



Research Article

## CURCUMIN A NF- $\kappa$ B INHIBITOR WITH CONCURRENT CHEMO-RADIATION IN LOCALLY ADVANCED HEAD AND NECK CANCERS

Rajasekaran Pooruli Neelakantan and Jebasingh Joseph\*

Department of Medical Oncology, Madurai Medical College, Madurai, Tamilnadu, India

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Curcumin, NF-KB, Chemoradiotherapy, Head and Neck Cancer

### ABSTRACT

**Aim:** To study the role of addition of Curcumin to conventional chemo-radiotherapy in locally advanced Head and Neck cancers

**Subjects and methods:** In this prospective study, 55 patients with Stage III / IV Head and Neck cancers excluding Nasopharynx were treated with Cap. Curcumin 500 mg 2 bd from Day 1 of radiation along with weekly Cisplatin 40 mg/m<sup>2</sup> and External radiation 66 Gy in 200 cGy per # at a tertiary hospital in South India. Response was assessed at the end of radiation therapy and 1 month later.

**Results:** All 55 completed the treatment. Male : Female ratio was 84 % : 16 % and the median age was 48years ( range 28 – 65). Hypopharynx was the site of cancer in 33 % of the patients while Oropharynx comprised 31 %, Larynx 24 % and Oral cavity 12 %. 24 % of the patients had Stage III disease while 76 % were in Stage IV. Complete response was seen in 78 % of patients within 1 month of completion of radiation therapy. Overall response rate was 91 %. There were no Grade 3 / 4 toxicities.

**Conclusion:** Concurrent administration of NF- $\kappa$ B inhibitor Curcumin at 2 g/day along with weekly Cisplatin as radio-sensitizer was found to increase the complete response rates in locally advanced Head and Neck cancers treated with radiation therapy compared to historical data without Curcumin with no added toxicities. It would be a cheaper alternative to Bortezomib as a NF- $\kappa$ B inhibitor.

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### INTRODUCTION

Head and Neck cancers are the commonest cancers of men in India. Most of them present in Stage III / IV. Though Concurrent chemoradiation has improved the results in such cases, there is a high percentage of patients who do not respond. NF- $\kappa$ B an initiator and promoter of cancer and also an inhibitor of apoptosis has been found to be constitutively expressed actively in all Head and Neck cancers. We have used a safe NF- $\kappa$ B inhibitor **Curcumin** along with conventional chemoradiation for locally advanced Head and Neck cancers to know its advantage. Curcumin topical application has been proved to clear superficial epithelial cancers. Curcumin also has the ability to arrest cells in the G2/M phase which increases the radiosensitivity of cancers.

### SUBJECTS AND METHODS

This study was undertaken in a tertiary care centre, Government Rajaji Hospital in South India. A nonfunded and epidemiological nature of the study deemed an ethical committee clearance unnecessary, as per the institutional protocols. The center was so chosen that its draining patient population was representative of the entire southern part of

India. All Head and Neck cancer patients registered in the Department of Medical Oncology of the hospital, between January 1, 2015 and December 31, 2017 were taken up for this study. In this study, 55 patients with Stage III / IV Head and Neck cancers excluding Nasopharynx were treated with Cap. Curcumin 500 mg 2 bd from Day 1 of radiation along with weekly Cisplatin 40 mg/m<sup>2</sup> and External radiation 66 Gy in 200 cGy per # at a tertiary hospital in South India. Response was assessed at the end of radiation therapy and 1 month later. The data were prepared on an Excel sheet and analyzed manually for the interpretation of the results.

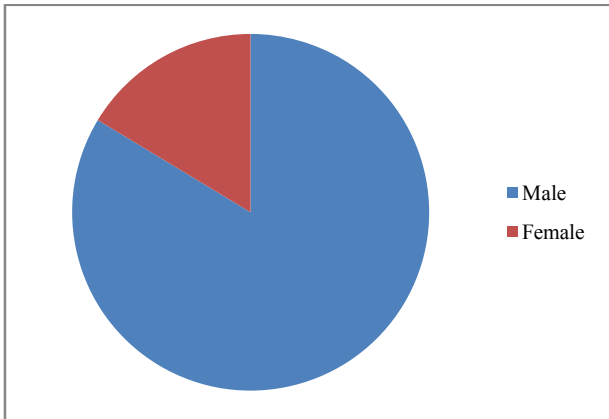
### RESULTS

Over a period of two years, 62 patients with locally advanced head and neck cancer were initially identified for the study. Since, 7 patients did not agree to the protocol, 55 patients were given Curcumin as per schedule during their course of chemoradiotherapy. All 55 completed the treatment. Median age was 48years (range 28 – 65).

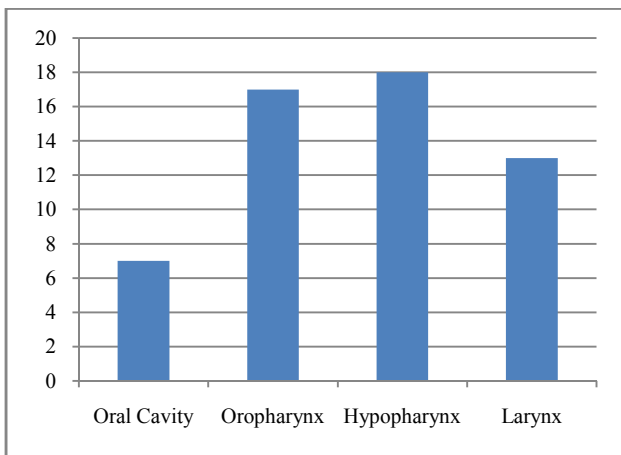
\*Corresponding author: **Jebasingh Joseph**

Department of Medical Oncology, Madurai Medical College, Madurai, Tamilnadu, India

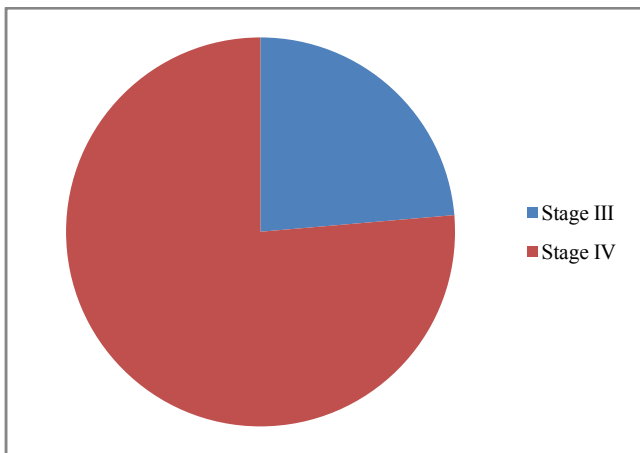
Out of the 55 patients, 46 were males and 9 females



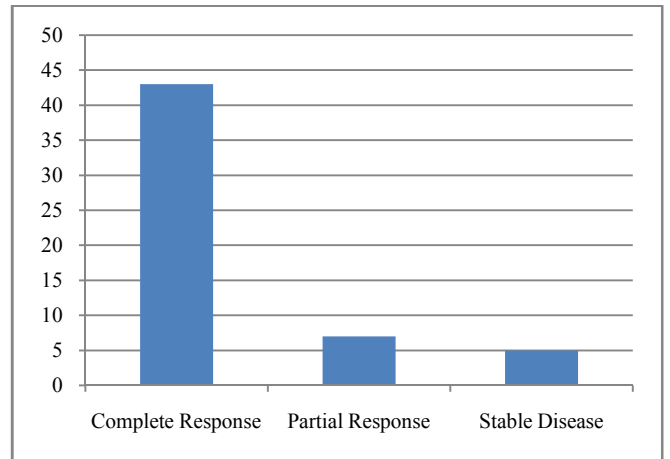
Hypopharynx was the site of cancer in 33 % of the patients while Oropharynx comprised 31 %, Larynx 24 % and Oral cavity 12 %



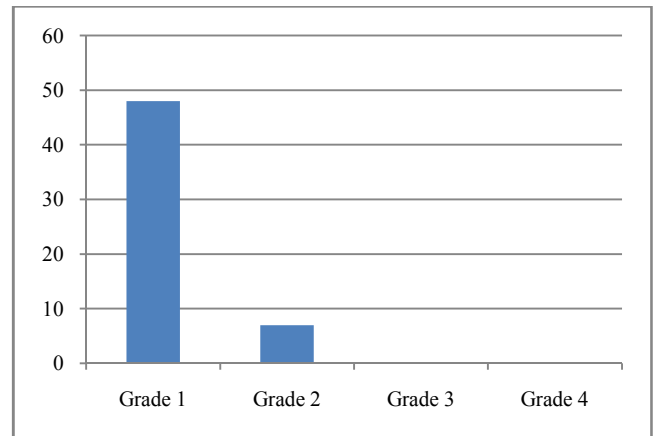
24 % of the patients had Stage III disease while 76 % were in Stage IV.



Complete response was seen in 78 % of patients within 1 month of completion of radiation therapy. Overall response rate was 91 %.



There were no Grade 3 / 4 toxicities.



## DISCUSSION

Multimodality of treatment using combination of surgery, radiation, chemotherapy has become the preferred treatment for HNSCC, more so in the advanced tumours. Chemotherapeutic agents are commonly used as an adjuvant along with radiation. They play a key role of radiosensitiser. The most commonly used radiosensitisers are cisplatin, 5 – fluorouracil, paclitaxel and gemcitabine. Cytotoxic action of radiosensitiser are usually associated with damage to normal cells with varying consequences, which can be acute or delayed. Randomised trials RTOG 9501 and EORTC 22931 have shown satisfactory evidence of improvement in terms of loco regional control and disease-free survival in patients undergoing chemotherapy along with EBRT, but grade 3 toxicity was reported in 77% and 44% of patients.<sup>11</sup> Hence there is a continued search for potential alternatives with less toxicity profile, one such agent of interest is curcumin.<sup>1</sup> The inhibitory action of curcumin was shown to be mediated via inhibition of NFkB and STAT3 signalling protein<sup>2</sup>. Curcumin as a radiosensitiser has been studied only in human cancer cell lines and in animal models. Curcumin significantly enhanced the effect of gamma radiation in xenograft nude mice models with colon cancer by suppressing NF-kB activity. In prostate cancer cell line PC-3, curcumin showed anti-cancer and radio sensitising effect by down regulating MDM2 levels, and also by inhibition of TNF- $\alpha$  mediated NF-kB activity<sup>3</sup>. The mechanism of radiosensitisation by curcumin in this study was attributed to the inhibitory action on COX-2 pathway and also on phosphorylation of EGFR. Studies have shown COX-2 and EGFR up regulation in most head and neck cancers. Curcumin as a combined inhibitor of COX-2 and EGFR has a potential

role in the treatment of these cancers. The down regulation of COX-2 expression has also shown to enhance chemo radiotherapy response while sparing the normal tissues<sup>4</sup>. Curcumin has been shown to cause alteration in the mitotic spindle structures and arrest cells in G2/M and S phase of cell cycle, which is the most radiosensitive phase of cell cycle. This mechanism is very similar to the action of taxols, which are potent radiosensitisers. In a phase I trial on 14 patients of advanced/metastatic breast cancer, combination of docetaxel and curcumin have shown to arrest progression of cancer. Out of the 14 patients enrolled in the study, 5 patients had PR, and 3 patients had SD and none of the patients had progressive disease<sup>5</sup>.

## CONCLUSION

Concurrent administration of NF- $\kappa$ B inhibitor Curcumin at 2 g/day along with weekly Cisplatin as radio-sensitizer was found to increase the complete response rates in locally advanced Head and Neck cancers treated with radiation therapy compared to historical data without Curcumin with no added toxicities. It would be a cheaper alternative to Bortezomib as a NF- $\kappa$ B inhibitor.

## References

1. Geiger JL, Lazim AF, Walsh FJ, Foote RL, Moore EJ, Okuno SH, *et al.* Adjuvant chemoradiation therapy with high-dose versus weekly cisplatin for resected, locally-advanced HPV/p16-positive and negative head and neck squamous cell carcinoma. *Oral Oncol.* 2014;50(4):311-8
2. Aggarwal BB, Surh YJ, Shishodia S. The Molecular Targets and Therapeutic Uses of Curcumin in Health and Disease. *Adv Experimental Med Biol.* 2007;595:159-161.
3. Khafif A, Lev-Ari S, Vexler A, Barnea I, Starr A, Karaush V, *et al.* Curcumin: a potential radioenhancer in head and neck cancer. *Laryngoscope* 2009;119(10):2019-26
4. Wilken R, Veena MS, Wang MB, Srivatsan ES. Curcumin: A review of anti-cancer properties and therapeutic activity in head and neck squamous cell carcinoma. *Mol Cancer.* 2011;10:12
5. Bayet-Robert M, Kwiatkowski F, Leheurteur M, Gachon F, Planchat E, Abrial C, *et al.* Phase I dose escalation trial of docetaxel plus curcumin in patients with advanced and metastatic breast cancer. *Cancer Biol Ther.* 2010;9(1):8-14

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