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Original Research Paper

Oncology

A PROSPECTIVE STUDY OF EVALUATION OF RESPONSES, TOXICITIES AND SURVIVAL OF PATIENTS WITH CONVENTIONAL EXTERNAL BEAM RADIOTHERAPY VERSUS INTENSITY MODULATED RADIOTHERAPY AFTER NEO ADJUVANT CHEMOTHERAPY IN LOCALLY ADVANCED OROPHARYNGEAL CANCERS.

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ABSTRACT Head and neck cancer (HNC) is one of the most common cancers in India. The present study analyzed the responses and toxixities comparing conventional radiotherapy [EBRT] and the state of art technology[IMRT]. Complete and partial responders after neoadjuvant chemotherapy, were randomized into Arm A and Arm B and definitive radiation 70Gy/ 35 fractions/7weeks in the form of conventional EBRT in arm A and IMRT in arm B as per institution protocol were delivered. Radiation related toxicities were assessed and documented as per the RTOG criteria. LRF, DFS, and OS at the end of last follow up found to be 10% versus 5%; 70% versus 90%; and 80% versus 95% respectively in arm A versus arm B. The future scope of management of advanced stage oropharyngeal carcinoma lies in judicial utilization of systemic chemotherapy and radiation therapy according to individualized patient centric approach to enhance therapeutic ratio and treatment success.

KEYWORDS : oropharyngeal, carcinoma, EBRT, IMRT, RTOG.

INTRODUCTION

Head and neck cancer (HNC) is one of the most common cancers in India [1]. It is the most common cancer of males and the fifth most common in females in India [2]. Head and neck cancer in India varies geographically due to tobacco consumption, food habits, varied demographic parameters and personal history [3]. As per the hospital based cancer registry of Kamala Nehru Memorial Hospital, Regional Cancer Centre, Allahabad, incidence of total head and neck cancer patients constituted 45.43% of all cancer patients reported from 2014-2015. Among them 5.12% were exclusively oropharyngeal cancers of both the sexes [4].

In Indian scenario, head and neck cancer (HNC) is attributed mostly to tobacco addictions either in the form of smokeless or smoking tobacco. A group of oropharyngeal cancer patients has been considered in our study because of rising trends of its incidence due to increasing popularity of smokeless tobacco in the form of pan, gutka, supari etc. even in very younger age groups. The present study attempted to analyze the response and clinical outcomes after neoadjuvant chemotherapy followed by definitive radiation therapy as loco-regional therapy in locally advanced oropharyngeal carcinoma

OBJECTIVES

The study design has set the following objectives with regards to-

1. Demographic profile of patients and clinical characteristics of oropharyngeal cancers.
2. Restaging evaluation after NACT
3. Acute and late toxicities as per RTOG criteria in both groups.
4. Clinical outcome with respect to loco- regional failures (LRF), disease free survival (DFS) and overall survival (OS).

RESEARCH METHODOLOGY

Material and methods

The present study has been conducted in the Department of Radiation Oncology, Kamala Nehru Memorial Hospital, Regional Cancer Centre (RCC), Allahabad, Uttar Pradesh. The study was conducted from February 2014 to January 2015 and the last follow up was assessed and recorded at the end of October 2017.Total number of oropharyngeal cancer patients of both sexes reported to our institute were 118, and among them 54 patients were eligible for study as per patient eligibility criteria.

Patient Eligibility

✓ **Inclusion Criteria**

- Histologically proven squamous cell carcinoma of all sites of oropharynx.
- AJCC Stage III and Stage IVA.
- Complete and partial responders to neoadjuvant chemotherapy.
- Patient age 21 years.
- Patient of both sexes.
- Karnofsky performance status (KPS) of ≥ 70.
- Weight loss ≤ 10% in the 3 months before diagnosis.
- No prior systemic chemotherapy / radiotherapy.
- Granulocyte count 4,000/ml
- Platelet count 1,50,000/ml
- Hemoglobin 10mg/dl
- Bilirubin ≤ 1.5 x normal
- Creatinine clearance > 50ml/min.

✓ **Exclusion Criteria**

- Age > 80 years.
- Histology other than squamous cell carcinoma
- Non responders to neoadjuvant chemotherapy
- Progressive disease to neoadjuvant chemotherapy.
- AJCC Stage I, II, IVb and Ivc.
- Patients with active concurrent malignancy, serious medial / psychiatric illness, or history of serious cardiac and renal diseases.

Study Design

The present study was a prospective, comparative, randomized double arm study which included patients of AJCC Stage III and Stage IVA oropharyngeal cancer of both the sexes. They were subjected to neoadjuvant chemotherapy as per institution protocol. According to WHO criteria NACT response was assessed [5], and complete and partial responders as per WHO criteria were included and randomized in two arms. After 3 weeks of neoadjuvant chemotherapy local treatment was given in arm A as conventional external beam radiotherapy (EBRT) and in arm B as intensity modulated radiotherapy (IMRT) according to institution protocol.

Statistical Method:

Statistical analysis was performed using SPSS, Version14. Patients and tumor related characteristics were observed and analyzed using Chi-Square Test.

Data Collection:

A mandatory work up of each patient included in the study was carried out prior to the commencement of treatment. It assisted in the staging the disease, evaluation of performance status and the

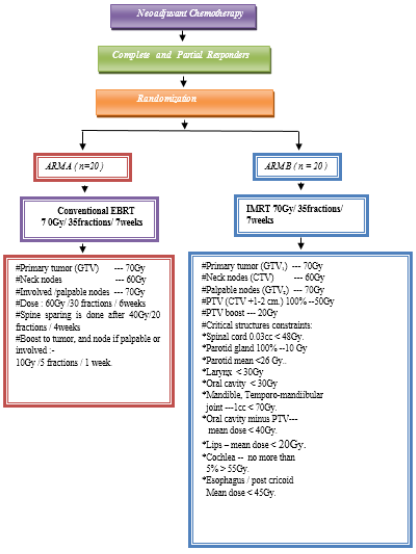
eligibility of the patient to undergo the proposed treatment.

Ethical Consideration:
Informed consent has been taken from the participants' and their relatives describing the treatment protocol and management in both vernacular & English languages. The study has been reviewed and approved by the scientific and ethical committee.

Pretreatment Dental evaluation
Dental checkup including complete clinical examination about status of teeth, condition of mucosa, gingival tissue, prosthesis, charting of all dental findings like caries tooth, root canal treatment, oral sepsis, metallic tooth, complete hygiene instructions and precautions about trauma and premature use of prosthesis. Removal of teeth which are non-viable before radiation therapy.

Pretreatment Diagnostic Work Up
- Routine blood profile – Hb, TLC, DLC, Platelets, BUN, Serum creatinine, random blood sugar, LFT, thyroid function tests,Serum electrolytes and a base line ECG.
- Radiological examination- Xrays, CT scans and MRI wherever indicated.
- Histopathological investigation- Biopsy from primary tumor and FNAC from neck nodes.
- Metastatic work up- Bone scans, PET-CT ,USG whenever indicate

TreatmentProtocol



Treatment Procedure
The patients were subjected to induction chemotherapy as per the institution protocol [inj. 5 FU 750mg/m2 i.v. infusion over 1 hour + inj. CDDP 30mg/m2 i.v. infusion over 1 hour with adequate hydration and diuresis for 3 days, q3 weekly x 3 cycles]. Local treatment has been planned after 3 weeks of NACT. The machine used for both the arms was Siemens Linac with 6 MeV photons. Prior to a course of radiotherapy, patients were simulated on CT for optimal radiotherapy planning. Patients were positioned supine, with a thermoplastic mask with an extended head position. The shoulders were positioned as caudally as possible to allow adequate exposure of the neck.

In Arm A, based on the location of the primary tumor and the area of lymphatic drainage , the volume to the treated and the radiation portal arrangement is determined. A margin of 1 to 2cm on the gross tumor and a minimum margin of 1cm around electively treated regional lymph node will be determined. Once the target volume was determined, bilateral parallel opposing field will be used, and a dose of 70Gy in 7 weeks in 35 fractions will be delivered, calculating the dose at the midline or by shrinking field technique. Tumor volumes and critical structures were contoured as per ICRU 62 guidelines.

In Arm B, inverse planning step and shoot IMRT was executed. ICRU 62 guidelines were followed in delineating the tumor volumes and critical structures. Gross Target Volume {GTV}is a primary tumor and any lymph nodes over 10mm in short axis dimension or smaller nodes with necrotic centers or rounded contours that contain tumor. Clinical Target Volume {CTV} is a tissue volume that contains a GTV and/or subclinical microscopic disease. Planning Target Volume {PTV} is a geometrical concept, and is defined to select appropriate beam sizes and arrangements, taking into consideration the net effect of all possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV. As per the institution protocol, 1-2 cm margin around GTV and CTV was constructed to form CTV and PTV respectively.

As per the institution protocol, treatment isocentre on lateral and anterior DRRs from the CT stimulation to be compared with the EPIs from the treatment machine taken on days 1-3 and weekly thereafter. An off-line correction is made relative to the isocentre position if the mean error in any plane is > 3mm. if there is a > 5mm error on any one day the patient should not be treated until the error has been corrected. Re-verification in the simulator or a repeat planning CT scan may be required. Total dose as scheduled was executed - 70Gy in 35 daily fractions given in 7 weeks. Patients are treated daily from Monday to Friday, 5 days per week.

RESULTS

The patient characteristics, socio-demographic profile and tumor parameters were assessed and tabulated [Table1]. Out of 54 patients, 46 patients (85%) has completed induction chemotherapy, 4 patients (7%) could not tolerate it, 3 patients (6%) lost during induction and 1 patient (2%) died. The most common side effect encountered during neoadjuvant chemotherapy was nausea and vomiting (24%), followed by anorexia (20%). Chemotherapy induced toxicities in patients who completed NACT were in acceptable limits. After completion of neoadjuvant chemotherapy we found radio logically complete response in 11 patients (24%), partial response in 29 patients (63%) and no response /progressive disease in 6 patients (13%). Restaging evaluation was performed clinically (both physical examination and imaging) after completion of neoadjuvant chemotherapy. 74% patients were downstaged subsequent to NACT [fig.1].

Toxicities during treatment were recorded as per RTOG criteria. Since 4th week skin reactions and mucosal reactions were more prominent in arm A compared to arm B. The radiation morbidity at the end of 7th week of radiotherapy was assessed and documented [fig.2a and 2b]. Dryness of the mouth, nausea, ear pain, hoarseness of voice and pain due to radiation was a common problem in Arm A compared to Arm B. There were no Grade V radiation morbidities encountered during local treatment in

either of the arms. 45% patients in arm A were admitted in the hospital for supportive care during local treatment compared to arm B [10%]. The quality of life of the patients were better in arm B compared to arm A according to the study.

Clinical outcome at the end of 6months, 1 year and at the end of last follow up the were assessed and documented. LRF, DFS, and OS at the end of last follow up found to be 10% versus 5%; 70% versus 90%; and 80% versus 95% respectively in arm A versus arm B (p-value is .748093) [fig.3]. The results were not significant statistically. Late radiation toxicities were assessed and recorded at the end of 6 months, 1 year and at the end of last follow up and found to be not statistically significant.

Table 1: Patient profile and Clinical characteristics

S.No.	Characteristics	Data (n=54)
1.	Age at the time of diagnosis (mean)	55 years
2.	Sex: male versus female	89% Vs 11%
3.	Histology – WD : MD: PD	32% : 57% :11%

4.	Primary site: Base of tongue Tonsils Pharyngeal walls Soft palate + uvula	48% 31% 17% 4%
5.	Stage Grouping (AJCC 2010) Stage III Stage IVA	43% 57%
6.	ECOG Performance scale 0 1 2	41% 52% 18%
7.	Personal habits Smokeless tobacco only Smoking tobacco only Dual tobacco users Smokers + Alcoholics	33% 20% 28% 19%
8.	Demographic distribution Rural Urban	81% 19%
9.	Clinical Symptoms Neck node/ swelling Dysphagia Bleeding Persistence sore throat Earache Change of voice	76% 5% 2% 9% 4% 4%
10.	Hemoglobin levels (mg/dl) 10-12 12-14 >14	69% 24% 7%
11.	Neoadjuvant Chemotherapy[NACT] Completed NACT Not tolerated NACT Lost during NACT Died during NACT	85% 7% 6% 2%

Fig. 1: Restaging after completion of NACT

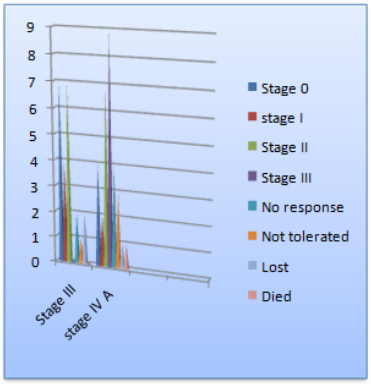


Fig.2a: Radiation morbidity at the end of 7th week in Arm A [Conventional EBRT]

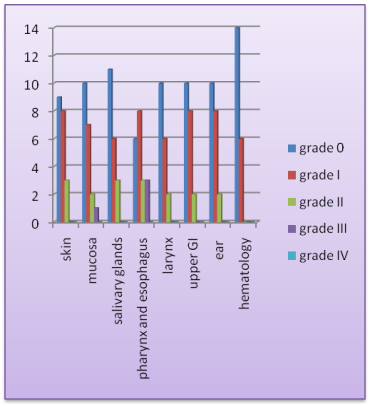


Fig.2b: Radiation morbidity at the end of 7th week in Arm B [IMRT]

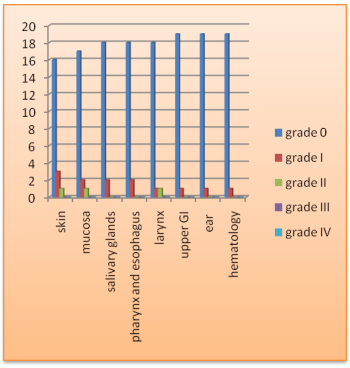
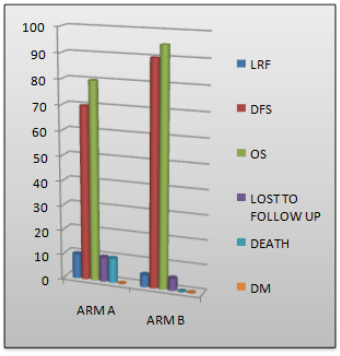


Fig.3: Clinical Outcome at the end of last follow up [October 2017]



DISCUSSION

Oropharyngeal carcinoma can be treated effectively with local therapy alone when it is presented in early stage. Unfortunately, advanced disease is the most common presentation and the prognosis tend to be poor. Management of such patients remains a challenge as quality of life becomes an important aspect in the oncology practice. Despite rapid pace of drug discoveries and clinical trials, the prognosis of loco-regional advanced HNSCC tends to be poor [6]. The 5 year survival rate of early stage oropharyngeal is approximately 80%, while the survival rate declines to 19% in advanced cases [7].

Neoadjuvant Chemotherapy has a limited role in the head and neck cancers and many studies have emphasized its significance recently in locally advanced stages of oropharyngeal cancers [8]-[10]. Chemotherapy combinations with 5FU + CDDP can produce response rates of 60-90%, with complete responses in 20 to 50% [11]. As per the study, 85% has completed the induction chemotherapy, 7% could not tolerate it and 74% has been down staged. Complete response to NACT was documented in 24%. NACT has improved the nutritional status, the psychological and emotional confidence of the patients and favorable compliance towards the assigned treatment protocol.

Various versatile studies have favored IMRT not only a worth mentioning sophisticated technique but also enhances quality of life of the patients. The recent addition to personalized medicine has been shifted to eradicate the disease with organ preservation. This maximizes therapeutic efficacy and treatment success [12]-[13]. This has been elucidated in the study. Patients treated with IMRT as loco regional therapy has less hospital admissions during the therapy (10%) and less treatment related toxicities. Although xerostomia , skin reactions, mucositis reactions were encountered in few patients, was a minor issue in patients treated with IMRT compared to conventional EBRT.

CONCLUSION

Neoadjuvant chemotherapy has its advantage in shrinking the tumor bulk and down staged the disease which helped the oncologist to attain a desired profile. There should be judicious use of chemotherapeutic drugs in this setting which outweighs the

demerits. Our evaluation depicted that there were quite a number of positive developments in the treatment of locally advanced squamous cell carcinoma of oropharynx but there was still much to improve. Variables such as patient condition, tumor biology, radiation dose, method of delivery and chemotherapeutic choice of drugs all influence treatment outcome and should be taken into account in attaining desired profile. Well differentiated studies should be undertaken balancing the possible positive effect of therapy and toxicity.

IMRT technique, as compared to conventional EBRT, has its advantages with respect to patient's compliance, tolerance and quality of life. The technique indeed required skilled personnel which decide the treatment delivery and outcome. Our present study has depicted that neoadjuvant chemotherapy was tolerated well with strictly selected patients' criteria. The patients in Arm B have less treatment related complications and improved quality of life than that of in Arm A. The study was compromised by the less number of patients and short duration. A long term study including more number of patients will be mandated to arrive at any conclusion statistically. The future scope of management of advanced stage oropharyngeal carcinoma lies in judicial utilization of systemic chemotherapy and radiation therapy according to individualized patient centric approach to enhance therapeutic ratio and treatment success.

ABBREVATIONS

NACT= Neo adjuvant chemotherapy; RTOG= Radio Therapy Oncology Group; EBRT= External Beam Radiotherapy; IMRT= Intensity Modulated Radio Therapy; HNSCCC= head and neck squamous cell carcinoma; QOL = quality of life; ICRU= International Commission on Radiological Units.

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FOOT NOTES

The authors declare there are no potential conflict of interests, including financial interests, relationships, and affiliation relevant to the subject of the manuscript in any way.

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