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Response Evaluation Of Accelerated Fractionation With Concomitant Boost Chemoradiation In Locally Advanced Squamous Cell Head And Neck Cancer

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Abstract: *Radiotherapy is often the primary treatment modality for unresectable squamous cell head and neck cancer ,but the optimal fractionation regimen has been controversial. The objective of this study was to evaluate and compare the efficacy and toxicity of accelerated fractionation with concomitant boost (group A) against standard fractionation regimen (group B). Patients were randomly assigned to receive radiotherapy delivered with accelerated fractionation with concomitant boost after 3 weeks of standard 30Gy/15fractions/3week, as 1.4 Gy/fraction twice daily with a 6-h interfraction interval ,5days/week for 3 weeks to 72 Gy/ 6 weeks and compared to standard fractionation at 2Gy/fraction/day,5days/week, to 70Gy/35fractions/7weeks .All patients in both treatment groups received concomitant chemotherapy in the form of weekly injection of cisplatin (30mg/m^2).Of the 100 patients entered ,only 90 patients were evaluable for outcome. The primary end point was locoregional control. chemotherapy was well tolerated, the overall complete response rate of 61.36% in group A vs 54.34% in group B. Results have showed an increased but non significant acute toxicity in group A. However , late effects were comparable . The Concomitant boost accelerated radiation plus concurrent weekly cisplatin is a feasible schedule in patients with locally advanced head and neck cancer, with moderate efficacy and acceptable toxicity particularly in limited-resource settings.*

Keywords: *Accelerated, Concomitant boost, Head and neck, Radiotherapy, Squamous cell.*

I. Introduction

The annual incidence of head and neck cancers worldwide is more than 550,000 cases with around 300,000 deaths each year . About 90% of all head and neck cancers are squamous cell carcinomas (HNSCC). HNSCC is the sixth leading cancer by incidence worldwide [1]. The prognosis of patients with locally advanced head and neck cancer is still poor, 5 year survival rate with conventional radiotherapy is 40%-50% [2]. Radiation therapy has served as an archetype for treatment of malignant epithelial squamous cell carcinoma. Standard fractionation schedules have arrived at delivering multiple fractions of 2 Gy each for five days in a week over seven weeks [3]. However, accelerated tumor clonogen repopulation during fourth to fifth week of conventional fractionation is one of the obstacles to cure of squamous cell carcinoma of the upper respiratory and the digestive tracts[4]. Various modifications in the fractionation schedules have been explored in attempt to improve local control and survival outcome in these patients. During the recent years schemes of radiotherapy incorporating multiple treatments in one day have been introduced. The prime object of fractionating the dose is to widen the response between normal tissue and tumor cells so as to get better tumor control and simultaneously sparing the normal tissue from severe radiation injury. Perhaps the most commonly used form of accelerated fractionation is to give "boost" treatments to reduced volumes concomitantly with the treatment of the large field. The dose delivery pattern need not be symmetric throughout the weeks of treatment. A biologically reasonable strategy would be to escalate the dose rate, delivering more of the concomitant boost doses toward the end of the course of radiotherapy. The reason for this is that acutely responding normal tissues are regenerating rapidly during the latter part of the treatment and would, therefore, be capable of withstanding more irradiation than they could at earlier times when they are still in steady state. Taking into account these considerations, the use of a radiotherapy schedule such as concomitant boost, implies a decrease in the total treatment duration by applying a second daily session to the macroscopic tumor ,which should begin just when tumor repopulation is supposed to occur. A landmark study by RTOG 90-03 compared three fractionation schedules with a standard fractionation schedule and demonstrated an advantage of 8% in the local control with hyperfractionation and concomitant boost technique. There was also a trend toward better disease free survival though it did not translate into a benefit in the overall survival. Though there was an increase in acute toxicity, the late toxicity was comparable [5].

Systemic chemotherapy applied to locally advanced SCCHN had demonstrated good indices of antitumor activity. Throughout the last two decades, a concurrent delivery of chemotherapy with radiation therapy has been tried and tested .The putative mechanisms of synergistic interaction of cisplatin with

radiotherapy in SCCHN include radiosensitizer (through inhibition of potentially lethal damage repair and sublethal damage repair); hypoxic cell sensitizer; cell cycle pertubator; ability to form deoxyribonucleic acid (DNA) adducts; and inhibition of angiogenesis[6]. Concurrent chemotherapy with radiation has now been recommended as the standard treatment for locally advanced head and neck cancer . Pignon et al, in a metaanalysis of 93 randomized trials showed that addition of chemotherapy was associated with 5% increased in overall survival. The use of concurrent chemotherapy with radiotherapy was the most effective modality with an absolute benefit in survival of 8% at five years[7].

In an attempt to assess the potential integration of these two modalities and to minimize accelerated tumour repopulation, the present study was designed to investigate the feasibility , efficacy and acceptability of the treatment regimen using accelerated fractionation for concomittant boost with concurrent chemotherapy with cisplatin versus conventional fractionated chemoradiation in locally advanced head and neck cancer, particularly in limited-resource settings.

II. Material And Methods

This prospective study was carried out in previously untreated histologically and cytologically proven patients locally advanced squamous cell carcinoma of head and neck (Stage III & IVA)**,** Age of patient 30-70 yrs, Previously untreated with chemotherapy or radiation therapy, Adequate Haematology, liver, and kidney function, Measurable or evaluable disease, Voluntarily given written informed consent, ECOG performance status 1 without evidence of metastasis were included in this study. Complete medical history and any significant past history or family history which attributed to malignancy, was asked. Physical examination with an assessment of the patient's performance was done prior to the start of any protocol treatment. General physical condition, nutritional assessment, complete dental evaluation, clinical evidence of lymphadenopathy. Local examination included inspection, palpation finding of visible growth in oral cavity, Indirect laryngoscopy, rhinoscopy , direct laryngoscopy will be done as per required for respective site. Systemic examination of nervous , cardiovascular , respiratory and gastrointestinal system and exclusion of any evidence of distant metastasis. Hundred patients selected, were randomly divided into two groups of 50 patients each. Of the 50 patients included in group A, 2 patient left treatment within the first 2 weeks of treatment and the one didn't come while receiving boost treatment. Two patients diagnosed with lung and liver metastasis respectively. And one patient died during the course of RT from local disease. While in group B , two patient left treatment and two diagnosed with lung metastasis. Thus total no. of patients evaluated 44 in group A and 46 in group B. Group A (concomitant boost group) patients were treated on external beam radiotherapy delivered by Cobalt-60 teletherapy machine (THERATRON 780E) at 80cm source to surface distance . Received accelerated fractionation for concomitant boost after 3 weeks ;30 Gy in 15 fractions, 5fractions/week in 3 weeks followed by 1.4 Gy twice daily fractions (time gap between 2 fractions were 6 hours) for 15 days in 3 weeks with a total of 72 Gy in 6 weeks , spinal cord shielding was done at 49.6 Gy/22fractions. Group B (conventional group) Patients were treated on external Beam Radiotherapy deliverd by Cobalt-60 teletherapy machine [THERATRON 780E] at 80cm source to surface distance . Dose of 2 Gy/ fraction/day, Monday to Friday to total dose of 70Gy, spinal cord shielding was done at 46Gy/ 23fractions .In most of the patients, lateral opposed fields were used to treat the primary tumor and involved lymph nodes. A third anterior field was used to treat the uninvolved supraclavicular nodes. Uninvolved level II to IV nodes were included in the initial treatment volume in all patients and uninvolved level I nodes were also included in oral cavity cancers to ensure microscopic coverage. For involved node coverage nodal targets were taken according to standard protocol.In both the groups Inj. Cisplatin 30mg/m^2 IV weekly (Ceiling dose 50 mg) started at the time of radiation till the radiation completed. During the entire course of treatment, the patients were under close monitoring and supportive care. Maintenance of adequate intake and nutrition, oral dental hygiene and hydration was taken care of. Radiation reactions were monitored. Radiation reaction were graded according to the RTOG grading system. Acute mucosal reactions were managed with daily cleaning with plain water ,acetyl salicylate gargles and xylocaine viscous for local relief. Nasogastic feeding was done in patients with severe odynophagia. Fluoride paste was advised to prevent dental caries. Oral analgesics, antibiotics and antifungals were prescribed wherever indicated. The patients were assessed every week for acute reactions. During the treatment frequent conversation were carried out and constant moral support was given. For end result reporting the response was assessed as Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD) [WHO criteria] at 4 weeks of completion of treatment. Monthly follow up visits by local examination, and if needed post chemoradiation CT scan imaging, hematological investigations at 2, 3, 6 and 9 months was carried out. The two groups were compared using the chi square test to check whether they were statistically comparable in terms of outcome and toxicity profile.

III. Results

Both the groups were statistically comparable. The age of the patients was ranged from 30-70 years, 43% were in age group of 30-49 yrs while 57% in 50-70 yrs. In our study group we had 13 females and 87 males. Cancer of the oral cavity was the primary site in 38% of the patients, cancer of oropharynx and larynx constituted 32% and 26% respectively. Majority of the patients i.e. 56% in group A and 48% in group B were moderately differentiated while grade I and III/UD constituted 40% and 8% respectively. Stage III disease was present in 46% and 44% of patients and stage IV disease was present in 54% and 56% of patients in group A and group B respectively.

Both local tumor and lymph nodal response was assessed at four weeks of completion of treatment. A statistically not significant complete local and nodal response was observed in 61.36 % patients in group A as compared to 54.34 % in group B. On assessing the nodal response it was observed that 63.63% of patients in group A and 60.86% of patients in group B had a complete clinical regression of involved lymph nodes (p=0.78). In two patients in group A and two patients in group B, there was no change in the size of involved lymph nodes. Two patient in group A and one patient in group B had clinical progression of disease at local site, while one patient in group A and 3 patients in group B had nodal progression of disease.

Weekly monitoring of radiation reactions was done, during the course of RT most patients had grade 1 and 2 acute toxicity. The maximum grade of reactions during the treatment was recorded. The most common sites of grade 3 or worse acute side effects were the pharynx and the mucous membrane which were statistically close to significant. Grade 2 dysphagia occurred in 54.54 % and 39.13 % in group A and B respectively and grade 3 dysphagia 27.27% and 10.86% in group A and B respectively.In group A 23 patients and 12 patients in group B required Ryle's tube feeding. Grade 3 mucositis was present in 59.09% and 39.13% patients in group A and B respectively. In group A 29.54% patients and 13.04% patients in group B had grade 4 mucositis. Grade 3 skin reactions was more in group A i.e 27.27% and in group B it was 6.52% while 3 patients in group A and 1 patient in group B had grade 4 skin toxicity . Grade 1 heamatologic toxicity was 27.2% and 19.5% in group A and B respectively. Six patients each in both the groups had grade 2 while one patient in group A had grade 3 heamatological toxicity which was statistically not significant. Radiotherapy was suspended in eight patients in group A and four patients in group B due to severe acute reactions. However all the patients completed the planned treatment.

Grade 2 mucositis was seen in 11.30% and 8.6% of patients in group A and group B respectively while 1 patient had grade 3 toxicity in group B. Grade 2 xerostomia was seen in 11.3% and 10.86% of patients in group A and group B respectively. 1 patient in group A and 2 patients in group B had grade 2 skin toxicity. Grade 1 subcutaneous tissue late side effect was seen in 15.9% and 13.04% patients of group A and B respectively. Grade 2 was present in 4.54% and 6.52% of patients in group A and group B respectively. While 1 patient in both the groups had grade 3 toxicity. None of them had spinal cord late side effects. Late effects in both the groups were statistically comparable. Median radiation days of treatment received in group A was 42 days while in group B it was 49 days. The mean gap during treatment in group A was 3.12 ± 4.74 days while in group B it was 2.57 ± 4.48 days. The median follow up in group A was 6 month while in group B it was 4.5 months.

IV. Figures And Tables

Table 1. Patient's characteristics

CHARACTER	TOTAL		GROUP A		GROUP B	
	NO.	%	NO.	%	NO.	%
AGE (YRS)						
30-49	43	43	21	42	2O	40
50-70	57	57	29	58	30	60
SEX						
FEMALE	13	13	6	12	7	14
MALE	87	87	44	88	43	86
SITE						
OC	38	38	20	40	18	36
OP	32	32	16	32	16	32
L	26	26	12	24	14	28
HP	4	4	2	4	2	4
GRADE						
I	40	40	17	34	23	46
II	52	52	28	56	24	48
III/UD	8	8	5	10	3	6
AJC STAGE						
III	45	45	23	46	22	44
IV	55	55	27	54	28	56

Table 2. Response after radiation therapy in both treatment groups.

RESPONSE	GROUP A[44]		GROUP B [46]		P value
	NO.	%	NO.	%	
OVERALL COMPLETE RESPONSE	27	61.36	25	54.34	P=0.51
PRIMARY CR	30	68.18	26	56.52	P=0.25
PR	12	27.27	18	39.13	
SD	0	0	1	2.1	
PD	2	4.54	1	2.1	
NODAL CR	28	63.63	28	60.86	P=0.78
PR	13	29.54	13	28.26	
SD	2	4.54	2	4.34	
PD	1	2.27	3	6.52	

Table 3. Acute adverse effects reported within 90 days after start of radiotherapy in both treatment groups.

ORGAN/TISSUE	GRADE	GROUP A		GROUP B		P VALUE
		NO.	%	NO.	%	
PHARYNX(DYSPHAGIA)	2	24	54.54	18	39.13	P =0.048
	3	12	27.27	5	10.86	
MUCOUS MEMBRANE (MUCOSITIS)	3	26	59.09	18	39.13	P=0.047
	4	13	29.54	6	13.04	
SALIVARY GLAND (XEROSTOMIA)	1	22	50	23	50	P =0.86
	2	14	31.81	12	26.08	
SKIN	3	12	27.27	3	6.52	P =0.046
	4	3	6.81	1	2.17	
HAEMATOLOGIC	1	12	27.2	9	19.5	
	2	6	13.63	6	13.04	P=0.85
	3	1	2.2	0	0	

Table 4. Late adverse effects of radiation therapy reported after 90 days after start of radiotherapy in both treatment groups.

ORGAN/TISSUE	GRADE	GROUP A		GROUP B		P VALUE
		NO.	%	NO.	%	
MUCOUS MEMBRANE	1	4	9.09	5	10.86	P=0.79
	2	5	11.30	4	8.6	
	3	0	0	1	2.17	
	4	0	0	0	0	
SALIVARY GLAND	1	6	13.63	5	10.86	P=0.97
	2	5	11.30	5	10.86	
	3-4	0	0	0	0	
SKIN	1	10	22.72	9	19.56	P=0.31
	2	1	2.27	2	4.34	
	3-4	0	0	0	0	
SUBCUTANEOUS TISSUE	1	7	15.9	6	13.04	P=0.47
	2	2	4.54	3	6.52	
	3	1	2.27	1	2.17	
	4	0	0	0	0	
SPINAL CORD	1-4	0	0	0	0	

V. Discussion

Concurrent chemoradiation with standard fractionated radiotherapy is considered the treatment of choice in locally advanced head and neck cancer. The evidence of this was derived from a number of large randomized control trials and metaanalysis which has not only shown a superiority in terms of improved local control along with organ preservation but has also shown a benefit in the overall survival in these patients. On the other hand, various fractionation schedules have been intensely explored in the treatment of head and neck cancers. In the landmark phase III trial by the Radiation Therapy Oncology Group (RTOG) 9003, a head to head comparison of accelerated fractionation with hyperfractionation in the four arm study clearly demonstrated a superiority of altered fractionation in terms of local control without affecting the late toxicity[5]. In a study by Ghoshal et al patients treated with concomitant boost had a better loco regional control rates 73.6% vs. 54.5% (p-0.0006) than with conventional fractionation. Grade 3 mucositis was seen in 35% patients in the concomitant boost arm whereas in the conventional arm only 19% had grade 3 mucositis (p-0.01) [8]. Thus both concurrent chemo radiation and altered fractionation regimens have individually shown an increase in the acute toxicity as compared to standard conventional fractionated radiotherapy alone [9,10,11]. Radical radiotherapy with

concurrent chemotherapy is contemporary standard of care in the non-surgical management of these loco-regionally advanced cancers ,based on large randomized controlled trials utilizing high-dose cisplatin regimen (80-100mg/m^2) cycled every three-weekly during definitive radiotherapy [9,10]. Although efficacious, this is associated with high acute morbidity necessitating intensive supportive care with attendant resource implications.

Thus keeping in mind the anticipated toxicity of concurrent chemotherapy with altered fractionation, we used Cisplatin to a dose of 30mg/m^2 weekly instead of the recommended dose of 100 mg/m^2 every three weeks. But despite that a significant increase in toxicity was observed in patients receiving concomitant boost with concurrent radiotherapy as a result an increased treatment interruption was observed in this group. However, all patients completed the planned treatment. In a study by Shaleen et al. 95 patients were treated with concomitant boost radiotherapy with concurrent cisplatin 35 mg/m^2 given weekly. A total dose of 70Gy in 38 fractions was delivered over 6 weeks with concomitant boost in the last fraction. Acute grade III/IV mucosal toxicity was seen in 79% of patients. Nasogastric tube placements were required in 26% (25/95) for an average duration of 19.3 days. Mortality during and within 30 days of treatment was seen in 14% [12]. In our study the total dose of radiation and chemotherapy were equivalent to Shaleen et al. The most significantly closed toxicities in our study were grade 2-3 dysphagia, 3-4 mucositis and dermatitis. The reported grade 2 and 3 dysphagia was observed in 54.54% and 27.27% patients in Group A respectively (p=0.048)while grade 3 and 4 mucositis was seen in 59.09% and 29.54% of patients respectively (p=0.048). Grade 3 and 4 dermatitis was seen in 27.27% and 6.81 % of patients respectively (p=0.046). This incidence is about the same as other reported studies with similar schedule [12,13]. Twenty three patients required Ryle's tube feeding in the concomitant boost group as compared to 12 in the conventional radiation group. Grade 2 xerostomia was seen in 31.81% and 26.08% of patients in group A and B respectively (p=0.86). The haematological toxicity of the chemotherapy was very low, with an excellent tolerance by the patient. Most of the patients completed the study treatment. This fact can be explained because the maximum mucosal toxicity was observed when the irradiation was already finished (between the fifth and sixth week). RT was suspended in eight patients with concomitant boost with mean gap of 3.12 ± 4.74 days while in conventional group 4 patients with mean gap of 2.57 ± 4.48 days itself showing the enhanced acute toxicities in group A also better compliance among concomitant boost patients were seen (median, 42 days). However, there were no treatment related deaths. Late toxicities were found to be insignificant in both the groups.

A non significant increase in complete clinical response (defined as a complete local and nodal response) was observed in patients who received concomitant boost with concurrent radiotherapy 61.36% vs 54.34 (p=0.51), which was seen lower than those reported for other concurrent chemoradiotherapy protocols in advanced head and neck malignancies[8,13,14]. A non significant Complete primary response was observed with concomitant boost group 68.18% vs 56.52% (p=0.25) while complete nodal response was found to be 63.63% vs 60.86% (p=0.78) .

VI. Conclusion

In the present study undertaken most patients received both radiation and chemotherapy according to protocol. As compared to conventional group the result of concomitant boost group were quite encouraging, we achieved overall complete response of 54.34% vs 61.36% respectively. The treatment outcome in terms of locoregional control was better in group A which was not statistically significantly due to smaller sample size. Results have showed an increased toxicity in the group A where patients received concomitant boost with chemoradiation. Concluding the above observations this approach is feasible provided that patients are carefully selected and supportive care is introduced in a timely fashion. Considering the manageable toxicity and the satisfactory tumor control obtained, this regimen represents a good choice when considering implementation of an altered RT fractionation ie concomitant boost schedule as standard treatment for head-and-neck cancers. As in the present study the follow up was limited to the maximum period of 9 months and minimum period of 3 months (median 6 months), Firm and final comments on concomitant boost radiotherapy for survival benefit needs further clinical trial on large scale with a prolonged period of follow up. The optimal integration of chemotherapy with concomitant boost radiotherapy is not yet defined, and the results obtained in the present study support to carry out a randomised study which compares this type of schedule with more aggressive treatments.

References

[1]. Jemal A, Bray F, Center MM et al,Global cancer statistics,*CA Cancer J Clin 2011; 61(2):69-90.*

[2]. Cummings B, keane T, pintilie M et al. Five year results of a randomized trial comparing hyperfractionated to conventional radiotherapy over four weeks in locally advanced head and neck cancer, *radiother oncol,2007;85:7-16.*

[3]. Wither, H.R., L.J. Peters and J.M.G. Taylor.1995. Dose response relationship for radiation therapy of subclinical disease, *Int. J. Radiat Oncol. Biol. Phys., 31: 353-359.*

[4]. Peters, L.J., H. Goepfert, K.K. Ang, et al. Evaluation of the dose of post operative radiation therapy of Head and Neck cancer, First report of prospective concomitant boost with concurrent radiotherapy randomized trial, *Int. J. Radiat Oncol Biol. Phys., 26: 3-11.*

[5]. Fu, K.K., T.F. Pajak, A. Trotti, et al. Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003,*Int. J. Radiat Oncol. Biol. Phys., 48: 7-16.*

[6]. Marcu L, van Doorn T, Olver I: Cisplatin and radiotherapy in thetreatment of locally advanced head and neck cancer, *Acta Oncol 2003, 42(4):315-325.*

[7]. Pignon, J.P., A. le Maitre, E. Maillard et al. 2009. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomized trials and 17,346 patients, *Radiother Oncol., 92: 4-14.*

[8]. Ghoshal S., J.S. Goda, I. Mallik, et al. 2008. Concomitant boost radiotherapy compared to conventional radiotherapy in squamous cell carcinoma of the Head and Neck-a phase III trial from a single institution in India, *Clin Oncol., 20: 212-220.*

[9]. Pignon JP, Bourhis J, Domenge C et al. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data, *Lancet 2000, 355:949-955.*

[10]. Pignon JP, Ie Maitre A, Bourhis J, MACH-NC Collaborative Group: Meta-analyses of Chemotherapy in Head and Neck Cancer (MACH-NC), *Int J Radiat Oncol Biol Phys 2007, 69(2 suppl):S112-114.*

[11]. Wolden SL, Zelefsky MJ, Kraus DH et al. Accelerated concomitant boost radiotherapy and chemotherapy for advanced nasopharyngeal carcinoma, *Clin Oncol 2001 Feb 15;19 (4):1105-10.*

[12]. Kumar S, Pandey M, Lal P et al. Concomitant boost radiotherapy with concurrent weekly cisplatin in advanced head and neck cancers: a phase II trial, *Radiother Oncol 2005, 75:186-192.*

[13]. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves loco-regional control in advanced head and neck cancers treated with hyperfractionated radiotherapy, *J Clin Oncol 2004, 22:4665-4673.*

[14]. Medina JA, Rueda A, de Pasos AS et al. A phase II study of concomitant boost radiation plus concurrent weekly cisplatin for locally advanced unresectable head and neck carcinomas, *Radiother Oncol 2006, 79:34-38.*