ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
Index Copernicus Value: 49. 23
PubMed - National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 3, Issue – 6, November - 2018, Page No. : 189 - 194

A Comparison between Five versus Six Fractions per Week of Conventional Radiotherapy in Locally Advanced Head and Neck Cancers

Narendra Kumar Gupta[1] , H. S. Kumar[2] , Neeti Sharma[3], Neha Rawat[4], Rahul Kumar Rai[5] , Rajesh Sinwer[6]

[1,4,5] III-year PG Residents, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner

[2] Senior Professor and Head, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner

[3] Professor, Department of Radiotherapy, Acharya Tulsi Regional cancer Treatment and Reasearch Institute, S.P. Medical College, Bikaner

[6]Senior Resident, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner

Corresponding Author: Rahul Kumar Rai**,** III-year PG Residents, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner

Type of Publication: Original Research Paper

Conflicts of Interest: Nil

Abstract

Background: One of the important prognostic factor for locally advanced head and neck cancer (LAHNC) patients treated with radiotherapy is overall treatment time, a lesser overall treatment time is associated with better prognosis, if total dose is not compromised. In this study we are trying to compare toxicities of overall treatment duration reduction without affecting total dose.

Methods: This is a prospective randomized controlled study performed at Regional Cancer Centre (RCC) Bikaner, Rajasthan, in which total 50 cases LAHNC with no prior treatment were included. These cases were randomly divided into two arms: in Arm A received 2 Gray (Gy) / # (fraction) for 5 days in a week for a total of 33#, while cases in Arm B received 2 Gy / # for 6 days in week for 33#.Cases were followed at 1, 3 and 6 months after completion of treatment.

Results: Median overall treatment time in Arm A was 46 days and for Arm B was 39 days. Overall 6 months loco-regional control rates were 72% with loco regional control in both arms being equal (72%) (p value = .254). There were no significant differences observed in two arms in terms of primary, nodal or distant disease control. Primary control rates were 84 % and 68 % (p value = .061), Nodal control rates were 76 % and 88 % (p value = .858), while distant control rates were 100% and 96% (p value = .245) respectively in Arm A and B. Acute toxicities were significantly more common in Arm B (6 fraction / week arm) with p value = .002.

Conclusion: Reduction in overall treatment time resulted in similar disease control but increased acute toxicities.

Introduction

The incidence of squamous cell carcinoma of the head and neck (HNSCC) is increasing, and it is now the fourth most

common malignant disease in the world, with more than 70% of cases occurring in the developing world[1]. Over 200,000 new cases of head and neck cancers are registered every year in India.

HNSCC is a loco regional disease confined to the primary tumour and the regional lymph nodes; distant metastases are rarely seen at the time of diagnosis. Radiotherapy and surgery are thus the treatments of choice, with radiotherapy being the favoured treatment if organ conservation is required[2]. One of the most important biological factors related to the outcome of radiotherapy in squamous cell carcinoma is the proliferation of tumour stem cells during treatment[3]. A prolonged overall treatment time might reduce the chance of tumour control[4–6] and a substantial number of clinical reports show a reduction in overall treatment time might improve tumour control[7–9]. A shorter treatment time can be obtained by applying a higher dose per fraction, but this will result in a disproportionate increase in the incidence of late complications[10, 11].

The purpose of this study is to evaluate effectiveness of accelerated fractionation of radiotherapy for patients with HNSCC, in terms of local control (LC), progression free survival (PFS) and acute toxicities.

Materials and Methods

This study is a prospective randomized control trial performed in a RCC located in Bikaner, Rajasthan. A total of 50 patients of LAHNC (stage III and IVa) with squamous cell histology and no prior treatment history with an ECOG score [12] 0 – 2 were included. Cases with age ≤70 years with baseline organ functions (normal CBC, LFT, RFT, Blood Sugar) were then randomized into two arms: Arm A (Control Arm with conventional regime) and Arm B (Study Arm with Accelerated regime). Arm A patients received 2 Gy/#, 1#/day, 5 days a week (Monday to Friday) for a total dose of 66 Gy in 33# (completed in 46 days), while in Arm B patients received 2 Gy/#, 1#/day, 6 days a week (Monday to Saturday) for a total dose of 66 Gy in 33# (completed in 39 days).

Table [1]: Patient characteristics in both Arms

Patients Characteristics	Arm A	Arm B
Age:		
≤ 50 years	07	07
> 50 years	18	18
Sex:		
Male	22	21
Female	03	04
Primary Site:		
Larynx	04	06
Oropharynx	13	10
Hypopharynx	06	05
Oral Cavity	02	04
Group Stage:		
III	14	15
IV a	11	10
T stage:		
T_1, T_2	03	02
T_3	21	23
T_4	01	00
Nodal Status:		
Node Negative	08	08
Node Positive	17	17

Treatment

Patients were treated by External Beam Radiotherapy (EBRT) on Co^{60} ((Theratron -780c / Bhabhatron) units, with standard fields, including the primary tumour and lymph nodes. Spinal cord sparring was done after 44 Gy of EBRT.

In both Arms patients received a total of 66 Gy in 33#. A daily fraction of 2 Gy is given in both arms. All patients received treatment from Monday to Friday, patient in Arm B additionally received sixth # on Saturday.

Patients were followed for loco regional control and distant failure and acute toxicities. Definitions of response were adapted from RECIST criteria [13]. Local control, distant control, DFS, follow ups were calculated from beginning of treatment.

Statistical Analysis

For Statistical analysis IBM SPSS Statistics 25 software is used. Data's 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

All patients were followed up for 6 months after completion of treatment. In total out of 50 patients 43 (86%) were able to complete their treatment. Out of 7 patients who were unable to complete treatment 4 were expired (8% of total cases) and 3 lost from the treatment.

Table 2: - Pattern of Control

Pattern of Control	Arm A	Arm B	p Value
Local Control (LC)	84%	68%	.061
Regional Control	76%	88%	.858
Distant Control	100%	96%	.245

Six months LC rates in Arm A and Arm B were: 84% and 68% with p value of .061, while regional control rates were: 76% and 88% (p value .858) in Arm A and B respectively. Overall progression free survival (PFS) of the study was 68%, PFS in Arm A and B was: 72% and 64% (p value .084) respectively.

Table 3: - Toxicities

Toxicity	Arm A	Arm B	p Value
Gd III, IV Toxicities	32%	52%	.002

The rates of acute toxicities in Arm A and B were: 32% and 52% with a significant p value of .002. In both arms equal patients were suffered from grade I and II toxicities (15 in each arm) and most were recovered without any intervention. Rates of grade III and IV toxicities were: 32% in Arm A and 52% in Arm B with p value of .002, with mucositis being the most common complication. These toxicities were treated with hospitalization and proper antibiotic and other measures.

Pattern of Failure

Table 4: - Pattern of Failure

Type of Failure	Arm A (No. of Patients)					Arm B (No. of Patients)				
	T Stage			N Stage		T Stage			N Stage	
	T_1,T_2	T_3	T_4	N_0	N_+	T_1,T_2	T_3	T_4	N_0	N_+
Local Failure	0	3	1	1	3	1	7	0	2	6
Regional Failure	1	4	1	2	4	0	3	0	0	3
Distant Failure	0	0	0	0	0	0	1	0	0	1

Overall treatment failure rate in Arm A was 16%, 24% for local and regional sites. No distant failure is seen in Arm A. For Arm B failure rate was 32%, 12%, 4% for local, regional and distant sites.

Patients with local failure had T_3, T_4 disease at the time of treatment initiation in both Arms, while in case of regional failure patients had node positive as well as T_3, T_4 disease at beginning of treatment in each arm. The only patient which had treatment failure at distant site had T_3 and node positive disease at the start of treatment (Arm B).

Discussion

Squamous cell carcinoma of head and neck is predominantly a loco regional disease, and the primary treatment methods are surgery and radiotherapy [14]. Head and neck cancer can be cured by radiation, but tumours might be heterogeneous for intrinsic cellular radio sensitivity. This heterogeneity results in variation in the total dose needed to control the tumour, the presence of tumour hypoxia with the consequential hypoxic radio resistance, and tumour cell proliferation during treatment.

Dische et al[15] compared randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer and concluded that Similar local tumour control was achieved by CHART as compared with conventional radiotherapy despite the reduction in total dose from 66 to 54 Gy supporting the importance of repopulation as a cause of radiation failure though acute radiation mucositis was more severe with CHART, occurred earlier but settled sooner and was in nearly all cases healed by 8 weeks in both arms.

Dobrowsky et al[16] compared Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Their results have suggested that main toxicity resulted from accelerated fractionation is confluent mucositis (Grade 3-4 in 95%) requiring nasogastral tube feeding, analgesics and antibiotics in the majority of cases. Haematological toxicity Grade 3-4 was seen after MMC administration in 18%. MMC administration did not influence mucosal reaction. Overall duration of mucositis was not different in the three treatment groups. Loco-regional tumour control was 31% after CF, 32% after V-CHART and 48% after V-CHART+MMC, respectively (P<0.05). Overall crude survival was 24% after CF, 31% following V-CHART and 41% after V-CHART+MMC, respectively (P<0.05). Median follow up was 48 months (assessment performed in February 1999).

Sklodowsky et al[17] done Continuous accelerated 7-days-a-week radiotherapy for head-and-neck cancer: long-term results of phase III clinical trial their results suggested that Five-year local tumour control was 75% in the CAIR group and 33% in the control arm ($p < 0.00004$). Tumour-cure benefit corresponded with significant improvement in disease-free survival and overall survival rates. Confluent mucositis was the main acute toxicity, with the incidence significantly higher in CAIR patients than in control (respectively, 94% vs. 53%). When 2.0-Gy fractions were used, radiation necrosis developed in 5 patients (22%) in the CAIR group as a consequential late effect (CLE), but when fraction size was reduced to 1.8 Gy no more CLE occurred. Actuarial 5-year morbidity-free survival rate was similar for both treatments.

In trials in which shorter treatment times were applied, but the total dose was not reduced, (Dische et al and Dobrowsky et al) a better or equivalent tumour response in the accelerated fractionation group was found. Accelerated regimens, however, increase the treatment related acute morbidity, and if this effect becomes too severe it could also raise the frequency of late radiation effects. In trails in which the acceleration was more prominent (Sklodowsky et al) late morbidity became unacceptable if the total dose was not reduced.

Thus, the window of opportunity for the benefit of acceleration is narrow, so in our study we try to compare conventional radiotherapy and accelerated radiotherapy with 1 week reduction in total treatment time as this duration seems to provide optimum balance between improved tumour control and avoidance of excess late morbidity.

Conclusion

In the management of LAHNC with EBRT tumour repopulation is one of the important prognostic factor, that's why completion of treatment in shortest possible time is required. In our study the results are suggestive

that shortening of overall treatment time in LAHNC has produced equally significant results in terms of local and regional control though rates of toxicities were higher. These results in comparison to DHANCA 6 and 7[18] were failed to prove benefits of shortening of overall treatment time, short follow up period of this study could be the reason for it. Still the results of this study has allowed to use short treatment time in LAHNC, which could be beneficial for Indian scenario as longer treatment time is associated with higher numbers of patients lost from the treatment. Toxicity rates are higher in accelerated treatment but most are manageable.

Informed Consent

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

References

1. Globocan 2002 database. www-dep.iarc.fr/globocan/database.htm (accessed March 15, 2010).
2. Overgaard J, Sand Hansen H, Jørgensen K, et al. Pri mary radiotherapy of larynx and phar ynx carcinoma. An analysis of factors infl uencing local control and survival. Int J Radiat Oncol Phys Biol 1986; 12: 515–21.
3. Withers HR, Taylor JM, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27: 131–46.
4. Baumann M, Krause M, Hill R. Exploring the role of cancer stem cells in radioresistance. Nat Rev Cancer 2008; 8: 545–54.
5. Hansen O, Overgaard J, Sand Hansen H, et al. The importance of overall treatment time for the outcome of radiotherapy of advanced head and neck carcinoma. Dependency on tumour diff erentiation. Radiother Oncol 1997; 43: 47–51.
6. Overgaard J, Vendelbo Johansen L, Hjelm-Hansen M, An dersen AP. Comparison of conventional and split-course radiotherapy as primary treatment in carcinoma of the larynx. Acta Oncol 1988; 27: 147–52.
7. Overgaard J, Hansen HS, Specht L, et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet 2003; 362: 933–40.
8. Fu KK, Pajak TF, Trotti A, 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 2000; 48: 7–16.
9. Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. Lancet 2006; 368: 843–54.
10. Peters LJ, Ang KK, Thames HD. Accelerated fractionation in the radiation treatment of head and neck cancer. A critical comparison of diff erent strategies. Acta Oncol 1988; 27: 185–94.
11. Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches: pioneering new opportunities in head and neck oncology. Eur J Cancer 2003; 39: 560–71.
12. http://ecog-acrin.org/resources/ecog-performance-status
13. https://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf
14. Overgaard J, Sand Hansen H, Jorgensen K, et al. Primary radiotherapy of larynx and pharynx carcinoma: an analysis of factors influencing local control and survival. Int. journal Radiat Oncol Phys Biol 1986; 12: 515-21.

15. Dische S, Saunders M, Barrett A, Harvey A, Gibson D, Parmar M. A randomised multicentre trial of CHART versus conventional radiotherapy in head and neck cancer. Radiotherapy Oncol 1997; 44: 123-36.
16. Dobrowsky W, Naudé J. Continuous hyperfractionated accelerated radiotherapy with/without mitomycin C in head and neck cancers. Radiotherapy Oncol 2000; 57: 119-24.
17. Skladowski K, Maciejewski B, Golen M, Tarnawski R, Slosarek K, et al Continuous accelerated 7-days-a-week radiotherapy for head-and-neck cancer: long-term results of phase III clinical trial. https://www.ncbi.nlm.nih.gov/pubmed/17011446.