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NeoadjuvantChemotherapy Followed by Concurrent Chemoradiotherapy versus Chemoradiotherapy alone in Locally Advanced HNSCC –A Retrospective study in a Medical college in WestBengal India

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Abstract
Introduction: Locally advanced Head and neck cancers (LAHNSCCs) are commonest mode of presentation in HNSCC (Head neck squamous cell carcinoma) in Rural area in india.The use of induction chemotherapy for locoregionally advanced squamous cell HNC become to be an attractive treatment option . The dramatic tumor response seen in Treatment naïve patients after cisplatin-based chemotherapy regimens would definitely suggest that an improvement in. locoregional control and even survival should also result. In our study NACT(neoadjuvant chemotherapy) were given to all LAHNSCC patients followed by comparison between chemoradiation versus only radiation in rural medical college
Materials& methods:-Biopsy proven nonmetastatic LAHNCC were randomized in two arms. one arm received neo adjuvant chemotherapy with inj. Paclitaxel 175 mg/ m2 and inj. Carboplatin AUC 6 iv q21 days followed by concurrent chemoradiotherapy (66 Gy/33#/6week 3 days) & another arm received upfront concurrent chemoradiotherapy (66 Gy/33#/6week 3 days). Only patients received 3 weekly concurrent inj. Cisplatin 100 mg/m2 was included for data evaluation. We have evaluated retrospectively in last 5 years from year 2013-2018 all Histopathologically proven non-metastatic LAHNSCC attending Radiotherapy Outpatients Department of RGKAR Medical College and Hospital, Kolkata.Results: There were 213 patients in total selected for data analysis. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy received in 104 patients and 109 patients received upfront concurrent chemotherapy. After completion of full treatment we have found that 65% in neoadjuvant chemotherapy followed by concurrent chemo radiotherapy(ARM A) achieved complete response than 60% in upfront concurrent chemo radiotherapy arm (ARM B) There is no significant late toxicity observed between 2 arms. Conclusions: Our study failed to show any statistically significant improvement in Response rate by adding Neoadjuvant chemotherapy to standard treatment of chemradiotherapy in Locally advanced head neck cancer(LAHNSCC).

Key words-*LAHNCC, Neoadjuvant chemotherapy, chemoradiotherapy,*

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I. Introduction:

Head and neck cancer is common in several regions of the world. The primary risk factors associated with head and neck cancer include tobacco use, alcohol consumption, human papillomavirus (HPV) infection (for oropharyngeal cancer), and Epstein-Barr virus (EBV) infection (for nasopharyngeal cancer).Worldwide, head and neck cancer accounts for more than 650,000 cases and 330,000 deaths annually [1]. In the United States, head and neck cancer accounts for 3 percent of malignancies, with approximately 53,000 Americans developing head and neck cancer annually and 10,800 dying from the disease [2]. In Europe, there were approximately 250,000 cases (an estimated 4 percent of the cancer incidence) and 63,500 deaths in 2012 [3].Head and neck cancers are a significant problem in our country constituting approximately one-third of all cancer cases in contrast to 4–5% in the developed world.[4] Squamous cell carcinoma (SCC) is the most frequent histological type in head neck cancer including all subsides.Patients with advanced head and neck squamous cell cancer (HNSCC) have still a relative poor clinical outcome. [5][6][7]More than 50% of patients

with HNSCC will be diagnosed with locoregionally advanced and technically unresectable disease, or a resection will lead to a significant mutilation or a bad functional outcome. [8]. Randomized controlled trials have shown that cisplatin containing chemotherapy (CT) administered concurrently to RT improves OS in HNSCC-patients treated either by surgery and adjuvant RT-CT or definite treatment with RT-CT [9]. Conversely, adjuvant CT after completion of adjuvant or definite RT does not improve clinical outcome [9]. Induction CT with cisplatin and 5-FU before definite treatment with RT was associated with a small benefit in OS mainly as the consequence of a reduced distant failure rate. Neoadjuvant chemotherapy aims to reduce the initial bulk of disease with organ preservation, alleviating the symptoms and improving the quality of life. In addition NACT is beneficial in better control of distant metastases. This was rationality for using NACT in study. But the when coming to definitive treatment, chemoradiation or only radiation still remains unclear for subset of inoperable LAHNSCC patients presenting with bulky and fixed primary / nodal disease or complicated with co-morbidities. [10]. In our present study we aimed to reevaluate the data that neo adjuvant chemotherapy before definitive CTRT whether have any statistically significant difference than CTRT alone.

II. Material & Methods:

We have evaluated retrospectively in last 5 years from year 2013-2018 all Histopathologically proven non-metastatic LAHNSCC attending Radiotherapy Outpatients Department of RGKAR Medical College and Hospital, Kolkata. Eligibility criteria included patients of either sex, older than 18 years upto 70 years with normal baseline complete blood count(Hb > 10 gm/dl, ANC > 1500/µl, platelets > 100,000/µl,), liver and renal function tests (total serum Bilirubin <1.5 mg/dl and serum creatinine<1.5mg/dl), histopathologically proven head and neck squamous cell carcinoma, ECOG performance status 0-2, locally advanced disease (stage III & IVA, according to the AJCC 8th edition staging manual). Patients data were collected according to 2 arm , one arm received anterior neo adjuvant chemotherapy with inj. Paclitaxel 175 mg/ m2 and inj. Carboplatin AUC 6 iv q21 days followed by concurrent chemoradiotherapy (66 Gy/33#/6week 3 days) & another arm received upfront concurrent chemoradiotherapy (66 Gy/33#/6week 3 days). Only patients received 3 weekly concurrent inj. Cisplatin 100 mg/m2 was included for data evaluation. The data was collected in predesigned worksheet and analyzed using Microsoft Excel Office 2007 and SPSSv17, IBM Corp, Chicago. The study was conducted after institutional ethical committee approval

III. Results:

There were total two hundred and thirteen patients(n- 213) patients in total selected for data analysis. Neoadjuvant chemotherapy followed by concurrent chemoradiotherapy received in 104 patients and 109 patients received upfront concurrent chemotherapy. During analysis we have found 144 male patients & 69 female patients.

The baseline characteristics of the patients are tabulated in table no.1.

Residential Status of patient		
Category	Frequency	Percentage
Urban	125	58.7
Rural	88	41.3
Total	213(n)	100
Educational Status		
Category	Frequency	Percentage
Graduate	2	0.9
High school passed	16	7.5
Middle school passed	59	27.7
Primary school passed	70	32.9
Illiterate	66	31.0
Total	213(n)	100
Socioeconomic Status		
Category	Frequency	Percentage
Upper	0	0
Upper middle	62	29.1
Lower middle	89	41.8
Upper lower	57	26.8
Lower	5	2.3
Total	213(n)	100

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Illiterate	66	31.0
Total	213(n)	100
Socioeconomic Status		
Category	Frequency	Percentage
Upper	0	0
Upper middle	62	29.1
Lower middle	89	41.8
Upper lower	57	26.8
Lower	5	2.3
Total	213(n)	100

The location of the primary tumor was tabulated in table 2. Arm A received NACT followed by concurrent chemo radiotherapy & Arm B received upfront concurrent chemo radiotherapy

Table 2 : Location and Stage of the Primary tumor at diagnosis

PRIMARY SITE	Arm A	Arm B
ORAL CAVITY	**34**	**27**
OROPHARYNX	**32**	**35**
LARYNX + PHARYNX	**33**	**38**
MAXILLA	**5**	**9**
STAGE		
III	**41**	**40**
IV	**63**	**69**

After completion of full treatment we have found that 65% in neoadjuvant chemotherapy followed by concurrent chemo radiotherapy achieved complete response whereas 60% in upfront concurrent chemo radiotherapy arm.

Table 3: Response after complete treatment

RESPONSE AFTER COMPLETE TREATMENT	***Arm a***	***Arm b***	***p value***
CR	67	65	0.3329
PR	20	30	
SD / PD	17	14	

Table 4 showing the RTOG late toxicity observed between 2 arms. There is no significant late toxicity observed between 2 arms

Table 4. RTOG Late TOXICTIES			
ORGANS	**ARM A**	**ARM B**	**P VALUE**
DRYNESS of MOUTH			0.13
GR 1	37	28	
GR 2	28	10	
GASTROINTESTINAL			0.52
GR 1	18	10	
GR 2	6	2	
GR 3	2	0	
DYSPHAGEA			0.44
GR 1	30	17	
GR 2	10	8	
GR 3	2	0	
MYELOPATHY			0.53
GR 1	5	2	

GR 2	1	0	0.

IV. Discussion:

Data from the Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) illustrating that the major therapeutic benefit of platinum-based chemotherapy results from an improvement in locoregional disease control when the drugs are given concurrently with radiotherapy. No significant improvement occurs with induction chemotherapy followed by radiotherapy . Randomized controlled trials have shown that cisplatin containing chemotherapy (CT) administered concurrently to RT improves OS in HNSCC-patients treated either by surgery and adjuvant RT-CT or definite treatment with RT-CT [9]. Conversely, adjuvant CT after completion of adjuvant or definite RT does not improve clinical outcome [9]. Induction CT with cisplatin and 5-FU before definite treatment with RT was associated with a small benefit in OS mainly as the consequence of a reduced distant failure rate. Neoadjuvant chemotherapy aims to reduce the initial bulk of disease with organ preservation, alleviating the symptoms and improving the quality of life. In addition NACT is beneficial in better control of distant metastases. This was rationality for using NACT in study. But the when coming to definitive treatment, chemoradiation or only radiation still remains unclear for subset of inoperable LAHNSCC patients presenting with bulky and fixed primary / nodal disease or complicated with co-morbidities. [10]. In our present study we aimed to reevaluate the data that neo adjuvant chemotherapy before definitive CTRT whether have any statistically significant difference than CTRT alone. GORTEC 94-01 compares definitive Radiotherapy (70 Gray with 2 gray fraction) versus Chemoradiotherapy with concomitant Carboplatin & 5FU.There is significant improvement in Local control, DFS(disease free survival) & OS(overall survival). In our study addition of Neoadjuvant chemotherapy does not cause any statistical significant advantage in terms of response rate as well as Toxicity.So we usually prefer concomitant chemoradiotherapy without Neoadjuvant chemotherapy in the management of LAHNSCC(locally advanced head neck squamous cell carcinoma) .

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