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Study of Outcome and Response of Hypofractionated Radiotherapy with Concurrent Cisplatin for Treatment of Stage II to IVA Head and Neck Cancer

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ABSTRACT
The term "head and neck cancer" refers to cancers of the upper aerodigestive tract, including the lips, oral cavity, oropharynx, sinonasal cavities, nasopharynx, larynx, hypopharynx and salivary glands. to assess the response of hypofractionated radiotherapy with concurrent cisplatin for treatment of stage II to IVa head and neck cancer. The present prospective study was conducted in department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. This thesis was approved by ethical and scientific committee Pt. JNM medical college Raipur. Duration of study during July 2018-September 2019, Maximum number of patients are of oral cavity 36.59% followed by oropharynx 29.27%. It is due to people used to keep tobacco related products in mouth. Most patients presented with locally advance disease of stage IVA 58.54% and with early stage II 12.2%. it is due to in Chhattisgarh state patients came with locally advanced stage. It is due to illiteracy, poverty, lack of awareness, lack of health facility. In our study treatment should be completed within 1 week from estimated total duration (39 days) percentage are 41.4%, Rest of 58.6% patients delayed their treatment 39 days+2weeks. It mainly due to radiation-related toxicities other reasons are distance of the treatment facility from home, age of the patient, advance stage , illiteracy and particular disease sites. In our study we observe response at 6 weeks, 3 months and 6 months. In 6 months-there is complete response in 36.6% of cases, partial response in 39%, stable disease in 12.2% and progressive disease in 4.8% cases. It is due to 58.4% cases have presented to us with stage IVA and they not response completely and tend to progress even after treatment.

INTRODUCTION

The term "head and neck cancer" refers to cancers of the upper aerodigestive tract, including the lips, oral cavity, oropharynx, sinonasal cavities, nasopharynx, larynx, hypopharynx and salivary glands. They account for 4% of all cancers, and it is estimated that over 65,000 new cases will be diagnosed in the United States in 2017[1]. Approximately 27% of these patients are women. The usual time of diagnosis is after the age of 40 years, except for salivary gland and nasopharyngeal cancers , which may occur in younger age groups. This is 6th most common cancer of world wide scenario. For many primary sites, tobacco use is associated with an increased risk. Alcohol has also been implicated as a causative factor, the effects of alcohol and tobacco is synergistic[2]. Head and neck cancer patients have an increased risk for developing a second primary tumor , both within the head and neck and elsewhere (e.g., esophageal and lung cancers), attributed to the field effect associated with tobacco and alcohol use. Human papillomavirus (HPV) infection (most commonly HPV16) plays a role in the development of certain head and neck cancers, particularly those in the oropharynx. Patients with high-risk HPV positive head and neck cancer tend to be younger and less likely to have a strong history of tobacco and alcohol use, have a history of multiple sex partners (particularly oro-genital sex), have a better prognosis and appear to have a lower rate of second primary tumors. Prior tobacco exposure adversely affects the prognosis of HPV-related oropharynx cancers[3]. An increasing trend of oral tongue squamous cell carcinoma (SCC) in nonsmokers white women has been reported which does not appear to be driven by prior HPV infection, whereas the incidence of other oral cavity cancers is declining. There is a longstanding association between Epstein-Barr virus (EBV) and Nasopharyngeal carcinoma. EBV DNA is uniformly present in nasopharyngeal carcinoma in endemic areas like Southeast Asia, North Africa and the Middle East. Squamous cell carcinoma is most common cancer of head and neck region constitutes 45%. Other variety may be Lymphoepithelioma is an squamous cell carcinoma with a lymphoid stroma and occurs in the nasopharynx, tonsillar fossa and base of tongue; it may also occur in the salivary glands. In the spindle cell variant, there is a spindle cell component that resembles sarcoma intermixed with squamous cell carcinoma . It is generally managed like other high-grade squamous cell carcinomas[4]. Verrucosa carcinoma is a low-grade squamous cell carcinoma found most often in the oral cavity, particularly on the gingiva and buccal mucosa. It usually has an indolent growth pattern and is often associated with the chronic use of snuff or chewing tobacco. Radiotherapy and Surgery are the only curative treatments for head and neck carcinomas. Although chemotherapy alone is not curative, it enhances the effects of radiotherapy and is routinely used as part of combined modality treatment in patients with stage III or IV disease in concurrent setting and neoadjuvent setting in some sub sites.

Non Metastatic Head and Neck Cancers (Stages I-IVB):

- Goal of treatment is to achieve maximum cure rates with minimum morbidity
- Since head and neck cancers have implications for speech and swallowing, an attempt is made at organ preservation

Non surgical protocols showing similar cure rates as surgery. Hence this study was done to assess the response of hypofractionated radiotherapy with concurrent cisplatin for treatment of stage II to IVa head and neck cancer.

MATERIALS AND METHODS

The present prospective study was conducted in department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. This thesis was approved by ethical and scientific committee Pt. JNM Medical College Raipur. Duration of study was during July 2018-September 2019.

Inclusion Criteria:

- Patients with head and neck carcinomas
- Biopsy proven case of head and neck carcinoma
- stage II to IVA
- Normal blood profile
- Karnofsky performance scale (KPS)>70%

Exclusion Criteria:

- Patients with co morbidities (heart disease, lung disease etc)
- Patients with metastasis
- Total 41 patients of head and neck cancer (stage II to IVA) have been taken in this study.
- Informed written consent have been taken from every patient
- Detail history was recorded from each patient pertaining to the onset and duration of present complaint
- Physical examination was done on all patients including general, local and systemic examination.
- All the routine investigations including CBC, RFT, LFT, X-ray chest, CECT face and neck, ECG was done on all the cases
- Patients have been simulated with appropriate immobilization then planned with IMRT and VMAT. We have evaluated the plan for dose to

primary site and dose to organ at risk, better plan have been executed
- Treatment planning have been perform using VARIAN (eclipse V.S 13.6.23) treatment planning system
- Dose to PTV and OARs was calculated
- Treatment toxicities during course of radiation and after radiation have been compared using QUANTEC data and RTOG, CTC version 3.0 respectively
- Follow up was done for 6 month. Patients were evaluated for local response and toxicities
- The comparison of the doses delivered to PTV and OARs was done using paired wilcoxon sign rank test

RESULTS AND DISCUSSIONS

We have observed 41 patients treated for hypofractionated radiotherapy of stage II to IVA head and neck cancer. In our study maximum percentage of patients (70.7% patients) are males while females are 29.3%. In our study maximum percentage of patients (34.1%) are between 41-50 years of age group in which maximum percentage (29.6%) of male are between 51-60 yr of age group while maximum percentage (57.1%) of females are between 41-50 yr old. All patients have same morphology squamous cell carcinoma. In our study histopathological grading of primary tumour, grade I represent 58.5%, grade II-34.1% and grade 3 represents 7.4% of total cases. In our study maximum 36.5% cases of carcinoma oral cavity and minimum 9.7% cases of ca hypopharynx. In our study in oral cavity maximum no of case (40%) from ca tongue and ca buccal mucosa. In our study 58.54% cases are stage IVA, 29.27% are stage III and 12.20% are stage II cases. In our study there is maximum percentage of tumour located left side in 44% of cases followed by centrally in 34% of cases. In our study maximum patients are delayed there radiotherapy for 2 weeks from the stipulated time. In our study at 6 month there is complete response in 36.6% of cases, progressive disease in 4.8% cases. Radiotherapy is the main modality of treatment for squamous cell carcinoma of head and neck cancer. Routinely radiotherapy is given with conventional fractionation 60-70 Gy in 30-35 # in 6-7 weeks. This requires a long treatment duration, poor compliance and treatment results. We did an observational study in 41 cases of stage II to IVA head and neck cancer at Pt. JNM medical college and associated Regional cancer centre Dr. BRAM Hospital Raipur CG in the department of radiotherapy for assessing effectiveness and toxicity profile. The study included all the patient of head and neck squamous cell carcinoman treated with hypofractionated radiotherapy 2.34 Gy per fraction, 5 fraction in a week for 5weeks concurrent with cisplatin at day 1 and day 22. During radiation therapy patient have been assessed for acute toxicity weekly than after completion of chemo-radiotherapy patient were assesed for tumour response on 6 weeks, 3month and 6 month and late toxicity every month.

In our study Gender wise male patients represent 70.7% of case whereas female patients 29.3% with male to female ratio is 2.4:1. male patients are more prone to Head and Neck carcinoma than female. According to Warnakulasuriya *et al.* it might be due to the increased consumption of tobacco and tobacco related products in males[5]. according to study by Eliassen *et al.* head and neck squamous cell carcinoma (HNSCC) is typically considered to be a disease that predominantly affects older males, with a male: female ratio of approximately 4:1 which is more as compare to our study. Long term alcohol and tobacco use have been identified as the traditional risk factors for this disease[6]. In our study Age wise maximum number of patients (34.1%) belong to age group of 41-50 year. According to Stoyanov *et al.* The mean age of diagnosis was 63.84±12.65 years which is compatible to our study[7]. Study by Eliassen *et al.* It is due to the tobacco related products consumption for long period of time6. Study by Swati *et al.* suggest that in oral cavity cancers were traditionally being thought of as a disease mainly affecting people of older age group[8]. In our study Grade and morphology wise All patients were squamous cell carcinoma in which grade I represent 58.5%, grade II-34.1% and grade 3 represents 7.4% of total cases. In study by Doshi neena et al Squamous cell carcinomas (SCC) constitute more than 90% of all oral cancer. Other malignant tumors can arise from the epithelium, connective tissue, minor salivary glands, lymphoid tissue, and melanocytes or metastasis from a distant tumor. In this study they found that grade I were 58%, grade II-33%, grade III-9% which is closely resemble to our study[9]. According to Ramasamy padma *et al.* that 98 (49.5%) participants had grade I carcinoma, 68 (34.3%) had grade II and 32 (16.2%) had grade III cancers[10].

In our study SUBSITE WISE carcinoma oral cavity represent maximum percentage of patients (36.59%) followed by oropharynx 29.27%, larynx 24.4%, hypopharynx 9.76%. It may be due to people used to keep tobacco related products in mouth. According to Sankaranarayanan *et al.* In India, oral cavity is the predominant site[11]. In our study LATERALITY WISE maximum percentages of patients have left sided disease (44%) followed by central (34%). Study by anil D kruz *et al.* it may be due to most people are right handed and they used to keep tobacco related products in left side of oral cavity[12]. In our study STAGE WISE there are 58.5% cases of stage IVA, 29.2% cases of stage III, 12.2% cases of stage II cancer. In Chhattisgarh state patients came to us with locally advanced stage. It is due to illiteracy, poverty, lack of awareness, lack of health facility. Study by Kailash

Table 1: Subsite wise distribution

Site	Subsite	N	Percentage
Oral cavity	Total	15/41	36.59
	Tongue	6/15	40
	Buccal mucosa	6/15	40
	Gingivo buccal sulcus	3/15	20
Oropharynx		12/41	29.27
	Base of tongue	6/12	50
	Tonsil	2/12	16.6
	Vallecula	2/12	16.6
	Pharyngeal wall	2/12	16.6
Hypopharynx		4/41	9.76
	Pyriform fossa	3/4	75
	Post cricoid	1/4	25
Larynx		10/41	24.4
	Aryepiglottic fold	8/10	80
	Epiglottis	2/10	20

Table 2: Distribution according to treatment Duration

Duration of treatment	Male	Female	Total
39 days+1 week	11	6	17 (41.4 %)
39 days+ 2 week	18	6	24 (58.6%)
Total	29	12	41 (100%)

Table 3: Overall response

	CR	PR	SD	PD	Death/Lost To Follow up	TOTAL
6 WEEKS	14 (34.1%)	20 (63.4%)	6 (14.6%)	1 (2.4%)	0	41 (100%)
3 MONTH	16 (39%)	17 (56.1%)	6 (14.6%)	2 (4.8%)	0	41 (100%)
6 MONTH	15 (36.6%)	16 (39%)	5 (12.2%)	2 (4.8%)	3(7.3%)	41 (100%)

Table 4: Site wise response (3 month)

	Response after 3 Months				
Site	CR	PR	SD	PD	Total
Oral Cavity	6/15(14.6%)	6/15(14.6%)	2/15(4.8%)	1/15(2.4%)	15
Oropharynx	5/12(12.2%)	6/12(14.6.%)	1/12(2.4%)	0	12
Hypopharynx	1/4(2.4%)	2/4(4.8%)	1/4(2.4%)	0	4
Larynx	4/10(9.7%)	3/10(7.3%)	2/10(4.8%)	1/10(2.4%)	10
TOTAL	16/41	17/41	6/41	2/41	41(100%)

Table 5: Site wise response in 6 month

	Response after 6 Months					
Site	CR	PR	PD	SD	LOST TO FOLLOW UP	Total
Oral Cavity	5/15(12.2%)	5/15(12.2%)	1/15(2.4%)	2/15(4.8%)	2/15(4.8%)	15
Oropharynx	5/12(12.2%)	6/12(14.6%)	0	1/12(2.4%)	0	12
Hypopharynx	1/4(2.4%)	2/4(4.8%)	(0%)	1/4(2.4%)	0	4
Larynx	4/10(9.7%)	3/10(7.3%)	1/10(2.4%)	1/10(2.4%)	1/10(2.4%)	10
TOTAL	15/41	16/41	2/41	5/41	3/41	41

Table 6: Stage wise response (3 month)

Stage	CR	PR	SD	PD	TotaL
II	3/5(7.3%)	2/5(4.8%)	0	0	5
III	6/12(14.6%)	5/12(12.2%)	1/12(2.4%)	0	12
IVA	7/24(17%)	17/24(41.4%)	5/24(12.2%)	2/24(4.8%)	24
TOTAL	16/41	17/41	6/41	2/41	41

Table 7: Stage wise response at 6 month

Stage	CR	PR	PD	SD	Lost to Follow up	Total
II	3/5(7.3%)	2/5(4.8%)	0	(0%)	0	5
III	5/12(12.2%)	5/12(12.2%)	0	1/12(2.4%)	1/12(2.4%)	12
IVA	7/24(17%)	9/24(22%)	2/24(4.8%)	4/24(9.7%)	2/24(4.8%)	24
TOTAL	15/41	16/41	2/41	5/41	3/41	41

Chandra Pandey et al found that head and neck cancer cases with stage I 0%, stage II 6%, stage III 6%, stage IVA 44% and stage IVB 44%[13]. Study by Jagruti a patel et al in their study reported that in head and neck cancers 27% in stage I and 14% in stage II, 11% in stage III, 39% diagnosed in stage IVA and 3% in stage IVB[14]. In our study TREATMENT DURATION WISE radiotherapy should be completed within 1 week from estimated total duration (39 days) percentage are 41.4%, Rest of 58.6% patients completed their treatment 39 days+2weeks. There was significant delay. It mainly due to radiation-related toxicities other reasons may be distance of the treatment facility from home, age of the patient, advance stage , illiteracy and particular disease sites all are contributing factors for total duration of treatment delay. According to Pujari

L it may be due to radiation-related toxicities, distance of the treatment facility from home, age of the patient, and particular disease sites[15]. According to Thomas *et al.* 58% patient delayed there radiotherapy from scheduled duration mainly due to radiation-related toxicities, treatment facility from home, cost issue[16]. In our study OVERALL RESPONSE we observe response at 6 weeks, 3 months and 6 months. In 6 months there is complete response in 36.6% of cases, partial response in 39%, stable disease in 12.2% and progressive disease in 4.8% cases. It may be due to 58.4% cases have presented to us with stage IVA and they not response completely and tend to progress even after treatment. According to somnath roy *et al.* CR in 76% cases , PR in 6.7% cases , SD in 6.7% cases and PD in 10% case which shows further intervention requires in our study[17]. A multi-institutional trial of hypofractionated intensity-modulated radiation therapy (IMRT) for early stage oropharyngeal cancer showed that hypofractionated radiotherapy for early oropharyngeal cancer is feasible, achieving high tumor control rates. Bakst *et al*. treated patients with carcinoma head and neck, using 2.34 Gy per fraction for a total of 70.2 Gy and treatment was well-tolerated[18]. According to Somanath Roy hypofractionated radiotherapy given to patients with HNSCC, results in similar to our study. The addition of concurrent chemotherapy in locally advanced stage with this hypofractionated regimen, therefore, offers an attractive method to improve tumor control probability[19].

Study by Pablo *et al.* observed that overall 5-year survival in a recently analyzed cohort of patients at Memorial Sloan-Kettering Cancer Center is 63%[19]. Study by Franzese *et al.* 1 and 2 year actuarial disease-free survival rates were 88% and 80%, respectively. The 1 and 2 year actuarial overall survival rates were 94% and 87%, respectively[18]. Study by Michelle L. Brown 2 year LC, DFS, and OS rates for the entire 80 cases were 80%, 63% and 66%, respectively[20]. In our study SITE WISE RESPONSE in 6 months in our study out of total CR (36.6%) oral cavity and oropharynx both site shows maximum (12.2%) CR followed by larynx (9.7%) CR. while out of total PR (39%) oropharynx shows 14.6% PR and oral cavity shows 12.2% PR. According to SOMNATH ROY On subgroup analysis in hypofractionated arm CR rate for larynx was 88% followed by oral cavity 75%,oropharynx 80% and hypopharynx 50%. Which shows more complete response than our study[17]. In our study STAGE WISE RESPONSE IN 6 MONTHS out of total CR (36.6%) Stage IVA patients shows maximum (17%) CR followed by stage III patients 12.2% CR. while out of total PR (39%) stage IVA patients shows 22 % PR and stage III patients shows 12.2% PR. According to Tonchev *et al.* They have found that overall 5-year survival rate by stage was found to be as follows-stage I (67%), stage II (51%), stage III (33%), stage IV (15%)[21]. According to Sanghera p The data from patients with squamous cell cancer of the larynx, oropharynx, oral cavity, and hypopharynx who received accelerated hypofractionated radiotherapy with chemotherapy[20].

CONCLUSION

In our study we observe response at 6 weeks, 3 months and 6 months. In 6 months- there is complete response in 36.6% of cases, partial response in 39%, stable disease in 12.2% and progressive disease in 4.8% cases. It is due to 58.4% cases have presented to us with stage IVA and they not response completely and tend to progress even after treatment.

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