Medical Journal of the
Islamic Republic of Iran

Volume 18
Number 3
Fall 1383
November 2004

DOES HYPERFRACTIONATED RADIOTHERAPY CHANGE THE OUTCOME OF HEAD AND NECK CANCER? A TRIAL COMPARING CONVENTIONAL WITH HYPERFRACTIONATED RADIOTHERAPY

A. MOSALAEI, M.D., N. AHMADLOO, M.D., S. OMIDVARI, M.D., AND M. MOHAMMADIANPANAH, M.D.

From the Radiation Oncology Department, Shiraz University of Medical Sciences, Shiraz, I.R. Iran.

ABSTRACT

The optimal fractionation schedule for radiotherapy of head and neck cancer has been controversial. The objective of this randomized trial was to test the efficacy of hyperfractionation vs. standard fractionation.

Patients with squamous cell carcinoma of head and neck organs were randomly assigned to receive radiotherapy delivered with A) standard fractionation at 2 Gy/fraction/day, 5 days/week, to 65-70 Gy/7 weeks; B) hyperfractionation at 1.2 Gy/fraction, twice daily, 5 days/week to 75 - 80 Gy/7 weeks. All patients but one completed the treatment. The median follow-up was 24 months for all patients.

Patients treated with hyperfractionation had significantly better local-regional control ($p<0.005$) than those treated with standard fractionation. Although acute morbidity was somewhat higher in the hyperfractionated radiotherapy group, late disturbing effect was much lower in this group.

In conclusion, hyperfractionation is more efficacious than standard fractionation for locally advanced head and neck cancer. Acute but not late effects are also increased.

MJIRI, Vol.18, No.3, 231-235, 2004.

Keywords: Head and neck, Radiotherapy, Fractionation

INTRODUCTION

Carcinomas of the mucous membranes in the head and neck often present with various signs and symptoms depending on the location of the primary site and the stage of cancer at presentation. Radiation oncologists, surgeons, and medical oncologists all are involved in the management of patients with head and neck cancer. The aim would be curing the patient while maintaining as much function of the involved organs as possible. If surgery and radiation therapy can offer similar cure rates, the cosmetic and functional outcome of the different treatment modalities influence the approach chosen. Radiation therapy is usually well tolerated and is a lesser physiologic insult than the alternatives of surgery or chemotherapy. Radiation therapy is also important in the treatment of the patient with head and neck cancer because most head and neck cancers are radiosensitive. [1]

Carcinomas limited to the mucosa have a high cure

Corresponding author: Ahmad Mosalaei, M.D., Radiation Oncology Department, Nemazee Hospital, Shiraz University of Medical Science, Telfax: +98 711 6260135
Email: mosalaa@sums.ac.ir

rate with radiation. Exophytic and well-oxygenated tumors are more radiosensitive than infiltrating and hypoxic ones.

For tumors considered to be unresectable, the treatment has traditionally been conventionally fractionated radiation therapy up to total doses of 60–75 Gy administered in 6–8 weeks and resulting in 2-year survival rates of less than 30%. [2,3]

However, nowadays, the schedules for administering the treatments and even the way the treatments are administered have changed.

Hyperfractionation is a different approach designed to maximize biologic effect and minimize negative adverse effects. This treatment regimen is derived from a better understanding of the cell cycle and the response of tumor cells to radiation therapy.

Based on this response, the department of radiation oncology initiated a prospective trial. The purpose of this study was to test the hypothesis that hyperfractionated radiotherapy will lead to better local control and prolongation of overall survival of patients with head and neck cancer than those who are being treated with conventional radiotherapy.

PATIENTS AND METHODS

One hundred patients with squamous cell carcinoma of the head and neck admitted to the Radiation Oncology Department of Shiraz University of Medical Sciences between March 1996 and February 1998 were chosen.

The median age of 75 male and 25 female patients was 52 years (range 21-80).

All patients had physical examination, panendoscopy and CT scanning of the primary tumor site and the neck, and were staged according to the guidelines of the TNM classification.

Patients had either locoregionally advanced carcinoma of the head and neck organs without distant metastases and were staged unresectable by head and neck surgeons or had refused operation if their tumor had been resectable and advised for operation. Therapy was given with curative intent. Before study entry, patients were evaluated by an interdisciplinary team of head and neck surgeons and radiation oncologists. In all patients, tumor biopsy had been performed and histologically squamous cell carcinoma had been proved. Patients had not received prior chemo-and/or radiation therapy. Performance status was 70 or higher in Karnofsky scale. Baseline laboratory requirements included a WBC count greater than 3,500 cells/mL, with an absolute neutrophil count greater than 1,500 cells/mL, and a platelet count greater than 100,000 cells/mL. Staging procedures included computed tomography (CT) and/or magnetic resonance imaging (MRI) of the head and neck region, ultrasound of the neck, chest X-ray, abdominal ultrasound, and bone scan.

The patients were assigned into two groups. Fifty patients (every other coming patient) were categorized in group A. They got 180-200 cGy radiation once a day and five fractions per week, up to a total radiation dose of 65-70 Gy. This dose was given to all sites of tumor and clinically involved lymph nodes (LN), including the whole regional lymphatic drainage. If the lymph nodes were not involved they received 50 Gy. The other 50 patients, who were balanced with patients in group A as much as possible and as far as location and stage of the disease was concerned, were gathered in group B. These patients got radiation twice daily. The time interval between the two daily fractions had to be 6 hours at minimum. The total dose to the tumor region and LN at risk was 60 Gy and to all sites of clinically proven tumor 75-80 Gy in 7-8 weeks. The total dose to the spinal cord should not exceed 46 Gy in both groups. Radiotherapy was delivered with Co^{60}.

The planning goal was to provide adequate coverage of the primary target and involved LN, while sparing as much volume as possible of the surrounding normal tissues.

RESULTS

Seventy-five men (38 in group A and 37 in group B) and twenty-five women (12 in group A and 13 in group B) were entered into the study. The sites and stage of tumors have been shown in Table I.

T_3 and T_4 lesions were found in about 75% of the patients and 90% of these cases had nodal disease as well. Only 10 cases out of those who had T_1 and T_2 lesions had clinical nodal involvement.

The acute morbidity during radiotherapy included severe (confluent) mucositis in 22%, moderate (spotted) mucositis in 56% and mucosal redness in 22% of group A patients. Meanwhile morbidity in group B patients included 54% confluent mucositis, 30% spotted mucositis and 12% mucosal redness. There was no treatment related mortality in each group (Table II).

Late treatment related morbidity included dental caries in 34%, loss of taste in 64% and xerostomia in 66% of group A patients. These figures for group B patients were 12%, 22% and 34% consecutively (Table III).

The two treatment groups were balanced as much as possible for site and TNM stage. At the time of writing of

Table I. Patients' site and stage of the tumors.

Site	TNM staging	Group 1	Group 2
Nasopharynx	$T_{1-2}N_0M_0$	1	0
	$T_{1-2}N_+M_0$	4	2
	$T_{3-4}N_0M_0$	2	1
	$T_{3-4}N_+M_0$	9	10
Glottic	$T_{1-2}N_0M_0$	3	3
	$T_{1-2}N_+M_0$	1	2
	$T_{3-4}N_0M_0$	1	3
	$T_{3-4}N_+M_0$	7	6
Supraglottic	$T_{1-2}N_0M_0$	2	3
	$T_{1-2}N_+M_0$	0	0
	$T_{3-4}N_0M_0$	1	0
	$T_{3-4}N_+M_0$	6	10
Hypopharynx	$T_{1-2}N_0M_0$	2	0
	$T_{1-2}N_+M_0$	0	0
	$T_{3-4}N_0M_0$	0	0
	$T_{3-4}N_+M_0$	8	9
Anterior 2/3rd of tongue	$T_{1-2}N_0M_0$	1	0
	$T_{1-2}N_+M_0$	0	0
	$T_{3-4}N_0M_0$	0	0
	$T_{3-4}N_+M_0$	0	0
Soft palate	$T_{1-2}N_0M_0$	0	0
	$T_{1-2}N_+M_0$	0	0
	$T_{3-4}N_0M_0$	0	0
	$T_{3-4}N_+M_0$	1	0
Tonsil	$T_{1-2}N_0M_0$		
	$T_{1-2}N_+M_0$	0	1
	$T_{3-4}N_0M_0$	0	0
	$T_{3-4}N_+M_0$	0	0
Nasal cavity	$T_{1-2}N_0M_0$	0	0
	$T_{1-2}N_+M_0$	0	0
	$T_{3-4}N_0M_0$	0	0
	$T_{3-4}N_+M_0$	0	0

this study the median time from the end of radiotherapy to last follow-up was 24 months for all surviving patients. The patients were visited every two months in the first year after treatment, every 4 months in the second year, every six months in the third year and annually thereafter.

Table II. Number (%) of cases with acute morbidity (mucositis).

Acute Morbidity	Mucosal redness	Spotted mucositis	Confluent mucositis
Conventional RT	11 (22%)	28 (56%)	11 (22%)
Hyperfractionated	6 (12%)	15 (30%)	27 (54%)

Physical examinations including indirect laryngoscopy were performed in each visit. Also periodic direct laryngoscopy and CT scan and/or MRI of head and neck disclosed any suspicious finding in the routine work-up.

After two years, 20 patients were alive in group one, out of which 18 cases were disease free and in the second group 31 patients were living while 29 of them were disease-free.

Table III. Number (%) of cases with late morbidity.

Late Morbidity	Dental caries	Loss of taste	Xerostomia	Hearing loss
Conventional RT	17(34%)	32(64%)	33(66%)	-
Hyperfractio-ated	6(12%)	11(22%)	17(34%)	1(2%)

Mean event free survival was 19.1 months (95%CI= 14.7-23.62) in group one and 28 months (95%CI=23.26-32.74) in group two (p=0.0282) and mean overall survival was 22.8 months (95% CI= 19.06-26.63) in group one and 30.7 months (95%CI=26.95-34.48) in group two (p=0.0226).

Overall survival after two years was 40% and 62% for group one and two respectively and disease free survival in the same period was 36% and 58% accordingly. Using log-rank tests this difference reaches statistical significance (p<0.05).

DISCUSSION

Patients with advanced carcinomas of the head and neck have a dismal prognosis. The natural history of advanced head-and-neck cancer is one of locoregional disease progression, which still accounts for the majority of disease-related mortality.

Altered fractionation regimens, such as hyperfractionation, were developed to deliver a higher biologically effective dose to the tumor and involved lymph nodes.

The strategy of hyperfractionation is to use an increased number of smaller doses per fraction than the conventional 1.8 to 2.0 Gy per day. This new fractionation method was designed to enhance the therapeutic ratio by improving tumor control without increasing late toxicity. Hyperfractionation exploits the difference in the fractionation sensitivity between rapidly and slowly renewing tissues, i.e., a higher total dose can be given when the dose/fraction is reduced. These smaller doses per fraction are most commonly given twice daily which allows for maintenance of the overall treatment time and a slight increase in the total dose delivered. Radiobiologically, hyperfractionation yields differential sparing of late-reacting normal tissue compared with acute reacting

malignant tissues. [4]

Based on this biologic data Ang [5] reviewed some randomized trials comparing altered fractionation schedules with standard fractionation, which showed up to a 15% improvement in locoregional control for intermediate-stage head and neck carcinomas (T_{2-3} N_{0-1}). Some other randomized studies also have confirmed the effectiveness of hyperfractionation in some cancer sites of the head and neck area [6-9] and also a statistically significant survival advantage. [7, 10]

The analysis of our survival data revealed the same outcome too. That means increasing two-year survival from 40% to 62%. These figures may be altered if some parameters such as: the number of cases, site of cancer in head and neck, grading of histology, and sex of the patients are meticulously matched.

Some authors [11,12] have reported that increasing the radiation dose improves both tumor control and survival. In our study, we also increased the dose using the hyperfractionation regimen and found better tumor control when the radiation dose was increased.

Cox et al. [13] reported similar benefit in patients with clinical N_2 non-small-cell lung cancer by increasing the irradiation dose to 69.6 Gy by hyperfractionation. Looking at the published literature of altered fractionation, there are multiple positive trials that have tested standard fractionation and altered fractionation radiotherapy. [9, 10, 14, 15]

In our patients radiotherapy compliance was excellent; all patients except one, completed radiation therapy within the planned dose. Although most patients showed severe mucositis and dysphagia during the radiation course that was the cause of noticeable weight loss in some, no one needed tube feeding and hospitalization. The mucositis was healed after about two weeks in most patients. In addition, more patients in the hyperfraction-ated radiation group survived than those in the conventional radiation category. Therefore, the hypothesis of better locoregional control and prolongation of survival among patients with head-and-neck cancer receiving hyperfractionated radiotherapy compared to conventional radiation was backed in this study especially for advanced cases. This gain was due to an improvement in locoregional control, but was associated with an increase in acute toxicity, especially regarding severe (confluent) mucositis. However, It seems fair that, relative to a conventional treatment the achievable gain in treatment outcome is quite worthy despite this morbidity.

CONCLUSION

Hyperfractionation radiation regimen seems to be superior to standard radiation in head and neck cancer particularly in advanced stages as far as locoregional control and survival is concerned. It also helps the patients improve quality of life by avoiding mutilating surgery in those who are likely to respond to radiation while eluding the late complications of high dose conventional radiation.

REFERENCES

1. Coutard H: Roentgen therapy of epitheliomas of the tonsillar region, hypopharynx, and larynx from 1920 to 1926. Am J Roentgenol Rad Therapy 28: 313-331, 1932.
2. Million RR, Cassisi NJ, (eds): Management of head and neck cancer. A multidisciplinary approach. Philadelphia: JB Lippincott, 1994.
3. Marcial VA, Pajak TF: Radiation therapy alone or in combination with surgery in head and neck cancer. Cancer 55: 2259 –2265, 1989.
4. Thames HD Jr, Peters LJ, Withers HR, et al: Accelerated fractionation vs. hyperfractionation: rationales for several treatments per day. Int J Radiat Oncol Biol Phys 9: 127-138, 1983.
5. Ang KK: Altered fractionation trials in head and neck cancer. Semin Rad Oncol 8:230 –23, 1998.
6. Ang KK, Trotti A, Garden AS, et al. Overall time factor in postoperative radiation: results of a prospective randomized trial. Radiother Oncol 40(Suppl. 1): S30, 1996.
7. Cummings BJ, Keane TJ, O'Sullivan B, et al: A prospective randomized trial of hyperfractionated versus conventional once daily radiation for advanced squamous cell carcinomas of the larynx and pharynx. Radiother Oncol 40 (Suppl. 1): S30, 1996.
8. Dische S, Saunders MI, Barrett A, Harvey A, Gibson D, Parmar MKB: A randomized multicenter trial of CHART versus conventional radiotherapy in head and neck cancer. Radiother Oncol 44: 123±136, 1997.
9. Horiot JC, Le Fur R, N'Guyen T, et al: Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: Final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. Radiother Oncol 25: 231-241, 1992.
10. Pinto LH, Canary PC, Araujo CM, et al: Prospective randomized trial comparing hyperfractionated versus conventional radiotherapy in stages III and IV oropharyngeal carcinoma. Int J Radiat Oncol Biol Phys 21: 557–562, 1991.
11. Tokars RP, Griem ML: Carcinoma of the nasopharynx: an optimization of radiotherapeutic management for tumor

control and spinal cord injury. Int J Radiat Oncol Biol Phys 5: 1741-8, 1979.

12. Vikram B, Mishra UB, Strong EW, Manolatos S: Patterns of failure in carcinoma of the nasopharynx: 1. Failure at the primary site. Int J Radiat Oncol Biol Phys 11: 1455-9, 1985.
13. Cox JD, Azarnia N, Byhardt RW, Shin KH, Emami B, Perez CA: N2 (clinical) non-small cell carcinoma of the lung: prospective trials of radiation therapy with total doses 60 of Gy by the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 20: 7-12, 1991.
14. Overgaard J, Sand Hansen H, Sapru W, et al: Conventional radiotherapy as the primary treatment of squamous cell carcinoma (SCC) of the head and neck. A randomized multicenter study of 5 versus 6 fractions per week–preliminary report from DAHANCA 6 and 7 trial. Radiother Oncol 40: 531, 1996.
15. Jackson SM, Weir LM, Hay JH, et al: A randomized trial of accelerated versus conventional radiotherapy in head and neck cancer. Radiother Oncol 43: 39 - 46, 1997.