Conventional Versus Accelerated Radiation with Concurrent Chemotherapy in Locoregionally Advanced Head and Neck Malignancy

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ABSTRACT

Introduction: The world wide incidence of Head and Neck malignancy exceeds half a million cases annually. In radiotherapy, conventional fractionation comprises of giving five fractions per week from Monday to Friday. Accelerated radiotherapy includes administration of six fractions per week is being advocated. It gives better loco regional control and the median overall treatment time is 39 days as compared to 46 days in conventional group. Our study involved comparison of conventional versus accelerated radiotherapy with concurrent chemotherapy, in evaluation of local control and toxicity in the two arms.

Material and Methods: Sixty patients of locally advanced squamous cell carcinoma head and neck region were studied. All the patients received Cisplatin (30mg/m^2) weekly during the therapy. The patients received radiotherapy dose of 70 Gray (Gy) in 35 fractions (#).

The patients were randomly assorted into two groups:

Group 1- Study Group (n=30) - Six fractions radiotherapy per week (Monday-Saturday).

Group 2- Control Group (n=30) - Five fractions radiotherapy per week (Monday-Friday).

During and after the treatment, locoregional control, acute and late radiation toxicity was assessed.

Result There was no significant difference between the two schedules regarding locoregional control rate. The grade 3 or higher acute toxicities were significantly higher in the accelerated arm although there was no significant difference in late toxicities between the two arms.

Conclusion: Accelerated fractionation regimen was not more efficacious than conventional fractionation in the treatment of previously untreated head and neck carcinoma.

Keywords: Head and neck carcinoma, Radiation therapy, Radiotherapy fractionation schedules, Accelerated radiotherapy.

INTRODUCTION

The world wide incidence of Head and Neck malignancy exceeds half a million cases annually.[1] The number of new cases of Head & Neck cancer in United States was 40,500 in 2006 accounting for about 3% of adult malignancy. Nearly 60% of this population presents with locally advanced disease, but not metastatic disease. In India, the most common Head and Neck cancers are those of Oral cavity & Pharynx. The age adjusted incidence for these sites in the Indian males range from 10.8 – 38.8 per 100000 males, and for females it is 6.4 – 14.9 per 100000 females. Mouth and Pharynx cancers stand as third most common cancer in males, and as fourth most common in females in developing countries. At the Institute Rotary Cancer hospital AIIMS, New Delhi, the Head and Neck cancers represent 25% of all registered new cases. Oral cancer is a major problem in India and accounts for 50-70% of all cancers diagnosed as compared to 2-3% in UK & USA. In Indian subcontinent, Central & Eastern Europe, Spain, Italy, Brazil, and among US blacks, the age standardised incidence rate exceeds 30/100000 related to Head & Neck cancer in males. In some areas like Indian subcontinent, Hong Kong, and Philippines even in females high rates of Head & Neck cancer (>10/100000) are found. Smoking is associated with most but not all Head & Neck cancers. Examples of cancers associated with smoking are Carcinoma Tongue including Base of Tongue, Floor of mouth, Tonsil, Larynx, and Pyriform sinus. On the other hand Carcinoma Parotid is not associated with smoking. There is general tendency of Head & Neck cancers to remain confined to site of origin & regional lymphatics with local invasion and spread to regional lymph nodes. A locally advanced cancer means that the cancer has spread to nearby tissue or lymph nodes but not elsewhere. The three modalities of treatment in Head and Neck malignancy are Surgery, Chemotherapy, and Radiotherapy. Out of these modalities Head & Neck cancers are predominantly treated by Surgery and/or Radiotherapy. However concomitant Chemotherapy and Radiotherapy appear to be the most effective approach for the treatment of Head & Neck cancers. Chemotherapy is the treatment modality for metastatic cervical lymph node with unknown primary, carcinoma Pyriform fosse & Nasopharynx because of their high rate of lymph node metastasis.

In Radiotherapy conventional fractionation (according to current practice in United States), for the curative treatment of most cancers comprises of a fractional dose of 1.8 – 2.0 Gy given once daily, Monday through Friday. Now a new regimen of radiotherapy which includes administration of six fractions per week is being advocated. It has shown better tumour control (76% vs 64% for six & five fractions respectively). In six day radiotherapy there is better loco regional control and the median overall treatment times is 40 days as compared to 47 days in five fraction group which is a major advantage in developing countries like India. Our study in-

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volved comparison of five radiation fractions per week versus six fractions per week with concurrent chemotherapy, in terms of locoregional control, acute and late radiation toxicities in the two arms.

Aims and Objectives: To compare conventional (5DRT) versus accelerated (6DRT) radiation with concurrent chemotherapy in locoregionally advanced head and neck malignancy in terms of locoregional control rate, acute and late radiation toxicities, and overall treatment time.

MATERIAL AND METHODS

The patients included in this study were mainly selected from the out patient department (OPD) cases. All of them belonged to mixed population from rural and urban areas.

Sample size & sample technique – The total number of patient included in this study was sixty (60). Thirty patients were included in *regimen 1 group (Accelerated RT)* and Thirty were included in *regimen 2 group (conventional fractionated RT)***.** These patients were selected randomly by computer. Below mentioned Exclusion Criteria was used for their selection. Sixty patients of locally advanced squamous cell carcinoma head and neck region were studied. Only the patients where external radical radiotherapy was the primary line of management were included for the study. After complete history taking and complete physical examination the patient underwent base line investigations including complete blood counts, renal function and liver function tests. Chest X-ray, X-ray soft tissue neck (lateral view) and X-ray PNS was done as per the requirement. To rule out distant metastasis or to assess the extent of the disease, USG abdomen and CT scan were done as per required. After examination and investigations all patients were staged according to International TNM classification of AJCC 2002. The exclusion criteria included patients previously operated, or treated with radiotherapy or chemotherapy, tumours classified as stage I&II, distant metastasis, and patients having some associated medical condition making them unfit for chemotherapy or radiotherapy. The patients received external beam irradiation on Cobalt-60 Teletherapy machine. All the patients received Cisplatin (30mg/m2) weekly during the therapy. The patients received 70 Gy in 35 fractions with each fraction being 2Gy. The patients were randomly assorted into two groups:

Group 1 (6DRT) - Study Group (n=30) - Six fractions radiotherapy per week (Monday-Saturday).

Group 2 (5DRT) - Control Group (n=30) - Five fractions radiotherapy per week (Monday-Friday).

During and after the treatment, locoregional control, acute and late radiation toxicity was assessed at following intervals-

a. Weekly during the course of radiotherapy
b. Within a week of termination of therapy
c. One month after termination of therapy
d. Three month after termination of therapy.

Acute toxicity was assessed using RTOG scoring and chronic reaction by RTOG-EORTC combined toxicity criteria.

STATISTICAL ANALYSIS

It was done using statistical tool SPSS 11.0. Two-tailed corrected chi-square test and unpaired *t*-test were used. The results were studied on an intention-to-treat basis.

RESULT

Total 60 patients were evaluated (30 in each arm). All the patients completed their treatment according to the protocol. The patient and tumor related details are given in Table 1. There was no significant difference between the two schedules regarding locoregional control rate. The locoregional failure details are given in Table 2. The grade 3 or higher acute and late toxicities were significantly higher in the accelerated arm although there was no significant difference in lower grade toxicities between the two arms. The acute and late radiation toxicities are detailed in Table 3 and Table 4. The median overall treatment time (OTT) in accelerated radiation arm was 40 days (range – 38 – 44 days) and conventional radiation arm was 47 days (range – 45 – 53 days). There was significant difference in OTT between the two arms and this is one the most important advantage with accelerated radiation.

DISCUSSION

Radiotherapy (RT) along with concurrent chemotherapy has long been the standard nonsurgical therapy for locally advanced disease. The state of art regarding radiation dose fractionation has evolved from once daily treatment to hyper fractionation and accelerated fractionation.[1-4] These newer strategies lead to a 7% to 10% improvement in loco regional

Characterstics	5-DRT	6-DRT
Median age (yrs)		
<50	07	10
50-60	16	17
>60	07	03
Primary site		
Oral cavity	04	04
Oropharynx	13	17
Larynx	10	07
Hypopharynx	03	02
Nodal status		
N0	04	06
N1	08	05
N2	17	05
N3	01	04
Tumor status		
T1	08	06
T2	08	09
T3	12	11
T4	2	04
Tumor stage		
Stage III	10	09
Stage IV A	19	15
Stage IV B	1	06

Table-1: Patient and Tumor related details

Failure	5-Day RT	6-Day RT
T Failure	02	00
N Failure	02	03
T + N Failure	02	00
Total	06	03

Table-2: Locoregional Failure Rate in both Arms

Radio dermatitis in 6-DRT						
Grade of Toxicity	1ST WK	2ND WK	3RD WK	4TH WK	5TH WK	6TH WK
Grade 0	26	10	01	00	00	00
Grade 1	04	17	21	12	03	02
Grade 2	00	03	06	16	19	16
Grade 3	00	00	02	02	08	12
Grade 4	00	00	00	00	00	00
Grade 5	00	00	00	00	00	00
Total	30	30	30	30	30	30
Radio dermatitis in 5-DRT						
Grade of Toxicity	1ST WK	2ND WK	3RD WK	4TH WK	5TH WK	6TH WK
Grade 0	30	28	21	07	02	02
Grade 1	00	02	08	21	15	06
Grade 2	00	00	01	02	12	20
Grade 3	00	00	00	00	01	02
Grade 4	00	00	00	00	00	00
Grade 5	00	00	00	00	00	00
Total	30	30	30	30	30	30
Mucosal Toxicity in 6-DRT						
Grade of Toxicity	1ST WK	2ND WK	3RD WK	4TH WK	5TH WK	6TH WK
Grade 0	24	02	00	00	00	00
Grade 1	06	22	10	01	00	00
Grade 2	00	05	15	18	11	04
Grade 3	00	01	04	09	18	19
Grade 4	00	00	01	02	01	07
Grade 5	00	00	00	00	00	00
Total	30	30	30	30	30	30
Mucosal Toxicity in 5-DRT						
Grade of Toxicity	1ST WK	2ND WK	3RD WK	4TH WK	5TH WK	6TH WK
Grade 0	29	28	14	05	00	00
Grade 1	01	01	15	22	11	04
Grade 2	00	01	01	03	17	22
Grade 3	00	00	00	00	02	04
Grade 4	00	00	00	00	00	00
Grade 5	00	00	00	00	00	00
Total	30	30	30	30	30	30

Table-3: Acute Radiation Toxicities in both Arms

Grade	5-DRT (n = 30)	6-DRT (n = 30)
Skin		
0	10	6
1	15	16
2	4	6
3	1	2
Subcutaneous tissue		
0	15	10
1	12	14
2	2	5
3	1	1
Mucous membrane		
0	6	6
1	7	3
2	15	14
3	2	7

Table-4: Later Radiation Toxicities in both Arms

control relative to once daily treatment scheme. Most randomized clinical trials show the superiority of combined radiotherapy and chemotherapy to RT alone for the treatment of locally advanced, nonmetastatic squamous carcinoma of head and neck. The Meta-Analysis of Chemotherapy on Head & Neck Cancer {MACH-NC}involving more than 10,000 participants related to 63 trials conducted prior to 1993, demonstrated that the addition of chemotherapy to RT in both concurrent and adjuvant settings lead to a 12% reduction in the risk of death from Head and Neck Cancer corresponding to an absolute improvement of 4% in 5-year survival.[5] Later on an update of MACH-NC including an additional 24 trials showed that it was concurrent chemotherapy which gave the maximum benefit, resulting in a 19% reduction in the mortality risk, and an overall 8% improvement in 5-year survival as compared to radiation alone (p<.0001).[6] The Radiation Therapy Oncology Group (RTOG) conducted a three-arm trial in carcinoma larynx. The three arms included radiation alone versus radiation and concurrent chemotherapy versus neoadjuvant chemotherapy followed by irradiation. Concurrent therapy resulted in best disease control and significantly better larynx preservation although there was no significant gain in survival.[7] Concurrent therapy also resulted in significant increase of acute mucositis. It is the most significant impediment to timely delivery of concurrent therapy. Because prolongation of total treatment time adversely affects the success of RT in Head and Neck Cancer,[8-10] a major challenge has been the development of treatment schedules that integrate RT and chemotherapy and yet do not excessively increase total treatment time. The Christie Hospital in Great Britain evaluated RT and 100mg/m2 of single agent methotrexate (MTX) given at the commencement of and after 2 weeks of a 3weeks course of treatment.[11] Most of the 313 patients in this protocol received 50-55Gy in 15 or 16 fractions. Mucositis was significantly greater in the patients receiving MTX, but there was no difference in long term toxicity. The addition of MTX increased local control from 50 to 70%(p=.02) and survival from 37 to 47% (p=.07). The greatest benefit was seen in patients with oropharyngeal primaries which constituted one third of study population. Local control rate with RT/MTX was 78% versus 38% with RT alone (.002) in this patient subset. Survival was 25% with RT alone and 50% with RT/MTX (p=.009). Browman *et al* compared RT and continuous infusion 5-FU against RT alone in a placebo- controlled randomised trial sponsored by the National Cancer Institute of Canada.[12] All 175 patients received 66Gy in 2Gy fractions. 5-FU was given in a dose of 1,200mg/m2/day for the first 3 days of the first and third week of irradiation. Confluent mucositis was more frequent in the 5-FU arm than in the placebo arm(32% vs 11%;p=.001) as was weight loss >15% from pre treatment baseline (41% vs 11%;p<.0001). This increased acute toxicity did not prolong the delivery of RT in the RT/5-FU arm relative to the RT/ placebo arm. The multi-institutional French trial, GORTEC 94-01, was performed with patients who had stage 3/4 oropharyngeal carcinoma.[13,14] Radiotherapy was given in both arms via conventional 2Gy, once daily fractions to a total dose of 70Gy. Patients on the combined modality arm also received three cycles of concurrent carbo-

platin (70mg/m2) and continuous infusion 5-FU(600mg/m2/day x 4days). There was significant improvement in 5-year locoregional control (48% vs 25% p=.002), Disease Free Survival (27% vs 15% p=.01) and Overall Survival (23% vs 16%;p=.05) with combined modality treatment. There was also significant increase in acute mucositis (grade>2) (39% vs 72% (p=.05). The DAHANCA trial tested accelerated radiation of 70Gy / 6weeks against conventional radiation of 70Gy / 7weeks with 2 Gy per fraction.[4] Patient's assigned with conventional radiation – 5DRT were given one daily fraction from Monday to Friday. Patient's assigned accelerated radiotherapy – 6DRT were given one fraction daily from Monday to Friday, and the sixth fraction was given on Saturday or Sunday, or as an extra fraction on weekdays at least 6hrs after the first fraction. The percentage of patients receiving the planned total dose was more than 97%. There was significant difference in median overall treatment times {39 days (6DRT) vs 46 days (5DRT)}. The 5- year loco regional control rates were 70% and 60% for the 6DRTand 5DRT groups, respectively (p=0.0005). This benefit of decreased treatment time was mainly observed for primary tumour control (76% vs. 66% for 6DRT and 5DRT respectively, p=0.0001). It was non significant for regional neck node control. 6DRT compared with 5DRT also significantly improved the voice preservation among patients with laryngeal cancer (80% vs 68%, p=0.007). There was significant improvement in Disease specific survival (73% vs 66% for six and five fractions, p= 0.01) but not in overall survival. Acute radiation toxicities were significantly more with accelerated than with conventional radiation, but were transient.

In our study, there was no significant difference in locoregional control of head and neck cancer, between conventional and accelerated fractionation of patients similar to the Toronto randomized trial.[15] There are less consistent results of randomized trials of accelerated fractionation as accelerated treatment is given by different ways.[2,4,16] We adopted the concept of pure acceleration using, six instead of five treatment days in a week because it has shown to significantly increase the locoregional control rate with a trend towards improved disease free survival. In our study there was no significant difference between accelerated fractionation and conventional fractionation, which is similar to previous findings.[17] On the other hand, when Ang *et al*[18] and Johnson *et al*[16] compared accelerated fractionation with conventional fractionation, they concluded significantly better locoregional control and survival rates. The improvement in therapeutic gain with accelerated fractionated radiation was also confirmed by the results of RTOG 9003 trial.[1] The patients which were treated with accelerated fractionation had significantly better locoregional control compared with standard fractionation, although the overall survival was not significantly different. Similar to other studies, in our study also mucous membrane was the most common site of Grade 3 acute reactions.[1,2,17,19] Grade 3 mucosal toxicity was also the most common late side effect. Contrary to this, according to RTOG 9003 trial[1] the pharynx and the salivary gland were the most common sites to have Grade 3 late effects. In our study, Grade 2 and lower acute reactions of skin and mucous membrane of patients in the accelerated fractionation group were not significantly different from those in the conventional fractionation group. Contrary to it, there was significant acute reaction related to mucous membrane in the altered fractionation groups of Horiot *et al*[2] and Johnson *et al.*[16] In our study, both acute and late Grade 3 and high mucosal reactions were significantly more in the accelerated fractionation group as compared to the conventional group. Similarly according to Fu *et al*[1] and Horiot *et al,*[2] the difference in late mucosal reactions between altered fractionation group and conventional fractionation group was also significant. According to Antognoni *et al*,[17] accelerated fractionation as compared to conventional radiation did not produce any significant reaction in normal tissues other than skin and salivary gland which showed slightly more mild complications. There is definite improvement in survival when chemotherapy is added concurrently with irradiation as compared to radiation alone.[20] The severe acute normal tissue reactions are increased when more toxic concurrent radio chemotherapy protocols and altered fractionated schedules are used, and these become the limitation of the before mentioned treatment modalities.[21] With the introduction of more conformal and intensity-modulated radiation techniques, these acute side effects in normal tissues are minimized. Conformal radiotherapy improves target coverage and also minimizes the dose to and volume of adjacent normal tissues.[22] Intensity-modulated radiotherapy delivers higher doses per fraction to the target and lower doses per fraction to normal tissues, thus maximizes total doses in tumors while spares more of normal tissue resulting in increased therapeutic gain.[23]

We used Cobalt-60 machine for irradiation and this may be one of the possible limitations related to our study. The use of new, more sophisticated linear accelerator machines may produce better results. Small sample size and short follow up are also other limitations of our study.

CONCLUSION

In conclusion, there is no significant difference in the therapeutic effects of accelerated fractionation schedule as compared to conventional treatment schedule. However, the use of conformal radiotherapy in previously untreated head and neck squamous cell carcinoma will increase the possibility of better outcome.

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