Title: A randomized trial comparing adjuvant chemoradiation 60 vs 66Gy in post operative head and neck cancer patients with presence of pathological extranodal extension.

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Background and objectives (200 words)

The presence of pathological extranodal extension (ENE) reflects aggressive inherent tumor biology, increases the likelihood of positive surgical margins, the risk of distant metastasis and also impacts the overall survival. Results from a historical series from MD Anderson of post operative head & neck cancers depicted that there is no clear dose response relationship for tumor control for radiation dose above 57.6 Gy but a subset of patients with ENE had better local-regional control with ≥ 63 Gy. However in the 20-year follow-up of this trial, ENE was still predictive of worse outcomes, but a dose response relationship could not be established.

Most of the prospective adjuvant trials stipulate a prescription of 60 Gy in 30 fractions with an optional boost of 6 Gy. In the National cancer database analysis, high dose of radiation (> 60 Gy - < 70 Gy) was delivered in 58.4% patients with ENE but this did not improve the overall survival compared to the standard dose schedule (≥56.64 Gy and ≤60 Gy). There is a paucity of evidence for identifying the subset of patients who will benefit from dose escalation, particularly in combination with concurrent chemotherapy. This randomised study aims to compare the outcomes of two widely practised radiation dose schedules of 60 Gy and 66 Gy in head and neck cancer patients with presence of pathological ENE.

c) Methods (maximum - 100 words)

Study design

Patients with pathologically proven ENE planned for adjuvant radiation with weekly concurrent chemotherapy will be included. Patients will be randomized to two arms, the standard arm will receive dose of 60 Gy and the experimental arm will receive 66 Gy.

Inclusion criteria

1. Age ≥ 18- ≤ 70 years
2. ECOG performance status 0-2
3. Patients fit for concurrent chemotherapy
4. Histopathologically proven head and neck cancer
5. Presence of ENE

Exclusion criteria

1. Patients with any previous history of malignancy
2. Presence of gross residual disease

c) Outcomes (maximum 100 words)

Baseline patient, tumor and treatment related factors will be recorded and subsequently analysed. Response status and toxicities will be assessed at 4 weeks after completion of

treatment and subsequently at 3, 6, 9, 12, 18 and 24 months. Toxicity will be graded according to the CTCAE grading criteria.

The primary end point will be locoregional control (LRC). LRC will be defined as the duration between time of randomization and the first proven evidence of locoregional recurrence. The secondary end points will be toxicity (xerostomia, dysphagia, mucositis, dermatitis), disease free survival, overall survival and quality of life (QOL) . The toxicity will be assessed using validated scales like xerostomia inventory, MDADI, RTOG and CTCAE scales. QOL will be assessed using EORTC QLQ C30 and HN 35. The difference in outcomes amongst the two groups will be analysed for statistical significance.

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e) Feasibility (30 words)

The proposed study duration is around two years with an aim for accrual of around 200 patients. Manipal Comprehensive care centre is a tertiary cancer hospital and registers 3000-4000 new patients per year. Yearly about 400-500 head and neck cancer patients receive radiotherapy of which >50% are in adjuvant setting.

f) References: (please list 3 key references)

1. Peters LJ, Goepfert H, Ang KK, et al. Evaluation of the dose for postoperative radiation therapy of head and neck cancer: first report of a prospective randomized trial. *Int J Radiat Oncol Biol Phys* 1993;26(1):3–11

2. Avkshtol V, Handorf EA, Ridge JA et al. Examining adjuvant radiation dose in head and neck squamous cell carcinoma. Head Neck. 2019 Jul;41(7):2133-2142. doi: 10.1002/hed.25680. Epub 2019 Feb 9. PMID: 30737968; PMCID: PMC7830814.

3. Matsumoto F, Mori T, Matsumura S et al. Prognostic significance of surgical extranodal extension in head and neck squamous cell carcinoma patients, Japanese Journal of Clinical Oncology, 2017,47 (8): 699–704