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RESEARCH ARTICLE

Evaluating the Response of Hypofractionated Radiotherapy verses Conventional Radiotherapy with Concurrent Cisplatin in Advanced Fixed Node Head and Neck Carcinoma

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Abstract

Background: The evolution of radiotherapy over recent decades has reintroduced hypofractionation for many tumor sites, with outcomes similar to those of conventional fractionated radiotherapy. While the use of hypofractionation in locally advanced head and neck cancer (LAHNC) has been explored, its application remains limited to a few countries. This trial aimed to assess the safety and feasibility of moderate hypofractionated radiotherapy (HYP-RT) in combination with concomitant cisplatin (CDDP). **Objectives:** The objectives of this study were to evaluate the efficacy of hypofractionated radiotherapy in advanced unresectable head and neck cancer, specifically in terms of response rate. Additionally, the study aimed to assess the local and systemic toxicities associated with the hypofractionated regimen, as well as evaluate the symptomatic improvement of radiotherapy and treatment compliance. **Methods:** A total of 50 cases of locally advanced head and neck cancer (stage cT4b and/or N3) without any evidence of distant metastasis were included in this study. These 50 cases were randomly assigned to the study and control groups, with 25 patients in each group. The radiotherapy regimen consisted of a single fraction of 6 Gy per week, administered over a total of 6 weeks. Patients who received less than 6 weeks of treatment were excluded from the study. The total dose administered was 36 Gy in 6 fractions. All patients were treated using unilateral or bilateral portals until a dose of 24 Gy was reached, at which point off-cord planning was implemented. For patients who exhibited complete disease regression after the initial planned dose of 36 Gy, further dose escalation was offered based on tumor regression status, tolerability, and toxicity, following institutional guidelines. Partial responders received no additional treatment until the end of the treatment period. **Results:** Among the study and control groups, the incidence of carcinoma of the tonsil was 12% and 20%, carcinoma of the base of the tongue was 24% and 16%, and carcinoma of the larynx was 16% and 24%, respectively. Hematological toxicities (as referenced by blood hemoglobin level) and renal toxicities (as referenced by blood urea) were assessed according to WHO toxicity criteria in all cases weekly for a duration of six weeks. In the study group, 8% had no acute hematologic reactions, 56% had grade I hematologic reactions, 28% had grade II hematologic reactions, and 8% had grade III hematologic reactions. No patients experienced grade IV hematological toxicity. Similarly, in the control group, 12% had no acute hematologic reactions, 48% had grade I hematologic reactions, 36% had grade II hematologic reactions, and 4% had grade III hematologic reactions. No patients from either group developed grade II, III, or IV renal toxicity. The rate of acute renal toxicity was comparable between the study and control groups. **Conclusions:** HYP-RT with concomitant CDDP was found to be feasible for LAHNC, with the rate of acute toxicity comparable to that of standard concomitant chemoradiation. The use of feeding tubes was necessary for most patients during treatment. Further investigation of this treatment strategy is warranted.

Keywords: Head and neck neoplasm- Accelerated radiation therapy- Hypofractionated radiotherapy

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Introduction

Concomitant chemoradiotherapy (cCRT) improves locoregional control (LRC) and overall survival (OS) in locally advanced head and neck cancer (LAHNC) compared with radiotherapy (RT) alone; consequently, chemoradiation is the standard of care for these patients [1]. Three-week 100 mg/m^2 cisplatin concomitant with conventional fractionation radiotherapy (CFRT - 35 2-Gy fractions over 7 weeks) is the most studied regimen and is associated with significant toxicity, which compromises patient compliance and may not be suitable for all patients [2-5].

Altered fractionation is an alternative for patients who are not suitable for cCRT and can improve OS compared with CFRT alone [6, 7]. Accelerated RT, in which the total dose is delivered in a short period of time, has radiobiological advantages and is also associated with improved clinical outcomes [8, 9]. Hypofractionation is an attractive method for accelerating RT and has been used with success with other tumor sites, showing comparable outcomes and a reduced cost compared to those of CFRT [10-13]. A remarkable moderate hypofractionated RT (HYP-RT) schedule for head and neck cancer, which delivers 55 Gy in 20 fractions (2.75 Gy per fraction) for 5 days per week, has been described in Birmingham/ Edinburgh [14]. The biologically effective dose (BED) of the HYP-RT is approximately the same of CFRT [15]. The United Kingdom Head and Neck (UKHAN1) trial was one of the largest trial to demonstrate the superiority of cCRT over RT alone for LAHNC. In the UKHAN1 trial, almost 50% of patients were submitted to hypofractionated RT, including the HYP-RT schedule, and hypofractionation did not affect event-free survival compared with CFRT. The chemotherapy regimen used in the UKHAN1 trial was non-platin-based and, to the best of our knowledge, no data exists regarding HYP-RT concomitant with CDDP [16].

Patients from low- and middle-income countries (LMIC) have limited resources for RT and face long waiting times to be treated [17, 18]. Consequently, in addition to the radiobiological and clinical benefits of accelerated RT, hypofractionation regimes can also be an important strategy to shorten treatment times and thus improve access to RT. Additionally, a short RT schedule is associated with better patient compliance [19].

According to various studies, the prevalence of head and neck cancer with respect to total body malignancies ranges from 9.8% to 42.7% with an estimated annual global incidence of 533,100 cases. Most of the diagnosed head and neck cancers are histologically squamous cell carcinomas, which is sixth most common malignancy globally. Approximately 30% to 40% of patients diagnosed with head and neck cancer eventually die from disease. In India head and neck cancers constitutes 25% of all cancer registered in a year [20].

The most common head and neck cancer is oropharyngeal carcinoma (28.6%) followed by oesophageal and oral cavity cancers (19.4%) and (16.3%), respectively. Carcinoma of the ear is the least common (0.4%). With respect to oral cavity and oropharynx, the most common site of involvement is the tongue (32.7%). Carcinoma of the cheek and tonsils accounted for more than 20% of oral cavity malignancies [21].

Acharya Tulsi Regional Cancer Treatment and Research Institute registry recorded 1741 cases of head and neck cancer in the year 2009 which Constituted 28.3% of total cancer registrations with a male preponderance (4.3:1) and more than 50% of cases presenting with advanced disease. The most common enrolled were carcinoma Tongue: 287 (16.48%), larynx: 214 (12.29%), tonsil: 160 (9.19%), laryngopharynx: 66 (3.7%), Nasopharynx: 24 (1.38%) and post cricoids 71 (4.08%) respectively, but above all most common cases registered were with secondary neck squamous cell carcinoma with unknown primary. In accordance with global figures, in our centre vast majority of patients of head and neck cancer clinically present in advanced, incurable stage, with >50% dying of uncontrolled loco-regional disease [22, 23].

The aim of this study to evaluate the efficacy of hypofractionated radiotherapy in advanced unresectable head neck cancer, in terms of response rate and evaluate the local and systemic toxicities of hypofractionated regimen with symptomatic improvement of radiotherapy and treatment compliance.

Materials and Methods

This study is a prospective randomized control trial performed in a regional cancer center located in Bikaner, Rajasthan. - A total of 50 cases of locally advanced head and neck cancer (stage cT4b and/or N3) without any evidence of distant metastasis were included in this study. These 50 cases were randomly distributed into study and control group containing 25 each.

Criteria for patient selection

1. Histopathopathologically proved squamous cell cancer of head and Neck (Biopsy or FNAC proved cases).
2. Locally advanced disease (stage cT4b and/or N3), where radical approach was not possible because of either unrespectability or those Patients who had denied for surgery and clinically present with hard, fixed node.
3. No evidence of distant metastasis at the time of presentation.
4. Previously untreated cases.
5. ECOG performance status 0/1/2
6. No evidence of second malignancy.
7. Adequate baseline organ function and haematological function.
8. Age limit 20-65 years.
9. Patient must have no other serious medical or psychiatric illness that would limit the ability of the patient to receive protocol therapy.
10. No history of allergic conditions.
11. No evidence of any dermatological disease or aphthous ulcer at time of start of radiotherapy.
12. Pregnant and lactating mother were not included.
13. Men/women of reproductive age group must agree to use an effective contraceptive method during treatment.

14. Patients were informed of investigational nature of this study and asked to provide written informed consent in accordance with institutional guide lines prior to initiation of therapy.

15. Patients who had not completed at least six weeks of treatment were excluded from both groups and fresh cases were registered to a total of 25 in each study and control group.

Summary of pre-treatment evaluation

All the cases were subjected to detailed clinical examination. A proforma was prepared for each patient in which history, general physical examination, systemic and local examination of head and neck and investigation reports were recorded.

History- Detail history of patient with special reference to presenting complaints, (main distressing complaint was noted) and graded (mild, moderate, severe). All patients were specifically asked about the specific symptoms that are associated with head neck malignancy such that they could also be assessed during and after treatment.

General physical examination and systemic examination- The general condition and state of nutrition, anaemia, oral hygiene, clinical evidence of lymphadenopathy, clinical examination of other organs to exclude any evidence of distant metastasis and other significant medical/surgical conditions were performed. Examination of cardiovascular system, respiratory system, abdomen and nervous system was also performed.

Local examination- Detailed local examination (ENT examination) of oral cavity, oropharynx, Nasopharynx, hypopharynx and larynx was performed under aseptic condition. Primary site of malignancy was inspected for site, size, shape, surface, borders, margins, base, infiltration into surrounding tissue, sign of inflammation and any bleeding/discharge from growth. All the inspectory findings were confirmed on palpation, where ever possible. Careful examination of lymphatic system of head and neck was performed documenting the level of lymph nodes involved unilateral/bilateral, size, shape, surface, mobility/fixity, consistency and tenderness.

Investigations- Routine laboratory investigations like complete blood counts, renal function test, liver function, x-ray chest, x-ray soft tissue neck and ultra sound of abdomen and pelvis were done.

Corroborating the clinical examination, findings and investigations, staging of malignancy was done using TNM staging system by AJCC 2002.

Treatment Plan

Radiotherapy protocol

All the 50 cases of study and control group were treated by external beam radiotherapy. Megavoltage radiation (Co- 60 gamma rays, average energy 1.25MeV) with SSD technique was used. Before the treatment was started prophylactic or emergency tracheostomy was done as per indication. Nutritional support through naso-gastric tube was given for needy patients. All these patients were immobilized with thermoplastic mould. Tissue compensator (TC) and appropriate wedges were used if necessary. The treatment volume was consisted of primary plus involved nodes. Appropriate conservative portals were used with margin of 2 centimetres from gross disease. Nodal irradiation was compulsory and whenever possible radiation to primary site was included in nodal field. Where bilateral disease was present or where disease crossed the midline opposed lateral fields were planned and the dose was prescribed to the midline. Bolus was used where there was dermal involvement or skin fungation.

(A) Dose prescription of study group

Patients who were randomized to be included in the study group received both chemotherapy and radiotherapy. Radiotherapy consists of a single fraction of 6 Gy Per week for a total of 6 weeks. If the patient received less than 6 weeks of treatment, he/she was excluded from study. Total dose given was 36 Gy in 6 fractions. All the patients were treated by unilateral or bilateral portal till 24 Gy and then off cord planning was done. Patients with complete disease regression after initially planned 36 Gy (BED-57.6 Gy, considering alpha/beta of 10 and corresponding EQD2-48Gy) were offered further dose escalation depending upon tumour regression status, tolerability and toxicity according to institutional guidelines. Partial responders are given no treatment up to end of treatment period.

(B) Dose prescription of control group

Patients who were randomized to be included in the control group received chemotherapy plus radiotherapy. Patients were treated by 2 Gy per fraction, 5 days a week (Monday to Friday) over 5 weeks to a total dose of 50 Gy with a gap of one week (at fourth week), in order to equalize time of treatment and biological equivalent dose. This is done to nullify the effect of tumour repopulation in either arm.

All the patients were treated by unilateral or bilateral portal till 44 Gy and then off cord planning was done. Patients of this group were treated to a total dose of 64-66 Gy.

Chemotherapy protocol

Both study and control groups received concurrent weekly cisplatin after assessment of baseline organ function and haematological status. Injection cisplatin: 40mg/m^2, with a ceiling dose of 50mg was given IV over three-hour infusion, preferably one hour before radiation dose. Hence a total of six cycles were given to each group respectively along with radiation. Appropriate premedication measures were taken during drug infusion.

Calculation of BED for late responding tissue (spinal cord)

By applying same equation as above, off cord planning dose was calculated from conventional schedule, which is 44-48 Gy. The newly calculated dose was 24 Gy, so in study arm off cord planning was done after 24 Gy (four fractions of 6 Gy). This was done intentionally to provide a good quality of life to the patients of study group i.e. to

decrease the morbidity associated with myelitis.

Observation and evaluation

All patients were reviewed at least weekly till the completion of treatment for assessing skin and mucosal toxicity (RTOG toxicity guidelines). After 6 weeks of completion, patients were assessed for response in terms of disease control (nodal regression as well as primary) using W.H.O criteria. Again, response was measured at end of treatment and at close out date (one month after completion of treatment) in both arms. Patients also have been asked to quantify the symptoms relief in percentage during every review verbally. Patients having metastatic disease or having persistently abnormal base line organ function were excluded from the study and received further treatment according to departmental protocol.

A). Objective response:

1. Complete response (CR): complete disappearance of all demonstrable disease.

2. Partial response (PR): More than 50% reduction in the measurable disease with no demonstrable progression elsewhere.

3. No response (NR): No change in size of measurable lesion or less than 50% reduction.

4. Stable Disease: Tumour size has not changed; no progression, no new lesions

5. Progression: More than 50% increase in measurable disease.

B) Evaluation of side effects:

The management of malignancy with chemotherapy and radiotherapy is associated with significant side effects or complications. Side effects like general weakness, anorexia, nausea, vomiting, alopecia, pain throat, dryness of mouth and skin reactions were noted regularly during treatment. All patients were recommended high protein diet, multivitamins, haemetonics, proper water intake and proper oral hygiene. Toxic side effects were assessed according to World Health Organization (WHO) toxicity criteria.

Toxicities to be monitored and protocol modification: Treatment modifications were needed if occurrence of grade 4 hematological toxicity was noted. For grade III & II hematological toxicity fresh blood transfusion was recommended. If Grade III & IV Non hematological toxicities occurred (nausea, vomiting, stomatitis and dermatitis) then also treatment was modified & supportive treatment was given.

Statistical Analysis

For Statistical analysis IBM SPSS Statistics 25 software is used. Data were tabulated in MS Excel 2015. Statistical significance of difference in proportions was calculated by the Chi-square test. Local control, disease -free survival, overall survival and late complication rates were calculated by Kaplan–Meier method, and the differences between the two arms were analyzed by log-rank test. p value <0.05 was considered to be statistically significant.

Results

As shown in Table 1, majority of the patients enrolled in study as well control were males. Table 2 shows the age distribution of patients included in the study. 18 patients (36%) were in the 41-50-year age group and 32 (64%) were in the 51-65-year age group, respectively out of 50 patients. The majority of patients were in the age group of 51-60 in both the groups. Among the study and control group, incidence of carcinoma of tonsil was 12% and 20%, carcinoma of base of tongue was 24% and 16%, carcinoma larynx 16% and 24%, respectively and Hematological toxicities (reference to blood hemoglobin level), Renal (reference to blood urea) were assessed according to WHO toxicity criteria in all cases weekly up to six weeks Among the study and control group, 8% and 12% had no acute hematologic reactions ($\chi2 = 0.22$, $p > 0.05$), 56% and 48% had grade I hematologic reactions ($\chi2 = 0.32$ $p > 0.05$), 28% and 36% had grade II hematologic reactions ($\chi2 = 0.36$, $p > 0.05$) and 8% and 4% had grade III hematologic reactions ($\chi2 = 0.35$, $p > 0.05$) respectively. No patient had had grade IV hematological toxicity (Table 3). Among the study and control group, 80% and76% had no acute renal toxicity. ($\chi2 = 0.11$, $p > 0.05$), 20% and 24% had grade I hematologic reactions ($\chi2= 0.11$

Table 1. Sex Distribution

Sex	No. of patients		Percentage (%)	
	Study Group	Control Group	Study Group	Control Group
Male	23	21	96	84
Female	2	4	4	16

Table 2. Age Distribution

	No. of patients				Percentage (%)			
Age Group	Study Group Stage III	Control Group Stage III	Study Group Stage IV	Control Group Stage IV	Study Group Stage III	Control Group Stage III	Study Group Stage IV	Control Group Stage IV
30-40	-	-	-	-	-	-	-	-
41-50	-	-	8	10	-	-	32	40
51-65	-	2	17	13	-	8	68	60

p > 0.05). No patients from either group develop grade II, III and IV renal toxicity (Table 4). Table 5 shows the distribution of patients according to primary response based on T-stage. Among the study and control group the complete response for the primary based on T-stage was T3: 36% and 48% and T4: 20% and 12%, the partial response for the primary based on T-stage was T3: 16% and 12% and T4: 28% in each group. No patient had stable disease and/or progressive disease in the study. Table 6 shows the distribution of patients according to nodal response based on N-stage. Among the study and control group the complete response for the node based on N-stage was N1:0% and 8%, N2: 28% and 36%, N3:20%and 12% respectively. The partial response for the node based on N-stage was for N2: 12%in each group and for N3:40% and 32% respectively. No patient had progressive/stable disease in the study.

Analysis of treatment response evaluation for disease control using W.H.O. criteria after sixth week, at completion of treatment and follow up after one month. At end of sixth week of treatment, 9 patients had complete response in both the study and control arm for stage IV disease, respectively and 2 patients from control group (stage-III), showed complete response Table 7. Just after completion of sixth week of treatment, 16 and 14 patients had partial response respectively in the study and control arm for stage IV disease. Table 8 shows the distribution of patients according to primary response based on T-stage. Among the study and control group the complete response for the primary based on T-stage was T3: 36% and 48% and T4: 20% and 12%, the partial response for the primary based on T-stage was T3: 16% and 12% and T4: 28% in each group. No patient had stable disease and/or progressive disease in the study. Table 9 shows the distribution of patients according to nodal response based on N-stage. Among the study and control group the complete response for the node based on N-stage was N1: 0% and 8%, N2: 28% and 36%, N3: 16%and 12% respectively. The partial response for the node based on N-stage was for N2: 12%in each group and for N3: 44% and 32% respectively. No patient had progressive/stable disease in the study. Table 10 shows the distribution of patients according to overall treatment response at close out date or at first month follow up. Among the study and control group the complete response is 32% and 44%, ($\chi 2 = 0.76$, $p>0.05$) the partial response is 68% and 56% ($\chi 2 = 0.76$, $p >0.05$. No patient had progressive and/or stable disease in the study. At end of treatment and one month follow up, 8 and 11 patients had complete response respectively in the study and control arm for stage IV disease ($\chi 2 = 0.36$, $p =>0.05$). At one month follow up, 17 and 14 patients had partial response respectively in the study and control arm for stage IV disease.

Discussion

Altered fractionation is a well-established alternative of RT in the LAHNC treatment because many studies have demonstrated its superiority in disease control and survival compared with CFRT [7]. By reducing the OTT, the accelerated repopulation effect is minimized, which may explain the improved outcomes when treatment is accelerated [8, 9, 15].

Hypofractionation is a remarkable method for accelerating cancer treatment and is associated with better RT compliance [19]. Additionally, radiobiological and long-term clinical data have suggested that the HYP-RT regimen of 55 Gy in 20 fractions is, at least, equivalent to CFRT for LAHNC [15, 16]. However, despite recent technological RT advances and successes in other tumour sites [10-12], the use of hypofractionation regimens with radical intent in LAHNC is modest and restricted to a few countries, particularly the United Kingdom [14, 16, 24-26]. The main reason for this restriction is the toxicity concern regarding the high dose per fraction, notably with concomitant chemotherapy [27]. Moreover, whether concomitant CDDP improve outcomes in the context of hypofractionation for LAHNC is unknown.

The long-term outcomes of the UKHAN1 trial, which included CFRT and HYP-RT, demonstrated good compliance, a low rate of late toxicity, improved disease control, fewer new tumours and reduced mortality when cCRT was compared to RT alone [15]. Nevertheless, the chemotherapy used in the UKHAN1 trial was non-platin based. Although Madhava and colleagues have already demonstrated the feasibility of carboplatin with HYP-RT, to the best of our knowledge, our trial is the first to address the feasibility of concurrent CDDP with hypofractionation in LAHNC [13]. With a 95% of completion rate, our early data demonstrate the good compliance and suggest the feasibility of this protocol for patients from a middle-income country.

There are several distinctive characteristics of advanced head and neck cancer that contribute to the complexities in choice of appropriate management strategies [28]. Oncologists differ in their goal of treatment. Even when the prognosis is distinctly poor, head and neck surgeons, radiation oncologists and medical oncologists are likely to pursue aggressive treatments with intention to cure [29]. These modalities of treatment did not achieve the goals as were expected rather they ended with new grades of toxicities and also the family of the patient was financially overburdened.

One of the most difficult tasks for head and neck clinicians is deciding which patients are not suitable for radical / curative treatment. The reason for not treating patients radically usually falls into one of two categories.

Table 3. Toxicity Profile

Toxicity	Grade 0		Grade I		Grade II		Grade III		Grade IV		TOTAL
Group	Study	Control	Study	Control	Study	Control	Study	Control	Study	Control	
Hemoglobin	2	3	14	12	7	9	2	1	0	0	50
Renal	20	19	5	6	0	0	0	0	0	0	50

Table 4. Statistical Table

Hematologic Toxicities		
Grading	$\chi 2$	p
0	0.22	>0.05
I	0.32	>0.05
II	0.36	>0.05
III	0.35	>0.05
IV	0	-
Renal toxicities		
0	0.11	>0.05
I	0.11	>0.05
II	0	-
III	0	-
IV	0	-

The first is that the patient's general physical condition is too poor for radical treatment. This may be due to severe medical co-morbidities. The second category is of those patients with very advanced disease that is either unresectable or involving sites that preclude radical radiotherapy. Although they are incurable, patients who are assessed as unsuitable for radical treatment often require symptom palliation [30]. It is suggested that incurable/unresectable head and neck cancer may be identified on the basis of clinical and radiological staging and through a systematic team approach [29]. This was the basis of selection of cases for palliative radiotherapy in present study. The decision regarding palliative care was taken since, most of the primaries were unresectable and few patients were unwilling for surgery, once the surgical procedure and associated morbidities were explained. One of the main reasons that patients came to our centre with such advanced disease are because of poverty and illiteracy (most of them are from rural area) and their occupation did not permit them to stay away from home for such a long time and weekly visit to hospital did not disrupt their work. Considering these facts and with knowledge of different fractionated schedule, it was assumed that such a weekly hypofractionated concurrent radiotherapy would be cost effective and equally efficacious.

Applying the relevant results of concurrent chemo radiotherapy from clinical trials, it was decided to add chemotherapy (cis dichoro diamino platinum, CDDP) as a radio sensitizer and a combination of treatment was designed for study with the aim to get maximum regression as well as quick and sustained relief.

In the present study efficacy of hypofractionated concurrent radiotherapy was compared with conventional concurrent radiotherapy, as well as with different palliative schedules used for advanced, unresectable head and neck cancer. Patients enrolled in the study group were given external beam radiotherapy of 6 Gy weekly for continuous six weeks whereas control group received conventional radiotherapy, 2 Gy per fraction, 5 fractions a week up to six week with radiation rest on fourth week. All the patients were given injection cisplatin 50 mg i.v, weekly for 6cycles.

At primary site we observed that 14 (56%) &15 (60%) had complete response and 11 (44%) &10 (40%) had partial response in study and control group respectively after sixth week of treatment. At secondary site (nodal disease) we observed that 12 (48%) &14 (56%) had complete response and 13 (52%) &11 (44%) had partial response in study and control group respectively after sixth week of treatment. Overall responses as observed at end of sixth week revealed that 9 (36%) & 11 (44%) patients had complete response and 16 (64%) &14 (56%) had partial response at primary site of disease in study and control group respectively At end of treatment and first month follow up, it was observed that 14 (56%) &15 (60%) had complete response and 11 (44%) &10 (40%) had partial response at primary site of disease in study and control group and at secondary site (nodal disease), 11 (44%) &14 (56%) had complete response and 14 (56%) &11 (44%) had partial response in study and control group respectively.

The Overall responses as observed at end of treatment and first month revealed that 8 (32%) & 11 (44%), ($\chi 2$ = 0.76, p>0.05) patients had complete response and 17 (64%) &14 (56%) had partial response in study and control group respectively. There were no statistically significant differences in both groups.

Porceddu et al. [31] in a multicentric study reported on 35 patients treated with a novel hypofractionated

Table 5. Primary Response Based on T-Status (At End of Sixth Week)

T-Status	CR		PR		SD	
	Study	Control	Study	Control	Study	Control
T3	9	12	4	3	-	-
T4	5	3	7	7	-	-

Table 6. Nodal Response Based on N-Status (At End of Sixth Week)

N-Status	CR		PR		SD	
	Study	Control	Study	Control	Study	Control
N0	-	-	-	-	-	-
N1	-	2	-	-	-	-
N2	7	9	3	3	-	-
N3	5	3	10	8	-	-

Table 7. Treatment Response (At End of Sixth Week)

	No of Patients (%)	
Response	Study Group	Control Group
CR	9 (36)	11 (44)
PR	16 (64)	14 (56)
SD	-	-

radiotherapy regimen (30 Gy/5Fractions /2Fractions per week, at least 3days apart with additional boost of 6 Gy for limited volume disease. The overall objective response rate was 80%. In present study an overall objective response of 100% (CR+PR) was found. When primary site evaluation was done for 27 patients, 15 (56%) had a complete response, 5% (19%) had a PR, 4 (15%) had SD,0 (0%) had PD and 3 (11%) died before 2 weeks of radiotherapy with a primary objective response (CR+PR) of 74% (20/27) in former. In present study 14 (56%) had a complete response, 11 (44%) patients had partial response & no patients had SD or PD. The overall objective response was 100%. When nodal status was assessed out of 27 patients, 12 (44%) had a complete response 5% (19%) had a PR, 4 (15%) had SD, 3 (11%) had PD and 3 (11%) died before 2 weeks of radiotherapy with a primary objective response (CR+PR) of 63% (17/27). Reports of present study Showed that 11 (44%) had complete response &14 (56%) had partial response with overall objective response of 100%. The overall objective response rate of 100% was very high and this could be due to the fact that patients were assessed clinically rather than radio logically. When compared with the results of primary plus nodal disease, out of 16 patients,4 (25%) had complete response, 4 (25%) had partial response, rest showed either SD or PD in either of the sites. Present study results figured higher percentage of cure in this regard. This could be due to combination of cisplatin with radiation. There were differences in nature of cases also. In the former group, 5 patients with metastatic and 14 patients of recurrent (primary site-5 &regional-9) disease were included. Patients of stage-I, II and III were included in study, their strength was13 (35%). In this study 100% Patients of stage –IV and non-metastatic primary patients were selected.

The only randomized trial, which was done in year 1982 by Weissberg et al. compared the efficacy of high fractional dose (400 cGy / 10-12 Fractions/2-3 week/ 4 Fractions per week) and conventional radiotherapy (60-70 Gy/30 -35 Fractions / 6-7 weeks). No stastical differences of results were found in either arm. Results of this study were also similar in outcome as shown by Weissberg. Complete regression was obtained in two third of the treated patients in former where as in later one third of cases only. The outcome could be due to dissimilar staging population. The percentage of T4, T3, N3 and N2 patients were 73%, 24%, 42% & 21% respectively. In present study these figures were48%, 52%, 60% & 40% respectively.

Paris KJ et al. [32] analyzed 37 patients in a non-randomized Phase I-II trial, used twice a day fraction (370 cGy per fraction) for 2 consecutive day's totalling 1, 480 cGy per course. Previously untreated malignancies were present in 24 lesions, primary recurrent diseases in six patients, metastasis to the head and neck in five patients and skin primaries in the remaining two cases. At presentation 15 of 37 patients (or 17 of 39 lesions) were in operable due to poor medical status, eight patients were considered technically in operable due to extent of disease, 10 patients had distant metastasis and four patients refused surgery. Three courses were given at 3-week intervals for a final tumour dose of 4,440 cGy in twelve fractions over 8-9 weeks. After completion of therapy, 11/39 (28%) complete response; 19/39 (49%) partial response; 4/39 (10%) no response & 3 /39 (8%) had progressive disease. These figures in present study are better in terms of outcome.

In this study majority of patients were males 23 (92%) and only few were females 2 (8%) this wide diversity is mainly due to the habits of tobacco, betel nut Chewing which was more common in male patients and also due to social structure of male dominated society where women were even deprived of health care facilities. Claire et al [33] in a chemo-radiotherapy study for locally advanced head and neck cancer from developing countries had shown higher survival in laryngeal tumours compared to other sites. In present study, it was found that carcinoma tonsil showed good regression when compared with other primaries as well as in terms of nodal regression (3/3). The T and N status of these cases at initial visit

Table 8. Primary Response Based On T-Status (At End of Treatment and First Follow Up)

T-Status	CR		PR		SD	
	Study	Control	Study	Control	Study	Control
T3	9	12	4	3	-	-
T4	5	3	7	7	-	-

Table 9. Nodal Response Based On N-Status (At End of Treatment and First Follow Up)

N-Status	CR		PR		SD	
	Study Group	Control Group	Study Group	Control Group	Study Group	Control Group
N0	-	-	-	-	-	-
N1	-	2	-	-	-	-
N2	7	9	3	3	-	-
N3	4	3	11	8	-	-

Table 10. Overall Treatment Response

	No of patients (%)	
Response	Study Group	Control Group
CR	8 (32)	11 (44)
PR	17 (68)	14 (56)
SD	-	

were T3N3, T4N3 and T4N2 respectively. 8/25 (32%) of patients in study group showed COMPLETE RESPONSE at close out date, raising the possibility that in patients with locally advanced disease without distant metastases this regime may offer a curative chance. However longer follow up studies are necessary to accept or refute its role. Patients having performance status ECOG grade I showed good compliance to hypofractionated schedule. When impact of age as a prognostic marker was studied, no statistical difference was noted. Complete responders when matched for degree of differentiation, it was seen that, well and moderately differentiation patients had better outcome. At the end of sixth week as well as follow up period, it is observed that nodal site was lagging behind primary disease site in response evaluation. There were 5 patients who presented with nodal fungation at the time of enrollment. One patient showed complete healing of fungated lesion.

Side effects of chemotherapy and radiotherapy treatment were also observed during the study period. When we compared the mucosal and skin reactions between study and control group, no stastical difference was noted up to 4th week of treatment, but during fifth- and sixth-week oral mucositis and skin reactions were more in control group. At the end of 5th week, in control group, skin reactions and oral mucositis of grade I were seen in 6 and 5 patients, grade II in 14 and 13 patients and grade in 5 & 7 patients respectively. Study group had skin reactions and oral mucositis of grade I reactions in 19 and 14 patients ($\chi2$= 13.52, p= <0.05and $\chi2$= 6.87, p= <0.05), grade II reactions in 6 and 7 patients ($\chi2$= 5.33, p= <0.05and $\chi2$= 4.02,p= <0.05), grade III in 0 and 2 patients ($\chi2$= 5.55, p= <0.05 and $\chi2$= 3.84, p= <0.05) and no grade IV toxicities was observed in either group.

At the end of 6th week, in control group, skin reactions and oral cavity mucositis of grade I were seen in 5 and 5 patients, grade II in 14 and 12 patients, grade III in 6 and 8 patients respectively. In study group grade I reaction were observed in 17 and 17patients ($\chi2$=11.68, p=<0.05and $\chi2$=11.68, p=<0.05), grade II in 7 and 6 patients ($\chi2$=4.02, p=<0.05 and $\chi2$=3.84, p=<0.05), grade III in 1 and 2 patients ($\chi2$=4.15, p=<0.05and $\chi2$=4.5, p=<0.05). The lesser degree of skin and mucosal reactions in study group were due to the time factor, where acute reacting tissues repopulate themselves completely. Traditionally acute toxicity has not been a problem for hypofractionation regimen. This analysis also showed similar results.

In a multicentric study reported on 35 patients, Cureus et al. [34] found acute skin and mucosal reactions of grade 3 were 4 (11%) & 9 (26%), grade 2 in 13 (37%)of patients. In this study at the end of sixth week, grade 3 skin and mucosal reactions were found in 1 (4%) & 2 (8%) patients respectively. None of the patients developed grade IV skin or mucosal toxicity, the lower percentage of reactions could be due to protracted course of treatment given with sufficient time for repopulation. Study results were superior to other hypofractionated schedules, where total dose was given within 2 or 3 weeks.

Hematological toxicities (reference to blood hemoglobin level), Renal (reference to blood urea) were assessed according to WHO toxicity criteria in all cases weekly up to six weeks. Hematological toxicities (reference to blood hemoglobin level), Renal (reference to blood urea) were assessed according to WHO toxicity criteria in all cases weekly up to six weeks Among the study and control group, 8% and 12% had no acute hematologic reactions ($\chi2$ = 0.22, p > 0.05), 56% and 48% had grade I hematologic reactions ($\chi2$ = 0.32 p > 0.05), 28% and 36% had grade II hematologic reactions ($\chi2$ = 0.36, p > 0.05) and 8% and 4% had grade III hematologic reactions ($\chi2$ = 0.35, p > 0.05) respectively. No patient had had grade IV hematological toxicity.

Among the study and control group, 80% and 76% had no acute renal toxicity. ($\chi2$ = 0.11, p > 0.05), 20% and 24% had grade I hematologic reactions ($\chi2$ = 0.11 p > 0.05). No patients from either group develop grade II, III and IV renal toxicity. So, we concluded cisplatin in weekly dose of 50 mg used as a radio sensitizer was tolerated well by patients of both groups.

In any clinical trial, there are certain advantages and disadvantages. Hence it is necessary to enumerate the drawbacks to make this study more suitable as well as realistic in future trials. Though this study was aimed for a palliative intent, there were patients who responded very well and got cured of disease and outcome of such patients should be addressed in terms of overall survival, disease free survival and progression free survival on subsequent follow up. These parameters are yet to be reported by the author and co-authors. Hypofractionated radiotherapy utilizes a small number of fractions with a larger dose per fraction. The overall time is usually shorter than an accelerated protocol. In this study a protracted (6 weeks) time frame was used to equalize the biologic equivalent dose and time with conventional schedule as well as to measure response after 50Gy of concurrent chemo radiotherapy, which was considered the minimum dose to observe response. So, in a strict sense it can be considered as a hybrid regime targeted at such patients of advanced bulky fixed node disease. Acceptability or Compliance of any regime also depends upon certain patients' characteristics. In this study, it was observed that patients who travelled from a long distance (Punjab, Uttar Pradesh) lost follow up once they went to their native place, so we recruited fresh cases against them. Hence this protocol was unsuitable for patients who were staying far away from hospital. During a course of radiation, fraction size is the dominant factor in determining late effects and overall treatment time has little influence on these effects. As in the study group, large dose per fraction was prescribed, it was expected that late effects will occur. Hence off cord planning was done to avoid myelitis, where as other late responding

tissue reactions like skin fibrosis, xerostomia are yet to be reported by the author and co-authors. Though in patients having poor survival these late effects are meaningless, it is a determining factor in providing good quality of life for those having good probability of survival. Thus, majority of our patients in whom disease progressed in spite of hypofractionated concurrent radiotherapy were offered palliative symptomatic treatment. In such cases letter was given to local physician so that this procedure can avoid unnecessary expenses and travel from their local place to treating hospital. Thus, improved communication between professionals and the aims of treatment at time of diagnosis would improve decision for advanced cancer patients.

Limitation

Small sample size and short follow-up.

In conclusion, treatment of LAHNC with HYP-RT concurrent with cisplatin appears feasible and safe and is associated with a good response rate. These data highlight the potential usefulness of hypofractionation for LAHNC, especially for LMIC, where access to RT is poor. Long-term outcome data from the HYPNO and COMPARE trials are expected to provide definitive conclusions about HYP-RT for LAHNC.

Evaluation for acute toxicity showed that there was a significant increase in the incidence of grade I/II/III mucosal reactions in the control group ($p<0.05$). Also, there was a significant increase in the incidence of grade I/II/III skin reactions in the Control group ($p<0.05$). No significant differences in haematological toxicities were observed in the study group as compared to control group. Although immediate results in both the arms were statically non-significant, to reach a definite conclusion larger studies with longer follow up are required.

Advanced head and neck cancer with fixed node are unsuitable for curative treatment except for few cases who responds well to therapy. There is a strong necessity for prospective trial in such patients to address various unresolved issues regarding standard fractionation, identification of proper cases for such regimens, palliative treatment related toxicities and most importantly the issues relating quality of life. Judicious use of appropriate fractionation schedule with or without adjuvant therapy acceptable early and late reactions will provide a good quality of life to those patients where complete remission is achieved.

This study tries to strike a balance between economic burden, treatment time and hospital stay and machine load.

Informed Consent

Research involving human participant – Informed consent was obtained from all individual participants included in the study

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