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Research Paper

Comparison of Acute Toxicities in Head and Neck cancer treated with 5 days vs 6 days a week Radiotherapy

Authors
Narendra Kumar Gupta[1], H. S. Kumar[2*], Neeti Sharma[3], Shankar Lal Jakhar[4] Rahul Kumar Rai[5], Neha Rawat[6]

[1,5,6]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 Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner

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

*Corresponding Author
H. S. Kumar
Senior Professor and Head, Department of Radiation Oncology, Acharya Tulsi Regional Cancer Treatment and Research Institute, S.P. Medical Collage, Bikaner, India

Abstract

Background: *Squamous-cell carcinoma of the head and neck is predominantly a locoregional disease, and the primary treatment methods are surgery and radiotherapy. A cause of treatment resistance could be radiation induced accelerated proliferation of clonogenic tumour cells. Reduced overall treatment time is expected to counteract the accelerated growth and thereby improve loco-regional control. Such shorter overall treatment time without a dose reduction can be achieved either by applying a higher dose per fraction or by applying more fractions per week. The aim of the study was to compare acute toxicities between the patients treated with 5 day vs 6 day a week radiotherapy.*

Material and Methods: *This was a prospective randomized controlled study performed at Regional Cancer Centre (RCC) Bikaner, Rajasthan, in which total 50 cases of LAHNC with no prior treatment were included. These cases were randomly divided into two arms: in Arm A patients received 2Gy/fraction(#) for 5 days in a week for a total of 33#, while cases in Arm B patients received 2Gy/# for 6 days in a week for 33#. Patients were assessed during treatment, at the end of treatment, 3 and 6 months after completion of treatment for acute toxicities according to the RTOG guidelines.*

Results: *Median overall treatment time in Arm A was 46 days and for Arm B was 39 days. Grade I and II skin reactions were seen in 19 cases of Arm A and 14 cases of Arm B (p value = .998). Grade III skin reactions were significantly high in Arm B patients (11 patients in Arm B vs 6 in Arm A, p value = .034) at treatment completion. Though skin reactions were disappeared at 3 months follow up, patients in Arm B required more time to heal then Arm A. In both arms patients had most commonly grade I, II mucositis (21 patients in Arm A and 16 in Arm B, p value = 0.902). Grade III mucositis was present in 4 patients of Arm A and 9 patients of Arm B (p value = .031) at treatment completion. All patients recovered at 3 months follow up. No grade IV toxicity seen in any of the arm. Local tumor control was significantly higher in Arm B compared to Arm B (p value = 0.03)*

Conclusion: *This study concluded that reduction in overall treatment time resulted in improved local tumor control at the cost of increased acute toxicities.*

Introduction

Cancers of the head and neck arise from the lining membrane of the upper aero-digestive tract. Ninety percent of the head and neck cancers are of squamous cell type[1] and includes the common squamous-cell carcinomas of the oral cavity, pharynx, and larynx, and the less frequent tumors of the nasal cavity, paranasal sinuses, and the salivary glands. One of the major oncological problems in Indian population is head and neck malignancies[2]. The age adjusted incidence for head and neck cancers in Indian male population range from 10.8 to 38.8 per 100000 population and in 6.4-14.9 in 100000 female population[3]. The incidence of HNSCC is on the rise and is now the sixth common malignant disease in the world and eighth common cause of cancer death with nearly 650000 people have head and neck cancer each year with approximately 350000 deaths[4]. Approximately 70%-80% are diagnosed as locally advanced disease, with lymph node involvement in up to 30%-50% of the cases accounting for significant morbidity and mortality[5]. Radiation therapy remains the mainstay of treatment offered nearly 75% of all head and neck cancers with either curative or palliative intent, alone or as a part of multimodality approach in the Indian scenario. The prognosis of patients with locally advanced head and neck cancer (LAHNC) is still poor, 5-year survival rate with conventional radiotherapy is 40-50% [6].

Division of radiotherapy dose into multiple spares normal tissue through repair of SLD (Sub-lethal damage) & repopulation of cells. Concurrently, fractionation increases tumor damage through re-oxygenation & redistribution of tumor cells. Hence a balance is achieved the response of tumor & early & late reacting normal tissue. Most common fractionation for curative radiotherapy is 1.8 to 2.2Gy[7]. It evolved as conventional regimen because it is Convenient (no weekend treatment), Efficient (treatment every weekday), Effective (high doses can be delivered without exceeding either acute or chronic normal tissue tolerance) and logistically it allows upkeep of machines. Rationale for using conventional fractionation is perhaps that it is the most tried and trusted method with well documented tumoricidal and tolerance doses[8].

Hyper fractionation - The delivery of radiation in small-dose fractions (2-3 times per day). It aims to improve the therapeutic ratio by reducing the dose given in each fraction, so as to reduce the late side effects while also permitting an increased total dose to the tumor.

Accelerated fractionation

It is an alternative to hyper fractionation. The rationale is to reduce repopulation in rapidly proliferating tumors by reducing overall treatment time. It can be classified into a) Pure accelerated treatment where the same total dose delivered in half the overall time by giving 2 or more fractions per day ,here acute effects might become a limiting factor. b) Impure accelerated treatment – dose is reduced, or rest period is interposed in the middle of treatment

Hypofractionation

High dose is delivered in 2-3 week. Rationale of hypofractionation is that the treatment completed in a shorter period and logistically the machine time well utilized for busy centers. Radio biologically higher dose gives better control for larger tumors. Higher dose also useful for hypoxic fraction of large tumor but it comes with the potential for increased late normal tissue complications.

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[9]. A prolonged overall treatment time might reduce the chance of tumour control[10-12] and a substantial number of clinical reports show a reduction in overall treatment time might improve tumour control[13-15]. 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[16,17].

The purpose of this study was to evaluate and compare acute toxicities between patients treated

with accelerated fractionation vs conventional fractionation radiotherapy in HNSCC.

Material and Methods

This study was 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 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 regimen) and Arm B (Study Arm with Accelerated regimen). 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). Patients in each arm also received weekly cisplatin (40 mg/m^2).

Patients were assessed during treatment, at the end of treatment, 3 and 6 months after completion of treatment for acute toxicities according to the RTOG guidelines.

Results

Table 1 shows age distribution of patients enrolled in the study. Mean age of patients in Arm A was 55.28±9.96 Years and mean age in Arm B was 56.08±10.38 years. Both groups were comparable.

Table 1 Age distribution of patients enrolled in the study

Age group	Arm A	Arm B
≤50 Yrs	7	7
>50 Yrs	18	18
Total	25	25
Mean age ± SD	55.28±9.96	56.08±10.38

Figure 1 shows sex distribution of patients entitled in the study. 88.00% patients were male, and 12.00% patients were female in Arm A and 84.00% patients were male and 16.00% patients were female in Arm B. Both groups were comparable.

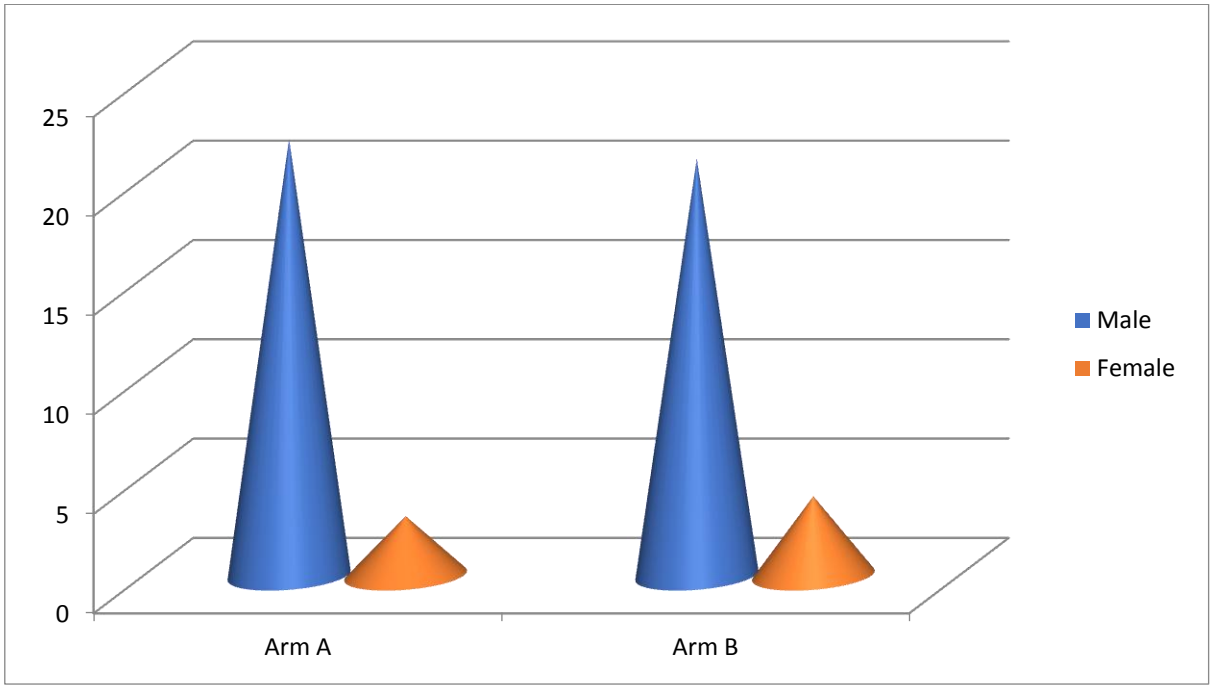

Figure 1 Sex distribution of patients enrolled in the study

Table 2. shows primary site wise distribution of patients in both arms. Fifty two percent patients had oropharyngeal, 24% patients had hypopharyngeal, 16% patients had laryngeal and 8% patients had oral cancers in Arm A. 40% patients had oropharyngeal, 24% patients had laryngeal, 20% patients had hypopharyngeal and 16% patients had oral cancers in Arm B.

Table 2 Primary site wise distribution of patients

Primary site	Arm A	Arm B
Larynx	4(16.00%)	6(24.00%)
Oropharynx	13(52.00%)	10(40.00%)
Hypopharynx	6(24.00%)	5(20.00%)
Oral cavity	2(8.00%)	4(16.00%)
Total	**25(100.00%)**	**25(100.00%)**

Figure 2 shows Smoking history wise distribution of patients in the study. Sixty four percent patients were non-smoker, 28% patients were current smoker and 12% patients were former smoker in Arm A. Twenty percent patients were non-smoker, 76% patients were current smoker and 4% patients were former smoker in Arm B.

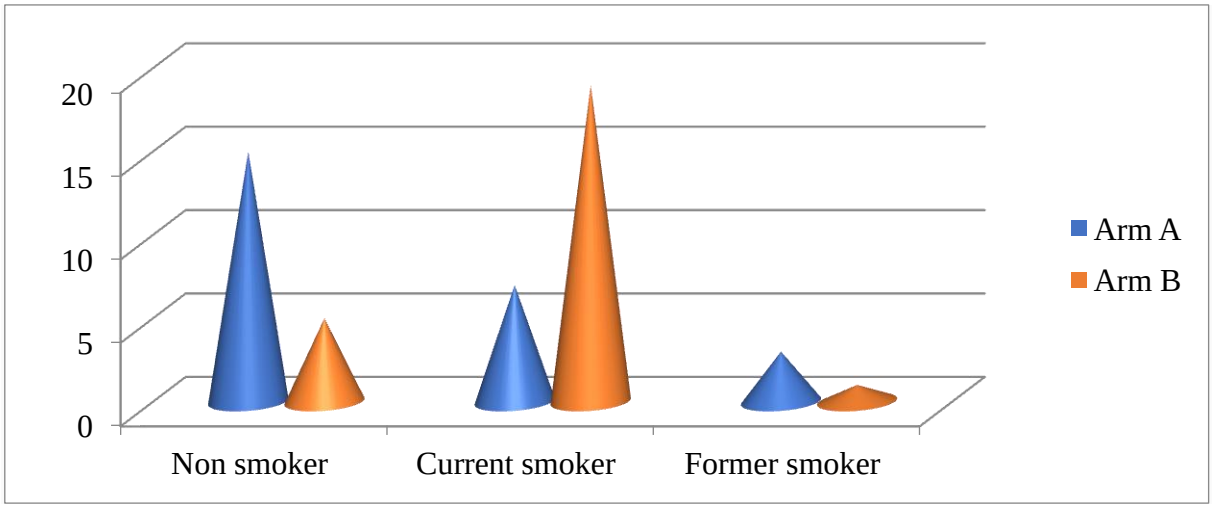

Figure 2 Smoking history wise distribution of patients

Table 3 shows distribution of patients according to the histopathological differentiation of tumor. Seventy two percent patients in arm A and 76.00% patients in arm B had moderately differentiated SCC, 16.00 % patients in arm A and 12.00% patients in arm B had poorly differentiated SCC while 12.00% patients in arm A and arm B had well differentiated SCC respectively.

Table 3 Histopathological Differentiation of tumor

Histopathological Differentiation	Arm A	Arm B
Well differentiation SCC	03(12.00%)	3(12.00%)
Moderate differentiation SCC	18(72.00%)	19(76.00%)
Poor differentiation SCC	4(16.00%)	3(12.00%)
Total	25(100.00%)	25(100.00%)

Table 4 shows group stage wise distribution of patients in the study. Fifty six percent patients had stage III and 44% patients had stage IV a in Arm A. Sixty percent patients had stage III and 40% patients had in stage IV a in Arm B.

Table 4 Group stage wise distribution of patients

Stage	Arm A	Arm B
III	14(56.00%)	15(60.00%)
IV a	11(44.00%)	10(40.00%)
Total	25(100.00%)	25(100.00%)

Table 5 shows grade of acute skin reaction occurred in both arms. Higher grade (grade III) acute skin reactions were more in arm B compared to arm A both at 3rd week of treatment and end of treatment. Grade I and II skin reactions were seen in 19 cases of Arm A and 14 cases of Arm B (p value = .998). Grade III skin reactions were significantly high in Arm B patients (11 patients in Arm B vs 6 in Arm A, p value = .034) at treatment completion. Though skin reactions were disappeared at 3 months follow up, patients in Arm B required more time to heal then Arm A.

Table 5 Incidence of acute skin reactions

Grade – Skin Reaction	Arm A					Arm B				
	0 day	3rd week	End of treatment	3rd month	6th month	0 day	3rd week	End of treatment	3rd month	6th month
0	25	2	0	12	17	25	0	0	0	21
I	0	9	11	8	6	0	8	3	10	04
II	0	11	8	5	1	0	7	11	15	0
III	0	3	6	0	0	0	10	11	0	0
IV	0	0	0	0	0	0	0	0	0	0

Table 6 shows incidence of acute mucositis in both the arms. In both arms patients had most commonly grade I, II mucositis (21 patients in Arm A and 16 in Arm B, p value = .902). Grade III mucositis was present in 4 patients of Arm A and 9 patients of Arm B (p value = .031) at treatment completion. All patients recovered at 3 months follow up. No grade IV toxicity seen in any of the arm.

Table 6 Incidence of acute mucositis

Grade	Arm A					Arm B				
	0 day	3rd week	End of treatment	3rd month	6th month	0 day	3rd week	End of treatment	3rd month	6th month
Mucositis										
0	25	1	0	18	24	25	0	0	17	23
I	0	12	10	6	0	0	12	5	7	2
II	0	10	11	1	0	0	9	11	1	0
III	0	2	4	0	0	0	4	9	0	0
IV	0	0	0	0	0	0	0	0	0	0

In present study complete response for local site at treatment completion and at 1st month was 44 % in Arm A and 80% patients in Arm B. At 3rd and 6th month complete response was 56 % in arm-A and 84 %patients in arm-B (p value at 6 months = .033).

Nodal control was seen in 44% and 32% patients in Arm A and B at treatment completion. at 1 and 3rd month in Arm A 44%, and in Arm B 36% patients were able to achieve nodal CR. At 6-month nodal control was 46% in Arm A and 36% in Arm B (p value at 6 months = 0.855). Nodal CR was seen in 8 out of 17 patients (44%) in Arm A and 7 out of 18 patients (36%) in Arm B.

Only one case of distant metastasis was seen in study population (in Arm B) at 5 months (site = L5 vertebra).

Discussion

Squamous-cell carcinoma of the head and neck is predominantly a locoregional disease, and the primary treatment methods are surgery and radiotherapy[18]. 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[19,20]. A cause of treatment resistance could be radiation induced accelerated proliferation of clonogenic tumour cells [21]. Reduced overall treatment time is expected to counteract the accelerated growth and thereby improve loco-regional control[22]. Such shorter overall treatment time without a dose reduction can be achieved either by applying a higher dose per fraction or by applying more fractions per week[23,24].

DAHANCA 6&7[25] randomised controlled trial which was multicentre, controlled, randomised trial. Between January 1992, and December 1999, of 1485 patients treated with primary radiotherapy alone, 1476 eligible patients were randomly

assigned five (n=726) or six (n=750) fractions per week at the same total dose and fraction number (66–68 Gy in 33–34 fractions to all tumour sites except well-differentiated T1 glottic tumours, which were treated with 62 Gy). All patients, except those with glottic cancers, also received the hypoxic radiosensitiser nimorazole. Analysis was by intention to treat. More than 97% of the patients received the planned total dose. Median overall treatment times were 39 days (six- fraction group) and 46 days (five-fraction group). Overall 5-year locoregional control rates were 70% and 60% for the six- fraction and five-fraction groups, respectively (p=0·0005). The whole benefit of shortening of treatment time was seen for primary tumour control (76 vs 64% for six and five fractions, p=0·0001), but was non-significant for neck-node control. Six compared with five fractions per week improved preservation of the voice among patients with laryngeal cancer (80 vs 68%, p=0·007). Disease-specific survival improved (73 vs 66% for six and five fractions, p=0·01) but not overall survival. Acute morbidity was significantly more frequent with six than with five fractions but was transient. Results were comparable with our study.

In our study we used two fractionation regimens and compared acute toxicities between them. Acute toxicities were the most common complications seen in the study population. Grade III skin reactions were significantly high in Arm B patients (p value = 0.034) at treatment completion. Though skin reactions were disappeared at 3 months follow up, patients in Arm B required more time to heal then Arm A. Grade III mucositis was present in 4 patients of Arm A and 9 patients of Arm B (p value = 0.031) at treatment completion. All patients recovered at 3 months follow up. No grade IV toxicity seen in any of the arm. All toxicities were manageable and good treatment adherence was seen with all patients completing their treatment with no loss of follow up.

We observed that accelerated radiotherapy improves local tumor control but has no effect on nodal control. Accelerated radiotherapy is also associated with increased acute toxicities. Overall disease response was similar in both conventional and accelerated regimes. So, any of the regime can be used in patient depending upon patients general condition and work-load of institute.

To understand the long-term control and toxicities when using accelerated radiotherapy, a longer follow-up and a larger sample size is required. Tumor heterogeneity is another factor which affects outcome of results, so it should also be considered before deciding regimens.

Conclusion

This study concluded that reduction in overall treatment time resulted in improved local tumor control at the cost of increased acute toxicities.

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