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Original Research Article

A Comparative Evaluation of Toxicity and Tumor Control in Well Lateralized Oral Cavity and Oropharyngeal Carcinoma Treated with Ipsilateral Versus Bilateral Irradiation Techniques

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Abstract

Background: There is growing evidence in the literature that patients with early oropharyngeal and oral cavity cancer have a low incidence of contralateral node involvement, hence, radiation therapy can be limited to the ipsilateral neck, without compromising loco-regional control. Aim of this study to document comparison of toxicity and tumor control for well lateralized carcinoma of oral cavity and oropharynx treated with the ipsilateral versus bilateral radiation techniques.

Material and Methods: A total 50 patients with well lateralized carcinoma of oral cavity and oropharynx were randomly divided in two groups; group A and B patients which were treated ipsilaterally and bilaterally respectively at our centre ATRCTRI, Sardar Patel medical college, Bikaner. Concurrent chemotherapy with cisplatin 100mg/m2 every three weeks as per standard indications were given.

Inclusion Criteria: Histologically proven SCC of oral cavity (RMT, Lateral alveolar ridge, BM, GBS) and oropharynx (Tonsil, Tonsillar pillar), Stage included T1-3, N1-2a.

Results: Age, gender, socioeconomic status, cancer stage and other baseline characteristics were comparable between both groups ($p>0.05$). Grade-3 mucositis was found in 36% patients in arm A and 56% in arm B, Grade-3 skin toxicity in 12% patients in arm A and 32% in arm B and Moderate dysphasia was found in 20% patients in arm A and 64% in arm B at the end of treatment. Xerostomia was statistically insignificant. Loco-regional control at the end of the treatment was found in all patients.

Conclusion: According to the findings of our study, individuals with HNC who underwent unilateral radiotherapy experienced less toxicity and no statistical significant recurrence was found over 6-month follow-up period. It is recommended to confirm a large RCT that involves longer follow-up at multiple centers.

Keywords: Ipsilateral and bilateral irradiation, Head and neck cancers, well lateralized, Toxicity, Tumor control.

Introduction

Cancers listed among the leading cause of morbidity and mortality worldwide, with approximately 19.2 million new cases and 9.95 million cancers related deaths in 2020 and 50.5 million prevalent cases in all age groups GLOBOCAN [1]. On the Indian scenario, 1.3 million new cancer cases were estimated, indicating India as a single country (of the 185 countries) contributing to 10.43% of the global cancer burden; mortality figures were 8,51,678 contributing to 7.05% of global cancer deaths in 2020 GLOBOCAN. Head and neck malignancies are the seventeenth most common malignancies, worldwide and second most common malignancy in India (1st most common in males while 4th most common in females. The main risk factors associated with HNSCC are environmental and lifestyle factors such as chewing tobacco, alcohol

consumption and smoking. Recently epidemiological studies have emerged a strong association with human papillomavirus (HPV) in subset of HNSCC and in non-smoking cases.

Other risk factors associated with prevalence of HNSCC are poor dental hygiene, poor nutrition, immunosuppressant, sub-mucous fibrosis, gastrointestinal reflux, different inherited syndromes and chronic iron deficiency anemia. Population based cancer registry in India projects that the number of tobacco related cancer and head and neck cancer would be 3,16,734 and 2,18,421 respectively by 2020.

Head and neck cancers (HNC) are the malignancies arising from the base of skull to the thoracic inlet. Quality of life in this patient is poor as they suffer from socially awkward condition. They are persistently symptomatic which includes pain, bleeding, mucositis, dysphagia, difficulty in swallowing, excessive salivating and most disturbing is proliferative growth that disfigures the face.

The optimal management of head and neck cancer requires a multidisciplinary approach. Surgery and radiotherapy are the major treatment modalities. The major goal of radiotherapy is to achieve local control of the tumor while minimizing damage to the critical organs. [2]

Radiotherapy is the main non-surgical treatment for squamous cell carcinoma of head and neck (HNSCC) [3]. High rates of local tumor control can be achieved with 5-year survival greater than 80% for stage 1 and 2 and 60-70% for stage 3 and 4 tumors [4].

However, long-term sequelae of radiotherapy are highly prevalent and have severe adverse effects on quality of life (QOL) [5].

In our institute, Total patients of head and neck cancer registered in the last 5 years from 2016-2020 was 14776, last year from Jan 2020 to Dec 2020 the total patient count was 3071(20.7% of total cancers), from which more than 1000 (32.5%) cases were oral cavity and oropharynx (oral cavity, Buccal Mucosa, gingivobuccal sulcus, tongue, lateral borders of tongue, tonsil and tonsillar fossa)

Aim and Objectives: To document comparison of toxicity and tumor control for well lateralized carcinoma of oral cavity and oropharynx treated with the ipsilateral versus bilateral radiation techniques.

Material and Methodology

A total of 50 patients with well lateralized carcinoma of oral cavity and oropharynx were included and randomly divide in in two groups with arm A patients treated unilateral and arm B patients treated with bilateral radiotherapy on Linac Accelerator by 3DCRT with or without chemotherapy as per the standard criteria.

Study Timeframe: Between 2021 – 2023.

- Concurrent chemotherapy with cisplatin 100mg/m2 every three weeks as per standard indications were given.

Radiotherapy Technique:

Two dosing schedules of radiotherapy in head–neck cancer patients:

1. Postoperative: 60 Gy at 1.8-2.0 Gy/fraction if margins are negative 64-66 Gy at 1.8-2.0 Gy/fraction if margins are positive
2. Definitive: 66-70 Gy at 1.8-2.0 Gy/fraction

Inclusion Criteria:

Patients with histologically proven well lateralized squamous cell carcinoma of oral cavity and oropharynx Stage T1-3, N1-2a.

Node positive or close margins (1-5mm) or lymphvascular invasion positive, perineural invasion positive and/or depth of invasion >10mm if post operated. Location of primary: Malignancies of head and neck cancer region, i.e., oral cavity and oropharynx.

1. Oral cavity: Retromolartrigone (RMT), Lateral alveolar ridge, Buccal mucosa (BM), GBS.
2. oropharynx: Tonsil, Tonsillar pillar.

Normal base line organ function test (CBC, RBS, RFT, LFT& ultrasound) if chemotherapy required.

No previous history of radiotherapy or chemotherapy , Age >18 years, European co-operative oncology group (ECOG) performance status (0-2), Normal base line organ function test (CBC, BLOOD SUGAR, RFT, LFT& ultrasound) if chemotherapy required, Informed consent of patient, No previous history of radiotherapy or chemotherapy

Exclusion Criteria:

- Patient with multiple malignancies.
- Patient who has bilateral node involvement
- Patients who will not complete planned radiotherapy. Patients with metastatic disease.
- Previous history of radiotherapy. Continued smoking during radiotherapy.

Characteristic:

Table 1: Characteristics of patients.

	Group A		Group B	
Age	**Count**	**%**	**Count**	**%**
less than or equal to 40 years	5.00	20.00	8.00	32.00
41-60 years	17.00	68.00	11.00	44.00
> 60 years	3.00	12.00	6.00	24.00
Gender	4.00	16.00	2.00	8.00
Female	21.00	84.00	23.00	92.00
Male				
Socioeconomic status	13.00	52.00	17.00	68.00
Lower	3.00	12.00	1.00	4.00
Lower middle	9.00	36.00	7.00	28.00
Middle				
Site	25.00	100.00	22.00	88.00
Oral cavity	0.00	0.00	3.00	12.00
Tonsil				
History	6.00	24.00	10.00	40.00
Smoking	4.00	16.00	2.00	8.00
Alcohol	21.00	84.00	15.00	60.00
Tobaco chewing				
Operation	24.00	96.90	21.00	84.00
Operated	1.00	4.00	4.00	16.00
Non operated				
Cisplatin injection	20.00	80.00	19.00	76.00
Not taken	5.00	20.00	6.00	24.00
taken				

- Age, gender, socioeconomic status, education, cancer stage and other baseline characteristics (smoking/alcohol/Tobacco chewing history, weight, height, BMI, site of cancer) were comparable betweep>0.05).
- Out of 50 patients of oral cavity versus oropharynx in group A 100% of oral cavity and in group B 22 (88%) had oral cavity cancer and 3(12%) had oropharynx carcinoma (tonsil). (p-value =0.235)

Most common stages for post-op patients were PT2N1, PT3N1 and PT1N1 and for nonoperated patients wcere cT3N1 and cT2N1 stages and 5 patients (20%) in group A and 6 patients (24%) took 3-weekly concurrent chemotherapy due to positive margins.(p- value =0.733)

Results

Disease control and toxicity: In this study, no statistically significant difference in skin toxicity was found between both group at 1st week, 2nd week, 4th week of follow- up and end of the treatment. However a high skin toxicity of grade 2 (in 100%, 100% patients) and similarly grade 3 (in 12%, 32%) was found respectively in group A and B. In this study, no statistically significant difference in Mucositis toxicity was found between both groups at each of follow-up.

However a high Mucositis toxicity of grade 2 ((in 100%, 100% patients) and grade-3 (in 36%, 66% patients) was found respectively in group A and B.

However moderate dysphagia in 5 patients (20%) and 16 patients (64%) was found respectively in group A and B during follow-up. and grade-1 xerostomia was found in group B patients at 3 and 6 month of follow-up (p- value=0.0001) which is statistically significant.

Table 2: Toxicity and Response

	Skin Toxicity		Mucositis		Dysphagia	
	Grade-2	**Grade-3**	**Grade-2**	**Grade-3**	**Mild**	**Moderate**
Group A	22 (88%)	3 (12%)	16 (64%)	9 (36%)	18 (72%)	5 (20%)
Group B	17 (68%)	8 (32%)	11 (44%)	14 (56%)	9(36%)	16 (64%)

Table 3: Response

	Response	
	Disease Control	**Recurrence**
Group A	25 (100%)	1 (4%)
Group B	25 (100%)	0

Discussion

Head and neck squamous cell carcinoma (HNSCC) are characterized by a relatively orderly spread to regional cervical lymph nodes. Generally, elective neck irradiation is not recommended when the risk of subclinical disease is less than 15-20% [6]; there is growing evidence in the literature that patients with early oropharyngeal and oral cavity carcinoma have low incidence of contralateral node involvement, hence, radiation therapy can be limited to the ipsilateral neck, without compromising loco-regional control.

In this study, out of the 25 participants in group A, maximum 15 (60%) had Well differentiate SCC followed by 6 (24%) had moderately differentiate SCC and out of the 25 participants in group B, maximum 15 (60%) had moderately differentiate SCC followed by 7 (28%) had Well differentiate SCC. This difference was found to be statistically significant. (p-0.039) In this study, out of the 25 participants in group A, all 25 had oral cavity cancer and out of the 25 participants in group B, 22 (88%) had oral cavity cancer.(p-0.235)

Cerezo L et al. [7] did a similar kind of study and twenty patients were included in the study. Out of 20 patients 12(60%) had oral cavity and 8(40%) had oropharyngeal cancer. Total dose prescribed to primary tumor was 66-70 Gy for patients with gross disease and 54-64 Gy for patients treated with adjuvant setting. For elective radiotherapy, 50 Gy was administered to the ipsilateral regions at risk for subclinical disease both for radical and postoperative radiotherapy.

Vergeer MR et al. [9] did a study to assess contralateral nodal control (CLNC) in postoperative patients with oral and oropharyngeal cancer. In this study, out of 123 patients majority of patients (41%) oropharyngeal and buccal mucosa (21%) malignancies the median total dose to primary tumor bed was 63Gy (50-70), In case of wide surgical margins (>5mm) the median total dose was 56Gy and the lymph node areas that contain pathologic lymph node with ENS received a median total dose of 66Gy (60-80).the elective nodal areas irradiated up to 46-50Gy in 23-25 fractions.

Kim Y et al. [12] compared the effects of postoperative ipsilateral neck radiotherapy (INRT) versus bilateral neck radiotherapy (BNRT). In this study out of 70 patients in INRT arm maximum 9(6.42%) had Well differentiate SCC followed by 39(27.85%) had moderately differentiate SCC and out of the 70 participants in BNRT arm, maximum 5(3.57%) had moderately differentiate SCC followed by 45(32.14%) had Well differentiate SCC. In this study, out of the 25 participants in group A, maximum 9 (36%) illiterate followed by 6 (24%) were educated up to 8th class, maximum 13 (52%) were belongs to Lower class followed by 9 (36%) belongs to middle class, and out of the 25 participants in group B, maximum 10 (40%) were illiterate followed by 7 (28%) were educated upto 8th class, maximum 17 (68%) were belongs to Lower class followed by 7 (28%) belongs to middle class. In our study education status (p-0.470) and socioeconomic status (p-0.410) were also comparable and no statistically significant difference was present.

In this study, out of the 25 participants in group A, 21 (84%) had history of tobacco chewing, 6 (24%) had smoking history and 4 (16%) had alcohol history and out of the 25 participants in group B, 15 (60%) had history of tobacco chewing, 10 (40%) had smoking history and 2 (8%) 6 had alcohol history. These differences were not found to be statistically significant. Kim Y et al compared the effects of postoperative ipsilateral neck radiotherapy (INRT) versus bilateral neck radiotherapy (BNRT). In this study out of 140 patients (70 in each arm) in INRT arm 29(20.7%) patient and in BNRT arm 35(25%) patients had smoking history

In this study, mean age of study participants in group A and B was 50.7±10.8 years and 49.9±14.8 years respectively and out of the 25 participants in group A, maximum 17 (68%) were belongs to age group of 41-60 years and out of the 25 participants in group B, maximum 11 (44%) were belongs to age group 41-60 years. Age was comparable in both groups and no statistically significant difference was present. (p-0.836)

In this study, out of the 25 participants in group A, maximum 21(84%) were male participants and out of the 25 participants in group B, maximum 23 (92%) were male participants. This difference was not found to be statistically significant.(p-0.384)

Cerezo L et al. [7] did a similar kind of study and twenty patients were included in the study. Mean age of study participants was 60 years. In this study male participants were 60% and female participants were 40%. Rath S et al did a similar kind of study and included a total 100 patients of head and neck cancer. In this study mean age of the participants was 59 years and male participants were 73% and female were 27%.

In This study there were no statistical significant difference was found in both the groups in terms of disease control in all patients and one patient (4%) in group- A presented with contralateral level-2 nodal recurrence at 6 month of follow-up. Vergeer MR et al. [9] did a study to assess contralateral nodal control (CLNC) in postoperative patients with oral and oropharyngeal cancer. In this study, the majority of patients (41%) oropharyngeal and buccal mucosa (21%) malignancies. The ipsilateral neck was operated on in the vast majority of cases (n = 102; 83%). Seventy-one percent of patients with contralateral metastases were candidates for successful salvage. In the end, it was determined that certain patients with oral or oropharyngeal cancer who underwent initial surgery and postoperative ipsilateral radiation had very high CLNCs and had a high chance of being successfully saved in the event of contralateral metastases. However, in cases of multiple lymph node metastases in the ipsilateral neck, particularly in the presence of extranodal dissemination, bilateral irradiation should be used. After bilateral irradiation, there is a noticeably decreased incidence of radiation- induced morbidity.

Kim Y et al. [12] In this study, contralateral neck recurrence was more frequent in the INRT group than in the BNRT group for 79 patients with N2b (7.9% vs. 0.0%), although the difference was not statistically significant.

Wirtz MM et al. [10] did a study and Complete resection (R0) was achieved in 85.8% of cases.

Ipsilateral ND was performed in all patients and contralateral ND in 144 patients (73.1%). Concurrent chemotherapy was given to 59 patients (30.0%). A total of 45 patients (22.8%) suffered from a loco-regional recurrence, lymph node metastases of the contralateral neck developed in 12 patients (6.1%) only. There was no significant difference in contralateral nodal failure rate with or without performance of contralateral ND.

Rath S et al. [11] analyze the failure patterns and survival in buccal mucosa cancers treated with adjuvant ipsilateral RT. This study revealed that crude rates of local failure, regional failure, and contralateral neck failure were 9.4%, 10.3%, and 3.4%, respectively. The 2-year contralateral neck control rate was 94.9%.

In this study, no statistically significant difference in skin toxicity was found between both group at 1st week, 2nd week, 4th week of follow-up and end of the treatment

However a high skin toxicity of grade 2 (in 88%, 68% patients) and similarly grade 3 (in 12%, 32%) was found respectively in group A and B. In this study, no statistically significant difference in Mucositis toxicity was found between both groups at each of follow-up.

However a high Mucositis toxicity of grade 2 ((in 64%, 44% patients) and grade-3 (in 36%, 56% patients) was found respectively in group A and B. In this study, no statistically significant difference in nausea/ vomiting was found between both groups at each of follow-up. In this study, no statistically significant difference in dysphagia toxicity was found between both group at 1st week to 4th week and 3rd month and 6th month. However moderate dysphagia in 5 patients (20%) and 16 patients (64%) was found respectively in group A and B. (p- value=0.0001)

In this study, no statistically significant Hb, TLC, blood urea difference was found between both groups at each follow-up interval.

Kim Y et al. [12] compared the effects of postoperative ipsilateral neck radiotherapy (INRT) versus bilateral neck radiotherapy (BNRT). Overall grade 2 toxicities in the INRT group were lower: acute (45.7% vs. 74.3%) and late (4.3% vs. 31.4%).

Rusthoven KE et al. [11] did study bilateral irradiation and found that no toxicity of late Grade 3 or higher was noticed. At the most last checkup, no patient was still reliant on a feeding tube.

In this study, a statistically significant xerostomia was found of grade-1 in group-B patients at 3 and 6 month of follow-up (p- value=0.0001)

Cerezo L et al. [7] found that the average dry mouth score on the 0-100 QLQ-H & N35 scale was 28.1. 87.5% of patients reported grade 0-1 subjective xerostomia on the CTCAE v3 scale, while 12.5% had degree 2 xerostomia. 81.2% of patients had unstimulated salivary flow more than 0.2 ml/min, whereas 19% had it between 0.1 and 0.2 ml/min. None of the patients had xerostomia of grade 3. However this study did not compare the ipsilateral irradiation with bilateral irradiation.

Rusthoven K.E. et al. [11] did study bilateral irradiation and found that one patient (5%), with Late Radiation Therapy Oncology Group grade 2 xerostomia, experienced it. No toxicity of late Grade 3 or higher was noticed. At the most last check up, no patient was still reliant on a feeding tube Vergeer MR et al. [9] did a study to assess contralateral nodal control (CLNC) in postoperative patients with oral and oropharyngeal cancer. In this study At 5 years, 2.6% of patients had xerostomia of Grade 2 or higher.

Kim Y. et al. [12] compared the effects of postoperative ipsilateral neck radiotherapy (INRT) versus bilateral neck radiotherapy (BNRT). Overall grade 2 toxicities in the INRT group were lower: acute (45.7% vs. 74.3%) and late (4.3% vs. 31.4%)

Conclusion

- According to the findings of our study, individuals diagnosed with early and moderate stages, well lateralized head and neck cancer, who underwent ipsilateral irradiation treatment of the primary site and ipsilateral neck experienced less toxicity and only single patient faced recurrence over the 6-month follow-up period.
- The major benefit of ipsilateral radiation treatment is to provide an opportunity for salivary protection by exclusion of contralateral major salivary glands and a part of the oral cavity mucosa without compromising locoregional control.
- It is recommended to conduct a study on a large group of patient and longer follow-up that involved multiple centers

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