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HYPOFRACTIONATED RADIOTHERAPY WITH CONCURRENT CHEMOTHERAPY WITH WEEKLY CISPLATIN IN LOCALLY ADVANCED RELATIVELY RADIORESISTENT SUBSITES OF HEAD AND NECK CANCERS

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Background. *Locoregionally advanced head and neck cancers are more aggressive and locoregional failure rate after conventional radiotherapy is high.*

Objective. *The aim of the study is to assess the tumor response and toxicities of hypofractionated radiation therapy with concurrent chemotherapy in treatment of four relatively radioresistent tumor sites of head and neck.*

Methods. *A prospective randomised control trial was conducted in 27 head and neck cancer patients. All patients were treated with hypofractionated radiotherapy at 250cGy/fraction once daily to a maximum of 62.5Gy in 25 fractions with concurrent cisplatin 30 mg/m^2. Data were evaluated with SPSS version 21.0 for Windows with p-value <0.05.*

Results. *Complete and partial responses were achieved in 15 (57.7%) and 8 (30.8%) patients respectively with an overall response rate of 88.5% and three patients having stable disease. Grade 3 and 4 acute mucositis was experienced by 17 patients (65.4%) and seven patients (27%), respectively. Grade 3 dysphagia was found in 21 patients (80.7%) and grade 3 and 4 skin reactions – in 11 and 2 patients, respectively. Most patients had manageable acute toxicities. Most of the late complications were of grade 2 and 3. The median time to locoregional recurrence was 12 months and one year progression-free survival attained by 61.5% patients.*

Conclusion. *Treatment with hypofractionated radiotherapy with concurrent cisplatin appears feasible and safe and is associated with a good response rate. Although grade 3 and 4 toxicities were comparatively high but it was manageable. Late toxicities were within tolerable levels.*

KEYWORDS: **head and neck cancer; hypofractionated; radioresistent; response; mucositis.**

Introduction

The term "Head and Neck Cancers" usually refers to the variety of neoplasms arising from upper aero-digestive tract with majority (approximately 80%) of head and neck malignancies of squamous cell carcinomas [1]. Oral cavity and laryngeal cancers are the most common head and neck cancers globally [2]. In India, age adjusted rate (AAR) of incidence for head and neck squamous cell carcinoma (HNSCC) is approximately 988.9 per 100000 populations with male to female ratio 3:1. In North-East of India, AAR incidence of HNSCC is 459.7 per 100000 populations, hypopharyngeal cancer being the commonest cancer [3]. HNSCC have been a disease of older males with heavy life-long tobacco use, high alcohol consumption, poorly preserved diet, and bad dentition usually presents with pain, dysphagia, neck mass etc. [4].

Locoregionally advanced (LA) HNSCC is treated by multimodality approaches combining surgery, radiotherapy and chemotherapy; radiotherapy being the main modality for unresctable tumors [5]. Nevertheless, the outcome of conventional radiation was disappointing, especially in advanced stage (i.e., stage III or IV) with a 5-year survival less than 60% only [6, 7]. One of the important causes of failure of conventional radiation is accelerated repopulation of tumor clones which usually starts around the 4th week of radiotherapy. To prevent this an altered fractionation scheme was introduced [8].

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Tumor hypoxia is a major concern in HNSCC causing treatment failures with radiation therapy. Whereas many sites of head and neck are radiosensitive like nasopharynx or larynx, few inherently radioresistant tumors of base of tongue, vallecula, pyriform sinus, retromolar trigone are associated with increased metastases and decreased sensitivity to ionizing radiation [9]. Hence, hypofractionated schedules by using a small number of fractions with a larger dose per fraction and shortening of the overall treatment duration have been tried to counter the tumor hypoxia and repopulation [10]. A meta-analysis of 16 randomized clinical trials demonstrate that optimized hypofractionation can markedly improve tumor control probability by 35% to 49% for late-stage head and neck cancer by overcoming tumor repopulation in fast-growing tumors [11]. Addition of concurrent chemotherapy to radiation would increase the efficacy of the treatment along with tumor control [12].

The aim of this study is to assess the tumor response and toxicities of hypofractionated radiation therapy with concurrent chemotherapy in treatment of four relatively radioresistent tumor sites of head and neck. After reviewing the literature and surveillance data, we have selected four subsites for this study retromolar trigone (RMT), base of tongue (BOT) and vallecula and pyriform sinus (PFS) because of their rarity and aggressive behaviour along with increased incidence of treatment failure and less long-term survival. Cancer in these sites is more hypoxic.

Methods

A prospective non-randomized experimental study was undertaken in the Department of Radiation Oncology, Regional Institute of Medical Sciences, Imphal, Manipur for two years starting from October 1, 2019 to September 30, 2021 among 27 patients. The permission of the Research Ethics Board (REB), RIMS, Imphal, Manipur was obtained (No. A/206/REB-Comm(SP)/RIMS/2015/597/75/2019) before initiating the study.

Inclusion criteria:

1. Patients aged between 30-75 years of age.
2. Patients with histopathologically confirmed squamous cell carcinoma of the selected head and neck subsites of base of tongue, vallecula, pyriform sinus, retromolar triangle (AJCC 8th edition stage III, IVA & IVB).
3. Patients who were not eligible for curative resection due to advanced stage.
4. Karnofsky performance status (KPS) ≥60%.
5. Normal complete blood count, liver and kidney function, blood glucose and normal audiometry.

Exclusion criteria:

1. Subsites other than those included in inclusion criteria.
2. Patient not willing to give consent.
3. Patient with second malignancy, previously treated with radiation therapy / chemotherapy and / or surgery.
4. Patients with uncontrolled co-morbid illness, psychotic disease, pregnant and lactating women.

All patients were treated with external beam radiotherapy by THERATRON 780-C, Telecobalt machine administered on a 5-week schedule by shrinking field technique and hypofractionated radiotherapy at 250 Gy/fraction once daily to a maximum of 62.5 Gy in 25 fractions (BED=78.12). Primary tumor and whole neck were irradiated up to a dose of 45Gy in 18 fractions. Doses equivalent to conventional fractionation were calculated for late reacting tissue and spinal cord shielding was performed after 40Gy in 16 fractions (BED=73.33), which was biologically equivalent with 46 Gy/23 fractions (BED=76.66) in conventional radiotherapy. Clinically uninvolved areas were excluded after 45 Gy. Primary tumor with metastatic nodal regions was irradiated up to 62.5 Gy. Concurrent cisplatin was administered at a dose of 30 mg/m^2 weekly for a total of 5 doses. The patients received standard hydration, mannitol infusion and prophylactic antiemetic medications for cisplatin therapy. Laboratory requirements before the dose of cisplatin were Granulocytes ≥1,500/μL, Platelets ≥100,000/μL and serum creatinine ≤1.5 mg/dL and normal audiometry.

During the whole period of treatment, the patients were reviewed every to note any adverse or untoward side effect, performance status, subjective response. Tumor response was assessed in 6 weeks after the completion of radiotherapy using RECIST Criteria (version 1.1) [13] with local examination and contrast enhance computed tomography (CECT) imaging. Acute radiation toxicities were assessed during each week of the radiation treatment and graded according to the RTOG acute radiation toxicity grading. Late radiation toxicities were assessed in 3 months after completion of treatment and thereafter every 3 months till 1 year (minimum 6 months) using the RTOG late radiation morbidity grading [14].

Statistical analysis: SPSS-version 21 for Windows (IBM Corp, Armonk, NY, USA) was used for statistical analysis. Variables like age, Karnofsky performance scores were presented as descriptive analysis using mean, median, mode and standard deviation. Categorical variables like gender, primary site, staging, histology, tumor response and toxicity profile were presented in terms of percentages and proportions as frequency tables or charts. Test of significance was done with Chi-square test using p-value 0.05 for assessing the association of multiple factors with treatment response and progression-free survival (PFS). PFS was analyzed using Kaplan-Meier survival curve and descriptive survival table.

Results

Total 27 cases of confirmed locoregionally advanced HNSCC were studied during the study period. One patient stopped treatment in between and lost follow up was excluded from the study. Hence data assessment was done for the 26 patients who completed their full coarse treatment.

Seventeen patients completed the treatment within the planned period of 35 days. The median time of delivery for these patients was 37 days (range, 33–65 days). Delay in the treatment contributed by environmental factor (Covid-19 Pandemic), social factors (lockdown), patient factors (noncompliance), treatment factors (side effects) and mechanical factors (machine break down).

Characteristic features of the patients and tumor are presented in Tables 1 and 2, respectively. 19 out of 26 patients had history of tobacco consumption whereas 16 patients had history of alcohol consumption and 9 patients had consumed both tobacco and alcohol. Median follow up period was 11 months with a range of 18 months (6-24 months). There were 16 patients of Pyriform sinus (5 stage III, 7 stage IVA and 4 stage IVB patients), 5 patients of Retromolar trigone (3 stage III and 2 stage IVA patients), 3 patients of vallecula (2 stage IVA and 1 stage IVB patients) and 2 patients of base of tongue (both stage IVA).

Table 3 shows the overall treatment response at the end of 6 weeks after completion

Table 1. Patients characteristics

Variables	Sub variables	Frequency (n=26)	Percentage (%)
Median Age in years		58.5	
Sex	Male	20	77
	Female	6	23
KPS	60	2	7.7
	70	9	34.6
	80	10	38.5
	90	5	19.2

Table 2. Tumor characteristics

Variables	Sub variables	Frequency (n=26)	Percentage (%)
T stage	T1	2	7.7
	T2	10	38.5
	T3	10	38.5
	T4	4	15.4
N stage	N0	3	11.5
	N1	4	15.4
	N2	13	50.0
	N3	6	23.1
Stage Grouping	III	8	30.8
	IV A	13	50.0
	IV B	5	19.2
Grade	Well differentiated	7	26.9
	Mod differentiated	12	46.2
	Poor differentiated	6	23.1
	Un differentiated	1	3.8

Table 3. Response rate in the patients according to Response Evaluation Criteria in Solid Tumor (RECIST) criteria after 6 weeks of completion of treatment

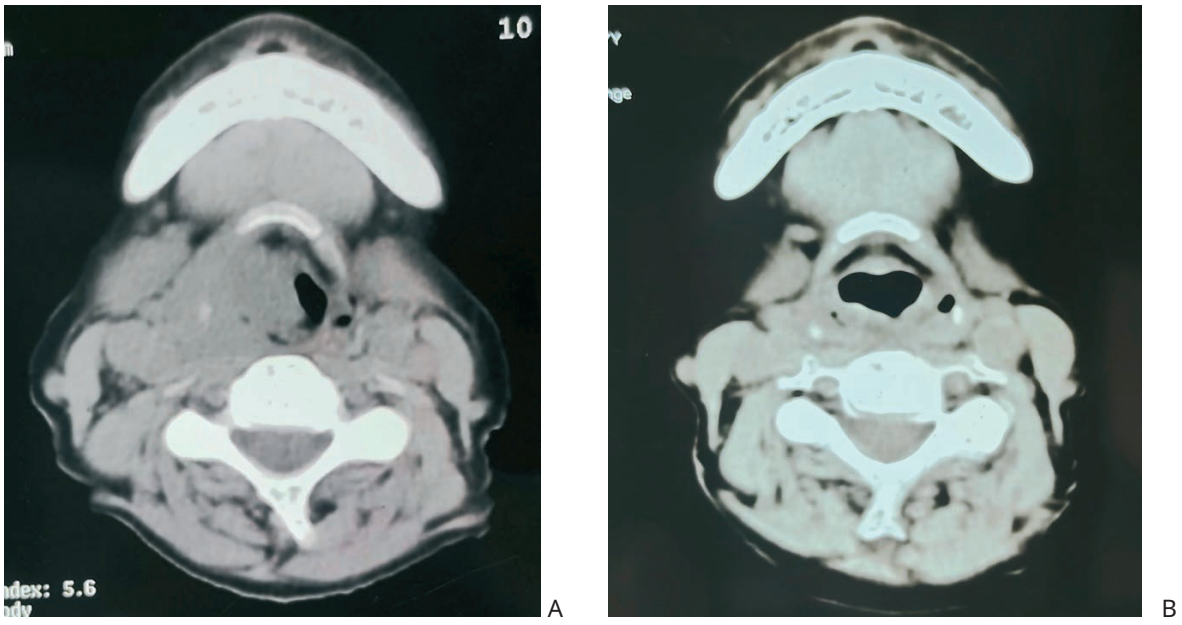
Tumor response	Frequency (n=26)	Percentage (%)
Complete response (CR)	15	57.7
Partial response (PR)	8	30.8
Stable disease (SD)	3	11.5
Overall response rate (ORR) [CR + PR]	23	88.5

of treatment in the study population. All the 26 patients were available for assessment at the end of the 1st month. The patients were evaluated with local examination and CECT imaging. CR was disappearance of all target lesions in primary site as well as secondary nodes whereas PR was defined as at least 30% decrease in size of target lesions. Complete and partial responses were achieved in 15 (57.7%) and 8 (30.8%) patients respectively with an overall response rate of 88.5% and 3 patients were having stable disease. One patient with T4 disease and two patients with N3 disease had radiological CR.

All patients were assessed weekly during treatment. Most of them had no hematological toxicity. Grade 2 anemia occurred in four patients, grade 2 neutropenia was in three patients for which they received blood transfusion and granulocyte colony stimulating factors. Grade 3 and 4 mucositis was experienced by 17 patients (65%) and seven patients (27%), respectively. Grade 3 dysphagia was evidenced in 21 patients (80.7%). The patients suffering from grade 2 and 3 skin reactions were 9 and 11, respectively. More than 88 % experienced grade 2 hoarseness, and grade 2 and 3 acute salivary gland reaction was found in 11 and 15 patients, respectively. Grade 3 and 4 toxicity developed after 3 weeks of radiation which corresponds with 3750 cGy in 15 fractions dose. Most patients had manageable acute toxicity.

Late complications were assessed at the 3rd, 6th and 9th month after completion of radiation. Grade 2 and 3 dysphagia was seen in 19 (73%) and 5 (19%) patients, respectively, and grade 2 mucositis was experienced by 38.5% of the study population. Grade 2 xerostomia was present in 20 patients at the 3rd months and reduced on further follow up. Grade 2 subcutaneous reaction was evidenced in 12 patients at the 3rd month. Almost all the toxicities were reduced on further follow up.

The median time to locoregional recurrence was 12 months (ranging 2-24 months). In Total 10 patients experienced recurrence. Three patients had recurrence at primary as well as nodal site and six patients – at nodal site only.



A B

Fig. 1. (A) Axial CT image of neck showing extensive pyriform fossa mass; (B) Response in the same patient in 6 weeks after completion of treatment.

Table 4. Acute radiation toxicity in study population according to the RTOG criteria, n=26 (%)

Toxicity	Grade	Week 2	Week 3	Week 4	Week 5
Anemia	Grade 2	0	2 (7.7)	3 (11.5)	2 (7.7)
	Grade 3	0	0	1 (3.8)	0
	Grade 4	0	0	0	0
Leucopenia	Grade 2	0	1 (3.8)	3 (11.5)	0
	Grade 3	0	0	1 (3.8)	1 (3.8)
	Grade 4	0	0	0	0
Mucositis	Grade 2	3 (11.5)	12(46.2)	8 (28.6)	7 (27.0)
	Grade 3	0	12 (46.2)	13 (50.0)	17 (65.4)
	Grade 4	0	0	7 (27.0)	2 (7.7)
Skin reaction	Grade 2	0	6 (23.1)	9 (34.5)	7 (27.0)
	Grade 3	0	0	6 (23.1)	11 (42.3)
	Grade 4	0	0	2 (7.7)	1 (3.8)
Dysphagia	Grade 2	3 (11.5)	13 (50.0)	4 (15.4)	7 (27.0)
	Grade 3	0	12 (46.2)	21 (80.7)	20 (76.9)
	Grade 4	0	0	0	0
Hoarseness	Grade 2	0	12 (46.2)	23 (88.5)	18 (69.2)
	Grade 3	0	0	1 (3.8)	4 (15.4)
	Grade 4	0	0	0	0
Salivary gland	Grade 2	0	17 (65.4)	11 (42.3)	11 (42.3)
	Grade 3	0	3 (11.5)	15 (57.7)	14 (53.8)
	Grade 4	0	0	0	0

Table 5. Late radiation toxicity in study population according to the RTOG criteria, n=26 (%)

Toxicities	Grade	3rd month	6th month	9th month
Skin reaction	Grade 1	17 (65.4)	19 (73.1)	11 (42.3)
	Grade 2	4 (15.4)	5 (19.2)	2 (7.7)
	Grade 3	0	0	0
Subcutaneous fibrosis	Grade1	13 (50.0)	9 (34.6)	4 (15.4)
	Grade 2	12 (46.2)	13 (50.0)	9 (34.6)
	Grade 3	0	0	0
Mucositis	Grade 1	13 (50.0)	12 (46.2)	4 (15.4)
	Grade 2	11 (42.3)	10 (38.5)	6 (23.1)
	Grade 3	0	0	0
Dysphagia	Grade 1	6 (23.1)	6 (23.1)	2 (7.7)
	Grade 2	19 (73.1)	13 (50.0)	8 (30.7)
	Grade 3	1 (3.8)	5 (19.2)	3 (11.5)
Hoarseness	Grade 1	13 (50.0)	16 (61.5)	10 (38.4)
	Grade 2	13 (50.0)	9 (34.6)	1 (3.8)
	Grade 3	0	0	0
Xerostomia	Grade 1	5 (19.2)	7 (27.0)	5 (19.2)
	Grade 2	20 (76.9)	16 (61.5)	7 (27.0)
	Grade 3	1 (3.8)	2 (7.7)	1 (3.8)

Recurrence with distant metastasis was evidenced in one patient. The patients with recurrent disease were planned for further salvage treatment.

When we have evaluated the dependence of progression free survival on the different factors related to patient and disease, tobacco consumption in any form along with the stage at presentation were found to be the two most important factors affecting the PFS with significant *P*-value (*P*=0.038 and 0.004 respectively).

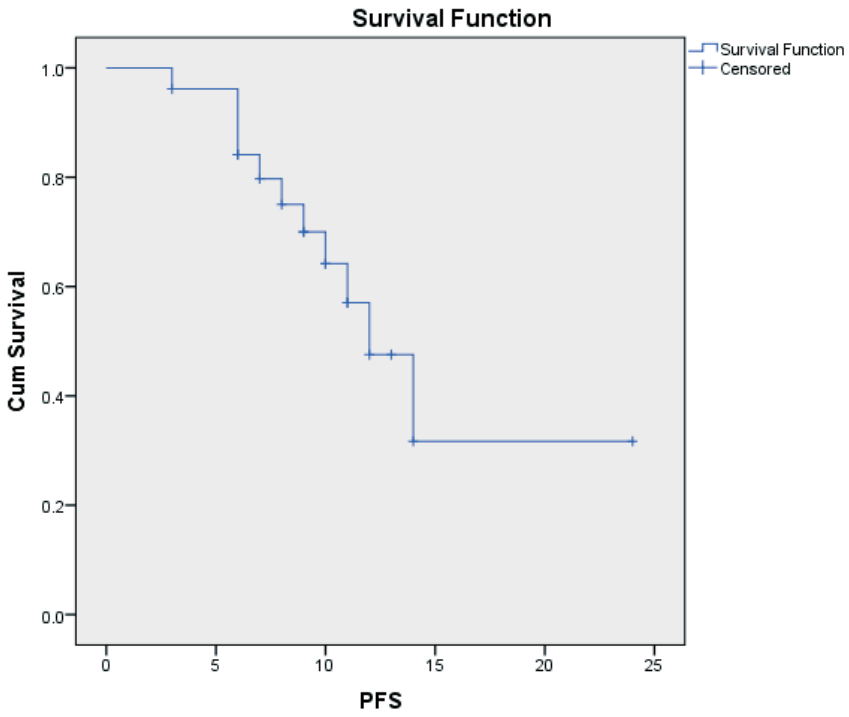


Fig. 2. Progression free survival (PFS) of the study population.

Discussion

National Comprehensive Cancer Network (NCCN) recommends for surgical resection of primary tumor in T3-T4a, N0 tumor along with neck dissection in N+ patients followed by RT, but for patients with stage T4b, N0-3, unresectable nodal status and unfit of surgery patients should be treated with concurrent chemoradiotherapy [15].

Prevalence of the head and neck malignancy in North Eastern part of India is high due to their continuous use of tobacco in various forms and their lifestyle. Most of them come with the advanced stage due to their negligence, unawareness, and poverty. Achieving long-term local control (LC) in locally advanced squamous cell carcinoma of the head and neck remains a challenge [16].

From radiobiological, economic and logistical points of view, a hypofractionated schedule would be the most suitable option. First, the treatment is completed before accelerated repopulation becomes a significant radiobiologic factor. Second, the reduction in the number of fractions also allows a more efficient use of resources, which can help avoid long waiting times for other patients; and lastly, considering that this group of patients are usually of elderly age and often have a poor performance status as well as significant co-morbidities, it is almost mandatory to keep the overall treatment time (OTT) as short as possible [17].

Moreover, during the recent first peak of the COVID-19 pandemic, many radiotherapy departments had reviewed their protocols for chemoradiation to make the OTT short by using hypofractionated schedules [18].

The patients characteristics were comparable with other studies [5, 19]. In this research by study design, PFS was the most common subsite followed by the RMT, Vallecula and BOT. Comparison between these subsites are not available in the literature for references. Other tumor characteristics were consistent with the previous studies [10, 20].

Response:

In this study, clinical complete response was observed in 15 (57.7%) patients and partial response in 8 (30.8%) patients with overall response rate of 88.5%. This report is consistent with the study by Proceddu et al. where 56% patients had complete response to the primary site and overall objective response rate was 80% [10]. Similarly, in the study by Teckie et al. 79% patients showed response to hypofractionated RT [21]. Our study has shown better result than the study by Nguyen NTA et al., where patients were treated with 8 Gy per fraction on the 0,7

and 21st day and documented complete response in only 30.9% patients with ORT of 81.8%, which means hypofractionated protocol of 62.5 Gy in 25 fractions is superior [20].

Koukourakis MI et al. studied Conformal hypofractionated RT with amifostine combined with cisplatin and cetuximab in patients with LAHNC, where the complete response rate was 68.57% [22]. The discrepancy is due to use of conformal hypofractionated RT, the use of amifostine, which reduced mucositis, that contributed to less interruption in treatment and some patients underwent nodal dissection.

The study by Valentina K et al. using conventional radiotherapy showed complete response in 72.3% patients which was superior than the present study findings. Use of 3DCRT with Linear accelerator in patients' treatment could be a factor for such result [23].

RT at either preoperative or post-operative stage in advanced HNSCC cases may influence the control rates, but many investigators in prospective studies have shown better response with concurrent chemoradiotherapy practice at any condition [24]. This suggests that patients undergoing accelerated RT with bulky lymph nodes sometimes may require neck dissection to gain benefit compare to conventional fractionation.

Toxicity:

Acute radiation reactions were high as expected, it contributed the major and minor deviation in the treatment plan for some patients and increase in overall treatment time.

In this study, grade 3 and 4 acute toxicities especially mucositis, skin reaction and dysphagia were high and developed after 3 weeks of radiation which is almost concordance with the previous studies [25, 26]. Study by Paul sanghera et al. [27] using hypofractionted RT with carboplatin showed Minimal Grade 3 mucositis was experienced by 60 patients (74%), with 5 (5%) patients with Grade 4 mucositis. Grade 3 dysphagia was evidenced in 44 patients (54%). The incidence of acute toxicity was very low in the patients treated with amifostine as observed by Koukourakis MI et al. [22].

The incidence of late side effects assessed at the 3rd, 6th and 9th months of treatment completion within a median of 11 months of follow-up was within acceptable levels, despite the use of hypofractionation. Longer follow-up is certainly needed to better estimate late adverse events. Reducing overall irradiation time by hypofractionation is an applicable alternative to conventional regimens with concerns that large fraction sizes may lead to greater toxicity in late-responding tissue supported by earlier studies. The reduction in number of fractions avoids long waiting times. There is no doubt that hypofractionation offers major potential advantages to patients and to the economy of health systems [19, 28, 29].

Progression free survival:

The median progression free survival in this study was 12 months. 38.5% patients had developed recurrence during the study period. PFS at the 6th and 12th month was 84.6% and 61.5%, respectively. This finding is almost similar with the study by Agarwal JP et al. [5] where 1-year PFS was 55%. Another study by Teckie et al. [21] demonstrated a locoregional PFS rate of 70% at the 6th month, 43% at the 12th month, and 29% at the 2nd year with median follow up of 11.9 months. Though overall response rate is good in this study, the sites chosen for the study are prognostically bad due to more hypoxia and less radiation responsiveness leading to poor progression free survival.

Of the various prognostic factors studied, tobacco consumption and higher stage had significantly affected the PFS. Other prognostic factors like age, sex, KPS, weight, site of tumor, T and N stage and the tumor grade did not show statistically significant difference on the PFS.

All the patients who had loco-regional failure presented with N3 node at initial presentation. This denotes that patients with a large nodal burden are probably less likely to be benefited by hypofractionation. This outcome is well-corroborated with MARCH collaborative group meta-analysis, which showed that the effect of altered fractionation was significantly more pronounced on the primary tumor than on the nodal disease [30].

Limitations of our study include a limited follow-up time, small sample size, treating with 2-D Cobalt-60 teletherapy machine. In view of the non-randomized single arm nature of the study, it would not be correct to draw any definite conclusions regarding local recurrence and survival patterns from this study. The use of neck dissection and the ability to complete treatment within the prescribed overall treatment time would have contributed better results.

Conclusion

Treatment of locoregionally advanced head and neck cancer (LAHNC) with hypofractionated RT with 62.5 Gy in 25 fractions concurrently with

cisplatin is feasible and safe and is associated with a good response rate. Although grade 3 and 4 toxicities were comparatively high but it was manageable. Late toxicities were within tolerable levels. These data highlight the potential usefulness of hypofractionation for LAHNC, especially for low to medium income countries, where access to advanced techniques of RT is poor. Long-term follow up with more sample size and comparative trials are needed for further recording of late response as well as toxicities to provide definitive conclusions about hypofractionated RT in the selected subsites LAHNC.

Conflict of Interests

Authors declare no conflict of interest.

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Author's Contributions

Kishalay Baidya, Yumkhaibam Sobita Devi, Yengkhom Indibor Singh – conceptualization, methodology, formal analysis, writing – original draft; *Kishalay Baidya, Akoijam Sunita Devi, Deepsikha Das* – data curation, writing – reviewing and editing; *Rahul Mahawar, Nongmaithem 0ima Devi* – investigation, formal analysis.

РОЛЬ ГІПОФРАКЦІОНОВАНОЇ ПРОМЕНЕВОЇ ТЕРАПІЇ З ОДНОЧАСНОЮ ХІМІОТЕРАПІЄЮ ЦИСПЛАТИНОМ ПРИ ЛОКАЛЬНО ПОШИРЕНОМУ ВІДНОСНО РАДІОРЕЗИСТЕНТНОМУ РАКУ ГОЛОВИ ТА ШИЇ

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Вступ. *Місцево-поширений рак голови та шиї є більш агресивним, і частота невдач терапії після звичайної променевої терапії є високою.*

Мета. *Оцінити реакцію пухлини та токсичність гіпофракціонованої променевої терапії з одночасною хіміотерапією при лікуванні чотирьох відносно радіорезистентних пухлин голови та шиї.*

Методи. *Проспективне рандомізоване контрольне дослідження було проведено за участю 27 пацієнтів з раком голови та шиї. Усі пацієнти отримували гіпофракціоновану променеву терапію в дозі 250 сГр/фракція один раз на день до максимуму 62,5 Гр у 25 фракціях з одночасним цисплатином 30 мг/м^2. Дані були оцінені за допомогою SPSS версії 21.0 для Windows із значенням p<0,05.*

Результати. *Повна та часткова відповіді були досягнуті у 15 (57,7%) та 8 (30,8%) пацієнтів відповідно із загальною частотою відповіді 88,5%, а у трьох пацієнтів захворювання було стабільним. Гострий мукозит 3 і 4 ступеня мали 17 пацієнтів (65,4%) і 7 пацієнтів (27%) відповідно. Дисфагію 3 ступеня спостерігали у 21 пацієнта (80,7%), а шкірні реакції 3 і 4 ступеня — у 11 і 2 пацієнтів відповідно. Більшість пацієнтів мали керовану гостру токсичність. Більшість пізніх ускладнень були 2-го та 3-го ступенів. Середній час до локального рецидиву склав 12 місяців і однорічну виживаність без прогресування захворювання досягли 61,5% пацієнтів.*

Висновки. *Лікування гіпофракціонованою променевою терапією з одночасним прийомом цисплатину видається можливим і безпечним і пов'язане з хорошим рівнем відповіді. Хоча 3 і 4 ступені токсичності були порівняно високими, але це можна було контролювати. Пізня токсичність була в межах допустимого рівня.*

КЛЮЧОВІ СЛОВА: **рак голови та шиї; гіпофракціонована; радіостійкий; відповідь; мукозит.**

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