IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 4 Ver. 13 (April. 2018), PP 11-14
www.iosrjournals.org

Conventional versus Hyperfractionated Radiotherapy in Locally Advanced Head and Neck Cancer: A Prospective Randomized Study

Arnab Adhikary [1], Praloy Basu[1]
[1](Department of Radiotherapy, Medical College & Hospital Kolkata, India)
Corresponding Author: Arnab Adhikary

Abstract:
Background *- In most patients with advanced head and neck cancer, conventional radiotherapy does not produce locoregional control. Therapeutic ratio may be improved by modifying dose fractionation. The rationale of hyperfractionation is to increase the total dose by using multiple smaller dose fractions without increasing the overall treatment time, that allows to increase the probability of tumour control within the tolerance of late – responding normal tissues.*
Materials and methods - *From June 2016 to December 2016, 80 patients with locally advanced squamous cell carcinoma of the head and neck were randomly assigned in this prospective study into two arms.*
Patients of both arms were treated with 3 cycles of cisplatin and 5-fluorouracil, repeated 3 weekly and randomized to receive either Conventionally Fractionated or Hyperfractionated Radiotherapy.
Response was assessed six weeks after completion of radiotherapy by clinical, endoscopic and radiological evaluation. Acute toxicities were graded according to RTOG criteria.
Results - *The study showed, HFRT had an overall response rate of 82.3% vs 61.5% in CFRT and complete response rate of 53% vs 32.7.7% respectively (p = 0.007).*
Patients treated with HFRT had greater acute side effects.
Conclusion - *Hyperfractionation is more efficacious than conventional fractionation in locally advanced head and neck cancer.*

Date of Submission: 10-04-2018 Date of acceptance: 24-04-2018

I. Introduction

The annual incidence of head and neck cancer worldwide is more than 550,000 cases with around 300,000 deaths each year.[1] Head and neck squamous cell cancer (HNSCC) is the sixth leading cancer by incidence worldwide. Most HNSCCs arise in the epithelial lining of the oral cavity, oropharynx, larynx, and hypopharynx.[2,3] These cancers are strongly associated with certain environmental and lifestyle risk factors such as tobacco and alcohol consumption.

More recently, a new disease has emerged related to several strains of human papillomavirus 16, 18.[4] The prognosis of these patients is substantially better than those associated with tobacco.

About one‐ third of patients present with early‐ stage disease (T1–2, N0) and remaining present with locally advanced stage.

Radiation therapy 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.[5]

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]

One of the important causes of failure is accelerated repopulation of tumour clonogen, which usually starts around the 4th week of radiotherapy.[7] To combat this, 60 cGy of extra dose per day is needed.[7] Hence to increase local control and survival, several strategy of altered fractionation is used.

Another reason to deliver radiation therapy with altered fractionation schedules was designed as a means of maximizing the therapeutic ratio. The use of small multiple daily fractions allows to increase the therapeutic differential between late‐ responding normal tissues and acutely responding tumours with the advantage that the overall treatment time is shortened, thereby limiting the opportunities for proliferation.[7]

The aim of this study was to evaluate whether after preceding induction chemotherapy, hyperfractionated radiotherapy (HFRT) is better than conventional fractionated radiotherapy (CFRT) and to assess the loco-regional response and the toxicity profile.

II. Material And Methods

Study Design: Prospective randomized study

Study Location: This was a tertiary care teaching hospital based study done in Department of Radiotherapy, at Medical College & Hospital, 88 College Street, Kolkata, India.

Study Duration:June 2016 to December 2016.

Sample size:80 patients.

Subjects & selection method:From June 2016 to December 2016, 80 patients with locally advanced biopsy proven squamous cell carcinoma of the head and neck who attended OPD of Radiotherapy, Medical College & Hospitals, Kolkata were randomly assigned in this prospective study into 2 arms, A and B.

Inclusion criteria:

1. Patients of either sex older than18 years.
2. Histologically proved squamous cell carcinoma of the head and neck.
3. Karnofsky performance status (KPS) >60.
4. Locally advanced non metastatic stage III, IV (according to UICC/ AJCC stage classification for head and neck cancer).
5. No evidence of coexistent synchronous or previous malignant disease.
6. No h/o of head and neck radiotherapy, previous chemotherapy or previous surgery except biopsy only.

Exclusion criteria:

1. Patients younger than 18 years.
2. Histological subtypes other than squamous cell carcinoma.
3. Karnofsky performance status (KPS) <60.
4. Non metastatic stage I, II (according to UICC/ AJCC stage classification for head and neck cancer.
5. Presence of metastasis.
6. Evidence of coexistent synchronous or previous malignant disease.
7. H/o of head and neck radiotherapy, previous chemotherapy or surgery.

Procedure methodology

Pre-treatment evaluation included complete history, physical examination, head and neck examination including mirror and panendoscopic examination, histopathologic examination of the primary tumour and/or cervical lymph nodes, complete blood count, liver function tests, and kidney function test ,computed tomography of the head and neck to define the extent of the disease and metastatic workup including chest x-ray and imaging of liver by ultrasound or computed tomography in all patients.

Induction chemotherapy consisting of 3 cycles of cisplatin 100mg/m^2 IV on day 1 and 5-fluorouracil 1000mg/m^2 on days 1 to day 4 by continuous infusion, to be repeated every 3 weeks.

Radiotherapy began within 3 weeks of completion of the last cycle of induction chemotherapy.

Out of 80 patients, only 77 patients completed 3 cycles of induction chemotherapy.

All 77 patients were randomly assigned into two treatment arms :

(1) Arm A (n=38) treated by conventional fractionated radiotherapy (CFRT) to total dose of 66 Gy in 33 fraction.

(2) Arm B (n= 39) treated by hyperfractionated radiotherapy (HFRT) to total dose of 79.2 Gy, 1.2 Gy / fraction, 2 fractions /day with 6- h interval between fractions, 5 days / week. Treatment time for both arms was 6.5 weeks.

The primary tumour and draining lymphatic system were irradiated in most patients by two parallel-opposed lateral fields. In the initial lateral fields: arm A received 45 Gy (2 Gy / fraction / day, 5 days / week), however, arm B received 48 Gy (1.2 Gy / fraction, 2 fractions / day, 5 days / week) after that these initial fields were reduced for spinal cord shielding. Patients were treated by Cobalt-60 teletherapy machine (THERATRON 780C). However, the supraclavicular nodes and nodes in the lower part of the neck were treated with the use of a single anterior field with midline block. Anterior lower neck field doses were prescribed at depth of 3 cm with a total dose of 50 Gy (2 Gy / fraction / day, 5 days/week). The inferior border of the lateral fields and the superior border of anterior lower neck field coincided on the skin.

All patients were instructed to maintain meticulous oral hygiene and change their eating habits. During RT, the patients were assed for acute toxicity weekly according to RTOG criteria.

Mucositis was treated by saline mouth washes, pain management, antimicrobials (antibiotics, and antifungal) and maintaining nutritional intake.

Response was assessed six weeks after completion of radiotherapy by clinical examination, endoscopic examination, and CT and/or MRI of head and neck.

Criteria for response were as follows:

1. Complete response (CR) - Complete regression of all evidence of tumour.
2. Partial response (PR) - Estimated decrease in tumour size of 50% or more.
3. Statble disease (SD) - < 50% decrease in tumour size or < 25% increase in pre-treatment tumour size.
4. Progressive disease (PD) - > 25% increase in pre-treatment tumour size.

Statistical analysis

Data was analyzed using SPSS version 21 (SPSS Inc., Chicago, IL). All significance tests were done usingPearson Chi-Square Tests and statistical significance was accepted for a calculated p-value <0.05.

III. Result

All 80 patients with locally advanced squamous cell carcinoma of the head and neck received induction chemotherapy but 77 patients completed their 3 cycles of chemotherapy. All the baseline profiles in two arms were comparable (p value NS).

In the CFRT arm, 37 patients completed their treatment as one patient died from disease after 2 weeks from beginning of RT. While in HFRT arm, only 37 patients completed their protocol as the remaining 2 patients dropped out during the course of RT.

The overall response rate after induction chemotherapy was 73.6%, including 13.2% complete response rate, 60.4% partial response rate and 26.4% stable disease.

However, the overall response rate 3 weeks after the completion of radiotherapy was 61.5% in arm A versus 82.3% in arm B; whereas 32.7% complete response rate in arm A vs 53% in arm B; 29% partial response rate in arm A vs 30.8% in arm B. However, 25% had stable disease in arm A vs 16% in arm B and 13.1% had progressive disease in arm A and none in arm B.

Tables*:*

Table 1 : Response after radiation therapy in both treatment arms:

RESPONSE	CFRT ARM	CFRT ARM(%)	HFRT ARM	HFRT ARM (%)	P value
Complete response	12	32.7	19	53	0.007
Partial response	11	29	12	30.8	
stable disease	9	25	6	16	
Progressive disease	4	13.3	0	0	

Table 2 : Acute adverse effects of radiation therapy in both treatment arms:

ORGAN	GRADE	CFRT(NO)	CFRT(%)	HFRT(NO)	HFRT(%)	P value
DERMATITIS	1 2 3 4	25 11	67 33	13 20 3 1	35 55 7.8 2.2	0.024
MUCOSITIS	1 2 3	12 19 5	30 52.7 17.3	2 15 18	5.4 40.5 48.6	0.007
XEROSTOMIA	1 2 3	12 24	33.3 66.6	10 24 3	27. 64.8 8.1	0.299
DYSPHAGIA	1 2 3	11 19 6	30.5 52.7 16.8	- 27 10	- 72.9 26.1	0.007
NECK EDEMA	1 2	14 1	38.8 2.7	19 2	48.6 5.4	0.627

IV. Discussion

Locoregional control represents the major end‑ point of any curative radiotherapy. This randomized trial demonstrates a significant Locoregional response rate benefit of a HFRT regimen over a conventional regimen in locally advanced head and neck cancer. These findings had been seen in many large randomized trials that had compared HFRT with CFRT.[8-13]

The RTOG 90‑ 03 altered fractionation randomized trial comparing conventional fractionation to hyperfractionation, split‑ course, and concomitant boost technique demonstrated a significant improvement in disease‑ free survival for the hyperfractionation and concomitant boost arms.[14] These altered fractionation regimens were associated with higher incidence of grade 3 or worse acute mucosal toxicity.

Pinto et al. reported a 10% improvement in locoregional response with HFRT over CFRT.[9].

Our study demonstrated an approximately 20% increase in complete response rate with HFRT which was statistically significant.

At the present time, the major limitation of HFRT or combined radiotherapy and chemotherapy for head and neck is increased acute reaction primarily acute mucositis.[15] In our study, hyperfractionated schedules resulted in increased acute toxicity more than standard fractionation which correlate with RTOG trial.[12]

The most common Grade III acute reactions were mucositis and dysphagia, which was in accordance with other studies.[9,10,12]

Several toxicity antagonists are under active investigation. In the future, some of these agents may decrease the acute and late effects of cancer therapy.

The therapeutic ratio may also be improved by conformal and intensity‐ modulated radiotherapy, which has the capability of the high‐ dose tumour target coverage while minimizing the dose to the volume of the surrounding normal tissues irradiated.

The only notable drawback of our study was the small sample size. Another potential drawback was the lack of long term follow-up data. However in a tertiary care centre in our country, with a number of patients defaulting on follow-up, pure long term data is difficult to obtain.

V. Conclusion

After induction chemotherapy, hyperfractionated radiotherapy is more efficacious than conventional fractionated radiotherapy in locally advanced squamous cell carcinoma of the head and neck, by increasing significantly the loco-regional control.

However, HFRT was associated with significantly increased acute toxicity, but it was tolerable and manageable.

References

[1]. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin2011;61:69‐ 90.
[2]. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin2007;57:43‐ 66.
[3]. Boyle P, Levin B. World Cancer Report 2008. France: International Agency for Research on Cancer; 2008.
[4]. Kreimer A, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: A systematic review. Cancer Epidemiol Biomarkers Prev2005;14:467‐ 75
[5]. Parkin DM, Pisani P, Ferlay J. Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 1999;80:827‐ 41.
[6]. Cummings B, Keane T, Pintilie M, Warde P, Waldron J, Payne D, et al. Five year results of a randomized trial comparing hyperfractionated to conventional radiotherapy over four weeks in locally advanced head and neck cancer. RadiotherOncol2007;85:7‐ 16.
[7]. Hall Eric J, Giaccia Amato J. Time, Dose and Fractionation in Radiotherapy, Radiology For The Radiologists. 6th edition. E. J Hall, Lippincott Williams and Wilkins; 2006. p. 378‐ 397.
[8]. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, Aleksandrovic J, et al. Hyperfractionated radiation therapy with or without concurrent low‐ dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: A prospective randomized trial. J ClinOncol2000;18:1458‐ 64.
[9]. Pinto LH, Canary PC, Araújo CM, Bacelar SC, Souhami L. Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. Int J RadiatOncolBiolPhys1991;21:557‐ 62.
[10]. Horiot JC, Le Fur R, N'Guyen T, Chenal C, Schraub S, Alfonsi S, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. RadiotherOncol1992;25:231‐ 41.
[11]. Cummings B, O'Sullivan B, Keane T, Pintilie M, Liu FF, Mclean M, et al. 5‐ year results of 4 week/twice daily radiation schedule‐ the Toronto trial abstract. The 19th annual meeting of the European Society of Radiation Oncology. Istanbul, Turkey; 2000. [Abstract 22].
[12]. Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL, et al. A 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 RadiatOncolBiolPhys2000;48:7‐ 16.
[13]. Santamaria RG, Inglada AB, Oliveros JG, Pujolet MM, Orpi JN, Nin RM, et al. retrospective study of head and neck cancer on hyperfractionated radiotherapy for head and neck cancer. Rev Oncol2004;6:424‐ 34.
[14]. Trotti A, Fu KK, Pajak TF. Long term outcomes of RTOG 90‐ 03: A comparison of hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinoma. Int J RadiatOncolBiolPhys 2005;63:S70‐ 1.
[15]. Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, Hars V, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. N Engl J Med 1998;338:1798‐ 804.

Arnab Adhikary "Conventional versus Hyperfractionated Radiotherapy in Locally Advanced Head and Neck Cancer: A Prospective Randomized Study."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 4, 2018, pp 11-14.