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A Comparative Evaluation of Accelerated Radiotherapy Versus Concomitant Chemoradiotherapy in Management of Locally Advanced Head and Neck Cancer

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Abstract

Background: The purpose of this study was to prospectively evaluate and compare the outcome of accelerated radiotherapy versus conventional chemoradiation in patients of head and neck cancers.

Methods: The study was conducted on patients with squamous cell carcinoma of head and neck region. The patients were randomly divided into two groups. Patients were treated with radical external beam radiotherapy (EBRT). Group I was given accelerated radiotherapy with dose of 66 Gy/33 fractions/5.3weeks/6 fractions per week and Group II was given conventional radiotherapy with dose of 66 Gy/33 fractions/6.3weeks/ 5 fractions per week along with cisplatin weekly. The response of primary tumor and lymph node were assessed. Acute radiation reactions were assessed on weekly basis. All the patients were re-examined monthly after the completion of treatment and analysed till six months of follow up.

Results: Patients were followed for six months after the completion of treatment. At the end of treatment, grade II & grade III acute skin reactions were seen in 53.3% of the patients in group I and 43.3% of the patients in group II. In group I, 63.3% of the patients experienced severe acute mucosal reactions, in comparison to 46.7% in group II. Overall the complete response was seen in 63.3% (19/30) of the patients in group I and in 73.3% (22/30) of the patients in group II.

Conclusion: The arm with conventional treatment with weekly cisplatin has shown slightly better outcomes in terms of disease control and toxicity profile in comparison to the arm with accelerated radiotherapy.

Keywords: head and neck, cancer, accelerated, conventional, radiotherapy, cisplatin

1. Introduction

Radiotherapy with or without chemotherapy remains the mainstay of treatment of locally advanced head and neck cancers (Mendenhall et al., 2006; Perez et al., 1991). In the past 20 years, many strategies have looked at improving the effectiveness of radiotherapy in advanced squamous cell carcinoma (SCC) of the head and neck region. This is because even the most effective radiotherapy regimen for advanced head and neck cancer results in local control rates of 50% to 70% and disease-free survival of 30% to 40% only. These have included incorporating the use of other treatment modalities such as surgery, chemotherapy and biological modifiers (Overgaard, Horsman, 1996; Peters, Ang, 1992; Withers et al., 1988). Because of high incidence of advanced

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disease at presentation and locoregional recurrences, the management of these patients is very disappointing and remains a challenge (Stupp et al., 1994).

The rationale for accelerated fractionation is that reduction in overall treatment time decreases the opportunity for tumor cell regeneration during treatment and therefore increases the probability of tumor control for a given total dose. The limitation of accelerated hyper-fractionation is acute toxicity (Withers, 1985).

Based on the information and literature available so far; the present work assessed and analysed the differences in tumor control and treatment induced toxicity by accelerated fractionation therapy (six fractions per week) and concomitant chemoradiation with cisplatin in cases of locally advanced head and neck carcinoma (LAHNC).

2. Materials and methods

The study was conducted on sixty previously untreated, histopathologically proven patients of squamous cell carcinoma of head and neck. These patients were randomly divided into two groups, group I and group II. Simple randomization was done by draw of lots.

Pre treatment Evaluation

The pre treatment evaluation in all patients included complete history, general physical examination and complete systemic examination. The assessment of patient's general condition was done using Karnofsky Performance Status (KPS). Haematological assessment was done by a complete hemogram including hemoglobin, total leukocyte count (TLC), differential leukocyte count (DLC), platelet count and peripheral blood film. Biochemical assessment to assess the kidney and liver functions was done by estimation of blood urea, serum creatinine, SGOT and SGPT levels. Radiological assessment including chest X-ray, X-ray soft tissue of neck was done in all patients. Whenever clinically indicated, computed tomography scan of face and neck was done. The patients were staged according to AJCC (American Joint Committee on Cancer) 2010.

Eligibility criteria includes KPS >70, Hb >8gm/dL, TLC >4000/cmm, platelet count > 100,000/cmm, blood urea <40mg/dL, serum creatinine <1.5mg/dL, SGOT <35 IU/L and SGPT <40 IU/L, AJCC stage III/IV and a positive biopsy for squamous cell carcinoma of head and neck.

Exclusion criteria includes distant metastases, prior radiation, surgery or chemotherapy for the disease, KPS<70, pregnant or lactating patient, associated medical conditions such as renal disease, liver disease or heart disease, patients having a primary in thyroid / salivary glands.

Group I

These patients were treated with radical external beam radiotherapy (EBRT). The accelerated treatment is being delivered with dose of 66 Gy/ 33 fractions/5.3weeks/6 fractions per week.

Group II

These patients were given concomitant radiation therapy. Conventional radiotherapy is being delivered with dose of 66 Gy/33 fractions/6.3weeks/ 5 fractions per week along with cisplatin 40 mg/m^2 on weekly basis.

Radiotherapy Technique

All the patients were treated in supine position and radiotherapy was delivered by Cobalt-60. The patients were planned by bilateral parallel opposing fields to face and neck and the dose was prescribed to the mid plane at the central axis. The shrinking field technique was used and the spinal cord was excluded from the radiation field after 44Gy.

EXAMINATION DURING TREATMENT

During the treatment, each patient was evaluated weekly. Primary tumor and lymph node response were assessed as per World Health Organization (WHO) criteria. Acute reactions that were specifically observed, included skin reactions and oral mucosa reactions, and were graded according to the Radiation Therapy Oncology Group (RTOG) criteria whereas nausea, vomiting and hematological parameters (Hemoglobin, TLC, platelets, blood urea, serum creatinine, SGOT/SGPT) were graded according to the WHO criteria. The weight loss was graded according to the SWOG (South West Oncology Group) criteria.

FOLLOW UP

All patients were followed monthly after the completion of treatment and analysed till six months of follow up. The response of tumor (primary and nodal) was assessed based on WHO criteria whereas late skin and mucosal reactions were graded based on RTOG criteria.

STATISTICAL ANALYSIS

The data thus obtained were assessed, analysed and compared to find out the differences in the two groups in terms of tumor response and toxicity using chi- square test.

3. Results

Patient characteristics

Patient characteristics are described in Table 1. Mean age of patients in group I and II was 53.9 years and 52.2 years respectively. Male: female ratio was 13:1 in both the groups. Overall 81.67% patients were from rural areas while 18.33% of the patients belonged to urban background. Overall 90% patients were smokers while 10% patients were non-smokers. Overall, base of tongue was the most common primary site; 46.67 % in Group I and 36.67% in Group II. Stage wise distribution of patients is summarized in Table 2. The baseline investigations were normal and comparable in both the groups.

Treatment

All patients were divided into two groups, group I and group II of 30 patients in each group. Group I was treated with accelerated radiotherapy (66Gy/33 fractions/5.3weeks/6 fractions per week). Group II was given conventional radiotherapy with dose of 66 Gy/33 fractions/6.3weeks/5 fractions per week along with cisplatin 40 mg/m^2 weekly.

Acute skin toxicity

All patients have developed cutaneous radiation reactions by the end of treatment. By the end of first week, 40% versus 20% of the patients in group I and group II respectively developed grade I cutaneous reactions. At the end of treatment, grade II & grade III reactions were seen in 53.3% of the patients in group I and 43.3% of the patients in group II. Though higher in group I but the difference in two groups was not significantly different.

Acute mucosal toxicity

By the end of first week, 20% of the patients in group I versus 13.3% in group II developed grade I mucosal reactions. By the end of third week, all patients developed mucosal reactions, Grade II reactions were seen in 56.7% of the cases in group I compared to 10% in group II. At the end of treatment, in group I, 63.3% of the patients experienced grade II & grade III mucosal reactions, higher than the corresponding figures of 46.7% in group II. Though higher in group I, the difference in two groups was not significantly different.

Tumor response

Overall, complete tumor response in group I and II was 70% versus 76.7% at the last follow up of six months. In T2 subgroup of patients, complete tumor response was observed in 75% (6/8) of patients in group I and 60% (3/5) of group II patients respectively. The observations were not statistically significant. In T3 subgroup of patients, complete tumor response was observed in 77.8% (14/18) of group I and 86.7% (13/15) of group II patients respectively. The observations were statistically not significant. In the T4 sub group of patients, complete tumor response was observed in 25% (1/4) of group I and 70% (7/10) of group II patients respectively. The observations were not statistically significant. Though small, the overall results were in favour of group II.

Nodal response

In N1 subgroup of patients, complete nodal response was observed in 66.7% (8/12) of group I and 91.7% (11/12) of group II patients respectively. In N2 subgroup of patients, complete nodal response was observed in 50% (4/8) of group I and 60% (3/5) of group II patients respectively. Overall, complete nodal response was seen in 60% (12/20) in group I and 82.4% (14/17) in group II patients. The observations were not statistically significant.

Stage wise response

Complete response in stage III was observed in 77.8% (14/18) of the patients in group I and 82.4% (14/17) in group II respectively. In stage IV subset, the corresponding complete responses were 41.7% (5/12) and 61.5% (8/13) respectively. For all stages, the complete response was seen in 63.3% (19/30) in group I and 73.3% (22/30) in group II patients. The observations were not statistically significant. The observations have been depicted in Table 3.

Late Radiation Toxicity

Mucosal reactions were comparable in the two groups. Though not statistically significant (p = 0.182), skin reactions were more in group I. Grade 2 skin reactions were seen in 20% and 13.3% of the patients in group I and II respectively. Grade 2 mucosal reactions were seen in 26.7% and 23.3% of the patients in group I and II respectively. None of the patients experienced grade 3 or 4 late toxicity.

4. Discussion

Meta-analysis of chemotherapy on Head and Neck cancer in 2009, based on 93 randomized trials and 17,346 patients has revealed an absolute survival benefit of 4.5% at 5-years by addition of chemotherapy to radiotherapy (RT+CT) as compared to radiotherapy (RT) alone. Out of the three groups studied (adjuvant, induction and concomitant), the maximum benefit of 6.5% in 5-year survival was observed with concomitant chemotherapy [8].

The concomitant chemoradiation has advantage in terms of local control as well as survival and is the standard of care for locally advanced HNSCC, but this is achieved at the cost of more acute toxicity, necessitating more supportive care, more treatment interruptions.

Accelerated radiotherapy applied to squamous-cell carcinoma of the head and neck yields better locoregional control than does a conventional schedule with identical dose and fractionation. There is evidence indicating that altered fractionation in the form of six fractions per week achieves better results than conventional radiotherapy in advanced head and neck cancer with acceptable toxicity (Overgaard et al., 2003; Wang et al., 2008; Lee et al., 2001; Skladowski et al., 2000; Kumar et al., 1992; Kumar et al., 2010).

Accelerated fractionated radiotherapy is known to produce more severe toxicity in head and neck cancer patients. Similar trend was seen in this study. In a study by Sharma A et al, grade III and IV toxicities were observed in 16% and 40% of the patients in RT and CRT arms, respectively (p= 0.01) (Sharma et al., 2010). In a study by Majumder D et al, grade 3 skin toxicity was observed in 47.36% of the patients on accelerated treatment, but in the concomitant group, they were 30%. Grade 3 mucositis was higher in the six fractions per week arm (63.16%) compared with concomitant arm (35%) but no statistical significance could be drawn. In our study, severe (grade 2 and 3) acute skin toxicity in group I, was seen in 53.3% of the patients and in group II, it was seen in 43.3% of the patients. Grade 2 and 3 mucositis in group I and II were seen in 63.3% and 46.7% of the patients respectively. Similar results were also observed by Majumder D et al (Cooper, Fu, 1995).

In the present study, response rate after six months of follow up was 63.3% in group I and 73.3% in group II. Similar results were also observed by Overgaard J et al and Sharma A et al (Overgaard et al., 2003; Sharma et al., 2010). Overgaard J et al observed that overall 5-year loco regional control rates were 70% and 60% for the six fraction and five-fraction group 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 (Overgaard et al., 2003). Sharma et al reported improved response rates (79.2% vs 69.7%, p < 0.05) and 3-year overall survival (62% vs 42%, p 0.024) for concurrent weekly cisplatin as compared to radical radiotherapy alone. This however, was achieved at the cost of increased grade III-IV toxicities (40% vs 16%, p < 0.05) (Sharma et al., 2010).

5. Conclusion

This may be concluded from the present study that in the management of locally advanced head and neck carcinoma, concomitant radiotherapy group is slightly better compared to accelerated treatment group in terms of disease control and toxicity profile. Though, no statistical

significant values were obtained, results favour the concomitant radiotherapy schedules over the accelerated fractionated radiotherapy group.

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Table 1. Patient characteristics

	Group I	Group II
Age (years)		
31-40	10%	20%
41-50	33.4%	26.7%
51-60	40%	23.3%
61-70	10%	30%
71-80	6.6%	0%
Gender		
Male	86.67%	13.33%
Female	86.67%	13.33%
Smoker	93.33%	86.7%
Non smoker	6.67%	13.3%
Site of tumor		
Oral cavity		
Anterior tongue	6.67%	3.33%
Floor of mouth	-	3.33%
Hard palate	3.33%	3.34%
Retromolar trigone	-	3.33%
Alveolus	-	3.33%
Oropharynx		
Tonsil	16.67%	26.67%
Base of tongue	46.67%	36.67%
Soft palate	-	3.33%
Hypopharynx	13.33%	6.67%
Larynx	13.33%	10%
Histopathology		
WDSCC	13.33%	3.33%
MDSCC	70%	76.67%
SCC,NOS	16.67%	20%
Stage		
III	60%	56.7%
IV	40%	43.3%

Table 2. TNM stage wise distribution at presentation (n=60)

	Group I (n=30) Number of patients (%)				Group II (n=30) Number of patients (%)			
	T1	T2	T3	T4	T1	T2	T3	T4
N0	0	0	9 (30)	2 (6.7)	0	0	8 (26.7)	5 (16.7)
N1	0	6 (20)	3 (10)	2 (6.7)	0	4 (13.3)	6 (20)	2 (6.7)
N2	0	2 (6.7)	6 (20)	0	0	1 (3.3)	1 (3.3)	3 (10)
N3	0	0	0	0	0	0	0	0
Stage III	18 (60)				17 (56.7)			
Stage IV	12 (40)				13 (43.3)			

Table 3. Tumor response (stagewise) at last follow up of six months

	Stage	Total number of patients	Disease status		
			CR	PR	NR
Group I	III	18	14 (77.8%)	02 (11.1%)	02 (11.1%)
	IV	12	05 (41.7%)	03 (25%)	04 (33.3%)
	All stages	30	19 (63.3%)	05 (16.7%)	06 (20%)
Group II	III	17	14 (82.4%)	02 (11.8%)	01 (5.8%)
	IV	13	08 (61.5%)	02 (15.4%)	03 (23.1%)
	All stages	30	22 (73.4%)	04 (13.3%)	04 (13.3%)