Introduction

As per data, published by the National Cancer Registry Programme, Indian Council of Medical Research (ICMR) India. Head and neck cancers constitute 18% of total cancer burden in India, it accounts for 26% of cancers in males and 10.27% in females. So in a vast country like India, though, 18% of cancer patients belong to head and neck region, its high time that we try to develop newer protocols for treating head and neck cancer patients, test them in our setup and have our own results, so that it we can understand what type of treatment best suits to the head and neck cancer patients of our country. The rationale for choosing Low Dose Fractionated Radiotherapy (LDFRT) as a potentiator of the Induction chemotherapy regimen. All along we have been taking the help of chemotherapy to sensitise radiation therapy, why not try sensitising induction chemotherapy with our radiation.!!! The textbook of Basic Clinical radiobiology states that, the LQ model adequately describes the response of cells to radiation above about 1 Gy. But this model fails to account for the enhanced responses seen at doses < 1 Gy. The authors further state that due to the recent availability of FACS-Fluoreosence Activated Cell Sorter, it has become possible to plate the desired number of cells that we want, as well as, it is possible to identify the exact number of cells in a plate before and after a prescribed treatment, it is with the help of these technology, that it has been feasible to show that mammalian cells actually exhibit Hyper-radiosensitivity phenomenon (HRS). S.M.Arnold et al at the university of Kentucky, Lexington, USA, studied the combined effect of low dose fractionated RT, and taxanes on the growth of cell lines containing squamous cell carcinoma of head and neck, SQ-20B, a p53 mutant cell line and concluded that HRS phenomenon can be utilised in the clinical setting, based on demonstrated synergy between Taxol and LDFRT. It was tested whether radiosensitising effect of paclitaxel was better or the chemo-potentiating effect of low dose radiation was better. The result was that paclitaxel increased the effect of radiation 3 times in wild head and neck cancer cells and 1.08 times in p53 mutant H&N cancer cells, whereas low dose radiation enhanced the effect of paclitaxel 7.6 times in wild type H&N cancer cells and 2.9 times in mutant H&N cancer cells.
To ascertain whether these in-vitro studies translate to meaningful benefits in-vivo, S.M.Arnold et al designed a new study incorporating low-dose radiation and their results were published in International Journal of Radiation Oncology, titled: “Low-dose fractionated radiation as a chemopotentiator of neoadjuvant paclitaxel and carboplatin for locally advanced squamous cell carcinoma of the head and neck: results of a new treatment paradigm.”

**LDFRT-STUDY No.1**

In this study, 40 patients enrolled; 39 were evaluable. The long-term outcomes were initially reported with a median follow-up of 66 months. Locoregional control (LRC) is 79% and distant control (DC) is 77%. 5 yr overall survival (OS) and progression-free survival (PFS) are 62% and 58%, respectively.

**LDFRT-STUDY No.2**

Ultrafractionated Radiation Therapy (3 daily doses of 0.75 Gy) - A New and Promising Radiotherapy Schedule for Glioblastoma Patients

**LDFRT-STUDY No.3**


**Aim**

The aim of the present study was to evaluate the effectiveness of Low Dose Fractionated Radiotherapy (LDFRT) in augmenting the Paclitaxel-Carboplatin-based induction chemotherapy in the management of locally advanced head and neck malignancy.

**Primary Objective(s):**

To assess the immediate response of patients treated with Paclitaxel and Carboplatin followed by four small fractions (0.8 Gy b.d.) of radiation given within 36 hours of chemotherapy in patients with Stage III and IV H&N cancer.

**Secondary Objective(s):**

To assess acute toxicity to the treatment.
To assess the prognostic factors which determine response to treatment.
To assess the response at the completion of the definitive treatment after this initial induction regimen using LDFRT.

**Materials And Methods**

**Study Design:** The present study was a Single Arm study with previously untreated locally advanced Squamous Cell Carcinoma of head and neck region.

**Methodology:** Eligible patients will be treated as per schema given in fig 1.

**Sample Size:** 30 consecutive patients of locally advanced head and neck cancers attending our outpatient department were enrolled in our study.

- Histologically proven newly diagnosed SCCHN
- Age 18 - 65 years.
- ECOG 0-1.
- Stage III or IV (M0) non metastatic disease.
- Head & neck cancer except tumours arising from nasal cavity, nasopharynx and paranasal sinuses.
- Patients will be medically fit for undergoing chemotherapy.

**Exclusion Criteria**

- Non Squamous Histopathology.
- Inadequate hepatic and renal functions, bone marrow reserve.
- Patient not consenting to chemotherapy at any point in the treatment.
- Patients with a history of allergy to drugs containing Cremophor in the formulation.
- Patients with grade II or greater peripheral neuropathy will be excluded from study.

**Radiation Schedule and Dosage:** REFER FIG 1:

In phase I, all eligible patients were administered dose/fraction of 80 cGy bid, 1st dose, starting within 2 hours of chemotherapy (Paclitaxel 175mg/m2 and Carboplatin AUC 6) and dose 2 was administered 6 hours later. The third and fourth fractions were administered the next day, both dose3 and dose4 spaced six hours apart. The patient were treated with shaped fields encompassing gross disease only (including the primary and gross nodal disease) with a maximum 2cm margin. The spinal cord was excluded from the radiation field. The same sched-
ule of radiotherapy and chemotherapy was followed on day 22& day23. Assessment of response was done between 36-42 days. Time interval between phase I&II was 21 days.

Phase II will be surgery or, if radiation is definitive treatment then Phase II will treat macroscopic primary tumor and gross adenopathy and subclinical disease(40.0 Gy/2Gy/#). Followed by treatment in a field after off cord (40.0-60Gy), after which treatment will be delivered to only gross tumor and node up to 66 Gy along with weekly Cisplatin 40mg/sq .m., The total duration of the entire treatment(phase I & II) was 87 days.

**Toxicity Assesment After Each Cycle Of Induction:**

Chemoradiotherapy induced toxicity was graded using Common Toxicity Criteria version4.03 and RTOG acute radiation morbidity scoring criteria. Tumour response was evaluated between 36-42 days after the inception of first cycle schedule. Using clinical examination and after confirmation by CT neck, the response was graded using RECIST 1.1 Criteria.

**Response assessment after definitive therapy schedule:**

Same procedure as stated above will be followed to assess Tumor response after 2nd phase of the treatment. This time the response will be evaluated 4-6 weeks after 2nd phase.

**Follow Up Procedure:**

Patients will be assessed for disease status 1 month after the end of treatment and every month thereafter. During follow up, a thorough history, physical examination and a complete clinical examination will be done.

The probability test used to identify p value is FISCHER’S EXACT PROBABILITY TEST.

**Results**

Out of the total 30 patients enrolled in the study, 80% were male, 20% were female patients, all of them completed the planned protocol, the median age of the patients were 56 years, 50 % of the patients belonged to the 50-60 years age group.

**Site-Wise Distribution:**

Pre treatement staging was done clinically, endoscopically and radiographically, majority were the ones having their primary at the oro-pharyngeal sub-site. The site wise break-up were as follows:

- Oral cavity    5 (17%),
- Oropharynx    12 (40%),
- Larynx         9 (29%),
- Hypopharynx    4 (14%).

**Stage Wise Distribution:**

All the patients were either stage III or stage IV, none of the patients belonged to stage I or II. Of these the patients 23.3% were of stage III, 63.3% belonged to stage IVA and 13.30% were of stage IV B.

**Response Assessment:**

**Response at the primary involved site:**

23.3% of the patients had complete response at the primary site, 70.0% had a partial response and 6.6% had a stable disease as depicted in the fig 2

**Response at the nodal region:**

14 of the patients had a complete response at the nodal region, 13 patients reported a partial response, 2 of the enrolled patients had a stable disease, and one patient had a progressive disease (N0- N1), as depicted in the fig 3.

**Adverse effects:**

Toxicity was assessed and was graded according to RTOG and CTAE criteria and was tabulated as table -1 . Other adverse effects were that of alopecia which was seen in 18 of the patients, mucositis in 2 patients both of them had grade 1 mucositis, neuropathy in one patient who had...
Response to Definitive Chemo-RT [2nd phase] schedule:

Response to 2nd Phase of the treatment protocol, was undertaken, following the assessment of patients to the induction, patients were taken up for concurrent radiotherapy with inj.cisplatin 40mg/ m2 . The response of these patients were assessed following CRT.no patient opted for surgery. At the primary site 20 patients had a complete response, 8 patients had partial response. Stable disease and progressive disease was seen in one patient each.

At the secondary nodal region, 25 patients had a complete response, 3 patients had partial response one patient remained having stable disease and one of the patients progressed at the secondary. That case was N3 nodal disease at presentation.

Discussion

Low dose fractionated radiotherapy, was found to be an effective sensitiser of the induction chemotherapy in our study, with tolerable toxicity compared to the 3 drug induction chemotherapy. All of the patients included in our study were able to complete the intended induction protocol of 0.8 Gy bid at day1&2 with paclitaxel and carboplatin, and same schedule on day 22& 23 except for a lone patient whose 2nd cycle was started with a five days delay. Though 16.6% had grade 3 anemia and 10% reported grade 3 leukopenia, they were managable. This scheme of induction therapy with LDFRT has resulted in improving the loco-regional response by downstaging most tumours, making it more amenable for the definitive treatment that followed, the complete response with the induction therapy at the primary was seen in 7 out of the enrolled 30 patients and at the nodal region,nearly half of the subjects had complete response. The results are quite encouraging at the outset with 70% partial response at the primary and 43% partial response at the nodal region.

Prognostic variables associated with complete responders: It is a necessary exercise to assess the positive predictive factors in the subjects that we included in our study, so as that in future we patients with these favourable prognostic factors who be apt for this type of regimen can be picked up for still more better results.

Age: In our study, age was a better predictor of complete response as there were 5 complete primary site responders out of 8 patients in the 40- 50 years bracket where as there was only one in the 50-60 yrs group.

Performance status: This was also a better predictor of response as all the complete responders were from the ECOG-1 group, and those with ECOG-2 responded only partially or had a stable disease at the primary following induction therapy

AJCC staging of disease: Stage of the disease turned out to be the most important of these predictive variables in our study, the stage of the disease was significantly associated with the response both at the primary as well as the nodal region as evident below. Table-2 A & 2B

### Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>11</td>
<td>7</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>11</td>
<td>6</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>GI toxicity</td>
<td>7</td>
<td>2</td>
<td>0</td>
<td>0</td>
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### Table 2A

<table>
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<th>AT THE PRIMARY</th>
<th>III</th>
<th>IVA</th>
<th>IVB</th>
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<tr>
<td>CR</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>CASES TOTAL</td>
<td>7</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>p = 0.001</td>
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</tbody>
</table>

### Table 2B

<table>
<thead>
<tr>
<th>AT NODAL REGION</th>
<th>III</th>
<th>IVA</th>
<th>IVB</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>5</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>CASES TOTAL</td>
<td>7</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>p = 0.003</td>
<td></td>
<td></td>
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</table>

Site wise assessment for predictive factors:

Oral cavity: None of the patients in this group had a complete response, albeit 3 patients had a partial response, the reason might be probably due to
1)The well-differentiated nature of the tumour, as 4 out of total 5 patients has this differentiation.
2)Secondly, all these patients were N2 disease at presentation, as it is evident from Perez et al.'s. statement for oral cavity tumours which states that- "The most significant prognostic factor for outcome in oral cavity carcinoma is the presence of cervical metastases ".

Laryngeal & oro-pharyngeal sub-site: Both these sub-sites fared well almost equally, with 3 out of 9 complete responders in the laryngeal and 4 out of 12 patients in the oro-pharyngeal group responded, both had a 33% complete response rate each.

Hypo-Pharyngeal Site: All cases here had a partial response, inspite of the fact that one of the cases out of the 4 had a IVB disease with N3 node, there was a response, probably due to the poorly differentiated nature. No discus-
sion is complete without comparing our results with similar trials, hence it is necessary to compare our results with the primary study which formed the basis of our present trial. That study was done at the University of Kentucky published in: International Journal of Radiation Oncology April 2004, as well as a poster in ASTRO 2011, by J.F. Gleason et al. the comparision is depicted in table-3.

<table>
<thead>
<tr>
<th></th>
<th>Parent study</th>
<th>Our study</th>
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<tbody>
<tr>
<td>primary</td>
<td>62%</td>
<td>70%</td>
</tr>
<tr>
<td>neck</td>
<td>38%</td>
<td>43.3%</td>
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</table>

*Table 3*

In contrast both our study and the parent study produced a higher control rate both at the primary as well as at the neck in response to LDFRT based induction therapy, though the number of patients included in these studies are smaller, this comparison helps us to understand that future induction therapies can be proceeded in this direction as innovative studies like this utilising sound radio-biological principles can help us produce better loco-regional results and aid us in providing better survival for these suffering patients in the future.

**References**

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5. Low-Dose Fractionated Radiation as a Chemo-Potentiator, Clinical Cancer Research April 2003
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7. Low-Dose Fractionated Radiation Potentiates the Effects of Paclitaxel in Wild-type and Mutant p53 Head and Neck Tumor Cell Lines S Dey, Paul M. Spring, Suzanne Arnold, et al
8. LDFRT as a Chemopotentiator of Neoadjuvant Paclitaxel and Carboplatin for Locally Advanced Squamous Cell Carcinoma of the Head and Neck: 5 Year Results Of A Prospective Phase II Trial J. F. Gleason, J. Valentino, S. M. Arnold

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