or 4 hematological toxicity was observed. Eight patients developed Grade 1 leukopenia, and two developed Grade 1 thrombocytopenia, without any Grade 3 or 4 events. In the German trial, acute hematological toxicity was reported in 12% of cases [3]. None of the patients in our study developed neurological, hepatic, or urological toxicities.

The encouraging findings from this study, consistent with results from phase I and II trials, suggest that IMRT-SIB with concurrent capecitabine is well tolerated, with an acceptable and manageable toxicity profile [14]. The hypofractionated radiation schedule improved treatment compliance. The favorable tumor responses achieved in our study rendered seven out of twelve patients operable. The convenience of oral administration, shorter treatment duration, and good tolerability make

concurrent capecitabine and IMRT-SIB an attractive option for locally advanced rectal cancer [15].

CONCLUSIONS

Our study concludes that neoadjuvant chemoradiotherapy is practised all over the world for downstaging the tumor and making it operable. The radiation can be delivered by a conventional or a conformal technique. Now we are in the era of image-guided radiotherapy and intensity modulated radiotherapy. IMRT decreases the rate of bowel toxicity, as supported by various studies. IMRT-SIB is more focused on tumor tissue, along with reduced toxicity to organs at risk. In our research, we suggest that pre-operative radiation therapy with IMRT-SIB technique, concomitantly with capecitabine, was well tolerated, with acceptable toxicities and decreased treatment time, leading to increased patient compliance to the treatment protocol, good response of the tumor, and operability rate, so that IMRT-SIB could be an appealing option for the treatment of locally advanced rectal cancer. Long-term follow-up is needed to determine whether the favorable response to therapy and down-staging rate are translated into improved rates of local control, disease, and overall survival.

CONTRIBUTION OF AUTHORS

Research concept- Sunita Sethy

Research design- Suresh Kumar Rout, Sunita Sethy

Supervision- Sanjukta Padhi, Sunita Sethy

Materials- Suresh Kumar Rout, Sunita Sethy

Data collection- Suresh Kumar Rout, Sunita Sethy

Data analysis and interpretation- Suresh Kumar Rout, Sunita Sethy

Literature search- Sunita Sethy

Writing article- Sanjukta Padhi, Sunita Sethy

Critical review- Sanjukta Padhi, Sunita Sethy

Article editing- Suresh Kumar Rout, Sunita Sethy

Final approval- Suresh Kumar Rout, Sunita Sethy, Sanjukta Padhi

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