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A Prospective Study Comparing Induction Chemotherapy with Low Dose Fractionated Radiation Followed by Conventional Radiotherapy Versus Conventional Concomitant Chemoradiotherapy In Locally Advanced Head and Neck Cancers

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Abstract

Background: To study and compare response rate and toxicities of Induction chemotherapy with Low dose fractionated radiation followed by conventional radiotherapy versus conventional concomitant chemoradiotherapy in locally advanced head and neck cancer.

Materials & Method: Between February 2009 to August 2010 ,60 cases of locally advanced head and neck cancer were treated either inARM A receiving 2 cycles of induction therapy (q 3 weeks) with paclitaxel (day 1) and cisplatin (day 2), with Low dose fractionated radiation to gross disease followed by radiotherapy or in ARM B receiving chemoradiotherapy with 3 weekly cisplatin. After treatment all patients underwent clinical and radiological evaluation at the end of first three months, then six monthly till end point.

Result: The overall response rate (CR +PR) was (63% + 17%) 80% in the study arm (ARM A) and(50% + 13%) 73% in the control arm (ARM B).After a median follow up of 84 months out of the 30 patients in Arm A 16 are still alive while 14 patients died as compared to 12 patients being alive with 18 dead in the Arm B. The increase in CR, PR, OR was not however statistically significant (P= 0.43, P= 0.74, P= 0.76 respectably) due to the smaller sample size. The median overall survival for arm A is yet to be reached while that of Arm B is 36 months .The 5 yrs OS of Arm A is 60 months while that of arm B is 43.3 months. In our study acute reactions were more in Arm B. Hematological toxicitieswere more in Arm A with statistically significant p value for leucopenia & neutropenia but were manageable with G-CSF support. Late reactions were less in Arm A but not statistically significant.

Conclusion: Induction chemotherapy with Low dose fractionated radiation followed by conventional radiotherapy is a major treatment option in advanced upper aerodigestive tract cancer resulting in 63% CR with equivalent late toxicity & with less severe acute reactions apart from a higher but manageable incidence of hematological toxicities.

Key Words*: Lowdose fractionated radiation, carcinomas of head and neck, chemoradiotherapy, chemosensitiser*

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I. Introduction

Head neck cancers generally contributeto 25-30% of the total malignancies in India of which 80% are in the advanced stage. [1]Most advanced cancers in our country are treated with chemo-radiation with or without surgery. In spite of these approaches, about only 30% of patients achieve long-term remission and recurrence commonly occurs loco-regionally.[2] Neoadjuvant chemoradiotherapy and concomitant chemoradiotherapy are the two modalities that have been widely studied to improve the outcome and shown to produce response rates ranging from 60 to 90% [3] but unfortunately failed toproduce a significant impact on long-term patient survival. One novel approach to capitalize on the synergy between radiation and chemotherapy is the use of low doses fractionated radiation (LDFRT) as a chemotherapy enhancer along with paclitaxel and a platin.[4]

Rationaleof LDFRT: Until recently in the field of radiation biology, the initial slope of the radiation cell survival curve (doses of <1 Gy) was presumed to be an ineffective dose range for human tumor therapy. However, Joiner *et al.* [4, 5] revolutionized the way we think regarding low doses of radiation (<1 Gy) by demonstrating an initial phase of hypersensitivity to radiation (using doses <1 Gy). Increased resistance to

radiation was found from doses >1 Gy, a phenomenon termed Induced radiation resistance (IRR.) Low dose fractionated radiation (LDFRT) (defined as doses < 100 cGy) induces an initial phase of hypersensitivity called hyper-radiation sensitivity (HRS). This hypersensitivity is thought to be due to the induction of apoptosis without the initiation of pro-survival pathways that are seen at higher radiation doses. This phenomenon of HRS at low doses of radiation is most pronounced in radio-resistant cells, i.e. those with mutant p53 expression.[6, 7]The fact that HRS does not stimulate cellular repair mechanisms, such as those seen at higher doses, gives us a possible explanation of why there is no induction of radio resistance with HRS.

One of the functions of the tumor suppressor gene *p53* is the induction of apoptosis Wild-type p53 protein causes responseto radiation, by either G1 cell cycle arrest and/or apoptotic death. This effect of radiation is generally caused by activation of other downstream target genes, such as p21, waf1/cip1, and BAXwhich act as cross-point regulators that facilitates apoptosis [6, 8] Ionizing radiation also decreases BCL-2 protein(anti apoptotic) levels in p53 wild-type cell lines causing enhanced cell death [9].). However, it has been found that in cells with mutant p53 [10], no induction of p53 and p21waf1/cip1 protein occurs after radiation treatment. Rather exposure to radiation has shown to increase NF-kB activity. NF-kB activity targets the induction of BCL-2 protein and thereby produces radio-resistance among tumor cells [11]. This molecular signaling is considered to be the basis of Induced radiation resistance (IRR). Low doses of radiation(doses of <1 Gy) that induce hyper-radiation sensitivity (HRS) phenomenon were found to cause a significant increase in the pro-apoptotic protein BAX, with no induction of NF-kB activity, suggesting that the low doses of radiation have the potency to selectively induce proapoptotic pathways by inhibiting pro-survival pathways and thus eliminating the quandary of IRR.[12]

S A Krueger et al. in their study showed a relationship between apoptosis detected 24 h after low-dose radiation exposure and low-dose hyper-radiosensitivity in four mammalian cell lines and two normal human lymphoblastoid cell lines. This proved the hypothesis that enhanced sensitivity of cells to low doses of ionizing radiation is due to the failure of ATM-dependent repair processes to prevent the progression of damaged G_2-phase cells harboring unrepaired DNA breaks entering mitosis.[12]Shareef MM. et al in their study showed that LDFRT causes enhanced apoptosis when compared with the 2-Gy dose in squamous cell carcinoma oral cavity cell lines. They gave the evidence for the lack of induction of P-glycoprotein expression by LDFRT.[13]

It has been proven with evidence that p53 can be induced by a number of chemotherapeutic agents [14] .Paclitaxel is a chemotherapeutic agent (member of taxane family) that can to act as a cell cycle specific radiation sensitizer [14, 15] because it promotes and stabilizes premature microtubule assembly and consequently arrests cells in the radiosensitive G2 and M phases of the cell cycle [16, 17].This ability of Paclitaxel to arrest cells in G2-M is the backbone of the mechanism of Paclitaxel-induced radiosensitization[18].

In order to exploit the enhanced cell killing at low doses of radiation (at which HRS is observed) it was combined with systemic chemotherapy. LDFRT in combination with paclitaxel has been shown to enhance cell kill compared to either paclitaxel or LDFRT alone as shown in the study titled "Use of low-dose fractionated radiation (LDFRT) as a chemosensitizer of neoadjuvant paclitaxel (P) and carboplatin (CBCDA) for locally advanced squamous cell carcinoma of the head and neck (SCCHN): results of a new treatment paradigm" by Susanne Arnold, William Regine, Joseph Valentino, et al.[19]In another study bySwatee Dey et al. titled **"**Low-Dose Fractionated Radiation Potentiates the Effects of Paclitaxel in Wild-type and Mutant p53 Head and Neck Tumor Cell Lines" it was found that Paclitaxel caused enhanced radio-sensitization, irrespective of p53 status. Unfortunately, the chemo-potentiating effects of single 2 Gy dose radiation on Paclitaxel were not observed in p53 mutant cells. Low doses of 0.5 Gy in fractionated form significantly potentiated the effects of Paclitaxel and caused enhanced radiosensitization in both cell lines, irrespective of p53 function. [20]

II. Material and Methods

Study Design- Prospective Comparative Study

Study location-: Departmentof Radiotherapy, Medical College Hospital, Kolkata.

Study Population- Previously Untreated Patients with Biopsy Proven Squamous Cell Carcinomas of Head and Neck (Including Larynx, Laryngopharynx, Oropharynx, Hypopharynx, Oral Cavity, Tongue). They Will Be Locally Advanced (Stage III - IVB), With No Distant Metastasis, Attending the Outpatient Department of The Radiotherapy Department, Medical College Hospital, Kolkata.

Study Duration: February 2009 to August 2010

Sample size: Total 60 Patients, 30 Patients in Each Arm

Sample Design: Patients Attending Radiotherapy Department OPDwere distributed alternatively into Study Arm and Control Arm. Patients refusing toparticipate inthe study were excluded. Those patients not fulfilling the Inclusion Criterias were excluded.

Inclusion criteria:

1. Previously untreated patients with biopsy proven squamous cell carcinomas of head and neck (including larynx, laryngopharynx, oropharynx, hypopharynx, buccal cavity, tongue) that are locally advanced (stage III-IVB), with no distant metastasis, attending the outpatient department of the Radiotherapy department, Medical College Hospital, Kolkata.
2. Age >18 yrs to <75 yrs
3. An absolute neutrophil count of > 1000/uL and platelet count > 100,000/uL; serum total bilirubin < 1.5 mg/dL; Creatinine Clearance greater than 50 ml/min

Using an actual or calculated creatinine clearance using the formula:

$$\frac{(140 - \text{age}) \times (\text{weight in kg}) *}{(\text{Serum creatinine}) \times (72)}$$

*= multiply by 0.85 for females

4) Patients to sign a study-specific informed consent form prior to study entry.
5) ECOG performance status of 0, 1 or 2.

Exclusion criteria:

1. Patients suffering from cancer of salivary glands, nasopharynx & paranasal sinuses.
2. Associated uncontrolled co morbid conditions like diabetes mellitus, tuberculosis, and heart disease.
3. Pregnant / nursing females.
4. Patients with active infection not eligible for this protocol until the infection is treated and the symptoms have clinically resolved.
5. Prior induction chemotherapy, prior irradiation or surgery not to be allowed.
6. Patients with metastatic disease will not be eligible for this study.
7. Participation in any clinical trial simultaneously or in the last 30 days

Procedure methodology : Previously untreated patients, aged between 18 yrs to 75 yrs with biopsy proven squamous cell carcinomas of head and neck (including larynx, oropharynx laryngopharynx, hypopharynx, oral mucosa, tongue), who had locally advanced cancer (stage III - IVB), with no distant metastasis,ECOG performance status <3 and fulfilling all the inclusion criterias as mentioned later on were distributed into 2 arms in 1:1 ratio.

In study arm (**ARM A)** patients received two cycles of induction therapy with paclitaxel (175 mg/m2) over 3 hours on day 1 and cisplatin 75mg/m2 on day 2, every 3 weeks. On day 1 and day 2 of chemotherapy cycle, patients received two fractions of 80 cGy, separated by at least 6 hours. The first fraction was given within 2 hours of completing chemotherapy. The patient was given radiation therapy with fields encompassing gross disease only (including the primary and gross nodal disease) with a maximum 2cm margin. After 2 weeks of this induction therapy, patients received conventional radiotherapy (66 Gy in 33#). During radiation, parallel opposed fields with low anterior neck with central shielding were used along with thermoplastic masks for immobilization as far as practicable. The spinal cord was excluded from the radiation field after 44 Gy. CT based treatment planning was used as far as practicable when needed. External beam radiotherapy was delivered by the telecobalt machine Theratron 780C.

In control arm (**ARM B)** patients received conventional chemoradiotherapy (66 Gy in 33# with 3 weekly cisplatin -100 mg/m2 at day 1, 22, 43). During radiation, parallel opposed fields with low anterior neck with central shielding were used along with thermoplastic masks for immobilization as far as practicable. The spinal cord was excluded from the radiation field. CT based treatment planning was used as far as practicable when needed.. External beam radiotherapy was delivered by the telecobalt machine Theratron 780C.

Clinical response rates and safety were the primary and secondary endpoints, respectively.

Before starting therapy, all the patients were asked about any history of uncontrolled hypertension, gastrointestinal bleeding, gastrointestinal ulcer, hepatic and/or renal dysfunction, and/or insufficiency. All the patients were examined and Stages were assigned according to the 6 th edition of the American Joint Committee on Cancer (AJCC) TNM 2002 staging system. The patients' functional statuses were evaluated according to the ECOG performance status. Clinical examination, chest radiograph, ultrasonography of whole abdomen, computed tomography (CT) scan for primary tumor and the cervical lymph nodes and laboratory tests, including complete blood count (CBC), liver function tests (LFT), and renal function tests (RFT) were obtained from the patients as baseline as far as practicable.

For Arm A ie the study arm, clinical and radiological evaluation was done at end of Neoadjuvant chemotherapy with LDFRT, at end of radiotherapy treatment, 3 months after completion of treatment and then 6 monthly till end point. For Arm B ie the control arm, clinical and radiological evaluation was done at end of Concomitant chemoradiation treatment, 3 months after completion of treatment and then 6 monthly till end point. The patients were followed weekly during the radiotherapy treatment for both the arms. Grades of mucositis and dermatitis were determined based on the Radiation Therapy Oncology Group (RTOG) scoring

criteria. CBC, LFT, and RFT were checked weekly. The grades of the hematologic toxicities were also determined based on the RTOG scoring criteria. Complete response was defined as complete (100%) clinical and radiologic disappearance of the tumor. Partial response was defined as incomplete (less than 100% but more than 50%) clinical and radiologic shrinkage of the tumor. Less than 50% clinical and radiologic shrinkage of the tumor was considered as no response. The survival durations were calculated from the start date of RT or chemo till the events of treatment failure (locoregional control), death from any reason (overall survival) or the last follow-up.

III.Statistical Analysis -

The statistical analysis was done by first computing the observed and expected values from each of the observations, and then finding the chi-square value from the result. The Yates' continuity correction was done to make the chi-square approximation better. This was then utilized to calculate the two tailed p value and thus finding the significance of the result. P values < 0.05 were considered statistically significant. Our results were confirmed by the Fisher's test, which is a more exact test. The calculations were done using Statistical Package for Social Sciences, (SPSS Inc., Chicago,IL) software version 23.0 along with verification done at the website (www.GraphPad.com last accessed 17.01.2020).

IV. Results:

Total 60 patients were enrolled in the study (30 patients in each arm). The median age of the patients in ARM A was 57yrs while in ARM B it was 56. Distribution as per sex, performance status, presenting features, and histopathological grade were comparable in both arms as shown in Table 1, Table 2.

Table 1

VARIABLES		Arm A	Arm B
AGE	Between 40-50	4	3
	Between 50-60	15	16
	Between 60-70	11	11
SEX	Male	24	26
	Female	6	4
PERFORMANCE STATUS(ECOG)	0	14	15
	1	14	13
	2	2	2
DISEASE SITE	ORAL CAVITY(O)	4	4
	OROPHARYNX(OPX)	7	5
	HYPOPHARYNX(HPX)	4	5
	LARYNX(LX)	15	16

Table 2

VARIABLES		Arm A	Arm B
PRESENTING FEATURES	Dysphagia	27%	23%
	Odynophagia	7%	14%
	Hoarseness	23%	23%
	Foreign body sensation	17%	17%
	Neck mass	13%	10%
	Ulceration/ Ulceroproliferative mass	13%	13%
HISTOPATHOLOGICAL GRADE	Well differentiated	6	7
	Moderately differentiated	18	15
	Poorly differentiated	6	8

Distribution as per stage of disease was also comparable as shown in Table 3.

Table 3

ARM	T stage	N0	N1	N2a	N2b	N2c	N3
ARM A	**T1**	0	1	0	0	0	0
	T2	0	2	4	5	2	0
	T3	7	7	2	0	0	0
	T4	0	0	0	0	0	0
ARM B	**T1**	0	1	0	0	0	0
	T2	0	1	2	3	2	0

	T3	8	7	3	2	0	0
	T4	1	0	0	0	0	0

Grade III & IV mucositis was found to be 8(27%) in ARM A at 3 months, compared to 15(50%) in ARM B (**p=0. 1111**; not significant).Grade 3 & 4 dysphagia was 3(10%) in ARM A compared to 11(37%) in ARM B (**p=. 0326**; statistically significant). Grade II, III & IV skin reactions were12(40%) in the study arm at 3 months, while it was 24(80%) in the control arm (**p=. 0388**; statistically significant).AmongHaematological toxicities Grade III & IV Anaemia was found to be (27%) in ARM A at 3 months, compared to 15(50%) in ARM B (**p=0. 1111**; not significant). Table 4.

Table 4

ACUTE TOXICITY	ARM	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
ANAEMIA	**A**	**6**	**9**	**10**	**7**	**2**
	B	**9**	**10**	**8**	**3**	**0**
LEUCOPENIA	**A**	**2**	**2**	**8**	**13**	**5**
	B	**11**	**9**	**6**	**4**	**0**
NEUTROPENIA	**A**	**2**	**3**	**7**	**12**	**6**
	B	**9**	**10**	**6**	**5**	**0**
THROMBOCYTOPENIA	**A**	**15**	**7**	**6**	**2**	**0**
	B	**19**	**9**	**2**	**0**	**0**
MUCOSITIS	**A**	**0**	**5**	**17**	**8**	**0**
	B	**0**	**3**	**12**	**13**	**2**
DYSPHAGIA	**A**	**0**	**10**	**17**	**3**	**0**
	B	**0**	**6**	**13**	**9**	**2**
SKIN REACTION	**A**	**0**	**18**	**8**	**4**	**0**
	B	**0**	**6**	**15**	**7**	**2**

There were no statistically significant differences in late toxicities, Subcutaneousfibrosis (80% vs 83%; p=0.7386), Xerostomia (80% vs 83%; p=0.7386) and late laryngeal toxicity including edema (23% vs. 27%: p=0.7945) respectively. Table 5

Table 5

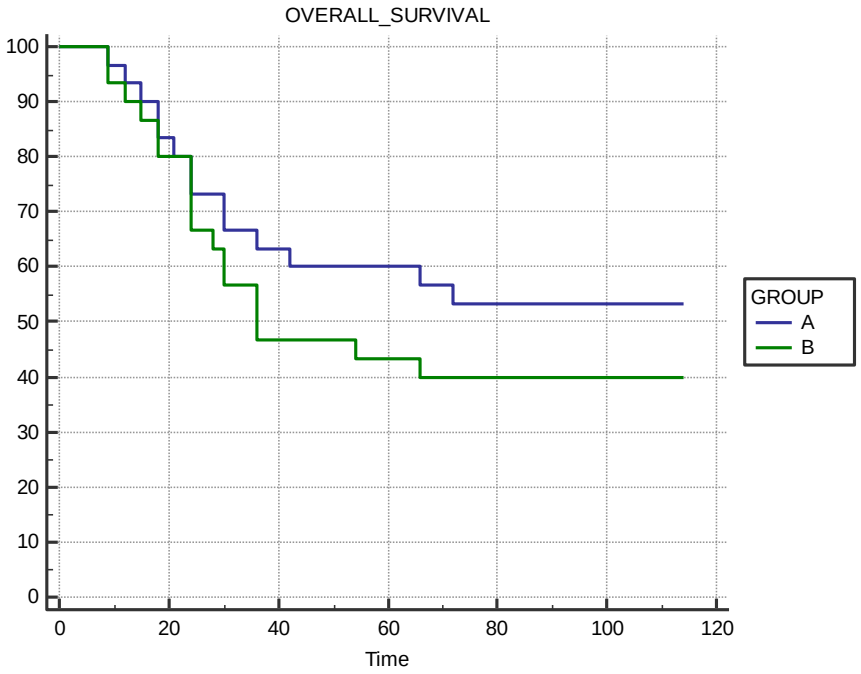
LATE TOXICITY	ARM	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SUBCUT FIBROSIS	**A**	**6**	**18**	**6**	**0**	**0**
	B	**5**	**17**	**8**	**0**	**0**
XEROSTOMIA	**A**	**6**	**17**	**6**	**1**	**0**
	B	**5**	**19**	**4**	**2**	**0**
LARYNGEAL TOXICITY	**A**	**12**	**7**	**0**	**0**	**0**
	B	**7**	**8**	0	**0**	**0**

Total 60 patients were enrolled in the study. The median follow up period was 84 months .The response rates (CR +PR) was (63% + 17%)80% in the study arm (ARM A) and(50% + 13%)73% in the control arm (ARM B).(Table 6)Of the 30 patients in Arm A 16 are still alive while 14 patients died as compared to 12 patients being alive with 18 dead in the Arm B. The increase in CR, PR, OR was not however statistically significant (P= 0.43, P= 0.74, P= 0.76 respectably) due to the smaller sample size.The median overall survival for arm A is yet to be reached while that of Arm B is 36 months .The 5 yrs OS of Arm A is 60 months while that of arm B is 43.3 months .

Table 6.

Arm A	Complete Response- 19 Pts. (63 %) Partial Response—5 Pts. (17%) No Response Or Progressive Disease 6 Pts (20%)	The Median Overall Survival Not Reached 5 YrsOs- 60%
Arm B	Complete Response- 15 Pts (50 %) Partial Response-7 Pts (23%) No Response Or Progressive Disease 8 Pts (27%)	The Median Overall Survival -36 Months 5 YrsOs- 43.3%

Figure 2. Kaplan meier curve analysis of survival in months



V. Discussion

Head neck cancer constitutes 25-30% of the total malignancies in India of which 80% are in the advanced stage. Affecting males about twice as much as females it is the 6th most common cancer for male and the 13th most common for female. Age of presentation is usually above 40 yrs. Most advanced cancers are treated with chemo-radiation with or without surgery. In spite of these approaches, about only 30% of patients achieve long-term remission and recurrence commonly occurs loco-regionally [1]. To improve the response and survival rate, emerged the concept of combining chemotherapy and radiotherapy. Neoadjuvant chemoradiotherapy and concomitant chemoradiotherapy are the two modalities that have been extensively studied to improve the outcome. Neoadjuvant chemotherapy has been administered prior to definitive therapy with response rates ranging from 60-90%, with pathologic CR rates documented in 30-70% of clinical responders. [2] However randomized trials have shown no improvement in overall survival. Because induction chemotherapy alone did not appear to improve long-term disease-free survival in advanced head and neck cancers with the previously available medicines, concomitant chemotherapy and radiation have been pursued in patients with, locally advanced head and neck cancers. The concept of synergy between radiation and chemotherapy is well established in vitro. Various schedules of radiation and chemotherapy have been utilized including weekly chemotherapy during radiation, chemotherapy given every three weeks during radiation and alternating chemotherapy and radiation.

One novel approach to capitalize on the synergy between radiation and chemotherapy is the use of low doses fractionated radiation (LDFRT) as a chemotherapy enhancer. In vitro data suggests that LDFRT enhances the response of both p53 wild type and p53 mutant cancer cell lines to chemotherapy. Not only was the cell death fraction increased, but there was no development of radioresistance in the cell lines studies when low doses of radiation were utilized as shown by Swatee Dey, Paul M. Spring, Suzanne Arnold, Joseph Valentino, et al. in their study titled "Low-Dose Fractionated Radiation Potentiates the Effects of Paclitaxel in Wild-type and Mutant p53 Head and Neck Tumor Cell Lines".[20] This strategy was translated into a clinical trial using four 80-cGy fractions of radiation with Carboplatin and Paclitaxel.

In the study titled "Use of low-dose fractionated radiation (LDFRT) as a chemosensitizer of neoadjuvant paclitaxel (P) and carboplatin (CBCDA) for locally advanced squamous cell carcinoma of the head and neck (SCCHN): results of a new treatment paradigm" by Susanne Arnold, William Regine, Joseph Valentino, et al. Of the 22 patients evaluable 36% had CR, 50% had PR ie overall 86% RR. Grade III or greater toxicities have included: neutropenia (43%), neutropenic fever (4%), non-neutropenic fever (8%), arthralgias / myalgias (12%) and allergic reaction (4%). No deaths have occurred during therapy. Conclusions: Chemosensitizing LDFRT combined with P and CBCDA provides a RR of 86%, with no disease progression and with tolerable side effects.[19] This effect of LDRT as a Chemosensitizing effect was also seen in tumours of upper abdomen(with gemcitabine) ,with pemetrexed in patients of NSCLC and also in patients of breast cancer, oesophageal cancer. [21, 22, 23]

The objective of this study was to expand our understanding of LDFRT and chemotherapy by using two cycles of induction therapy with paclitaxel (175 mg/m2) over 3 hours on day 1 and cisplatin 75mg/m2 on day 2, every 3 weeks with two fractions of 80 cGy radiation BID followed by conventional radiotherapy (66 Gy in 33#) and comparing the results with conventional chemoradiotherapy (66 Gy in 33# with 3 weekly cisplatin - 100 mg/m2 at day 1, 22, 43).

In our study during the course of the first 3 months, patients in the study arm were found to have lesser reactions in the acutely responding tissues than in the conventional concomitant chemoradiation arm. Grade III & IV skin reactions, dysphagia, mucositis was more in Arm B and first two mentioned toxicities were statistically significant. Among Hematological toxicities Anaemia (gr 3-4), leucopenia(gr 3-4) , neutropenia (gr 3-4) were more in Arm A withstatistically significant p value for leucopenia (p=0.0005) & neutropenia (p=0.0014)but those were manageable with GCSF support. 3 patients were lost on follow up of which 2 were in the control Arm.

We assessed the patients for locoregional control and toxicities to the late responding tissues. The overall response rates (CR +PR) was (63% + 17%) 80% in the study arm (ARM A) and(50% + 13%) 73% in the control arm (ARM B). Of the 30 patients in Arm A 16 are still alive while 14 patients died as compared to 12 patients being alive with 18 dead in the Arm B. The increase in CR, PR, OR was not however statistically significant (P= 0.43, P= 0.74, P= 0.76 respectably) due to the smaller sample size. The median overall survival for arm A is yet to be reached while that of Arm B is 36 months .The 5 yrs OS of Arm A is 60 months while that of arm B is 43.3 monthsLate reactions like Subcutaneous fibrosis (Grade III & IV) - (37% vs 43%; p=0.7921), Xerostomia (37% vs 40% ; p=0.7906), Late laryngeal edema - (40% vs. 47%; p=0.7945).were seen to be less (or equivalent) in Arm A but the results were not statistically significant. Again, this was consistent with most of the studies on this subject.

Our results reasonably match with the trials conducted on Low dose fractionated radiation however; the area where we have fallen short is that the number of the patients in the study is small only 60 patients. For statistically significant data we need to conduct the study among greater number of patients.

VI. Conclusion

Head and neck cancer constitutea major burden of cancers in India most of which are in the advanced stage.Surgery, radiation therapy & chemotherapy, alone or in combination have been the major forms of treatment. Radiotherapy used both in conventional fractionation or in altered fractionation regimes has formed the cornerstone of organ-preserving treatment practiced by radiation oncologist. The advent of concomitant chemotherapy with radiation therapy increased the response rates, but still the high recurrence risk and poor locoregional control (5-64%) results in low 5yr survival rate (rarely exceeded 40%). We wanted to expand our understanding of LDFRT and chemotherapy by using two cycles of Paclitaxel and Cisplatin plus LDFRT as induction therapy prior to definitive treatment (radiation). It was hoped that using LDFRT as a chemoenhancer would further increase the response rate seen with induction therapy in this population of patients thus adding an extra arsenal in our never-ending battle against Head and neck Cancer. Our studies indicated that the strategy of using LDFRT with chemotherapy can yield better response rate with minimal toxicities that can be easily countered. However, our study sample size was small for any remarkable statistical significance, hence larger randomized studies are to be done to explore this old but rather unexplored territory of radiation.

After a long follow up period we can conclude by saying that Induction chemotherapy with Low dose fractionated radiation followed by conventional radiotherapy is a major treatment option in advanced upper aerodigestive tract cancer, where upto 63% complete response rate can be obtained with equivalent late toxicity.

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