Original Research Article

Altered Fractionation Intensity Modulated Radiotherapy with concurrent chemotherapy in head and neck cancer : a feseability study

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Abstract

Purpose: To assess the loco regional response and toxicity of patients to concurrent chemo-radiation with 6 fractions/week using Intensity Modulated Radiotherapy in locally advanced head and neck cancers. (oropharynx and hypopharynx). **Materials and Methods:** 20 patients with Stage III and stage IV, squamous cell carcinoma of Head and neck were enrolled. Target Volume Delinetion was done in accordence with Danish Head and Neck cancer group (DAHANCA) contouring guidelines. Differential radiation dose of 70 Gy, 63Gy and 56 Gy in 35 fractions using IMRT, delivered to GTV, CTV1 and CTV2 with weekly cisplatin with weekly assessment of response and toxicity. **Results:** The median age of the patients was 54 years ranging from 40 to 65 years. 14 and 6 patients had Hypopharyngeal and Oropharyngeal malignancy of squamous cell origin. 95% of patients received 70 Gy in 35 fractions with 4 cycles of concurrent Cisplatin. 18 patients completed treatemnt within 45 days of OTT. 16 patients had complete response and 4 had partial response. Grade I, II dermatitis was observed in 70% and 30% of patients, respectively. 5 patienst developed Grade 2 and 1 patinet developed grade 3 leucopenia. 2 patients had weight loss of more than 10%. 85% oforopharyngeal cancers and 67% of hypopharyngeal cancers showed complete response. Nodal response was 100% complete in N1 & N2a, 92% and 0% in N2b and N3 lesions respicyively. TNM stage group wise the complete response rates were 100% in stage III, 92% & 0% IVA & IVB. **Conclusion:** Accelerated fractionation with IMRT and concurrent chemotherapy is a feasible in locoregionally adanced head and neck cancers with acceptable toxicities and good locoregional response rates.

Key words : Altered fractaionation, IMRT, Concurrent chemoradiation

Introduction

The incidence of squamous-cell carcinoma of the head and neck (HNSCC) is increasing, and it is the fifth most common malignant disease in the world, with more than 70% of cases occurring in the developing world (India) [1]. 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]. HNSCC is a loco-regional disease confined to the primary site and its regional lymph nodes, with distant metastasis being rarely found at diagnosis. Thus loco-regional treatments like Radiotherapy (RT) & Surgery are the primary modality of treatment. With the evolution of "Concept of organ and function preservation" RT is preferred over mutilating surgeries.

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However tumors being known for heterogeneity in intrinsic radio-sensitivity, attributable to tumour hypoxia and or tumour cell repopulation during treatment including dose of RT required for tumour cell ablation, loco-regional control rates are still low. One of the most important biological factors related to the outcome of RT in squamous-cell carcinoma is the tumour stem cells proliferation during treatment [3]. It is well known that the prolonged over all treatment time (OTT) would result in loss of tumour control by 0.6% per day, [4–6] and a substantial number of clinical reports show that reduction in overall treatment time might improve loco-regional control [7–9].

A shorter treatment time can be obtained by delivering higher dose per fraction, but this will result in disproportionate the incidences of late complications [10, 11]. Alternatively Accelerated fractionation is if the

weekly number of fractions is increased without increasing the dose per fraction. This was studied by Danish Head and Neck Cancer Group (DAHANCA) 6 & 7 trial which compared the same total dose of radiotherapy given to patients with HNSCC either conventionally (five fractions per week) or accelerated (six fractions per week using conventional technique [7].

The accelerated schedule enabled delivery of 66 Gy in 33 fractions, 8 days earlier than the conventional schedule, with an overall treatment benefit of around 15% more than the conventional schedule and an with manageable complications rate Thus, decrease in OTT can result in better tumour control, with the existing resources, provided the total dose is not reduced.

However this benefit associated with Accelerated fractionation by conventional 2D technique was masked due to associated higher normal tissue toxicities compromising the therapeutic gain. 12 However the benefit of AF using IMRT, is not so far evaluated which is the current standard of care in H/ N cancers.

The purpose of this study was to determine the feasibility and effectiveness of Accelerated fractionation using IMRT by assessing compliance of patients and the loco regional response comparing with concurrent chemoradiation.

Materials and Methods

In this prospective, non randomized, feasibility study, after obtaining ethical committee approval, 20 Patients with histologically proven invasive SCC of Oropharynx and Hypopharynx of Stage III to IVA, with performance status of WHO-0-2, with no history of prior RT or Surgery, deemed suitable for radical radiotherapy with curative intent were selected. Patients were staged according to TNM classification 7th edition after clinical, radiological and endoscopic evaluation (Table 1). All patients underwent orodental assessment including dental prophylaxis.

Patients were immobilized with thermoplastic mask in supine position. Computed tomography (CT) images indexed every 3 mm were obtained, ranging
from vertex to 5 cm inferior to the clavicular heads.

Primary and nodal target volumes along with critical stucutres were delineated as per RTOG and Danish Head and Neck Cancer Group (DAHANCA) contouring guidelines on a contrast enhanced CT superimposed plain images.

Treatment planning was performed using the inverse planning algorithm. IMRT plans were genarated using 7-9 fields with dMLC optimiszation and patients were treated with altered fractionation scheme with six fractions per week, from Monday to Saturday, with sixth fraction delivered on Saturday. Thus reducing the overall treatment timewithout reduction in the total dose.

The treatment prescription and dose specifications were in accordence with guidelines of ICRU 50 and 62.

Gross Tumor Volume (GTV) – includes measurable and demonstable Primary (GTVp) and Nodal (GTVn) disease.

Clinical Target Volume 1 (CTV1) – includes 5mm margin to GTV(p) and GTN(n) , edited at bone, air cavities and fascia with no radiological evidence of invasion.

Planning target volume 1 (PTV1) - 5mm margin for CTV1. PTV1 to recieve 70Gy in 35 Fr.

Clinical Target Volume 2 (CTV2) – Includes CTV 1 + entire nodal region.

Planning target volume 2 (PTV2) - 5mm margin for CTV 2 - PTV2 recieves 63Gy in 35 Fr.

Clinical Target Volume 3 (CTV 3) – Includes Low risk adjecent neck nodal region.

Planning target volume 3 (PTV3) - 5mm margin to CTV3. PTV3 to receive 56Gy in 35Fr.

All patients received concurrent chemothearpy with Cisplatin at a weekly dosage of 40mg/m2

Treatment plan analysis- Dose-volume histograms (DVHs) of the PTVs and the critical normal structures were analyzed accordingly. For PTVs, we evaluated the volume covered by 95% of the prescribed dose (V95%), Maximum point dose (D-max), Dose minimum (D-min), Mean dose (D-mean).

The aim was to achieve 95% of the PTV to receive 95% of the prescribed dose and no more than 1% of the PTV to receive >107% of the prescribed dose. For the critical organs with functional subunits organised in series such as brainstem, spinal cord, Mandible, D-max was evaluated. For critical organs with functional subunits organised in parallel such as cthe parotidsand cochlea, the D–Mean was evaluated. A QA program included a pre-treatment dosimetric check of all IMRT fields, using electronic portal imaging device (EPID).

Treatment Execution- All patients were given 6 fractions of radiation from Monday to Saturday and long with coucurrent Cisplatin at 40mg / m^2/ week. Treatment postion and adequecy of PTV margins were verified by pre-treatment EPID imaging on first 3 consecutive days of treatment and weekly, thereafter in order to calculate systematic and random error.

Response and Toxicity assessment- Response and Toxicity were assessed weekly. Tumour Response was assessed according to RECIST crieteria. Acute mucosal and skin toxicity was assessed and scored as per the RTOG Acute Radiation Morbidity Scoring system.

Chemotherapy induced renal and hematological toxicities were assessed as per the Common Toxicity Criteria for Adverse Events (CTCAE).

Follow-up- First follow-up was done at 4 weeks and subsequent follow-up at 3 months interval. During follow up, primary tumour and the nodal response were assessed separately along with radiological and endsocpic mapping. Acute mucosal and skin toxicity were assessed and scored respectively.

Statistical Methods- Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean SD (Min-Max) and results on categorical measurements are presented in Number (%).

Significance is assessed at 5% level of significance. Student t test (two tailed, dependent) has been used to find the significance of study parameters on continuous scale.

Results

In this study, the median age of the patients was 54 years ranging from 40 to 65 years. 17 were male and 3 were female. 16 (80%) patients gave history of tobbacco and alcohol addiction. 14 (70%) patients had Hypopharyngeal and 6(30%) had Oropharyngeal malignancy.

The T stage and N stage of the cohart is as per the table-2. Histologically, 12 (60%) patients had well differentiated SCC, 7(30%) were moderaratley differrentiated and 1(10%) poorly differentiated. 19 (95%) of patients received 70 Gy of radiation dose along with 4 cycles of concurrent Cisplatin. The Over all Treatment time (OTT) was 45 days in 18 (90%) patinets.

The most common acute toxicity was mucositis, which was grade II and grade III in 6 (30%) and 14 (70%) of patients, respectively. Mucositis negatively impacted swallowing ability and causing mean weight loss of 8.3% and 5 (25%) patients developed sever degrees requiring naso-gastric tube support.

Grade I, II dermatitis toxicity was observed in 14 (70%) and 6(30%) of patients, respectively. None had G-III or IV skin reactions. 5(25%) patients had Grade II and 1 (5%) patient developed Grade III Leucopenia. 4 (25%) of patients required G- CSF support after 4 cycles of chemotherapy.

None of the patients developed Renal toxicity. None of the patients had hemoptysis, dyspnea, or stridor nor required tracheostomy. 5 (25%) patients, grade 2 and 1 (2%) grade 3 developed leucopenia after 4 cycles of chemotherapy. 5 (25%) patients required tube feeding and or IV fluids for nutritional support.

Response Rates- Overall, complete response was seen in 80% (16/20) of the patients, partial response was seen in 20% (4/20) of the patients.

Tumor Response Based on Different Variables- Complete response was observed 100% in well deifferntiated, 66% in moderately differentiated and none in poorly differatiated carcinomas.

17 (85%) of oropharyngeal and 13 (65%) of hypoparyngeal cancers showed complete response. 100% of T2 and T3 and T4b tumors and 80% of T4a tumors showed complete response.

In nodal disease 100% complete response among patients with N1 and N2a lesions, while 91% in N2b and none in N3 disease.

TNM stage group wise the complete response rates were 100% in stage III, 92% in stage IVA, none in stage IVB.

Patient Characteristics

Table-1

Age in Years	**No.**	**Percentage**
41-50	5	25%
51-60	8	40%
61-70	7	35%
Sex		
Male	17	85%
Female	3	15%
Habits		
Smoking		
No	05	25%
Yes	15	75%
Alcohol		
No	4	20%
Yes	16	80%
Pan Chewing		
No	19	95%
Yes	1	5%
Betel Nut		
No	18	90%
Yes	2	10%

Tumor Response Based On Different Variables

Table-2: Correlation of study variables with overall response.

Variables	**Total number of patients**	**Overall Response**	
		Complete response	**Partial Response**
Site			
□ Hypopharynx	14	12	2
□ Oropharynx	6	4	2
Clinical Stage			
□ III	3	3	0
□ IVA	14	13	1
□ IVB	3	0	3
Tumor stage			
□ T2	2	2	0
□ T3	11	11	0
□ T4a	5	4	1
□ T4b	1	1	0
Nodal stage			
□ N0	2	2	0
□ N1	3	3	0
□ N2a	1	1	0
□ N2b	11	10	1
□ N3	3	0	3
Histology			
□ WD	12	12	0
□ MD	6	4	
□ PD	2	0	2

Discussion

The design and choice of an accelerated protocol was ba sed on results of the DAHANCA 7 trail [22] where Cisplatin was used concurrently with RT, as a single agent or in combination with 5-FU or Mitomycin-C) with stanadard dose schedule of 100mg / m^2 bolus on days 1, 22 and 43 of RT. Randomised clinical trials comprisng so called non-standard schedules of platinum based CRT against RT alone [13,14,15] have treated equivalent numbers of patients as those that have compared bolus CDDP CRT against RT alone [16,17,18].

It is clear that schedules that deliver drug in smaller doses on a more frequent basis are also quite effective in improving outcome.A common thread with respect to chemotherapy delivery in all of the sucessful RT / concurent single agent cisplatin schedules, both "standard" and otherwise is the delivery of a minimum cumulstive dose of 200mg / m2 during the couse of irradiation. Hence Cisplatin of weekly 40mg / m2 was used in this study. In this study 80% (16/20) of patients completed the intended treatment protocol of chemo-radiation in less than 45 days. The rate of compliance was comparable to study by Staar et al[19] which reported 90%.

The significant toxicity in our study was mucositis. 70% (14/20) of the patients had grade III mucositis and 30% (6/20) had grade II mucositis. No patients had grade IV mucositis. This incidence grade 3 or more mucositis is less (70% vs 80-85%) as compared to DAHANCA-7[20] and other studies with similar schedules [21,22,19] and where hyper fractionation was used [13], its reported as upto to 95%. All the cases with mucositis responded to conservative management. Mucositis appeared during the second week of treatment as hyperemia of the mucous membrane. Grade II mucositis was seen during the third week, while grade III mucositis was seen during the fifth week of treatment.

Mucositis compromised the ability to maintain nutrition with patients, on an average loss in baseline weight upto 8.3% which is comparable to study by Brizel et al which reported 10% mean weight loss. The proportion of patients who required and accepted a nasogastric tube was 20% (5/20), which was less compared to a multicentre randomized German trial [13] which mandated hospitalizing of all patients who were randomised to the chemotherapy arm (CDDP, 5-FU) and over half had a percutaneous gastrostomy for tube feeds prior to starting treatment.

70% (14/20) of the patients had grade I skin reaction, 30% (6/20) grade II skin reaction. 25% (5/20) of the patients had grade II hematological toxicity and 5% (1/20) of the patients had grade III hematological toxicity in comparison with study by Dobrowsky and Naude[22] that reported 18% of grade 3-4. None of the patients in our study had renal toxicity.

IMRT in head and neck cancer has proved better long-term preservation of salivary flow and better local-regional control [23] in comparisons with conventional radiation techniques. Chao et al [24] reported that using IMRT for Stage III and IV oropharyngeal cancers, after a median follow-up of 33 months, the 4-year estimate of loco-regional control was 87% and disease-free survival was 81%. With conventional radiation techniques, upto 95% of patients experience Grade 3 or higher mucositis after radiation therapy. The treatment in our study was well tolerated, with Grade 3 mucositis seen in 70% of patients.

Our study consisted of mostly advanced-stage study population, All the 20 patients (100%), received concurrent chemotherapy. Both meta-analyses and randomized trials have established the role of concurrent chemotherapy in improving outcomes in head-and- neck cancers [25]. The recent update from Denis et al [18] has shown an improvement in overall survival and Loco regional control at 5 years using combined modality therapy for advanced-stage Oropharyngeal cancers. It follows that the common use of concurrent chemotherapy in our study is likely a contributing factor to the observed rates of initial tumor response and acute toxicities.

When we analyzed by T size and N stage, our study produced good response rates. It was significant even for advanced stages like T4a and T4b tumors. The DAHANCA-7 reported that the whole benefit of acceleration came from improved T-site control, which further improved with chemotherapy.

Withers et al and Bentzen and Thames showed that a dose of 0.48 Gy per day was recovered by tumour during fractionated radiotherapy of HNSCC.

This was the reason why in our study in which overall treatment time was reduced by 1 week, produced higher response than conventional fractionation. By reducing overall treatment time by 1 week the 'dose recovery factor' of 3.3 was avoided.

Finally, all stages (except N3 nodes) showed improved response with accelerated radiotherapy using IMRT technique. The addition of chemotherapy has an added advantage. Patients with partial response of neck nodes underwent salvage neck dissection and are disease free till date. Long term follow-up is needed to look at the parameters like late toxicity, Loco-regional control, disease free survival and overall survival.

Conclusion

Accelerated fractionation in the form of 6 fractions a week using IMRT along with concurrent chemotherapy is a feasible in the treament of locally advanced head and neck cancer with good compliance. The loco-regional response rates and toxicity profile were acceptable and were similar when compared with DHANCA 7 study.

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