ORIGINAL RESEARCH PAPER
Volume-8 | Issue-9 | September - 2019 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EVALUATION OF TOXICITIES IN MULTIMODALITY MANAGEMENT OF LOCALLY ADVANCED HEAD AND NECK CANCERS: AN INSTITUTIONAL EXPERIENCE

Oncology

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ABSTRACT

INTRODUCTION: Head & Neck cancers accounts more than 644,000 cases and 320,000 deaths annually worldwide. The majority of cases are reported from South – East Asia region, where India is a major contributor. For Locally advanced Head and neck cancers, multimodal treatment is the standard of care.
The fractionated doses of radiotherapy are important because of the differences in the response of the tumor and normal tissue. Acute adverse effects continue to be an important concern in head and neck cancer patients which may be intense and debilitating but resolve over time.
MATERIAL AND METHODS: Observational Prospective Study, from2015 to 2017.100 patients enrolled. Three arms, 30 patients in each arm.
ARM A. ICT f/b CTRT
ARM B. ICT f/b RT
ARM C. RT alone
RESULT: Among 90 cases, male: female ratio was 1.6:1 with 62% were of age more than 40 years. Acute toxicities i.e. Nausea, vomiting, mucositis and myelo-suppression were significantly more in ARM-A than ARM –B and C, and radiation dermatitis was significantly more in ARM-C.
CONCLUSION: Treatment related toxicities and protracted treatment protocols are associated with high attrition rate but with good symptomatic, nutritional support and proper counseling it can be avoided successfully.
Treatment related toxicities can be minimized by using more conformal techniques of radiotherapy like 3D CRT, IMRT.

KEYWORDS

head and neck, induction chemotherapy, chemo radiation, toxicities.

INTRODUCTION

Oral and oropharyngeal cancers are important sub sites in Head and Neck cancers. Global estimated annual incidence of Oral and oropharyngeal cancers is around 440,000.[I] Head and Neck cancers accounts for more than 644,000 cases and 320,000 deaths annually worldwide.[ii][iii]The majority of cases are reported from South – East Asia region, in which India is a major contributor. The annual estimated incidence of these cancers in India is around 115,000.[ii]

For Locally advanced Head and neck cancers, multimodal treatment is the standard of care. Radiation therapy alone can be used with curative intent in selected cases. Most patients treated with radical intent receive 66-72 Gy.[iv] In addition to anti-tumor effects, radiation also affects critical normal structures.

The fractionated doses are important because of the differences in the response of the tumor and normal tissue to the radiation. Tolerance of the normal tissue around the tumor is important dose limiting factor in the radiation treatment.[v]Acute adverse effects continue to be an important concern in head and neck cancer patients which may be intense and debilitating but resolve over time.

AIM AND OBJECTIVES

AIM: To compare the toxicity profile in patients undergoing induction chemotherapy followed by CTRT, Induction chemotherapy followed by RT Vs RT alone in locally advanced head and neck cancer patients.

OBJECTIVES

1. To assess the toxicities arising due to chemo radiation in locally advanced head and neck cancer.
2. To analyze the co- relation of toxicities with treatment modality.

MATERIAL AND METHODS

Observational Prospective Study, from 2015 to 2017.100 patients enrolled. Three arms, 30 patients in each arm.

ARM A. ICT followed by CTRT
ARM B. ICT followed by RT
ARM C. RT alone

INCLUSION CRITERIA:
- Biopsy proven carcinomas of head and neck
- Patients whose treatment intent was radical.
- Age up to 65 years.
- Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) <=2.

EXCLUSION CRITERIA:
- Evidence of distant metastases.
- Previous therapeutic irradiation for Head and Neck cancer.
- Any medical or surgical condition precluding use of Radiotherapy or Chemotherapy.
- Pregnant or lactating mother.
- Patient with poor compliance.

STUDY PROCEDURE:
All study cases satisfying inclusion criteria were evaluated for the disease status by clinical examination, indirect and or direct laryngoscopy, CECT FACE + NECK. Sampling done with purposive sampling method based on reference studies

A. NEO–ADJUVANT CHEMOTHERAPY FOLLOWED by RADIOTHERAPY WITH CONCURRENT CHEMOTHERAPY
In this arm patient received taxane based Induction chemotherapy three cycles three weeks apart, then received 66 to 70 Gy in 1.8Gy to 2Gy per fraction respectively 5 days a week in 6 to 7 weeks along with injection Cisplatin 40mg/m2 weekly.

B.INDUCTION CHEMOTHERAPY FOLLOWED by RADIOTHERAPY
In this arm patient received taxane based Induction chemotherapy three cycles three weeks apart, followed by 66 to 70Gy in 1.8Gy to 2Gy per fraction respectively 5 days a week in 6 to 7 weeks.

C. RADIOTHERAPY ONLY
These patients received 66 to 70Gy in 1.8Gy to 2Gy per fraction

respectively 5 days a week in 6 to 7 weeks.

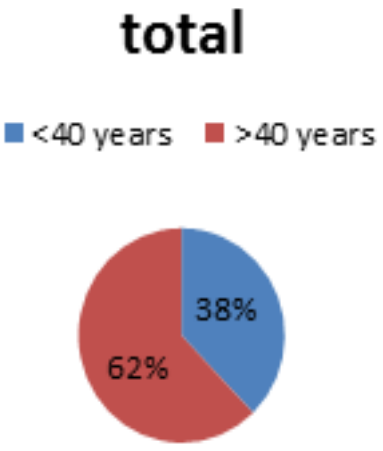
EVALUATION OF TOXICITIES:
Acute toxicities were assessed weekly till the completion of treatment and the toxicity of highest grade was recorded and graded according to CTCAE4.0 Criteria.

Proper required supportive treatment was given to each patient.

Post completion of treatment Patients were called for follow up every 3 months for assessment of treatment related late toxicities.

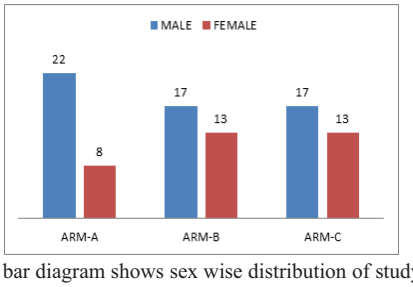
OBSERVATION AND RESULTS
Total 90 patients were evaluated 30 subjects in each arm.

DIAGRAM -1



The above Pie diagram shows that patients with age more than 40 years are 62 % of the study population.

DIAGRAM -2

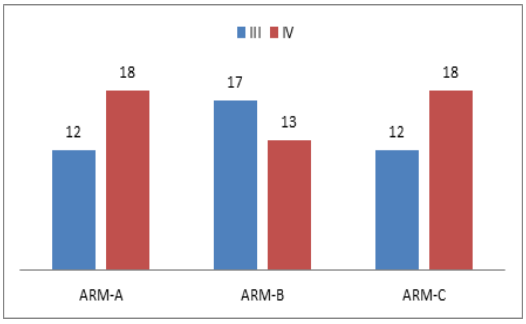


The above bar diagram shows sex wise distribution of study subjects with male population predominates in the study. M:F =1.6:1

ECOG PS	ARM-A	ARM-B	ARM-C
0	2	7	9
1	11	23	21
2	17	0	0

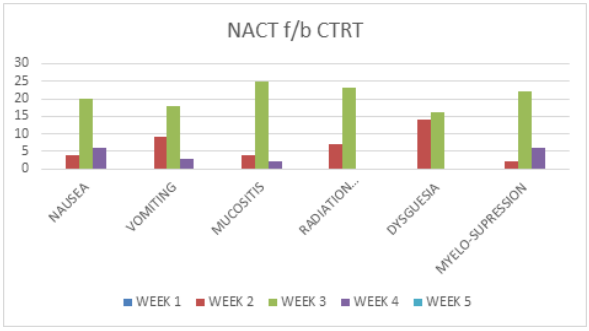
Maximum patients in the study were in ECOG 1.

DIAGRAM-3



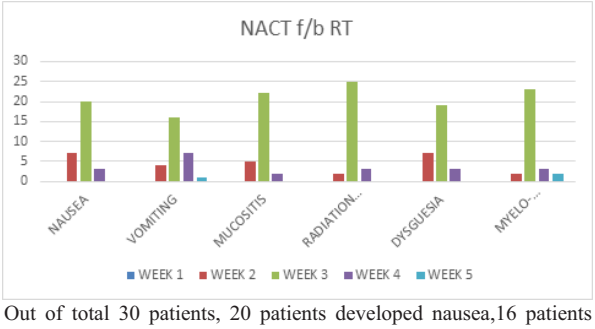
The above graph shows stage-wise distribution of study subjects and it reveals that 49 (54%) patients belong to stage IV almost equal in both the arms.

DIAGRAM -4 ARM-A



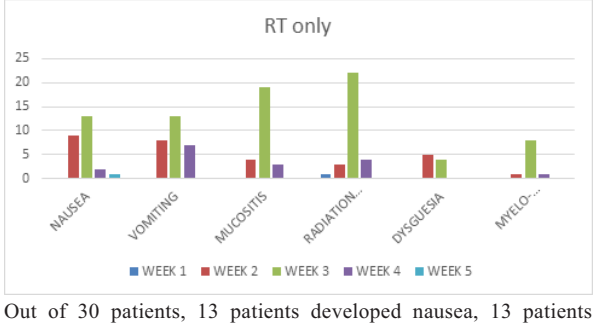
Out of total 30 patients, 20 patients developed nausea, 18 patients developed vomiting, 25 patients were developed mucositis, Radiation dermatitis was observed in 23 patient's dysguesia in 16 patients and 22 patients developed myelo-suppression in 3rd week of treatment.

DIAGRAM-5 ARM-B



Out of total 30 patients, 20 patients developed nausea,16 patients developed vomiting ,mucositis was observed in 22 patients ,almost 25 patients were developed radiation dermatitis,19 patients developed dysguesia ,23 patients developed myelo-suppression in 3rd week of treatment.

DIAGRAM-6 ARM-C



Out of 30 patients, 13 patients developed nausea, 13 patients developed, mucositis was observed in 19 patients, maximum numbers of patient's almost 22 patients were developed radiation dermatitis, 4 patients developed dysguesia and only 8 patients developed myelo-suppression in 3rd week of treatment.

TABLE - 1 MEDIAN GRADES OF TOXICITIES

	ARM – A	ARM - B	ARM – C
TOXICITIES	Median Grade	Median Grade	Median Grade
nausea	3	3	3
vomiting	3	3	2
mucositis	3	3	2
radiation dermatitis	3	3	3
dysguesia	1	1	1
myelo-suppression	3	3	1

From the above table it is obvious that grade 3 toxicities viz. nausea, vomiting, mucositis and myelo-suppression were significantly more with Kruskal-Walis Test(P value <0.05) in ARM-A as compared to ARM-B and ARN-C and radiation dermatitis was significantly more with Kruskal-Walis Test(P value <0.001) in ARM-C as compared to ARM-A and ARM-B.

TABLE- 2. WEEK 3 TOXICITIES

Week 3 toxicities				
TOXICITY	NACT-CRT	NACT-RT	RT alone	TOTAL
nausea	20	20	13	53
vomiting	18	16	13	47
mucositis	25	22	19	66
radiation dermatitis	23	25	30	78
dysguesia	16	19	4	39
myelo-suppression	22	23	8	53
total	160	169	118	447

Chi Square=	27.89
Degrees of Freedom=	14
p-value=	0.01469

The above table shows that the difference in toxicities in 3 different ARM's is found to be statistically significant with Chi square test. Toxicities including nausea, vomiting, mucositis, dysguesia and myelo-suppression are statistically more significant in ARM-A and Radiation dermatitis is statistically more significant in ARM-C .

DISCUSSION

Head and Neck cancer is the most common cancer in men and third most common cancer in women in India.

Due to habit of tobacco chewing, illiteracy, poverty and negligence most of the patients presented with advanced stage of the disease.[vi,vii]

The conventional methods of radiotherapy which exposes higher volume of tissue to irradiation and lower conformity have been thought to be associated with more normal tissue toxicities.

With this background, the current study aimed to assess the treatment related toxicities in advanced head and neck cancer patients.

The Sample size was 100 of which 90 patients were evaluated and completed the entire study. 3 patients died and remaining 7 patients defaulted. The most common cancer detected was of oral cavity and the study sample mostly comprised of males and most of the patients were having age more than 40 years. Toxicities were assessed weekly during the treatment in all the three arms. The grading of toxicities was done according to the CTCAE criteria version 4.0.

The highest grade experienced by the patient during the treatment was noted as a grade of toxicity for the respective patient.

NAUSEA and VOMITING

Nausea and vomiting was observed to be more in 3rd week of treatment in ARM – A as compared to ARM B and ARM – C, as evident from **table no.1**, that the median grade 3 nausea and vomiting was significantly more with Kruskal-Walis test (P value <0.05) in ARM – A. There was statistically significant difference between the nausea and vomiting observed between three treatment arm's as evident from **table no. 2**

Similar observations were found in studies done by Vermorken et al in 2007, Alber's AE et al in 2007 and TAX 324 trial.[viii][ix] [x]

MUCOSITIS

Mucositis was observed to be more in 3rd week of treatment in ARM – A as compared to ARM – B and ARM – C as evident from **table no.1** that the median grade 3 mucositis was significantly more with Kruskal-Walis test (P value <0.05) in ARM – A.

There was statistically significant difference between the mucositis observed between three treatment arms's as evident from **table no.2.**

Similar observations were found in studies done by Vermorken et al in 2007, Alber's AE et al in 2007 and TAX 324 trial.[viii][ix][x]

RADIATION DERMATITIS

Radiation dermatitis was observed to be more in 3rd week of treatment in ARM – C as compared to ARM – B and ARM– A

As evident from **table no. 1** that the median grade 3 radiation dermatitis was significantly more with Kruskal-Walis test (P value <0.001) in ARM – C.

There was statistically significant difference between the radiation dermatitis observed in three treatment arm's as evident from **table no2.** This study finding is in contrast to the study done by Saptarshi et al. in 2012.[xi]

DYSGUESIA

Dysguesia was observed to be more in 3rd week of treatment in ARM – B as compared to ARM – A and ARM – C as evident from **table no.1** that the median grade 1 dysguesia was significantly more with Kruskal-Walis test (P value <0.05) in ARM – B.

There was statistically significant difference between the dysguesia observed in three treatment arm's as evident from **table no.2.**Most of the times the dysguesia occurred as a consequence of acute salivary gland reactions.

Similar results were found by Vermorken et al in 2007.[viii]

MYELO-SUPRESSION

Myelo-suppression was observed to be more in 3rd week of treatment in ARM – A as compared to ARM – B and ARM – C as evident from **table no.1** that the median grade myelo-suppression was significantly more with Kruskal-Walis test (P value <0.05) in ARM – A.

There was statistically significant difference between the myelo-suppression observed between three treatment arm's as evident from **table no.2**

Similar results were found by Vermorken et al in 2007, Alber's et al in 2007, TAX 324 trial in 2011, Dr. Robert Haddad et.al.in 2008, EORTC phase 3 trial 22931 and GORTEC TRIAL 1994.[viii][ix][x][xii] [xiii][xiv]

SUMMARY :

Head and neck cancers are considered as a significant health burden. Radiation therapy is used for treatment in most of these patients. We conducted a prospective observational study in 100 patients with advanced head and neck cancer who have attended our department from August 2015 to July 2017.

Patients of different age groups were included with many patients were above 40 years of age mostly male. Most of the patients were of stage IV A and type 2 (exophytic) and type 3(ulcerative) growth patterns. Many patients had habit of taking tobacco in different forms.

The most common acute toxicities found during the study were nausea, vomiting, mucositis and myelo-suppression in ARM – A .

There was significant difference between the different arms of treatment for grade 3 hematological and non-hematological toxicities. Almost all patients with significant high grade toxicities were optimally treated in hospital and adequate nutritional support also been provided free of cost under government schemes.

CONCLUSION:

Head and neck cancers are rising in India and in era of organ and function preservation radiotherapy has shown good results though it is associated with significant amount of toxicities. Study shows that treatment related toxicities as well as more protracted protocols of treatments are associated with high attrition rate but with good symptomatic and nutritional support and proper counseling of the patients and their relatives it can be avoided successfully as in our study. Neo adjuvant chemotherapy is associated with more toxicities as compared to radical CTRT.

Treatment related toxicities can be minimized by using more conformal techniques of radiotherapy like 3D CRT, IMRT.

It's time to work on combination of treatments which are associated with fewer amounts of toxicities without compromising the treatment outcomes in view of both disease free survival and overall survival.

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