Study On The Risk of Mucositis Among The Head And Neck Cancer Patients Receiving Radiation Therapy In 3dcrt/Imrt And Chemotherapy By Cisplatin + 5-Fluorouracil Due To Protein Deficiency

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Abstract

This study aims to determine the severity of mucositis inpatient receiving radiotherapy with chemotherapy in head and neck cancer patients. 29 numbers of head and neck cancer patients enrolled in the study and assigned to treat with radiation therapy and chemotherapy. To analyze the severity of mucositis inpatient on concurrent chemoradiation therapy and to observe the other causes of mucositis including lack of protein in diet the subjects were monitored the severity of Mucositis due to lack of protein in the diet. As a result, good nutrition improves the symptoms of mucositis and reduces the severity of treatment, and also the protein level maintained within ranges seems the severity of mucositis can be reduced.
The consequences of mucositis which include, dysphagia, and weight loss were also reported.

Keywords — *Mucositis, IMRT, 3D-CRT, Cisplatin, 5- fluorouracil, Head and neck cancer*

I. INTRODUCTION

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body. HNSCC is the sixth leading cancer by incidence worldwide. The five-year overall survival rate of patients with HNSCC is about 40-50%. More than 90% of head and neck cancers are squamous cell carcinomas (HNSCC) that arise from the mucosal surfaces of the oral cavity, oropharynx, and larynx.

The three main types of treatment for managing head and neck cancer are radiation therapy, surgery, and chemotherapy. Concurrent chemoradiation therapy is the current standard of care for patients with locally advanced squamous cell carcinoma of the head and neck cancer. Chemotherapy is most effective at killing cells that are rapidly dividing. Chemotherapy drugs given are Cisplatin and 5- fluorouracil.

Radiation therapy is a type of cancer treatment that uses beams of intense energy to kill cancer cells. Radiation therapy is commonly applied to the cancerous tumor because of its ability to control cell growth. Ionizing radiation works by damaging the DNA of cancerous tissue leading to cellular death.

IMRT and 3D-CRT are the two types of radiation. Intensity-modulated radiotherapy (IMRT) uses linear accelerators to safely deliver precise radiation to a tumor while minimizing the dose to surrounding normal tissue. It manipulates photons and proton beams to the shape of the tumor. 3D-CRT (three-dimensional conformal radiotherapy) is to deliver a conformal dose distribution to tumors, which provides the 3-dimensional images of the tumor and provides the highest possible dose of radiation while sparing surrounding normal structures.

Up to 40% of head and neck cancer patients are malnourished. Malnutrition has a significant impact on morbidity, mortality, and quality of life of cancer patients. The major side effects caused due to concurrent radio-chemotherapy are sore mouth, weight loss, pain, dysphagia, hair loss, mucositis nausea, and vomiting.

Mucositis is the painful inflammation and ulceration of mucus membrane lining the digestive tract, usually as an adverse effect of radiotherapy and chemotherapy. Mucositis is dose-dependent; radiation doses used are 66-72 Gy (2.0 Gy/fraction; daily Monday-Friday in 7wk). Mucositis is not only painful but can also limit adequate nutritional intake and decrease the patient's willingness to continue treatment.

II. METHODOLOGY

Source of data: Patient Case Report Form.
Study location: Erode Cancer Centre Hospital
Duration: Feb 2019 –Jul 2019
Type of Study: Prospective observational study
Study population: 29 patients

INCLUSION CRITERIA:
- Age from 18yrs to 75 yrs.
- Patients newly diagnosed with head and neck cancer.
- Patients undergoing chemotherapy either with 5-flurouracil+Cisplatin and radiation therapy in Linear Accelerator (LINAC) or Patient undergoing chemotherapy with Cisplatin.
- ECOG performance status 0, 1, or 2.
- No prior hormonal, chemotherapy or radiotherapy is allowed.
- Patients can understand willingness and likely to comply with study procedures and restrictions.

EXCLUSION CRITERIA:
- Pregnant and lactating woman.
- A patient who is unwilling or unstable to follow the protocol requirements.
- Patients with brain metastatic.
- Patients having an untreated symptomatic dental infection.

STUDY PHASE - I:
- Literature survey
- Prepare suitable data collection forms.
- Obtain approval from the Institutional Ethical Committee.

STUDY PHASE - II:
- Newly diagnosed head and neck cancer patients undergoing radiotherapy and chemotherapy were allocated into study groups.
- An informed consent form was obtained from the patient.
- The data was collected from the patient using a well-structured data collection form.
- The patient's demographic history, medication chart, case history, laboratory parameters, and physical status of the patient were taken.
- The physical assessment of the patient was analyzed using ECOG (Eastern Cooperative Oncology Group) grading scale.
- Eligible patients were randomly assigned for the study, identical radiation therapy with concurrent bolus cisplatin with or without fluorouracil.
- And the patients in the group were continued with routine care. Oral mucositis was assessed on 1st, 5th, 10th, 15th, 20th, 25th, and 30th day of radiotherapy by using the WHO oral toxicity scale.
- A nutritional assessment of the patient was done for the assessment of mucositis due to a lack of protein in the diet.

WHO grading system for mucositis

GRADE	DESCRIPTION
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcer, solid diet tolerated
III (severe)	Oral ulcer, liquid diet only
IV (life-threatening)	Oral alimentation impossible

Note: Grading based on clinical appearance and functional status.

Dysphagia grading scale

GRADE	DESCRIPTION
1	Complaints of dysphagia, but still eating normally
2	Requires liquid with meals
3	Able to take semisolid, but unable to take solid foods
4	Able to swallow liquid food only
5	Unable to swallow liquid food, able to swallow saliva
6	Unable to swallow saliva

STUDY PHASE - III:
- Data analysis
- Result interpretation

III. RESULTS
TABLE NO.1

Age-wise distribution of patients

SL No	AGE GROUP	NUMBER OF PATIENTS (n=29)	PERCENTAGE (%)
1	40-50	7	24.14%
2	50-60	7	24.14%
3	60-70	9	31.04%
4	70-80	6	20.68%

TABLE NO.2

Distribution of patients based upon gender

GENDER	NUMBER OF PATIENTS (n=29)	PERCENTAGE (%)
MALE	19	65.51%
FEMALE	10	34.49%

TABLE NO.3

Type of head and neck cancer

SL NO	TYPE OF CANCER	NUMBER OF patients (n=29)	PERCENTAGE
1	OROPHARYNX	4	13.79%
2	BUCCAL MUCOSA	6	20.68%
3	HYPOPHARYNX	6	20.68%
4	SUPRAGLOTTIS	3	10.35%
5	LIP	2	6.8%
6	NASOPHARYNX	1	3.46%
7	TONGUE	4	13.79%
8	RETROMOLAR TRIGOME	1	3.44%
9	CHEEK	1	3.44%
10	PYRIFORM FOSSA	1	3.44%

TABLE NO.4

Eastern cooperative oncology performance status

ECOG GRADE	NUMBER OF PATIENTS (n=29)	PERCENTAGE (%)
GRADE 0	19	65.51%
GRADE 1	10	34.49%
GRADE 2	0	0%

TABLE NO.5

Social habits

SOCIAL HABITS	NO OF PATIENTS(n=29)	PERCENTAGE (%)
BETEL NUT	8	27.56%
SMOKING	5	17.24%
SMOKING & ALCOHOLIC	5	17.24%
BETEL NUT & ALCOHOLIC	3	10.34%
ALL THREE	6	20.66%
NONE	2	6.87%

TABLE NO.6

Tumour nodes metastasis staging

T- STAGING	NUMBER OF PATIENTS (n=29)	PERCENTAGE
T1	2	6.89%
T2	7	24.15%
T3	17	58.62%
T4	3	10.34%

TABLE NO.7

Nodes staging

N - STAGING	NUMBER OF PATIENTS (n=29)	PERCENTAGE (%)
N0	4	13.79%
N1	13	44.82%
N2	11	37.95%
N3	1	3.44%

TABLE NO.8

Type of radiation therapy

TYPE OF RADIATION THERAPY	NUMBER OF patients (n=29)	PERCENTAGE (%)
3D-CRT	17	58.63%
IMRT	12	41.37%

TABLE NO.9

Chemotherapy dosing chart

CHEMOTHERAPY DOSAGE	NUMBER OF PATIENTS (n=29)	PERCENTAGE (%)
CISPLATIN 30MG	4	13.79%
CISPLATIN 40MG	12	41.37%
CISPLATIN 50MG	8	27.59%
CISPLATIN 60MG	3	10.85%
CISPLATIN 40 MG + 5 FU 1000MG	2	6.89%

TABLE NO.10

Dysphagia in head and neck cancer patient undergoing IMRT

DYSPHAGIA GRADE	IMRT (n=12)	PERCENTAGE (%)
GRADE 1	0	0%
GRADE 2	7	58.34%
GRADE 3	4	33.33%
GRADE 4	1	8.33%
GRADE 5	0	0%
GRADE 6	0	0%

GRADE 3	8	47.05%
GRADE 4	2	11.77%
TOTAL	17	100%

TABLE NO.11

Dysphagia in head and neck cancer patient undergoing 3d-CRT

DYSPHAGIA GRADE	3D-CRT(n=17)	PERCENTAGE (%)
GRADE 1	0	0%
GRADE 2	0	0%
GRADE 3	8	47.05%
GRADE 4	5	29.43%
GRADE 5	3	17.64%
GRADE 6	1	5.88%

TABLE NO.16

The protein level in 3DCRT patients

No of patients(n=17)	During Cycle 1	During Cycle 6
1	7.8 g/dl	5.5 g/dl
2	6.0 g/dl	5.0 g/dl
3	5.7 g/dl	5.8 g/dl
4	8.0 g/dl	6.1 g/dl
5	7.4 g/dl	5.4 g/dl
6	7.4 g/dl	6.1 g/dl
7	7.1 g/dl	5.5 g/dl
8	7.6 g/dl	5.2 g/dl
9	7.7 g/dl	5.2 g/dl
10	7.4 g/dl	5.4 g/dl
11	7.8 g/dl	5.3 g/dl
12	8.0 g/dl	6.0 g/dl
13	7.6 g/dl	5.3 g/dl
14	6.9 g/dl	5.1 g/dl
15	7.8 g/dl	6.0 g/dl
16	7.9 g/dl	5.2 g/dl
17	8.0 g/dl	5.4 g/dl

TABLE NO.12

Weight variation graph

TYPE OF RADIATION	1 TO 3 (kg)	4 TO 6 (kg)	7 TO 9 (kg)	TOTAL
3D-CRT	2	12	3	17
IMRT	3	9	0	12
TOTAL	5	21	3	29

TABLE NO.13

Mucositis grading according to WHO grading

MUCOSITIS GRADE	NUMBER OF PATIENTS (n=29)	PERCENTAGE
GRADE 1	3	10.35%
GRADE 2	12	41.38%
GRADE 3	10	34.48%
GRADE 4	4	13.79%

TABLE NO.17

The protein level in IMRT patients

NO Of patients	During Cycle 1	During Cycle 6
1	7.3 g/dl	5.4 g/dl
2	7.8 g/dl	5.9 g/dl
3	8.0 g/dl	6.0 g/dl
4	7.6 g/dl	5.0 g/dl
5	8.1 g/dl	6.4 g/dl
6	6.5 g/dl	6.0 g/dl
7	7.1 g/dl	6.2 g/dl
8	6.6 g/dl	5.4 g/dl
9	6.8 g/dl	5.5 g/dl
10	6.9 g/dl	5.3 g/dl
11	6.5 g/dl	6.0 g/dl
12	5.9 g/dl	5.8 g/dl

TABLE NO.14

Mucositis percentage in IMRT patients

MUCOSITIS GRADE	IMRT (n=12)	PERCENTAGE (%)
GRADE 1	2	16.67%
GRADE 2	8	66.67%
GRADE 3	2	16.66%
GRADE 4	0	0%
TOTAL	12	100%

TABLE NO.15

Mucositis percentage in 3D-CRT patients

MUCOSITIS GRADE	3D-CRT (n=17)	PERCENTAGE (%)
GRADE 1	1	5.88%
GRADE 2	6	35.30%

IV. DISCUSSION

Cancer is a class of diseases; it is unlikely that there will ever be a single "cure for cancer" any more than there will be a single treatment for all infectious diseases.

In this study the age distribution was found higher in the age group of 60–70 years (31%) whereas it was found lower between the age 70-80 years(20%) which coincides with the study conducted by Lori smith et al.,(2018) The mean age of the included study participants was 61 years; 74% of participants were men and 26% were women. From this, we concluded that head and neck cancer were mainly occurring in-between the age group of 60-70 years (31%) as shown in (Table no:1).

Among the study population, 29-patients were selected according to inclusion and exclusion criteria which consist of 19 patients (66%) were male while 10 patients (34%) were female (Table no.2).

The primary site of the tumor was identified in the buccal mucosa in 6 patients (20.6%), oropharynx in 4 patients (13.79%), tongue in 4 patients (13.79%), hypopharynx in 6 patients(20.68%), supraglottis in 3 patients (10.35%), the lip in 2 patients (6.8%), nasopharynx in 1 patient(3.46%), retromolar trigone in 1 patient(3.44%), cheek in 1 patient(3.44%), pyriform fossa in 1 patient(3.44%) (Table no. 3) which coincides with the study conducted by Smith, et al.,(2018), and the most common cancers noted in the study population was of the oropharynx (46%), followed by the larynx (31%), oral cavity (13%), and the hypopharynx (12%). Nearly half of all patients studied were diagnosed with stage IV disease.

Subjects for concurrent chemoradiotherapy were selected based on the ECOG (Eastern Cooperative Oncology Group) performance status of the patient to assess the capability of the patient to withstand the chemotherapy drugs and radiation fraction. ECOG performance status scale in this study shows that there are 19 patients (65.51%) under Grade 0 and 10 patients (34.49%) under Grade 1 (Table no. 4).

As shown in table (Table no.5) mostly 93% of patients were alcoholics, smokers, and taking betel nuts. Rhona A Beynon et al., (2018) conducted a study, which suggests that smoking at the time of an HNC diagnosis may result in poorer clinical outcomes and reduced survival.

This study was conducted based on Tumour Node Metastasis staging and among 29 patients - 2 patients had T1 stage, 7 patients had T2 stage,17 patients had T3 stage and 3 patients had T4 stage (Table no.6) and 4 patients with N0, 13 patients with N1, 11 patients with N2, 1 patient with N1 (Table no.7).

Based on the tumor lesion in different sites, radiation fraction, and drug dose were chosen. The patient received concurrent radiation therapy 40 -70 Gy (Table no. 8) in IMRT and 3DCRT along with cisplatin /5 fluorouracil at a dose of 30-60mg/kg /1000mg weekly(Table no. 9). The prevalence of other causes varies from subject to the subject because of the inter-subject variability towards the drugs administered.

Out of 12 patients who underwent IMRT, Grade II dysphagia was found in 7 patients (Table no. 10) and out of 17 patients who underwent 3DCRT, Grade III dysphagia was observed in 8 patients (Table no.11). Lasrado, et al.,(2014) conducted a study and reveals that evaluation of acute toxicity revealed that 50% had grade II mucositis, 25% grade III mucositis, 2.5% grade IV mucositis. Sehi Kweon, et al., (2016) conducted a study and concluded an inflammatory reaction and the production of reactive oxygen species after CCRT can cause dysphasia, and patients show acute dysphagia within 4 to 5 weeks of starting therapy.

During this study weight loss was also observed, about which 21 patients lost weight up to 4-6kg (Table no. 12).

In this study oral mucositis was assessed on 1st, 5th, 10th, 15th, and 20th day of radiotherapy by using the WHO oral toxicity scale (Table no. 13). While Lambrecht et al., reported xerostomia in 23% with IMRT and 68% with 3D-CRT. Grade 3 or greater mucositis was 32% with IMRT while it is 44% with 3D-CRT as compared to xerostomia of 45% and 72.5% and grade 3 or greater mucositis of 40% and 57.5% in this group respectively. This study is to evaluate the severity of mucositis in patients undergoing concurrent chemotherapy and radiation therapy (Table no. 14, 15).

This study also revealed that there is a significant lowering of protein level in both 3DCRT and IMRT but there is more decrease of protein level in 3DCRT (Table no.16, 17). D. Hopanci Bicakli, et al.,(2017)conducted a study and concluded body composition parameters were better in head and neck cancer patients considered as compliant according to dietary intake than non-compliant ones during radiotherapy period.

V. CONCLUSIONS

All patients managed to complete all six cycles of chemotherapy and radiation therapy treatment. As compared to conventional radiotherapy, the IMRT technique with chemotherapy offers better sparing of normal tissue thus minimizing toxicity. The IMRT technique gives the ability to create treatment fields with varying beam intensity by using inverse planning and iterative optimization algorithms.

Patients who were treated with IMRT had grade 2 mucositis and patients treated with 3DCRT had grade 3 mucositis. The severity of mucositis was increased due to inadequate nutrition during the treatment.

Through this study, we concluded that patients receiving IMRT experienced low-grade

mucositis. However, this study may not be a sole guide in assessing the severity of oral mucositis but could be used as an adjunct to clinical oral examination at the assessment level in the future.

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