IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 4 Ser.9 (April. 2020), PP 31-36
www.iosrjournals.org

''A Study To Evaluate The Efficacy And Safety Profile of VMAT(Rapid Arc) Technique For The Treatment Of Post Operatedoral Cancer In A Tertiary Cancer Care Centre''

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Abstract-

Introduction- *Cancer of the Oral cavity is one of the most common malignancies in developing countries due to Tobacco and Alcohol use. Oral cavity carcinoma (OCC) is primarily a surgical disease. Depending upon the post surgical histopathology report patient requires adjuvant Radiotherapy alone or in combination with chemotherapy. Amongst the available treatment modalities thebiggest advantage of VMAT technique is in its delivery efficiency. Several investigators have reported significant reductions in both treatment times and MUs over conventional IMRT. Role of VMAT increases in a busy government aided centre with resource constrained settings. This study was done to assess the clinical outcomeand toxicity profile of the post operated carcinoma oral cavity patients.*

Material and method*- The present prospective study was conducted in the Department of Radiotherapy,Pt. JNM Medical College and Regional Cancer Center (RCC) of Dr. BRAM Hospital Raipur(C.G.) India during the period of July 2017 –july2019. Total 60 post operated patients of oral cancer eligible for radiotherapy alone were taken in this study from july 2017 to july 2018 and followed up to july 2019.. Patients were simulated with appropriate immobilization and delineation of various volumes were dome with consensus guidelines then planned with VMAT technique .Treatment outcome in terms of locoregional control and Acute toxicities related to the surrounding organs at riskwere assessed according to RTOG and EORTC criteria.*

Result- *In our study there were 30% cases of carcinoma buccal mucosa and tongue each followed by alveolus 23% and gingivobuccal sulcus 13%.In our study 40% cases were stage III, 26.7% were stage II, 20% were stage IV and 13% were in stage I. In our study there was complete response in 78.4% of cases, progressive disease in 23% cases at the end of 12 month follow up .After the completion of RadiationSignificant number of patient had (80%) grade I skin reaction, 76% cases of grade II salivary gland toxicity(xerostomia), 55% cases of grade 3 mucositis and 96% had low grade (I & II) dysphagia. There were 60% cases of grade II radiation fibrosis and 24% cases of grade II xerostomia at 12'month of follow up.*

Conclusion-*In the Treatment of post operated oral cavity cancer with adjuvant radiotherapy, treatment efficacy and toxicities profile with VMAT radiotherapy technique were within acceptable limit and were managed symptomatically. There is less time required with VMAT technique in comparison to IMRTcausing less intrafraction movement thus more precise dose delivery.. More number of patients can be recruited with a longer follow up to look for overall survival and other morbidities in post operated oral cavity cancer treated with VMAT technique.*

Keyword-*Oral cavity carcinoma, Intensity-modulated radiation therapy, Volumetric-modulated arc therapy*

Date of Submission: 11-04-2020 Date of Acceptance: 26-04-2020

I. Introduction

The oral cavity is a distinct site of the head and neck region that possesses complex functional anatomy with regard to speech, swallowing, and facial projection. Anatomically, the oral cavity is composed of the mucosal lip, oral tongue, floor of mouth (FOM), mandibular and maxillary gingiva, retromolartrigone, buccal mucosa, and hard-palate subsites. Although the oropharynx is often confused as a continuous extension of the oral cavity, it is imperative to separate the two because the etiologies, management, and outcomes of cancers arising in these two head and neck sites are drastically different.

There are Various modalities of external beam Radiotherapyat present which includes, Two dimensionalradiotherapy, Three dimensional conformal radiotherapy (3DCRT), Intensity modulated radiotherapy (IMRT) , Volumetric modulated arc radiotherapy (Rapidarc). Radiotherapy with IMRT is already established technique in the treatment of Head and Neck carcinoma. surgery+radiotherapy provides far better results than surgery or radiotherapy alone. In this study we assessed the efficacy and toxicity of more conformal VMAT technique in post operated oral cavity cancers.

II. Methodology

Total 60 post operated patients of oral cancer (stage I to IVA) werrtakenin this study. Informed written consent were 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 were simulated with appropriate immobilisation then planned with IMRT and VMAT. We evaluated the plan for dose to primary site and dose to organ at risk and the better plan was executed. Treatment planning was performed using VARIAN (eclipse V.S 13.6.23) treatment planning system, Dose to PTV and OARs was calculated in both thearms. Treatment toxicities during course of radiation and after radiation were compared using QUANTEC data and RTOG, CTC version 3.0respectively. Follow up was done for 6 month. Patients were evaluated for local response and toxicities. Data was compile in MS Excel and checked for its completeness and correctness. Then it was analyzed by using suitable statistical software.

III. Observation And Result

Table 1. Age and sex wise distribution of study subjects

Age group in years	**20-30**	**30-40**	**40-50**	**50-60**	**>60**	**Male**	**Female**
TOTAL	1.70%	20%	48.30%	20%	10%	85%	15%

Majority of patients belongs to 30-60yr age group. M:F=6:1. **[Table 1]**

Table 2. Histopathological grade and Risk wise number of patients

GRADE	**NO.**
I	61.7%
II	35%
III	3.3%
HIGH RISK	**PRESENT**
LVI	46.7%
PNI	53.3%

Histopathological grading of primary tumour, grade I represent 61.7%, grade II – 35% and grade 3 represents 3.3% of total cases. Lymphovascular invasion was present in 46.7% of cases &Perineural invasion present in 53.3% of cases. **[Table 2]**

Table 3. Subsites and Laterality Wise Persentage Of Patients

LATERALITY	**RIGHT**	**LEFT**	**CENTRAL**	**TOTAL**
BUCCAL MUCOSA	8.3	21.7	0	30%
TONGUE	15	13.3	1.7	30%
ALVEOLUS	13.3	3.3	6.7	23.3%
GB SULCUS	1.7	11.7	0	13.4%
LIP	0	0	3.3	3.3%
TOTAL	**38.3**	**50**	**11.7**	**100%**

In our study there is maximum percentage of tumour on left side in 50% of cases followed by right side in 38% and central in 11% of cases. In our study there are 30% cases of carcinoma buccal mucosa and tongue each followed by alveolus 23% and gingivobuccal sulcus 13%. **[Table 3]**

Table 4. Stage Wise Percentage Of Patients

COMPOSITE STAGE	TOTAL
I	13.3%
II	26.7%
III	40%
IVA	20%

In our study 40% cases are stage III, 26.7% are stage II, 20% are stage IV and 13% are in stage Icases. **[Table 4]**

Table 5. Response

	CR	PR	NR	PD	DEATH	TOTAL
1ST MONTH	91.7	0	0	8.3	0	100
3RD MONTH	90	0	0	10	0	100
6TH MONTH	78.4	0	0	21.6	0	100
9th MONTH	75	0	0	25	0	100
12TH MONTH	71.7	0	0	28.3	0	100

Table 6 Toxicities

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
SKIN					
6TH WEEK OF RADIATION	0	83.4	16.6	0	0
1ST MONTH FOLLOW UP	0	100	0	0	0
3RD MONTH FOLLOW UP	32	68	0	0	0
6TH MONTH FOLLOW UP	86.7	13.3	0	0	0
9TH MONTH FOLLOW UP	91.7	8.3	0	0	0
12TH MONTH FOLLOW UP	95	5	0	0	0
MUCOSITIS					
6TH WEEK OF RADIATION	0	13.3	28.3	55	3.4
1ST MONTH FOLLOW UP	41	55	4	0	0
3RD MONTH FOLLOW UP	96	4	0	0	0
6TH MONTH FOLLOW UP	100	0	0	0	0
9TH MONTH FOLLOW UP	100	0	0	0	0
12TH MONTH FOLLOW UP	100	0	0	0	0
SALIVARY					
6TH WEEK OF RADIATION	0	16.6	76.6	6.7	0
1ST MONTH FOLLOW UP	6.7	50	40	3.3	0
3RD MONTH FOLLOW UP	56.7	40	0	3.3	0
6TH MONTH FOLLOW UP	88.3	8.4	0	3.3	0
9TH MONTH FOLLOW UP	91.7	5	0	3.3	0
12TH MONTH FOLLOW UP	91.7	5	0	3.3	0
DYSPHAGIA					
6TH WEEK OF RADIATION	0	50	46.6	3.4	0
1ST MONTH FOLLOW UP	46.7	48.3	5	0	0
3RD MONTH FOLLOW UP	60	40	0	0	0
6TH MONTH FOLLOW UP	88.3	11.3	0	0	0
9TH MONTH FOLLOW UP	91.7	8.3	0	0	0
12TH MONTH FOLLOW UP	93.3	6.7	0	0	0

	GRADE 0	GRADE 1	GRADE 2	GRADE 3	GRADE 4
RADIATIONFIBROSIS					
6th month	40	60	0	0	0
9th month	20	70	10	0	0

12th month	10	75	15	0	0
MANDIBLE BONE					
6th month	100	0	0	0	0
9th month	100	0	0	0	0
12th month	100	0	0	0	0
XEROSTOMIA					
6th month	68.4	23.3	8.3	0	0
9th month	75	20	5	0	0
12th month	78.3	16.7	5	0	0
HOARSNESS					
6th month	100	0	0	0	0
9th month	100	0	0	0	0
12th month	100	0	0	0	0
SPINAL CORD	100	0	0	0	0
6th month	100	0	0	0	0
9th month	100	0	0	0	0
12th month	100	0	0	0	0
TM JOINT	100	0	0	0	0
6th month	100	0	0	0	0
9th month	100	0	0	0	0
12th month	100	0	0	0	0

According to our study 21.6% patients have progressive disease. It is due to 20% cases have presented to us with stage IVA & they tend to progress even after treatment. We have found that 55% cases have grade 3 mucositis. It is due to low immunity in the last week of radiation, absorbed radiation dose is more than tolerance dose of buccal mucosa & it is associated with superadded infection. In our study we found that dysphagia grade I contributed to 50%, grade II 46% and grade III 2%, grade IV 0%. In our study skin toxicity was reported as grade I 80%, grade II 20%. In our study we found that acute xerostomia of grade 0 contribute to 0% grade I 15%, grade II 78%, grade III 6.7% grade IV 0%. We have found that most of the acute toxicities regressed over 3-4 months & at 6th month there is development of late radiation fibrosis & xerostomia. **[Table 5,6]**

IV. Discussion

According to our study about 50% of cases were in the group of 40-50 year and it was due to the tobacco related products consumption for long period of time. In a study done by **SamanWarnakulasuriya et al** about 6% of oral cancers occur in young people under the age of 45 years.[7] In high-incidence countries of the world, many cases are reported before the age of 40.In Scotland, where this trend was first reported, the incidence rate between 1990 and 1999 in males under 45 has more than doubled from 0.6 to 1.3 per 100,000.7 Fortunately the disease is not more aggressive than that occurring in older adults either in the USA or in SouthernEngland. In a study done by**Swati et al**oral cavity cancers were traditionally being thought of as a disease mainly affecting people of older age group. In the present article, the pattern observed is different.[8] This increased incidence of oral cancer at a very young age group has been usually attributed to indiscriminate usage of substances, mainly tobacco and tobacco-related products, over a prolonged period of time, which leads to genetic damage. Immune surveillance reduces at age 20 and above.

According to our study male patients are more prone to Head & Neck carcinoma. It is due to the increased consumption of tobacco related products. **SamanWarnakulasuriya et al**, the ratio of males to females diagnosed with oral cancer, however, has declined over the decades and is now about 1.5:1 for the mouth and about 2.8:1 for cancer of oropharynx and **Swati et al**found that the incidence rate of oral cancer is more than twice as high in men as in women.[7,8] Age Adjusted Rates (AAR) mouth cancer was maximum in the central region among males (64.8%) in the 70- to 75-year age group followed by AAR in northeast and west regions of India (58.4%) in 60- to 69-year age group. Among females, development of mouth cancer was maximum in the northeast and central regions with AARs of 60.2% and 37.2%, respectively, in the 70- to 75-year age group. From our study we have found that about 60% of histopathological differentiation are well differenciated whereas 30% are moderately differenciated& 3% are poorly differenciated.

In a study done by **Pablo 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.[9]

In a study done by **Doshineena et al,**they have found that grade I contributed 58%, grade II – 33%, grade III –9%.[10] In our study lymphovascular invasion present in 46.7% of cases &Perineural invasion present in 53.3% ofcases. In a study done by **Yu-Tsai Lin,** there were 41 females and 513 males.[11] Patients with PNI, LVI, or ECS presented pathologically had 5-year overall survival rates of 58.4%, 50.4%, and 31.4%, respectively. Patients with both ECS and PNI or both ECS and LVI presented had 5-year overall survival rates

of 31.5% and 22.2%, respectively. Patients presenting with triple-positive status (PNI, LVI, and ECS) had only a 20.0% 5-year overall survival rate. The 5-year local/regional control rate for patients with both ECS and PNI or both ECS and LVI was 26% and 44.4%, respectively; for all three factors, it was 26.7%.

According to our study we observe that maximum number of patients are of buccal mucosa 30%, tongue 30% & alveolus 23%. It is due to people used to keep tobacco related products (Khaini, gudakhu&Betal nuts) in inner & outer side of alveolus which is constant touch with tongue, buccal mucosa & alveolus.

In a study done by **PadhiarRutvij Ajay et al,**Buccal mucosa was the most common site (36%), second most common site was alveolus 31%, followed by the tongue 21%, gingivobuccal sulcus 7.7%. The least affected site was palate and oropharynx (0.7%), lip 1.4%, palate 0.7%. The prevalence of OC did not differ between different sites.[12]

Naikbalachandraramachandra et al,reported buccal mucosa have 57.8% and tongue 24% contribution in oral cavity cancer.In our state patients came to us with locally advanced stage. It may due to illiteracy, poverty, lack of awareness, lack of health facility.[13]**Kailash Chandra Pandey et al,** found that oral cancer cases stage contribute stage I 0%, stage II 6%, stage III 6%, stage IVA 44% and stage IVB 44%.[14]**Jagruti a patel et al**have reported that early stage disease (3% in stage 0, 27% in stage I and 14% in stage II), 14% had locoregionally advanced curable cancer (11% in stage III, 3% in stage IV), while 42% cases had loco- regionally advanced incurable cancer (39% diagnosed in stage IVA, 3% in stage IVB).[15]

According to our study 21.6% patients have progressive disease. It is due to 20% cases have presented to us with stage IVA & they tend to progress even after treatment. **Franzese C et al**found that 1 and 2 year actuarial disease-free survival rates were 88% and 80%, respectively.[16]The 1 and 2 year actuarial overall survival rates were 94% and 87%,respectively.

In a study done by **Michelle L. Brown,** the 2-/3-year LC, DFS, and OS rates for the entire80+ cohort were 81/80, 69/63, and 68/66%,respectively.[17]**Myers et al**have found that 5-year disease-specific and overall survival rates for pathologically N0 patients were 88% and 75%, respectively; these decreased to 65% and 50%, respectively, if patients were node positive but without evidence of ECE. Patients who were node positive with evidence of ECE had 5-year disease-specific and overall survival rates of 48% and 30%, respectively.[18]

We have found that 55% cases have grade 3 mucositis. It is due to low immunity in the last week of radiation, absorbed radiation dose is more than tolerance dose of buccal mucosa & it is associated with superadded infection.

An explanation for the results in a study done by **Dean et al S. Yahyaetal**is that the duration of G3M scored as a patch of confluent mucositis may be a serial radiobiological phenomenon independent of dose bath to a putative parallel mucosal OAR.[19]

In a study done by **Rosario Mazzola et al**, Acute mucositis was recorded as follow: grade 0 (G0) in 4% of patients, G1 in 26%, G2 in 50%, G3 in 20%. No case of G4 toxicity was registered. The median week of onset was 3th (range, 2th -4th).[20]

In our study we found that dysphagia grade I contributed to 50%, grade II 46% and grade III 2%, grade IV 0%. In a study done by **Bhide et al**, showed a significant correlation between length of pharyngeal mucosa treated to 50 Gy and 60 Gy and the incidence of grade 3 dysphagia.[21]**Rosario Mazzola et al**showedthatacute dysphagia was recorded as follow: G0 in 24% (n=12), G1 in 32% (n=16), G2 in 38% (n=19), G3 in 6% (n=3). No case of G4 toxicity was registered.[20]

In our study skin toxicity was reported as grade I 80%, grade II 20%. **Gopaghosh et al** reported as grade I skin toxicity is 100%, grade II 92.5%, grade III 7.5% and grade IV 0%.[22]

In our study we found that acute xerostomia of grade 0 contribute to 0% grade I 15%, grade II 78%, grade III 6.7% grade IV 0% **Gopaghosh et al** reported acute xerostomia grade I contributed to 40% and grade II 18% of cases.We have found that most of the acute toxicities regressed over 3-4 months & at 6th month there is development of late radiation fibrosis & xerostomia.[22]

In a study done **MutlaySayan et al,**Seventy-six patients with Oral tongue cancer (45% males and 55% females) were treated with definitive surgical resection followed by adjuvant RT.[23] The median follow-up was 4.3 years. Combined late toxicities were reported in 38% of patients. Thirty-four percent of the patients had narcotic dependency and, 3.9% of the patients had Osteo-Radio Necrosis of the mandible. Thirteen percent of patients developed PEG tube dependency that was significantly associated with a higher 3D maximum radiation dose on univariate analysis ($p < 0.01$). On MV analysis, 3D maximum dose remained significantly associated with long-term PEG tube dependency ($p = 0.05$).

Shao-Hui Huang et alfound that severe muscular fibrosis rate was higher for POCRT (10% vs. 5%) but severe xerostomia was lower (14% vs. 22%). Spontaneous ORN is dose dependent and related to the volume of mandible receiving radiotherapy beyond 50~60 Gy (47). The incidence is generally low <15% with conformal radiotherapy.[24]

Gopaghosh et alreported grade I radiation fibrosis in 7.5% cases, grade I dysphagia in 7.5%, grade I xerostomia in 27.55, grade II xerostomia in 5% of the patients.[22]

V. Conclusion

In treatment of post operation oral cavity cancer with adjuvant radiotherapy, treatment efficacy and toxicities profile are similar with IMRT and VMAT radiotherapy technique. There is less time required wit VMAT technique in comparison to IMRT, so in our institution where patients load is more in that case we can deliver radiotherapy with VMAT technique to more patients compare to IMRT technique. Further follow up with more number of patients isrequired to evaluate therecurrance pattern, late toxicity andoverallsurvivalwith VMAT Technique to establish the fact.

Source of funding- None
Conflict of interest- None
Ethical permission- Ethical permission was granted from institutional ethical committee.

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