ejpmr, 2018,5(5), 225-231

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Research Article

ISSN 2394-3211

EJPMR

HYPOFRACTIONATED INTENSITY MODULATED RADIOTHERAPY WITH CONCURRENT CHEMOTHERAPY FOR LOCALLY ADVANCED SQUAMOUS CELL CARCINOMA OF HEAD AND NECK -A PILOT STUDY

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Article Received on 06/03/2018 **Article Revised on 27/03/2018** **Article Accepted on 17/04/2018**

ABSTRACT

Introduction: Head and neck carcinoma is common cancer in India often presenting in advanced stage and unresectable. These patients are usually relegated to palliative treatment. Study undertaken with the intention of treating these patients with radical intent using, hypo-fractionated IMRT and concurrent chemotherapy. Primary objective is to assess loco-regional response and post-treatment resectable status. Secondary objective is to assess the toxicity. **Methods and Materials:** 20 patients of stage III and IV Head and Neck squamous cell carcinoma (HNSCC) were treated with Hypofractionated IMRT and chemotherapy. RT of 45Gy in 15 Fractions delivered to the primary tumor and involved lymph nodes, 37.5Gy in 15 Fractions to low intermediate risk areas with simultaneous Integrated Boost (SIB), using 6MV photons with an overall treatment time (OTT) of 3 weeks. Infusion Cisplatin (70mg/m2) on day 1 and last day of treatment was given. Resectable tumors underwent surgery and remaining patients boosted to a radical dose of 16Gy in 8 fractions. **Results:** 90% (18/20) completed treatment & 45% (9/20) made resectable following hypofractionated neo-adjuvant chemoradition. 35%(7/20) underwent surgery. At three months, 50% (10/20) were loco regionally controlled.30% (6/20) developed grade II, 60% (12/20) grade III and 5% (1/20) grade IV mucositis. 20% (4/20) had grade I, 60% (12/20) grade II and (1/20) 5% Grade III skin reactions. **Conclusion and Discussion:** Neo-adjuvant Hypofractionated IMRT with concurrent chemo radiation is clinically feasible with good response rates in the treatment of locally advanced HNSCC with acceptable toxicities and conversion rates to surgery.

KEYWORDS: Hypofractionation, Locally advanced squamous cell cancer of head and neck, chemotherapy, cisplatin.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the fourth most common neoplasm worldwide with an estimated annual global incidence of more than 5,00,000 cases[1]. Patients with HNSCC are at considerable risk of mortality with more than 3,00,000 deaths yearly. It is one of the ten leading causes of cancer in India. According to population based cancer registry, accounting for 23% of all cancer in males and 6% in females.[2]

Surgery, Radiotherapy, Chemotherapy, and combinations of these treatment modalities are well-established methods of treatment. The modality of treatment depends on the site and stage of the disease and on the overall health status of the patient. Single modality treatment with surgery or radiotherapy is generally recommended for approximately 40% of patients who present with early stage disease (stage I or stage II) with similar local control and survival. In contrast, for the 60% of patients with locally advanced disease at diagnosis, combined modality treatment is generally recommended.[3]

Over the past two decades, there have been several major advances in the treatment of cancers of the head and neck. Effective chemotherapeutic agents have been developed for squamous cell carcinoma of the head and neck and are increasingly used sequentially or concurrently with radiation. Both standard and altered fractionation schedules have been used to treat unresectable cases and to promote organ preservation.[4,5,6,7] Even with multimodality treatments, 5-year survival rates are 40% for all locally advanced tumors with 30% recurring locally and 25% distally, and these survival figures are mainly dictated by prognostic factor either disease related or patient related.[8]

Recently certain strategies have emerged for the improvement of therapeutic outcome in the curative treatment of HNSCC, they include the development of altered fractionation, and intensity modulated radiotherapy and targeted biological therapy. Hypofractionation may be used in patients with locally advanced HNSCC with the goal of improving local

control and counteracting tumor repopulation by reducing the overall treatment time by increasing the dose per fraction without altering the total dose equivalent.

One of the most important biological factors governing the outcome of radiotherapy in squamous cell carcinomas is associated with the proliferation of tumor cells during treatment. The analysis suggests that clonogen repopulation in the human cancer accelerated at about 28 days after the initiation of radiotherapy in a fractionated regime. A dose increment of about 0.6 Gy (60 rad) per day is required to compensate for this repopulation. Such a dose increment is consistent with a 4-day clonogen doubling rate, compared with a median of about 60 days for unperturbed growth.[9] It is now well documented for head and neck cancer that local control is reduced by about 0.4% to 2.5% for each day that overall treatment time is prolonged and an improved tumor control with reduction in overall treatment time.[9,10,11]

In response to the findings that local control was dependent on the overall duration of the treatment, altered fractionation schemes have been devised to decrease the repopulation by tumour clonogen .There are various types of altered fractionation regimens which have been tested with advantages and disadvantages. Hence hypo-fractionated IMRT is less labor intensive as we intend to increase the dose per fraction thereby shortening the duration of treatment while at the same time obtaining the equivalent dose as when conventional doses were delivered. The rationale for altered fractionation is that reduction in overall treatment time reduces the opportunity for tumor cell repopulation during treatment and therefore increases the probability of local control for a given total dose. A shorter treatment time can be obtained by applying a higher dose per fraction, but this will result, in a disproportionate increase in the incidence of late complications. Intensity-modulated radiotherapy (IMRT) offers advantage in the treatment of head and neck cancers by its ability to conform the high dose to the target volume and simultaneously sparing critical structures, hence reducing the treatment toxicity and achieving high loco-regional control rates.

The present study was undertaken with the intention of treating these patients with a radical intent in the most appropriate manner by using optimal dose rates as designed in this study by using hypo-fractionated IMRT with concurrent chemotherapy.

The benefit of hypofractionated radiotherapy

In a study by Paul Sanghera et al , the tumor control rates in locally advanced head and neck cancer using accelerated hypofractionated radiotherapy [55Gy in 20 fractions at 2.75 Gy/fraction] with concurrent chemotherapy [carboplatin and methotrexate] were assessed. A total of 81 patients were analyzed of which 68 included stage III-IV squamous cell carcinoma of larynx, oropharynx, oral cavity and hypopharynx and the 2 year overall survival rate was 67.6%, the 2 year disease free survival rate was 64.1% and local control rate was 72%. The hypofractionated regimen was shown to benefit, especially when the treatment was designed so as to tackle the accelerated repopulation of tumor cells.[12]

Kiprian D et al, in a study evaluated the early results and toxicity of Simultaneous integrated boost (SIB)-IMRT given concomitantly with cisplatin for locally advanced head and neck cancer. The boost volume was limited to the GTV + 3mm margin (macroscopic tumor extension was defined on the basis of CT and/or MRI examinations). Dose per fraction given to this volume was 2.25 Gy up to 67.5 Gy of total dose. The PTV-CTV + 3mm - was defined as an area of increased risk of microscopic spread. Dose per fraction given to this volume was 2 Gy up to 60 Gy. The PTV1-ETV+ 3mm [electively irradiated volume] received dose per fraction -1.8 Gy up to 54-56 Gy. Overall treatment time was 6 weeks [5 fractions per week, 30 fractions]. Concomitant chemotherapy consisted of cisplatin in daily dose 100mg/m2 given two times during irradiation [1 and 22 day of treatment]. 99 patients with stage III and IV squamous cell carcinoma of head and neck were treated and found that overall survival rate to be 90% and the disease free survival to be 82%.[13]

H. Benghiat et al, in a study showed that Hypofractionated accelerated chemo radiotherapy in the conformal area achieved acceptable control rates for squamous cell carcinoma of the head and neck. This study reports outcomes for biologically staged oropharyngeal cancer treated using four-week intensity-modulated radiotherapy (IMRT) and synchronous chemotherapy. Patients with squamous cell carcinoma of the oropharynx treated with hypofractionated chemo-IMRT (55Gray in 20 fractions), with either carboplatin or cetuximab were prospectively identified. Outcome measures analyzed were 2-year loco-regional recurrence-free survival (LR-RFS) and overall survival (OS). The acceptable efficacy obtained with this schedule questions the need for synchronous cisplatin in good prognosis groups of oropharyngeal carcinoma. These results may also prompt the examination of a 4 weeks schedule of chemo radiotherapy in future randomized trials.[14]

THE BENEFIT OF NEO-ADJUVANT RADIOTHERAPY/CHEMOTHERAPY IN

Locally advanced head and neck cancers

Gus Totman et al, in their study CT/RT was used preoperatively in advanced Stage 111 and IV head and neck cancer. Fifty-three patients were entered prospectively into a Phase II study. Treatment consisted of 4500cGy of radiation therapy in 5 weeks combined with Cisplatin 20 mg/m^2 for 4 days during weeks 1 and 4 of radiation therapy. This was followed 4 to 8 weeks later by curative surgery.[15] In four patients, toxicity was seen; three episodes of skin reaction or stomatitis and

three episodes of leukopenia & causing a delay in CT/RT treatment in one patient. Three patients died of other causes during the preoperative interval, without clinical evidence of toxicity. Clinical CR was seen in 38 of 51 (75%) primary tumors and 21 of 27 (78%) positive cervical nodes. Forty-one patients (77%) underwent curative surgery. Postoperative morbidity was 32%. Five patients (12%) required additional surgery for their complications. With a follow-up of 8 years (median, 40 months), the median survival for all patients was 45 months. The 5-year actuarial survival rate was 43% for all patients and 55% for patients who had CT/RT and surgery. This multimodality treatment of advanced head and neck cancer had low toxicity and impressive survival. It rendered a significant number of patients tumor-free before surgery. These patients may be candidates for additional study trying additional CT/RT for complete CR only and surgery for PR and biopsy-proved residual disease.

MATERIALS AND METHODS

Sample Size

The Sample size had been estimated in consultation with a biostatistician. 20 patients were recruited into the study. This was estimated based on data obtained with the historical studies.

Table 1: List of Clinical Investigations done in the study.

Sl. No.	Investigations
1	Complete Blood Count.
2	A standardized data collection proforma was used for the study.
3	All the cases underwent biopsy or FNAC for confirmation of malignancy.
4	Clinical examination, Computer tomography (CT) or Magnetic Resonance Imaging (MRI) with contrast was carried out for staging.
5	X-ray Chest.
6	Complete Blood Count.
7	Renal Function Test

Inclusion Criteria include age group between 20 to 70 years, Performance Status-0-2(ECOG Criteria), locally advanced squamous cell carcinoma of Head and Neck with TNM stages III and IV.

Patients with Metastatic disease, ECOG Performance status more than 3, previous irradiation to head and neck area, and nasopharyngeal carcinoma were excluded from the study.

Informed written consent of the patient

When all the investigations were within the normal limits, patients written consent was taken after explaining the nature of the disease, its treatment options, duration of treatment and side effects in their own vernacular language. Patients were also explained about the clinical trial in depth. Patient was counselled about ill effects of tobacco and alcohol consumption and asked to discontinue the same. They were also explained regarding oral hygiene, nutrition and precautions to be taken throughout the treatment.

Chemotherapy Protocol

The drug Cisplatin was used as a single agent concurrently with the radiotherapy. The dosage used was 70mg / m^2 on day 1 and last day of treatment. The patient was started on chemotherapy after adequate hydration and pre medication. Cisplatin was administered with normal saline and given over 2 to 3 hrs IV infusion. It was followed by radiotherapy within 1 hr. after completion of infusion. Myelosuppression and renal toxicity was evaluated by doing complete heamogram, blood urea and serum creatinine weekly.

During treatment, the patient was explained about the care of irradiated site, precautions, and diet modifications. The weight of the patient was then checked on a weekly basis. Acute reactions like mucositis, pharyngitis, laryngitis, secondary infections, and skin reactions were observed on a weekly basis. The grading of acute reaction was done as in **RTOG – acute reaction morbidity criteria**. The patient was managed according to the toxicity profile. Tumor response was noted clinically at the end of RT and subsequently on follow up based on RECIST criteria. Patients were reassessed after 4 weeks for surgery with clinical examination & imaging. If they were still inoperable, the patients were re-simulated and dose was escalated to the radical dose with 16Gy in 8 fractions at 2 Gy per fraction to CTV.

In patients taken up for radical chemo-radiation, the response evaluation was done radiologically with the help of CT / MRI and fiber optic endoscopy at 3 months and 6 months after completion of treatment using RECIST criteria. In patients who undergo surgery the response was assessed by pathological examination.

Statistical analysis

Statistical Methods: Frequency distribution of response and categorical variables were determined. The qualitative data comparison was done using Chi-square test. P value less than or equal to 0.05 was considered statistically significant.

Statistical software: Data analysis: data were analyzed using SPSS version 20 for windows. Microsoft word,

Apple Pages and Excel have been used to generate graphs, tables etc.

RESULTS

During and at the completion of treatment, patients were evaluated for mucositis, skin toxicity, hematological toxicity and dysphagia. After completion of the treatment the patients were reassessed for surgery after 4 weeks of treatment.

In the present study of twenty patients of locally advanced head and neck cancers, the various characteristics are shown in the following pages.

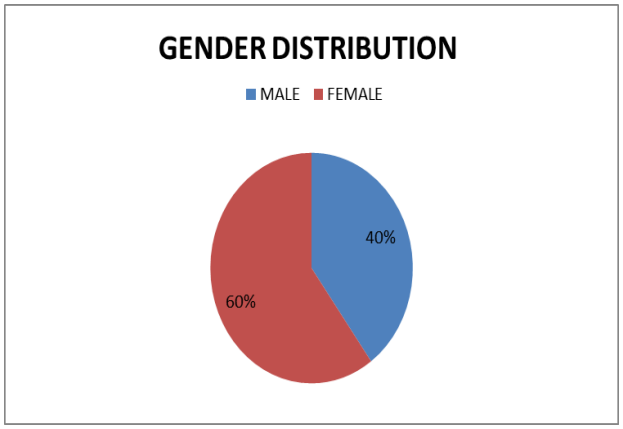

Figure 1: Showing Gender Distribution.

Table 2: Table representing the patient's characteristics i.e. Tumor Site, clinical Stage, sex.

Site	No of Patients
Oral Cavity	17
Oropharynx	1
Hypopharnyx	2
Clinical Stage	
IVA	8
IVB	12
Sex	
Male	8
Female	12

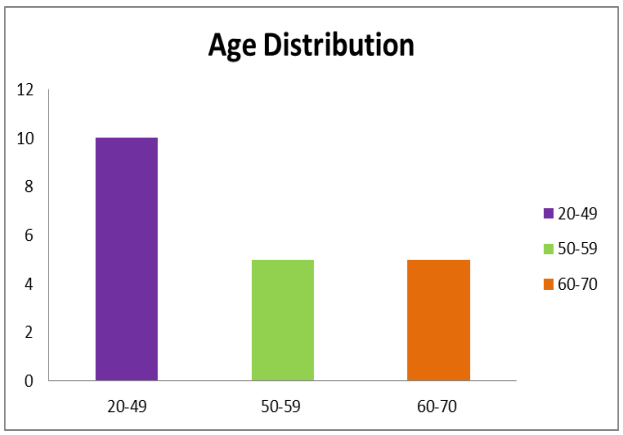

Figure 2: Age Distribution.

Table 3: Age distribution in terms of mean and Standard Deviation.

Report			
Age			
Sex	**Mean**	**Std.Deviation**	**N**
Female	49.50	8.252	12
Male	52.38	12.420	8
Total	50.65	9.197	20

Considering the distribution of primary site

Out of twenty patients:

- Patients with T4a lesions - 55% (11/20)
- Patients with T4b lesions - 45% (9/20)
- Patients with N1 Nodal status- 20% (4/20)
- Patients with N2 Nodal status -65% (13/20)
- Patients with N3 Nodal status - 15% (3/20)

Table 4: Representing the primary site of tumor distribution, tumor stage, Nodal Stage, TNM stage grouping.

Tumor Response	No of patients	Percentage (%)
Primary Site Distribution		
Oral Cavity	17	85
Oro pharynx	1	5
Hypo pharynx	2	10
Tumor Stage		
T4a	11	55
T4b	9	45
Nodal Stage		
N1	4	20
N2	13	65
N3	3	15
TNM Stage Grouping		
Stage IVA	8	40
Stage IVB	12	60

Out of twenty patients

- Patients with Stage IVA disease - 40% (8/20).
- Patients with Stage IVB disease - 60% (12/20).

TREATMENT ADMINISTRATION

Ninety-Five percent (19/20) of patients received the planned neo-adjuvant dose of 45 Gy in 15 fractions, with one patients progressing during treatment and died due to complications. Sixty-Five percent (13/20) received only 1 cycle of chemotherapy in view of haematological toxicity following 1st cycle of chemotherapy. 10% (2/20) did not receive chemotherapy in view of age and poor performance status.

Table 5: Treatment Administrations (Chemotherapy Cycles).

CT cycles	No of Patients	Percentage
2cycles	5	25%
1 cycle	13	65%
No CT	2	10%

Treatment interruptions were observed in 45% (9/20) patients in view of severe grade III mucositis and had a

treatment break ranging from 4-7 days. None of the patients had haemoptysis, dyspnea and stridor. All patients were on naso-gastric tube feeding from the start of treatment as a part of institutional protocol for all head and neck cancers. 55% (11/20) had an overall treatment time of 21 days for the neo-adjuvant treatment.

We also assessed various grades of mucositis during treatment and following RT in all the patients. We observed that:

At week 2 – 40% patients presented with grade 2 mucositis while other 45% developed grade 3 mucositis and 5% grade 4 mucositis.

At week 3 – 25% had grade 2 mucositis and 70% patients presented with grade 3 mucositis.

Mucositis subsequently healed by 1 month after RT and remained healthy even after 3 months of follow up.

Patients were assessed for skin reactions weekly during treatment and the reactions were noted. 20% (4/20) had grade I reactions, 60% (12/20) grade II and 10% (2/20) had grade III skin reactions. They were managed conservatively and all reactions healed subsequently.

At end of RT – 70% patients presented with grade 2 and 15% had severe grade 3 dysphagia.

Dysphagia reduced subsequently in 3 months follow up and remained normal in all patients.

30% (6/20) patients had Grade II neutropenia and 15% (3/20) had grade III neutropenia. 20% (4/20) of patients required G-CSF support. None had thrombocytopenia or renal toxicity.

Tumor Response

The patients were assessed for tumor response on completion of treatment and on subsequent follow up. The following are the observations seen: At completion patients were assessed clinically. Complete response was seen in 10% patients. Partial response was seen in 85% patients.

At 1 month after RT patients were assessed both clinically and radiologically.

Table 6: Tumor response on completion of treatment and subsequent fallow up for one month.

1 month	CR	PR	Death
Primary	5	14	1
Node	9	10	1

RESECTABILITY

The patients were assessed for resectability 4 weeks after hypofractionated neo-adjuvant chemo radiation and it was found that 9 patients out of 19 were resectable. 7 patients underwent surgery and two patients refused surgery and received the radical dose of radiation.

- Among the 7 patients who underwent surgery, 1 patient was treated with a boost dose of 16 Gy in 8 fractions and one cycle of Cisplatin in view of extra capsular extension on the post-op histopathological examination.
- Two deaths occurred before the completion of definitive treatment. One patient had progressive disease and died due to complications during the neo-adjuvant treatment and the other before the onset of boost radiation due to aspiration pneumonia.
- Among the patients who were not resectable, 5 did not receive the boost dose in view of poor performance status and remaining patients were treated with 16 Gy in 8 fractions.

Table 7: The patients were assessed for the respectability 4 weeks after hypo fractionated neo-adjuvant chemo radiation, site-wise and stage –wise as shown above.

	Resectability		P value
	Yes	No	
Site-wise			
Oral cavity	8	8	
oropharynx	0	1	
Hypo pharynx	1	1	0.53
Stage-Wise			
IVA	4	4	
IVB	5	6	0.53

At 3 months after definitive treatment, the patients were assessed for response and it was found that among the 7 patients who underwent surgery there was no recurrence seen.

Among the patients who did not undergo surgery 3/11 patients had complete response and 8/11 had partial response. 50% (10/20) patients had no evidence of disease. At 6 months after definitive treatment, the patients were assessed for response and it was found that 55 %(11/20) had no evidence of tumor at the 6 months follow-up.

Table 8: Tumor responses on completion of treatment and subsequent fallow up for 3 months and 6 months.

Tumor Response	Complete Response	Partial Response
3 Months		
Non-Surgical patients(N=11)	3	8
Surgical Patients(N=7)	0	0
6 Months		
Non-Surgical patients(N=11)	4	7
Surgical Patients(N=7)	0	0

DISCUSSION

In most patients with advanced head and neck cancer, conventional radiotherapy does not result in long- term loco regional control of the tumor, and this failure

ultimately proves fatal.[16] One of the ways to improve the therapeutic ratio is through modification of dose fractionation. Altered fractionation regimens were predicted to offer therapeutic advantage. The main rationale of hypo fractionation is to achieve the standard doses through the use of larger dose per fraction (3 Gy/ fraction) and by relatively reducing the overall treatment time. Reduction in overall treatment time reduces the opportunity for tumor cell regeneration during treatment and therefore increases the probability of tumor control for a similar total dose.

Achieving long-term local control (LC) in locally advanced squamous cell carcinoma of the head and neck remains a challenge. A great variety of treatment schedules have been reported. In a study by Paul Sanghera et al prescription with larger doses per fraction, such as 55 Gy in 20 fractions (2.75 Gy/fraction) has the theoretical advantage, that treatment is completed before accelerated repopulation becomes a significant radiobiologic factor. The reduction in the number of fractions also allows a more efficient use of resources, which can help avoid long waiting times. The combination of this accelerated regimen with chemotherapy, therefore, offers an attractive method to improve control rates and productivity.

In our study Cisplatin has been used concurrently with RT, as a single agent, with a dose schedule of 70mg/m^2 infusion on day 1 and last day of radiotherapy.

The radiotherapy dose of 4500cGy in 15 fractions were prescribed to PTV1 and 3750cGy to PTV2 were used concurrently with chemotherapy and the patients were assessed for feasibility of surgery after 4 weeks of neo-adjuvant hypofractionated chemo radiation.

In this study 90% (18/20) of patients completed the intended treatment protocol of neo-adjuvant hypo fractionated chemo-radiation. The rate of compliance appears to be in accordance with the study done by Abrahim et al.[17] 45% (9/20) patients were resectable following neo-adjuvant hypo-fractionated chemo radiation and 7/9 patients underwent surgery and two patients refused surgery and were subjected to the boost dose. 3/7 patients showed pathological complete response. One patient received a third cycle of chemotherapy and adjuvant RT 16Gy in 8 fractions following surgery in view of postoperative HPE showing extra capsular extension. The reduction in volume of tumor from areas where it was initially deemed unresectable were predictive of resectability post neo-adjuvant treatment.

The 11 patients who did not undergo surgery were boosted with 16Gy in 8 fractions to the radical dose. 5 patients in view of poor performance status did not receive the boost dose. Based on effective doses calculation models derived from LQ model, we have delivered 45 Gy in 3 weeks, which is equal to 54 Gy in conventional 2Gy fractionation and a boost of 16 Gy in 8 fractions were given in those who were not amenable for surgery. On subsequent follow-up at 3 months and 6 months 3/11 & 4/11 patients showed complete response respectively.

At the end of the definitive treatment at 3 months follow-up 50% (10/20) patients had no evidence of disease. Subsequently on the 6 months follow-up (11/20) 55% were free of any residual tumor.

The significant toxicity in our study was mucosal toxicity. Forty percent (8/20) of the patients had grade II mucosal toxicity, 45% (9/20) had grade III mucositis and 5% had grade IV mucositis. The incidence was in accordance with which it occurred in a study by Paul Sanghera and other studies with similar schedules where accelerated hypo fractionation was used, which ranged from 55 to 70% for grade III mucositis and 5 to 10% for grade IV mucositis. All the cases with mucositis responded to conservative management. The treatment time was prolonged in 45% of the patients due to mucositis.

Twenty percent (4/20) of the patients had grade I skin reaction, 60% (12/20) grade II and only 10% (2/20) of the patients grade III skin reaction. Thirty percent (6/20) of the patients had grade II hematological toxicity and 15 % (3/20) of the patients had grade III hematological toxicity after first cycle of chemotherapy. None of the patients had renal toxicity.

Given our mostly advanced stage study population and poor tolerability after first cycle, 65% of patients received only one cycle of chemotherapy. One patient progressed during treatment and died due to complications. The remaining patients completed the neo-adjuvant treatment and one patient died on follow-up due to complications.

Patients with locally advanced unresectable HNSCC who otherwise were treated with a Palliative intent were salvageable by surgery following neo-adjuvant hypo-fractionated IMRT showing good response with acceptable toxicity. Among the patients who completed the planned neo-adjuvant treatment equal response was seen in patients with stage IVA and IVB.

Hence we were able to achieve a similar result in patients with advanced unresectable stage IVB disease with the use of hypofractionated regimen and the patients were subjected to a better quality of life and were treated with a curative intent who otherwise would have been treated with a palliative intent.

A larger study with a comparative arm and longer follow up will shed more light on the outcome of such a regime, taking into account overall survival, disease free survival, and late toxicity profile.

CONCLUSION

This was a nonrandomized prospective study to assess the resectability of locally advanced HNSCC by using neo-adjuvant hypo-fractionated chemo radiation, assess response rates and also to report the acute toxicities.

1. Neo-adjuvant hypo-fractionated chemo radiation followed by either surgery or boost can be used as a curative treatment strategy in patients with locally advanced head and neck cancer who otherwise are deemed to a treatment with palliative intent. In our study fifty-five percent showed no evidence of disease at the subsequent follow-up.
2. Acute toxicity profiles seen in our study were acceptable and comparable to similar studies with hypo fractionated regimens.

ACKNOWLEDGEMENT- Nil.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

ROLE OF THE FUNDING SOURCE –Nil.

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