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Research Article

TO ASSESS ACUTE AND LATE TOXICITIES DURING NEOADJUVANT CONCURRENT CHEMO RADIOTHERAPY IN CARCINOMA STOMACH

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Abstract:

Background: The case-fatality ratio of gastric cancer is higher than for common malignancies like colon, breast, and prostate cancers because most patients experience vague and nonspecific symptoms in the early stages and the classic triad of anemia, weight loss, and refusal of meat-based foods is seen only in advanced stages. **Objective:** To assess acute and late toxicities during neoadjuvant concurrent chemoradiotherapy in carcinoma stomach**.** **Methods:** The present prospective observational study was conducted among all locally advanced biopsy proven carcinoma stomach presenting to at Department of Radiation Oncology, in tertiary care institute, regional cancer centre, Raipur, Chhattisgarh, India. Duration of study was two years: June 2021 - October 2022. The study was approved by the Ethical Committee of the Institute. **Result:** In present study, 8 patient developed grade II anemia and 12 patients developed grade I anemia in the 6th week post radiation., 8 patient developed grade I thrombocytopenia and 2 patient developed grade II thrombocytopenia in the 5th week post radiation. 12 patient developed grade I neutropenia and 3 patient developed grade II neutropenia in the 5th week post radiation. 7 patient developed grade I esophagitis in the 5th week post radiation. The most common toxicity in patients at 1 month follow up is

grade I skin lesions toxicity seen in 58 out of 60 patients, and the least common toxicities are grade I neutropenia seen in 2 patient each. Hand foot syndrome was seen in 30 patients with Grade I and 10 patients with Grade II toxicity

Conclusion: The acute toxicities with neoadjuvant therapy are less. Further follow-up is required to assess the late post op complications and disease free survival and overall survival.

Keywords: Acute and late toxicities, Neoadjuvant concurrent chemoradiotherapy, carcinoma stomach

INTRODUCTION: Carcinoma stomach can spread by local extension to involve adjacent structures and can develop lymphatic metastasis, peritoneal metastasis and distant metastasis. Extension can also occur by local invasion. [1]

Surgical resection is the only potentially curative treatment for GC. Adjuvant and neoadjuvant perioperative approaches, including chemotherapy and/or radiotherapy are now increasingly used in conjunction with surgery for locally advanced disease and even early stage disease; however, little consensus exists regarding optimal treatment sequencing. Indeed, competing approaches are supported by randomized data of variable quality. Compared with surgery alone, a survival advantage has been demonstrated with adjuvant chemotherapy in Asian trials, adjuvant chemoradiotherapy [CRT] in the largest North American study, and perioperative chemotherapy in the most cited European trial. [2]

The high rate of locoregional and distant relapse after gastric resection necessitates a multimodal treatment approach. Therefore, while surgery is the definitive curative therapy, chemotherapy and radiation are often used neoadjuvantly and adjuvantly to decrease the risk of recurrence and improve survival rates. Treatment regimens for patients with locally advanced, resectable gastric carcinoma continue to be evaluated to optimize the sequence and timing of chemotherapy, radiotherapy, and surgery. [3]

There has been tremendous improvement in the treatment of cancer over the years. But in case of gastric carcinoma overall response after all intervention has not improved significantly over the years. The five-year survival rate after surgery alone in resectable gastric carcinoma is 20-35% only.[4] Interventions like extended lymph node resection and pre and perioperative chemotherapy have been tried but not much have been achieved. Adjuvant CRT in post operated gastric carcinoma did not show any survival benefit. Most of the patients don't respond effectively to adjuvant chemotherapy and also there is increased toxicity due to same. Patient compliance is less in postoperative treatments. 40-60% patients do not complete treatment due to toxicities and disease progression and patient refusal. [4]

Radiotherapy helps in locoregional controls and chemotherapy prevents micro metastasis and adds to the effect of radiotherapy. Intact vasculature in preoperative settings helps in better chemotherapy delivery.

An article reported 70-100% R0 resection and pathological complete response of 7-29%in gastric carcinoma patient when treated with CRT. Several authors have reported benefits of preoperative radiochemotharapy also in unresectable gastric cancers, enabling radical resection in 25-50% of these patients with consequent survival benefit. [5]

Therefore, the present study was conducted to assess acute and late toxicities during neoadjuvant concurrent chemoradiotherapy in carcinoma stomach**.**

Material and Methods: The present prospective observational study was conducted among all locally advanced biopsy proven carcinoma stomach presenting to at Department of Radiation Oncology, in tertiary care institute, regional cancer centre, Raipur, Chhattisgarh, India. Duration of study was two years: June 2021 - October 2022. The study was approved by the Ethical Committee of the Institute.

SAMPLE SIZE: A total sample size of 55biopsy proven locally advanced gastric cancer patients was included in the study satisfying inclusion and exclusion criteria.

Out of total registered cases of stomach carcinoma each year, locally advanced stomach carcinoma is ~40%.

The present study was performed in the department of radiation oncology Regional Cancer Center, Dr. B.R.A.MH Raipur [C.G].

Sample size is calculated by using population correction method:

$$\mathbf{n}= \frac{x^2\ N\ p(1-p)}{d^2(\ N-1)+x2p(1-p)}$$

- n=sample size
- x^2 value is 3.84
- N=total population last [2018-2020]
- p=prevalence of stomach carcinoma= 0.037
- d=5% margin of error
- n= ≈ 55

Hence, a Sample size for study was 55 biopsy proven gastric cancer patients.

SAMPLING TECHNIQUE:

All biopsy proven locally advanced gastric cancer patients presentingto department were randomly selected qualifying inclusion criteria.

INCLUSION CRITERIA:

1. Age group 20-60 Years.
2. Histologically proven locally advanced carcinoma stomach.
3. Stage II - III.
4. WHO Performance Status of 0,1, 2.
5. With normal blood parameters.

EXCLUSION CRITERIA:

1. Patient with severe comorbidities.
2. Patients who have underwent surgery with curative intent or chemotherapy.
3. WHO Performance status >2.

METHODOLOGY:

- In the study enrolled all the locally advanced gastric cancer patients who are not operated and registered in the department after taking their consent.
- Patients were taken for neoadjuvant radiotherapy along with concurrent chemotherapy after detailed investigations.
- External beam radiation by RA technique to a total dose of 50.4 Gy @ 1.8 Gy per fraction for 28 fraction for 5 days a week combined with chemotherapy TAB.CAPECITABINE [625 mg/m2] day 1 to day 14 P/O AND INJ.OXALIPLATIN 85mg/m2 on day 1 and day 21 was given to the patients.
- Patients observed weekly during the therapy and toxicities are assessed.
- After 4 weeks of completion of chemoradiotherapy reassessing the patient through clinical examination, radiological investigation and endoscopically and assessment for operability is done.
- Toxicities assessed according to CTCAE 5.0

PATIENT IMMOBILISATION

- Patient undergoing conformal radiotherapy were planned and treated lying supine with arms above the head, ideally immobilized with thermoplastic cast.

CT SIMULATION:

- CT scanning was recommended for data acquisition.

- Radiation fields should encompass the tumor bed regional lymph nodal areas for locoregional control.
- Patients were usually scanned in supine position, arms overhead.
- Patientwas asked to come empty stomach.
- Iv and oral contrast was given.
- CT scan [3-5mm cut should be performed.
- For obese pts. prone belly board was used.
- For stomach radiation volume scanned extended from carina to iliac crest.

TARGET VOLUME DEFINITION

- GTV includes gross tumor and gross nodes as per CECT and Endoscopy finding.
- CTV included tumor bed with 2cm margin proximally and distally and the perigastric nodes on greater and lesser curvature.
- The phase 3 trial showed survival advantage of chemoradiation included para-aortic splenic hepatoduodenal and pancreatico – duodenal nodes.
- For tumors of fundus, the lower para oesophageal nodes should be included but pancreatico duodenal nodes can be omitted.
- For antral tumors splenic nodes can be omitted.
- To produce PTV 10 mm margin is added isotopically.The liver, kidneys and heart are countered as OARS.

Pretreatment evaluation

After patient's registration and after taking written informed consent complete clinical history were taken and all the patients were assessed clinically then investigation as follows.

Routine investigation: CBC, LFT, RFT, Serum electrolytes, Serum amylase, Serum lipase

Disease specific investigation: CXR, UGIE, CT Scan with contrast- thorax+ abdominal+pelvis scan.

After proper staging of patients as per AJCC TNM 8th edition patients were treated with LINAC using 6mv proton with RA technique for 50.4GY

In my study patients were treated by the following regime-

Radiotherapy planning-

All Patients have been simulated with appropriate immobilization according to the standard protocol

Planning CT scans was acquired with 3 mm axial images from thyroid to pubic symphysis and images will be transferred to contouring station. Treatment planning have been perform using VARIAN [eclipseV.S13.6.23] treatment planning system. TV and OARs will be contoured as per standard protocol The GTV was delineated by the using all available resources CT data, endoscopic reports, and diagnostic CT images, The GTV was expanded to the clinical target volume [CTV] by extending coverage 3 cm superiorly, 1 cm laterally, 3 cm inferiorly, and. The planning target volume [PTV] was the CTV plus a uniform 0.5-cm expansion margin. Organs at risk were outlined.

DOSE PRESCRIPTION

All patients are treated by RA Technique for a dose of 50.4Gy. All plans were constructed to deliver the target dose in 28 fractions using heterogeneity corrections. I so dose distributions were evaluated

FOLLOW UP- Treatment toxicities during course of radiation and after radiation have been compared using QUANTEC data and RTOG, CTC version 5.0 respectively. patients were followed weekly during treatment then after 1,3 and 6 monthly. During follow up examination, any recurrence and metastasis were carefully looked for and appropriate

chemotherapy has been given

PLANNING

- By RA technique, 50.4 Gy in 28 fractions of 1.8 Gy in 6 weeks with concomitant capecitabine and oxaliplatin.

Statistical Analysis:

- The data obtained was coded and entered into Microsoft Excel Worksheet. Data collected in the study was analyzed using statistical package for the social sciences [SPSS] software for windows version.
- The categorical data was expressed as rates, ratios and proportions and comparison was done using chi-square test or Fisher's exact test. The continuous data was expressed as mean ± standard deviation [SD].
- A probability value ['p' value] of less than or equal to 0.05 at 95% confidence interval was considered as statistically significant.

Results: In this study, majority i.e.80.00% of the patients are male, and the rest 20.00% are female. Patients evaluated belonged to age group between 30 – 70 years. Majority of the patients [46.67%] were of age group 40-50 years in which 23 [38.3%] were males and 5 [8.3%] females. The mean age is 52.58 ±9.92 years.

ACUTE TOXICITIES:

ANEMIA: In this study, 8 patient developed grade II anemia and 12 patients developed grade I anemia in the 6th week post radiation.

Table – 1: Anemia toxicity:

Anemia	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	18	25	15	02
2nd Week	42	10	08	00
3rd Week	22	28	10	00
4th Week	12	38	08	02
5th Week	22	25	13	00

6th Week	40	12	08	00

THROMBOCYTOPENIA

In this study, 8 patient developed grade I thrombocytopenia and 2 patient developed grade II thrombocytopenia in the 5th week post radiation.

Table – 2: Thrombocytopenia toxicity:

Thrombocytopenia	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	60	00	00	00
2nd Week	60	00	00	00
3rd Week	52	08	00	00
4th Week	52	05	03	00
5th Week	50	08	02	00
6th Week	60	00	00	00

NEUTROPENIA

In this study, 12 patient developed grade I neutropenia and 3 patient developed grade II neutropenia in the 5th week post radiation.

Table – 3: Neutropenia toxicity:

Neutropenia	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	60	00	00	00
2nd Week	60	00	00	00
3rd Week	42	15	03	00
4th Week	33	20	05	02

5th Week	54	12	03	00
6th Week	48	12	00	00

ESOPHAGITIS:

In this study, 7 patient developed grade I esophagitis in the 6th week post radiation.

Table – 4: Esophagitis toxicity

Esophagitis	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	60	00	00	00
2nd Week	60	00	00	00
3rd Week	60	00	00	00
4th Week	58	02	00	00
5th Week	45	15	00	00
6th Week	53	07	00	00

SKIN LESIONS: In this study, 55 patient developed grade I skin lesions and 5 patient developed grade II skin lesions in the 6th week post radiation.

Table – 5: Skin lesions toxicity

Skin lesions	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	55	05	00	00
2nd Week	60	00	00	00
3rd Week	45	15	00	00
4th Week	40	20	00	00
5th Week	25	35	00	00

6th Week	00	55	05	00

NAUSEA/ VOMITING: In this study, 45 patients developed grade I nausea/vomitingat 2nd week and 27 patients developed grade I nausea/vomiting in the 3rdweek post radiation.

GASTRITIS: In this study, 38 patients developed grade I gastritis at 2nd week and 10 patients developed grade II gastritis in the 2nd week post radiation.

Table – 6: Gastritis toxicity:

Gastritis	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	10	38	12	00
2nd Week	12	38	10	00
3rd Week	38	22	00	00
4th Week	48	12	00	00
5th Week	60	00	00	00
6th Week	60	00	00	00

DYSPHAGIA:

In this study, 55 patients developed grade 0 dysphagia and 5 patients developed grade I dysphagia in the 4thweek post radiation.

ABDOMINAL FULLNESS:

In this study, 53 patients developed grade I abdominal fullness and 2 patient developed grade II abdominal fullness in the 2nd week post radiation.

DIARRHOEA: In this study, 6 patients developed grade I diarrhoea in the 6th week post radiation.

CONSTIPATION: In this study, 7 patients developed grade I constipation in the 6th week post radiation.

LIVER DYSFUNCTION: In this study, 5 patients developed grade I liver dysfunction in the 6th week post radiation.

Table – 7: Liver dysfunction toxicity:

Liver dysfunction	Grade 0	Grade 1	Grade 2	Grade 3
1st Week	60	00	00	00
2nd Week	60	00	00	00
3rd Week	60	00	00	00
4th Week	60	00	00	00
5th Week	58	02	00	00
6th Week	55	05	00	00

PANCREATITIS: In this study, 7 patients developed grade I pancreatitis in the 3rd week post radiation.

HAND FOOT SYNDROME: In this study, 5 patients developed grade II pancreatitis in the 4thweek post radiation.

LONG-TERM TOXICITY:

The most common toxicity in patients at 1 month follow up is grade I skin lesions toxicity seen in 58 out of 60 patients, and the least common toxicities are grade I neutropenia.

Table – 8: Long-term toxicity:

TOXICITY-1	GRADE 0	GRADE 1	GRADE II	GRADE III	GRADE IV
Esophagitis	53	07	00	00	00
Skin lesions	02	58	00	00	00
Esophageal stricture	60	00	00	00	00
Esophageal perforation	60	00	00	00	00
Dysphagia	50	10	00	00	00
Ascites	60	00	00	00	00
Gastric stenosis	60	00	00	00	00
Pancreatitis	53	07	00	00	00
Liver dysfunction	53	07	00	00	00
Renal dysfunction	50	10	00	00	00

Anemia	35	20	05	00	00
Thrombocytopenia	60	00	00	00	00
Neutropenia	58	02	00	00	00
Hand Foot syndrome	20	30	10	00	00

In this study, all 60 patients completed 1 month follow up. Operability was observed among 48 [80.00%] patients.

Discussion: In this study, majority i.e. 80% of the patients are male, and the rest 20% were females. **K Sambasivaiah et al** [2004] observed among 151 patients with gastric cancer male to female ratio was 4:1. This finding was similar to present study. [6]

Patients evaluated belonged to age group between 30 – 70 years. Majority of the patients [46.67%] were of age group 40-50 years in which 23 [38.3%] were males and 5 [8.3%] females. The mean age is 52.58 ±9.92 years.

Arun Kumar Barad et al [2014] observed majority of the men were in the age group of more than 60 years [45.37%] and majority of females were of 51-60 years [44%]. [7]

ACUTE TOXICITIES: In present study, 8 patient developed grade II anemia and 12 patients developed grade I anemia in the 6th week post radiation., 8 patient developed grade I thrombocytopenia and 2 patient developed grade II thrombocytopenia in the 5th week post radiation. 12 patient developed grade I neutropenia and 3 patient developed grade II neutropenia in the 5th week post radiation. 7 patient developed grade I esophagitis in the 5th week post radiation. Among 60 patients, 55 patient developed grade I skin lesions and 5 patient developed grade II skin lesions in the 6th week post radiation. 45 patients developed grade I nausea/vomiting at 2nd week and 27 patients developed grade I nausea/vomiting in the 3rd week post radiation. 55 patients developed grade 0 dysphagia, 53 patients developed grade I abdominal fullness and 2 patient developed grade II abdominal fullness in the 2nd week post radiation, 7 patients developed grade I constipation in the 6th week post radiationand 5 patients developed grade I dysphagia in the 4th week post radiation, 10 patients developed grade II gastritis in the 2nd week post radiation. 3 patients developed grade II dysphagia in the 1st week post radiation. 53 patients developed grade I abdominal fullness and 2 patients developed grade II abdominal fullness in the 2nd week post radiation. 33 patients developed

grade I diarrhoea in the 6th week post radiation. 7 patients developed grade I constipation in the 3rd week post radiation. 5 patients developed grade I liver dysfunction in the 6th week post radiation. 7 patients developed grade I pancreatitis in the 3rd week post radiation. 25 patients developed grade II hand foot syndrome in the 4th week post radiation.

Similar findings were observed in **Shen-Bao Hu et al** [2019] observed 13 [13.7%] patients had grade 3–4 leukopenia, anemia, and thrombocytopenia, while 9 [9.5%] patients had grade 3–4 anemia, and 5 [5.3%] patients had grade 3–4 thrombocytopenia. [8]

Twisha Chakravarty et al in a study observed no patient had Grade 4 or higher acute toxicity, whereas Grade 3 acute toxicity developed in 14 [56%] patients. The Grade 3 acute toxicities included dehydration in 10 patients [40%], nausea in 8 [32%], anorexia in 5 [20%], fatigue in 2 [8%], dysphagia in 1 [4%], odynophagia in 1 [4%], and mucositis in 1 [4%].[9]

LONG-TERM TOXICITY:

The most common toxicity in patients at 1 month follow up is grade I skin lesions toxicity seen in 58 out of 60 patients, and the least common toxicities are grade I neutropenia seen in 2 patient each. Hand foot syndrome was seen in 30 patients with Grade I and 10 patients with Grade II toxicity.

Similar findings were observed in Shen-Bao Hu et al [2019] study observed Thirteen [13.7%] patients had grade 3–4 leukopenia, anemia, and thrombocytopenia, while 9 [9.5%] patients had grade 3–4 anemia, and 5 [5.3%] patients had grade 3–4 thrombocytopenia. [8]

Jing Shen et al [2022] in a study observed out of 95 patients Grades 3–4 leukopenia, anemia, and thrombocytopenia were observed in 13 [13.7%] patients, 9 [9.5%] patients, and 5 [5.3%] patients, respectively. Seven patients [7.4%] developed grade 3 nausea. [10]

Preoperative chemoradiation data for patients with gastric cancer **MD Anderson Cancer Center investigators** reported a study in which 33 patients Grade 4 toxicity occurred in 21% of patients. [11]

Compared with the previous literature, results of preoperative neoadjuvant chemotherapy for patients with gastric cancer, the application of radiotherapy combined with chemotherapy in neoadjuvant setting for patients with locally advanced gastric cancer can achieve improved clinical efficacy.

Conclusion: The acute toxicities with neoadjuvant therapy are less. Further follow-up is required to assess the late post op complications and disease free survival and overall survival. Further multi-institutional studies are required for improving p balue of study and significance. People need to be made aware about the disease by government programs and advertisements. Large scale screening programs are needed for early detection of diseases. Early presentation can offer much better prognosis which can be achieved by proper counselling and guidance.

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