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Original Research Article

RolesofConcurrentChemo-RadiotherapyandRadiotherapyAloneintheManagementofMalignanciesofHeadandNeckInaTertiaryCareHospital

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Abstract:

Background: Optimization of dose of radiation therapy (RT), fractionation, normal-tissue sparing, and technology has helped treating malignancies of the Head and Neck. Introduction of the combination of chemotherapy and radiotherapy has increased the tumor control and preservation of organ integrity. This study compares the final outcome of these two methods in treating the Head and neck cancers.

Aim of the study: To compare the outcome of the advanced stages of Head and neck malignancies with concurrent chemo-radiation and radiation alone in terms locoregional control (tumor regression), recurrence, survival and complications.

Materials: A randomized prospective study was conducted between Jan 2018 to Dec 2020 in the Department of Radiation Oncology, Viswabharathi Medical College and General Hospital, a tertiary teaching Hospital in Kurnool, Andhra Pradesh. 63 patients with advanced stages (stage III and IV) of Head and Neck Malignancies were included. Group A (33) patient with Head and Neck malignancies treated with Radiotherapy alone and Group B (30) patients treated with Concurrent chemotherapy and Radiotherapy. Patients to both the groups were allotted by a random number generated online at randomnumber.com. Patients diagnosed aged above 18 years were included. Patients of both the genders were included. Patients with histology of the tumors showing as squamous cell carcinoma were included. Patients with unresectable tumors were included. Patients with advanced stages (stage III and IV) were included. Patients with Eastern Cooperative Oncology Group (ECOG), (21), 1982 performance status between 0 and 02 were included.

Results: 63 patients Head and Neck malignancies were grouped as A (33) and B (30) patients. Group A received EBRT alone and B group concurrent chemo-radiation. There were 22 (34.92%) male patients in group A and 20 (31.74%) male patients in group B and there were 11 (17.46%) female patients in group A and 10 (15.87%) female patients in group B. The mean age in group A was 56.78±4.70 years and the mean age in the group B was 54.30±5.15 years. The age and gender, ECOG status, TNM staging and gross staging of the malignant diseases observed in the patients of both the groups included in this study had no statistical significant difference. (p- Value more than 0.05)

Conclusions: The advantage of Combine chemo-radiation versus Radiotherapy alone was found to be only marginal and failed to show any positive significant advantage of concurrent chemo-radiotherapy over EBRT alone. In terms of overall response rates at the end of 06 months was ranging from 85.3% to 93% in the study. The limitations to this study are relatively short follow-up and small sample size.

Keywords: Cancer, Head and Neck, Radiotherapy, Chemotherapy and Tumor Regression.

Introduction

The prevalence of Head and Neck malignancies is at 70% especially in the developing countries. [1] Head and Neck malignancies account for 4th largest group among all the other malignancies in human beings worldwide [2] More than 5, 50, 000 cases of Head and Neck malignancies are registered every year from all over the world and among them nearly 3, 00, 000 die due to failure and complications. [3] In India alone nearly 2, 00,000 new patients report to the cancer hospitals all over. [4] In India the malignancies of Head and Neck region account for second commonest malignant

tumors. [5] Among the males it is the most common and among the women it is the 4th largest group in India. [6] The Male to female ratio of Head and Neck malignancies ranges from 2:1 to 4:1 in India. [7] 90% of the Histopathology diagnosis of Head and Neck malignancies is squamous cell carcinomas (HNSCC). [8] This could be due to rampant usage of alcohol and tobacco either alone or in combination. [9]

In the treatment of Head and Neck malignancies, Radiotherapy helps in improving the clinical outcome, functional ability of the affected organ. Nearly 75% of the cancer patients are treated with it now either primarily or as an adjunct therapy either before or after surgery. [10] These patients can also be treated using concomitantly with chemo-radiotherapy when diagnosed in early stages which sometimes can replace surgery. [11] Radiotherapy could also be used to preserve the organ function by avoiding surgery especially in patients with carcinoma larynx. [12] Evaluation of the tumor mass by physical examination, multimodality imaging helps in obtaining 3-dimensional anatomic details. [13] Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography-computed tomography (PET CT) play important roles to evaluate and planning in the treatment based on volume of the tumor, its outline and surrounding normal tissues. [14] CT scan combined with MRI helps in better understanding soft tissue details whereas PET-CT scan helps in knowing the functional and metabolic details.[15] Gross tumor Volume (GTV) includes the primary cancer with its lymph node regions and considered as the areas of gross disease. [16] The microscopic cancer involvement of the tumor mass with its spread to the immediate neighboring tissues is called as the clinical tumor volume (CTV1). The total area of GTV and clinical tumor volume CTV1 enlarged to 2.5 to 10 mm was aimed for radiation called as planning target volume (PTV1). PTV1 is based on the microscopic evaluation of the surgical specimens. [17] The usual total dose of radiation is 66 to 74 Gy (Gray units) in 2 Gy fractions or 81.6 Gy in 1.2 Gy fractions.[18] Concurrent to radiotherapy many chemotherapeutic agents are used such as Cisplatin (DDP), 5-fluorouracil, Mitomycin, and Hydroxyurea. These are acting as radio-sensitizers and act as adjuncts to radiotherapy [20] such treatment was proved to be useful in the survival over treating with radiotherapy alone. This may be due to their role in producing good locoregional control. The present study was a randomized prospective study conducted at a cancer unit of tertiary teaching Hospital in Kurnool, Andhra Pradesh.

Materials: The present study was a randomized prospective study conducted at Department of Radiation Oncology, Viswabharathi Medical College and General Hospital, a tertiary teaching Hospital in Kurnool, Andhra Pradesh. Totally 63 patients diagnosed with advanced stages (stage III and IV) of Head and Neck Malignancies were included. They were divided into two groups. Group A consisted of 33 patients with Head and Neck malignancies treated with Radiotherapy alone and Group B consisted of 30 patients treated with Concurrent chemotherapy and Radiotherapy. Patients to both the groups were allotted by a random number generated online at randomnumber.com. An institution ethics committee approval was obtained before commencing the study. An ethics committee approved consent letter and proforma were used.

Inclusion Criteria: Patients diagnosed with malignancies of Head and Neck was included. Patients aged above 18 years were included. Patients of both the genders were included. Patients with histology of the tumors showing as squamous cell carcinoma were included. Patients willing to participate in this study were included. Patients with unresectable tumors were included. Patients with advanced stages (stage III and IV) were included. Patients with Eastern Cooperative Oncology Group (ECOG), (21), 1982 performance status between 0 and 02 were included.

Exclusion Criteria: Patients aged below 18 years and above 70 years were excluded. Patients with tumors not showing squamous cell carcinoma of histology were excluded. Patients with co-morbid conditions like, diabetes, hypertension, liver diseases, renal diseases, and endocrinal diseases were excluded. Patients with Immune-compromised diseases were excluded. All the patients were subjected to hematological, radiological and endocrinal investigations. Group B 30 patients received induction chemotherapy of three cycles with Inj. Paclitaxel 175 mg/m^2 on day 01, Inj Cisplatin 80 mg/m^2 in two divided doses given on day 01 and day 02 and Inj 5FU 1 Gm/m^2 on the day 01 & 02. Inj G-CSF was given after 48 hours of TPF chemotherapy cycle in all these patients in the study. Prophylactic Ciprofloxacin (500mg/ oral route twice daily) was given to all the patients from days 06 to 12 after TPF chemotherapy cycle. After a gap of 03 to 04 weeks the patients were subjected to two arms of either CTRT (arm A) or EBRT alone (arm B). Patients in arm A consisted of 66Gy in 33fr (2Gy per fraction), given daily (5 days per week) for 5 weeks (conventional fractionated radiotherapy) with 3 weekly Inj Cisplatin 80mg/m^2 divided in two days. PTV1 included primary tumor and neck nodes regions. Usually parallel right and left opposing lateral fields were planned. The dose was prescribed at midline. External beam radiotherapy (EBRT) was given with radiation therapy

parameter on cobalt-60 machines or Theratron 780E/ 780C/Bhabhatron II with photon energies of 1.25MeV. The minimum treatment distance planned was more than or equal to 80 cm SSD. Patients of group A (33 patients) received EBRT alone, same as arm B without concurrent chemotherapy.

All the patients were closely monitored after every course of chemotherapy and prior to & during radiotherapy. The response to the treatment was assessed by observing the control of symptoms and any treatment related morbidity. Regular laboratory tests were repeated like complete blood counts, biochemistry profile consisting of RFT & LFT, ENT examination, chest X-ray, USG Abdomen. Toxicity of the chemotherapeutic agents was closely monitored by doing Hematological, renal, bio-chemical, skin reactions and disease response were assessed. After completion of treatment follow up started 04-06 weeks later. Patients were again assessed for treatment response and symptoms relief by conducting clinical and general examination, ENT examination, Hemogram, RFT, RBS & CECT head and neck.

Toxicity was assessed by conducting metastatic workup using chest X-ray, USG Abdomen and LFT. In this study the primary object was to study and compare the efficacy of concurrent chemotherapy over EBRT alone. Result of both groups were analyzed and compared in terms of tumor response, symptom relief and treatment related toxicities.

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

N.B: Adopted from (21) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am. J Clin Oncol. 1982 Dec;5(6):649-655.

Results

The present study included 63 patients with different types of Head and Neck malignancies grouped as A and B, in the former 33 patients received EBRT alone, and the later B group 30 patients received concurrent chemo-radiation. There were 22 (34.92%) male patients in group A and 20 (31.74%) male patients in group B and there were 11 (17.46%) female patients in group A and 10 (15.87%) female patients in group B. The mean age in group A was 56.78±4.70 years and the mean age in the group B was 54.30±5.15 years. The youngest and eldest patients in the group A were aged 24 and 67 years and the similar ages of group B patients were 21 and 68 years. The ECOG status of patients of both the groups, TNM staging of both the groups and the types of statistical significance was observed in the study was tabulated in Table 1.

The age and gender, ECOG status, TNM staging and gross staging of the malignant diseases observed in the patients of both the groups included in this study had no statistical significant difference. (p- Value more than 0.05)

Table 1: Showing the age and gender, ECOG status, TNM staging and gross staging of the malignant diseases observed in the patients of both the groups (n-A group-33; n- B Group- 30)

Observations	Group A 33	Percentage	Group B 30	Percentage	P value
Age in Years					
18 to 37	03	09.09	01	03.33	
38 to 47	08	24.24	06	20	0.147
48 to 57	12	36.36	10	33.33	
58 to 67	09	27.27	11	36.36	
68 to 70	01	03.03	01	03.33	
Gender					
Male	22	66.66	20	66.66	0.243
Female	11	33.33	10	33.33	
ECOG					
0	02	06.06	01	03.33	0.311
01	18	54.54	16	53.33	
02	13	39.39	13	43.33	
Tumor staging					

T2	03	09.09	02	06.66	
T3	23	69.69	25	83.33	0.410
T4	07	21.21	03	10	
Nodal staging					
No	05	15.15	04	13.33	
N1	12	36.36	09	30	0.112
N2	14	42.42	16	53.33	
N3	02	06.06	01	03.33	
Anatomical site					
Oral cavity- 05	03	09.09	02	06.66	
Tongue-04	02	06.06	02	06.66	
Buccal mucosa- 05	02	06.06	03	10	
Tonsil- 07	04	12.12	03	10	
Oropharynx- 06	03	09.09	03	10	
Hypopharynx- 05	02	06.06	03	10	
Nasopharynx- 04	02	12.12	02	06.66	
Larynx					
Supra Glottis- 04	02	12.12	02	06.66	0.233
Glottis- 01	01	03.03	00	00	
Sub Glottis- 06	04	12.12	02	06.66	
Thyroid- 08	04	12.12	04	13.33	
Lymph nodes					
Hodgkin's- 05	03	09.09	02	06.66	
Non-Hodgkin's- 03	01	03.03	02	06.66	

There was no mortality in both the groups during the period of entire study. All the patients in both the groups received complete treatment. It was observed that in 06.06% (2/33) of the group A patients and 10 (3/30) patients showed loss of weight during the treatment. Totally 07.93% (5/63) patients showed loss of weight. All the patients were followed for 06 months starting from at 04 weeks, 03 months and at 06 months' time. At the end of 04 weeks follow up of the group A, 26/33 (78.78%) patients showed regressive disease, 01/33 (03.03%) patient found to have stable disease, 01/33 (03.03%) patient had progressive disease) which was not showing statistical significance (p value less than 0.05). At the end of 04 weeks follow up of the group B, 25/30 (85.33%) patients showed regressive disease, 03/33 (10%) patient found to have stable disease, 02/30 (06.66%) patient had progressive disease which was not showing statistical significance (p value less than 0.05). Follow up of group A patients for 03 months showed 28/33 (84.84%) patients showed regressive disease, 02/33 (06.06%) patient found to have stable disease, 03/33 (09.09%) patient had progressive disease) which was not showing statistical significance (p value less than 0.05). Follow up of group B patients for 03 months showed 28/30 (93.33%) patients showed regressive disease, 02/30 (06.66%) patient found to have stable disease, 01/30 (03.33%) patient had progressive disease which was not showing statistical significance (p value less than 0.05). At the end of the 6 months follow up in group A, it was observed that 30/33 (90.90%) patients showed regressive disease, 02/33 (06.06%) patient found to have stable disease, 01/33 (03.03%) patient had progressive disease) which was showing statistical significance (p value less than 0.05). Similarly in group B it was observed that 28/30 (93.33%) patients showed regressive disease, 01/33 (03.33%) patient found to have stable disease, 01/30 (03.33%) patient had progressive disease) which was showing statistical significance (p value less than 0.05). In the study there was no incidence of chemotherapy reactions or toxicity features, hematological and other than hematological complications were observed. Anemia, Neutropenia and GIT symptoms were manageable in all the patients. The incidence of Grade 3 neuropathy was observed in 05/63 (07.93%) patients, stomatitis in 09/63 (14.28%) patients and radiation dermatitis in 11/63 (17.46%) patients. (Table 2)

Table 2: Shows the response to the two modalities of treatment among the two groups (n-A group-33; n-B Group- 30)

Observations	**Follow up 4 weeks**		**Follow up- 03 months**		**Follow up- 06 months**	
	Group A	**Group B**	**Group A**	**Group B**	**Group A**	**Group B**
Regressive Disease	26	25	28	27	30	28
Stable Disease	03	03	02	02	02	01
Progressive disease	04	02	03	01	01	01
P value	0.114	0.341	0.221	0.114	**0.046**	**0.031**

Discussion

Treatment of head and neck cancer is a multidisciplinary involvement because Head and Neck cancers are complex with multiple sub sites. It requires participation of the surgeons, Radiation oncologist, medical oncologist, and physicists to plan and execute the successful treatment using chemotherapy and radiotherapy based on the nature of the malignant disease. These cancers also require therapies to include the need for support teams who give speech and swallow therapy, physical therapy, occupational therapy, smoking cessation programs, and nutrition. [22]

The treatment plan depends largely upon the site and stage of the tumor, neighbouring vital organs and the consent of the patients to accept radiation therapy alone or combined chemotherapy and radiotherapy. Radiation therapy can be administered in post-surgery patients either as definitive or adjuvant form, sometimes even for palliation of symptoms. A definitive concurrent chemo-radiation (CRT) could be used, keeping the choice of surgery as salvage therapy method, which is known as organ-preservation approach. [23] Overgaard et al. [23] from their multicentre randomized controlled trial (RTC), discussed the advantages of increasing the fractions of RT in a week from 05 to 06to achieve a better primary tumor control. In their study with 06 fractions a week demonstrated good primary tumor control at 76% vs. 64% (hazard ratio [HR] 0.63, 95% CI 0.49–0.83; p = 0.004). In this study 05 fractions per week was used in 07/33 (21.21%) of the group A and 07/30 (23.33%) of the group B showed a good tumor control in 85.3% of the cases each. Rosenthal et al [24] from their phase III RCT study with 264 subjects diagnosed with stage III-IV SCC of the oral cavity, oropharynx, or hypopharynx malignancies who were treated with radiation doses of 57.6 Gy or 63 Gy for low risk areas and 63 or 68.4 Gy for high-risk regions with over 1.8 Gy per fraction showed that the overall survival (OS) rates for 5- and 10-year marks were found to be 32% and 20%, respectively. They also suggested that by simply increasing the without adjuvant chemotherapy does not improve tumor control.

In this study the overall tumor control and functional preservation was found in 85.3% of the patients. However, the total treatment package time (TPT) less than 85 days demonstrated good results in terms of locoregional control compared to >85 days for dose levels >60 Gy. Shortening TPT in the study improved cancer specific survival (CSS), locoregional control (LRC). Review of literature showed that there was no clear role for adjuvant chemotherapy with RT for NPC patients. It gave mixed results and its efficacy and selection of chemotherapy are being evaluated in the NRG HN001 study based on EBV levels. [25] In this study 02/33 in group A and 02/30 in group B patients in each of the two groups were found to have equivocal results with good tumor control and disease free status till the end of the study in 89.32% of the cases. Forastiere et al [26] discussed several phase III trials for laryngeal cancer patients and supported both hyper fractionation and accelerated fraction treatments which demonstrated a 10–15% in LRC of the primary tumor. In this study 11/33 patients of group A and 08/30 of the group B patients were treated for carcinoma larynx and LRC was 93% in the group A and 93.22% in the group B patients.

The studies in the literature discuss about de-intensification of therapy for HPV and Oro-pharyngeal squamous cell carcinoma (OPSCC) patients when they are appropriately selected which had yielded promising results. Multiple clinical trials have shown that 2-year and 3-year PFS and OS are comparable to standard treatment with the benefit of reducing RT-related toxicities. Patients with Head and Neck malignancies with low recurrence risk are only likely to be benefited from (Stage <T4, <N2c disease, less than 2 packs per day smoking) from treatment de-escalation. Such reduced RT dose could significantly lessen the chances of patients developing swallowing and nutritional complications. [27]As per the results shown by Delaney et al. RT was indicated at some point in 74% of all patients with head and neck carcinoma. Using chemotherapy before radiotherapy as an induction was investigated elaborately during the last decade but there is no proof of survival benefit from it. [28] The chances of developing locoregional recurrences were found to be discouraging. In addition, patients receiving induction chemotherapy refuse local therapy with RT and for this reason their survival may also compromised. [29] No patient expired during the present study in both the groups during 6 month follow up. All the complications were treated successfully in the study with conventional medical treatment.

Conclusion

The advantage of Combine chemo-radiation versus Radiotherapy alone was found to be only marginal and failed to show any positive significant advantage of concurrent chemo-radiotherapy over EBRT alone. In terms of overall response rates at the end of 06 months was ranging from 85.3% to 93% in the study. The limitations to this study are relatively short follow-up and small sample size.

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