



Original Research Article

Conventional radiation therapy with hyperfractionated radiation therapy in cancer hypopharynx - A prospective comparative study

Vijayakumar S^{1,*}¹Dept. of Radiotherapy, Thanjavur Medical College Hospital, Thanjavur, Tamil Nadu, India

ARTICLE INFO

Article history:

Received 21-10-2021

Accepted 02-03-2022

Available online 31-07-2023

Keywords:

Hyperfractionation

Conventional fractionation

Hypopharyngeal carcinoma

chemotherapy Introduction

ABSTRACT

Introduction: Cancer treatment of the head and neck, the effectiveness of hyperfractionated radiation therapy (HFRT) has been revealed in recent randomized trials, mainly in their local control. As the hypopharynx is situated near the larynx, to achieve greater laryngeal preservation, local control of hypopharyngeal cancers should be achieved; it is very important to enhance the patient's quality of life. In this study, hyperfractionated radiation therapy results were compared with conventional radiation therapy (CFRT) results.

Materials and Methods: Patients with squamous cell cancer of hypopharynx (Stage II to IVA); were submitted with hyperfractionated (n = 34) or conventionally fractionated (n = 22) radiotherapy, with chemotherapy, between July 2018 to January 2020.

In conventional radiotherapy, each patient received 2 Gy per fraction with a total dose of 66 Gy at over 6.3 weeks, along with concurrent cisplatin (30 mg/m²) weekly. In hyperfractionated radiotherapy, each patient received 1.2 Gy per fraction two fractions per day six hours apart with a total dose of 72 Gy at over 6 weeks, along with concurrent cisplatin (30 mg/m²) weekly. The endpoints were tumor response and toxicities.

Results: Complete response rate in the HFRT group was 85.29% and that in the CFRT group was 68.18%. The most prevalent acute toxicities were skin, mucosal and dysphagia related. The acute skin toxicity was significantly higher in CFRT (54.55%) than in HFRT (44.12%).

Conclusions: This study suggests that for the treatment of locally advanced hypopharynx cancers, hyperfractionated radiation therapy with simultaneous chemotherapy can be a standard method of treatment and care.

This is an Open Access (OA) journal, and articles are distributed under the terms of the [Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprint@ipinnovative.com

1. Introduction

Cancer of the hypopharynx is a poor predictive cancer. The survival rate (OS) of five years is about 35%. Even if the survival rate has enhanced dramatically, the overall survival rate has been dramatically reduced for decades than oropharyngeal cancer related to the human papillomavirus.¹⁻⁵

Compared with conventional radiation therapy treatment, good treatment results can be achieved with the

hyperfractionated technique. Theoretically, this substitute could increase the total amount of radiation dose without increasing the frequency of toxic substances or extending the duration of general treatment.^{6,7} In addition, random clinical trials have shown that HFRT was better than CFRT in the treatment of head and neck cancers, mainly in local controls.^{8,9}

The reasons for the rise in hyperfractionation than other modified variants remain unclear, and hyperfractionation has not been the standard of care, mainly due to mobility problems, difficulty in finding 2 slots per day on machines or management of patient between fractions, which preferred

* Corresponding author.

E-mail address: sripushkakai@gmail.com (Vijayakumar S).

the delivery of simultaneous chemoradiotherapy over hyperfractionation.¹⁰

This study aimed to investigate tumor response in hypopharynx cancer using hyperfractionated radiotherapy compared with conventional fractionation with concurrent chemotherapy.

2. Materials and Methods

Data of 56 patients with biopsy-proven cancer of hypopharynx squamous cell (Stage II to IVA), who received either hyperfractionated (n = 34) or conventional fractionation (n = 22) radiotherapy, with concurrent chemotherapy, between July 2018 to January 2020 are analyzed.

The patient data includes patient age, stage, chemotherapy used with regimen details and the number of cycles administered, the radiation dose administered, overall treatment time, pre-and post-therapy contrast-enhanced computed tomography (CT) scan findings of head and neck, hematological, biochemical and chest X-ray findings, acute toxicity data.

Table 1 depicts the characteristics of patients. The mean age in the case of the HFRT group was 58.29 years. As per the classification of staging by UICC-TNM,¹¹ stage II cases were 19; stage III were 9 and 6 cases were of stage IVA. The mean age in the CFRT group was 56.45 years. As per the classification of staging by UICC-TNM, stage II cases were 13; stage III were 5 and stage IVA was 4. All cases are histologically proven to be cancers of squamous cells in both the HFRT and CFRT groups.

Table 1: Characteristics of patient's

	HFRT group	CFRT group
Number of patients	34	22
Mean age (years)	58.29	56.45
Gender (Male:Female)	29:5	19:3
Stage II	19	13
Stage III	9	5
Stage IVA	6	4

The treatment protocol is shown in Table 2. This study hyperfractionated radiation technique comprises 2 fractions per day at an interval of six hours apart of 1.2 Gy per fraction, 5 days in a week up to a total dose of 72 Gy in 6 weeks (Average of 6.3 to 7.4 weeks). Conventional fractionated radiation therapy comprises 1 fraction per day with 2.0 Gy per fraction, 5 days in a week up to the total dose of 66 Gy in 6.3 weeks (Average of 7.1 to 8.2 weeks). Chemotherapy was administered in all patients and received weekly Cisplatin 30 MG per m². Radiotherapy was delivered using CO 60 Teletherapy machine.

The outcome measures studied were tumor response and emphasis on toxicities as the primary outcome. Response evaluation was done periodically after completing treatment

based on contrast-enhanced CT scan of neck and head, clinical examination and chest X-ray findings in each patient. Biopsy or fine-needle aspiration cytology was taken from any suspicious clinical and or radiological residual tumor or to confirm recurrence at the primary and/ or nodal areas. Patients were then categorized as per Response Evaluation Criteria in Solid Tumors (RECIST) criteria (version 1.1) as having complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Patients were evaluated for toxicity weekly during radiation and after that during follow-up, initially monthly and subsequently at longer intervals.

Table 2: Characteristics of treatment

	HFRT group	CFRT group
Fraction size (Gy)	1.2/ 2	2.0
Total dose (Gy)	72	66
Overall treatment time (Weeks)	6 (6.3 to 7.4)	6.3 (7.1 to 8.2)
Chemotherapy	Cisplatin 30 MG per m ²	Cisplatin 30 MG per m ²

3. Results

Response evaluation was done periodically after the completion of treatment. After completing radiation therapy, the rate of responses of hypopharynx lesions was determined and shown in Table 3. As for hypopharynx lesions, there were 29 CRs and 3 PRs, 1 SDs and 1 PDs in the HFRT group. In the CFRT group, there are 15 CRs, 2 PRs and 3 SDs and 2 PDs. So the rate of complete response in the HFRT group was 85.29% and 68.18% in the CFRT group.

Table 3: Radiation response

Tumor response	HFRT	Percentage	CFRT	Percentage
Complete response (CR)	29	85.29%	15	68.18%
Partial response (PR)	3	8.82%	2	9.09%
Stable disease (SD)	1	2.94%	3	13.64%
Progressive disease (PD)	1	2.94%	2	9.09%

The rate of local control in the N0-N1 stages in the HFRT group was 88.24% and it was 72.72% for the CFRT group. Also, the rate of local control in node N3 was 0% for the HFRT group and 4.55% for the CFRT group (Table 4).

The most prevalent acute toxicities were skin, mucosal and dysphagia related. The acute skin toxicity was significantly higher in CFRT (54.55%) than in HFRT (44.12%). Acute oral mucositis was higher in HFRT (50%), while in CFRT, it was less (45.45%). Acute dysphagia was noticed in 22.72% in CFRT compared to HFRT. It was lesser to 17.65% (Table 5).

Table 4: Local control status of N stage

Nodal status	HFRT	CFRT
N0	23	16
N1	7	2
N2	4	3
N3	0	1

Table 5: Toxicity in HFRT and CFRT

Toxicity reactions	HFRT	CFRT
Acute skin reactions	15	12
Acute oral mucositis	17	10
Acute dysphagia	6	5

4. Discussion

For various types of cancer, dose-escalation radiation therapy achieves improved local control, according to many reports. To achieve dose escalation, a good knowledge of the biology and physics of radiation therapy is needed.^{12,13} Because of advances in physics, there is intensity-modulated radiation therapy (IMRT) and 3-dimensional conformal radiation therapy (3D-CRT) for the treatment of head and neck, prostate and lung cancers; by improved dose distributions, escalation of the dose was attained.^{14–16} Conversely, developments in biology have to steer to modified fractionated radiation techniques, including hyperfractionation therapy. Since the 1980s, HFRT has been performed to increase the total dose without extending general treatment.

Some recent experiments further supported the clinical efficacy of modified radiation therapy to treat carcinomas of the head and neck, mainly in their local control.^{8,9} Fu et al. showed that the rate of local control within two years for hyperfractionation at 81.6 Gy total dose with 1.2 Gy each fraction was 54.4% which shows statistically significant enhancement when compared to conventional fractionation at 70 Gy total dose with 2 Gy each fraction was 46.0% ($P = 0.045$).⁸ They further investigated and compared conventional fractionation, as per the protocol of Wang et al two modified fractionated radiation therapies that are accelerated fractionation and concomitant boost fractionation.¹⁷

This comparison showed that only concomitant boost fractionation was better than conventional fractionation. When compared to conventional fractionation, severe late toxicity in concomitant boost fractionation was more. These studies proposed that one of the best modified fractionated radiation therapies is hyperfractionated radiation therapy.

In our study, complete response (CR) was detected in 85.29% of patients receiving hyperfractionated radiation therapy, which is much higher than patients receiving conventional radiation therapy showing only CR of 68.18%. The rate of local control at the N0-N1 nodes in the HFRT (88.24%) was also better when compared to CFRT (72.72%) group.

In terms of acute toxicity, pharyngeal toxicity in the HFRT group had a greater tendency than in the CFRT group. Nevertheless, the hematological and skin toxicities were comparable between the groups (Table 5), indicating acceptable acute toxicity of the HFRT group. However, further research is needed to lessen acute toxicity.

5. Conclusion

To conclude, this study showed that hyperfractionated radiation treatment for hypopharyngeal cancer had achieved superior local control, better survival rates, acceptable toxicity and pharyngeal preservation. These findings indicate that HFRT is a promising treatment for hypopharyngeal cancer.

6. Conflict of Interest

There are no conflicts of interest in this article.

7. Source of Funding

None.

8. Acknowledgement

Authors acknowledge the immense help received from the scholars whose articles are cited and included in references to this manuscript

References

- Kim YJ, Lee R. Surgery vs. radiotherapy for locally advanced hypopharyngeal cancer in the contemporary era: A population-based study. *Cancer Med.* 2018;7(12):5889–900. doi:10.1002/cam4.1811.
- Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer.* 2014;120(10):1507–13. doi:10.1002/cncr.28588.
- Petersen JF, Timmermans AJ, Van Dijk B. Trends in treatment, incidence and survival of hypopharynx cancer: a 20-year population-based study in the Netherlands. *Eur Arch Otorhinolaryngol.* 2018;275(1):181–9.
- Newman JR, Connolly TM, Illing EA, Kilgore ML, Locher JL, Carroll WR, et al. Survival trends in Hypopharyngeal cancer: A population-based review. *Laryngoscope.* 2015;125(3):624–9. doi:10.1002/lary.24915.
- Wendt M, Romanitan M, Nasman A. Presence of human papillomaviruses and p16 expression in hypopharyngeal cancer. *Head Neck.* 2014;36(1):107–12. doi:10.1002/hed.23394.
- Niibe Y, Karasawa K, Mitsuhashi T, Tanaka Y. Hyperfractionated Radiation Therapy for Hypopharyngeal Carcinoma Compared with Conventional Radiation Therapy: Local Control, Laryngeal Preservation and Overall Survival. *Jpn J Clin Oncol.* 2003;33(9):450–55.
- Ang KK. Fractionation effects in clinical practice. *Textbook of Radiation Oncology.* 1998;47(1):26–52.
- Fu KK, Pajak TF, Trotti A, Jones CU, Spencer SA, Phillips TL. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiation therapy for head and neck squamous cell carcinoma: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys.* 2000;48(1):7–16. doi:10.1016/s0360-3016(00)00663-5.

9. Horiot JC, Fur LR, 'guyen N, Chenal T, Schraub C, Alfonsi S, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC Cooperative Group of Radiotherapy. *Radiother Oncol*. 1992;25(4):231–41. doi:10.1016/0167-8140(92)90242-m.
10. Lacas B, Bourhis J, Overgaard J, Zhang Q, Grégoire V, Nankivell M, et al. Role of radiotherapy fractionation in head and neck cancers (MARCH): an updated meta-analysis. *Lancet Oncol*. 2017;18(9):1221–37. doi:10.1016/S1470-2045(17)30458-8.
11. Sobin L, Wittekind C. International Union Against Cancer. Pharynx. In: TNM Classification of Malignant Tumours. New York: Wiley-Liss, Inc; 1997. p. 25–32.
12. Fletcher GH. Clinical dose-response curves of human malignant epithelial tumours. *Br J Radiol*. 1973;46(541):1–12. doi:10.1259/0007-1285-46-541-1.
13. Perez C, Pilepich M, Zivnuska F. Tumor control in definitive irradiation of localized carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 1986;12(4):523–31. doi:10.1016/0360-3016(86)90059-3.
14. Hunt MA, Zelefsky MJ, Wolden S, Chui CS, Losasso T, Tosenzweig CL, et al. Treatment planning and delivery of intensity-modulated radiation therapy for primary nasopharynx cancer. *Int J Radiat Oncol Biol Phys*. 2001;49(3):623–32. doi:10.1016/s0360-3016(00)01389-4.
15. Uematsu M, Shioda A, Suda A, Fukui T, Ozeki Y, Hama Y, et al. Clinical outcomes of 3D conformal hypofractionated single high-dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys*. 2001;51(4):666–70. doi:10.1016/s0360-3016(01)02731-6.
16. Nagata Y, Negoro Y, Aoki T, Mizowaki T, Takayama K, Kokubo M. Clinical outcomes of 3D conformal hypofractionated single high dose radiotherapy for one or two lung tumors using a stereotactic body frame. *Int J Radiat Oncol Biol Phys*. 2002;52:1041–1047.
17. Wang CC, Blitzer PH, Suite HD. Twice-a-day radiation therapy for head and neck. *Cancer*. 1985;55(9 Suppl):2100–4. doi:10.1002/1097-0142(19850501)55:9+<2100::aid-cnrcr2820551411>3.0.co;2-a.

Author biography

Vijayakumar S, Associate Professor

Cite this article: Vijayakumar S. Conventional radiation therapy with hyperfractionated radiation therapy in cancer hypopharynx - A prospective comparative study. *Panacea J Med Sci* 2023;13(2):476–479.