A Comparative Study of Maximum Mouth Opening amongst Postoperative Oral Cancer Patients with or without Radiotherapy

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ABSTRACT

Introduction: Restricted mouth opening is a long-term sequelae of head neck cancer treatment. This is a major concern as it leads to multiple problems in maintenance of oral hygiene, speech, chewing, swallowing, prosthetic rehabilitation, and follow-up intra-oral examination. In this study, our aim was to assess maximum mouth opening (MMO) amongst postoperative oral cancer patients with or without conventional radiotherapy over a period of one year.

Material and methods: A prospective longitudinal study was done in oral cancer patients, within three years, to compare effect of post-operative radiotherapy (PORT) on MMO over a follow-up period of one year with control of post-operative cases without radiation. Level of significance was set at alpha level 0.05.

Results: Among 18 patients of PORT and 19 patients of control group, repeated measure ANOVA were significant for the following parameters: within subject effect in each group; between subject effect and interaction effect of month and radiation. Multiple pairwise comparison showed MMO at 3rd, 6th, 9th and 12th month were significantly different in PORT group, in comparison to preoperative MMO. In the control group however, only postoperative MMO at 1st month was significantly different. After one-year, mean MMO, in PORT and control was 32.56±4.29mm and 46.37±4.65mm, respectively and total trismus in radiotherapy group was 66.67% and that of control group was nil.

Conclusion: Conventional radiotherapy in oral cancer patients can lead to high rate of trismus as a late effect. Strict exercise protocol along with close monitoring is recommended to have beneficial effect to the patients.

Keywords: Mouth Neoplasm, Radiotherapy, Adverse Effect, Trismus

INTRODUCTION

The goal of oral cancer treatment is attaining loco-regional control of the disease, restoration of normal form and function and ensuring acceptable quality of life for the patient.[1] Although there has been a lot of improvement in this field, long term sequelae of head neck cancer treatment by surgery, chemotherapy and radiation remains a challenge. Many of the patients develop multiple impairments like trismus, difficulty in chewing, speaking, swallowing, dryness of mouth etc.[2] However, the problem of restricted mouth opening or trismus requires more consideration, as it results in a multitude of other problems like difficulty in maintenance of oral hygiene, difficulty in speaking, chewing, swallowing, receiving further dental treatment, prosthetic rehabilitation and proper intra-oral examination during follow up.[1,3]

According to literature, significant association has been found between radiotherapy and trismus, however it can also result from the effect of surgery.[3–5] The effect of radiation does not become apparent during the course of radiotherapy, however over a period of 1-9 months, mouth opening rapidly decreases.[6,7]

This study was done with an aim to assess effect of ablative surgery with or without radiation in oral cancer patients on maximum mouth opening over a period of twelve months.

MATERIAL AND METHODS

A prospective longitudinal study was done in oral cancer patients, in the Department of Oral & Maxillofacial Surgery of a dental college within a duration of three years, to compare effect of post-operative radiotherapy (PORT) on maximum mouth opening, over a period of one year with control of post-operative cases without radiation. Institutional ethical clearance was taken prior to the study.

Non-probability sampling technique was employed to include histo-pathologically confirmed oral cancer patients, in sequence in the two groups. Preoperative maximum mouth opening (MMO_0) was recorded for all the patients between the edges of the central incisor teeth with the help of a graduated scale.

Post-operative patients with any of the following criteria were allocated to the Group I (PORT group) and sent for

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postoperative radiation (as per the institutional treatment protocols).

1) Positive resection margin or close margin (< 5 mm)
2) Extra-capsular spread in lymph node
3) >3cm size of involved node($N2_a$)
4) Multiple or bilateral node involvement ($N2_b$, $N2_c$)
5) Multicentric primary cancer
6) Perineural spread

Other patients who were not indicated for post-operative radiotherapy were allocated to the Group II (Control).

Radiotherapy

Radiotherapy was started for the patients of Group-I, between 4 – 6 weeks following surgery and thermoplastic immobilization system (Orfit®) was used during therapy. Patients received total dose of 60 Gy in 30 fractions in 2 Gy/day, 5 days a week schedule with cord sparing at 44 Gy.

All the patients were advised for mouth opening exercise at home and were followed up for a period of one year to record maximum mouth opening, at 1st month before starting radiation (MMO_1); 3rd month (MMO_3); 6th month (MMO_6); 9th month (MMO_9); 12th month (MMO_{12}).

Patients treated without surgical ablation, having evidence of metastasis, pre-existing oral submucous fibrosis or temporo-mandibular joint pathologies were excluded from the study. Written informed consent were taken from the patients to follow the study protocol and follow-up at least for a period of one year according to the schedule.

Among initially selected 40 patients (20 in each group), two patients were excluded from Group I, who died due to presence of co- morbidities within three months and another one patient from Group II were excluded due to non-compliance with the follow-up protocol.

Hypothesis

1) MMO would change over a period, within the groups.
2) Difference of change of MMO would be present between the groups.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS (Statistical Package for Social Sciences) version 20. Repeated measures ANOVA was done to test the effect of time on MMO within the groups. Unpaired *t*- test was done to measure effect of radiation on MMO. Results of calculation were regarded as significant at alpha level of .05.

RESULT

Relevant data related to sex, age, site of cancer, staging and previous treatment is presented in Table 1. In PORT group, majority (78%) of the patients were in stage IV and four patients had preoperative chemotherapy whereas in control group 89% were in Stage III without any previous treatment. Table-2 shows type of neck dissection, flap reconstruction and frequency of complication in both the groups. In PORT group, radical neck dissection was done in 12 patients (67%); in control group, majority (68%) of the patients had selective neck dissection. In both the

Characteristics	Group I: PORT (N=18)	Group II: Control (N=19)
Sex		
Male	12(67%)	12(63%)
Female	6(33%)	7(37%)
Age		
Range (Median) in years	38-59(46.5)	21-58(43)
Site of cancer		
Alveolus	5(28%)	7(37%)
Buccal Mucosa	7(39%)	7(37%)
Tongue and Floor of Mouth	3(17%)	5(26%)
Retro Molar Trigone	3(17%)	-
Stage of Cancer		
Stage II	-	1(5%)
Stage III	4(22%)	17(89%)
Stage IV	14(78%)	1(5%)
Previous treatment		
Chemotherapy	4	-
None	14	19

Table-1: Patient and tumour related characteristics

	Group I: PORT (N=18)	Group II: Control (N=19)
Neck Dissection Type		
Selective Neck Dissection	1 (6%)	13(68%)
Radical Neck Dissection	12 (67%)	-
Modified Radical Neck Dissection	5 (28%)	6 (32%)
Reconstruction		
Pectoralis Major Myocutaneous Flap (PMMC)	12 (67%)	17(89%)
Forehead Flap	2 (11%)	2(11%)
PMMC + Forehead Flap	1 (6%)	-
Delto Pectoral Flap	1 (6%)	-
PMMC + Deltopectoral flap	2(11%)	-
Post- Operative Complication		
Yes	6(33%)	4(21%)
No	12(67%)	15(79%)

Table-2: Treatment and Complication

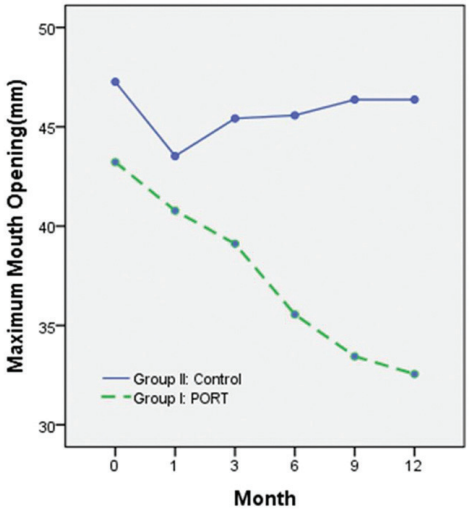

Figure-1: Maximum Mouth Opening vs Time

Effect Type	df	F	p-value	partial η^2
Within Subject effect				
Group I: PORT	(1.234,20.981)	31.375	< .001	0.649
Group II: Control	(2.476, 44.560)	13.439	< .001	0.427
Between Subject effect	(1, 35)	26.089	< .001	0.427
Interaction effect				
Month* Radiation	(1.702, 59.583)	31.893	< .001	0.477
Significant at the .05 level				

Table-3: Result of repeated measures ANOVA with Greenhouse-Geisser correction

	Group I: PORT						Group II: Control					
	MMO_0	MMO_1	MMO_3	MMO_6	MMO_9	MMO_{12}	MMO_0	MMO_1	MMO_3	MMO_6	MMO_9	MMO_{12}
MMO_0	-	.744	.026	< .001	< .001	< .001	-	.044	1	1	1	1
MMO_1	.744	-	.020	< .001	< .001	< .001	.044	-	.004	.022	.002	.001
MMO_3	.026	.020	-	< .001	< .001	< .001	1	.004	-	1	.663	.602
MMO_6	< .001	< .001	< .001	-	< .001	< .001	1	.022	1	-	.315	.018
MMO_9	< .001	< .001	< .001	< .001	-	.140	1	.002	.663	.315	-	1
MMO_{12}	< .001	< .001	< .001	< .001	.140	-	1	.001	.602	.018	1	-

* Based on estimated marginal means; The mean difference is significant at the .05 level. Adjustment for multiple comparisons: Bonferroni.

Table-4: Result of Pair wise comparison of MMO showing p- value*

MMO	Group	Mean± SD	t	df	Sig. (2-tailed)
MMO_0	Group I: PORT	43.22±10.5	-1.495	23.332	.148
	Group II: Control	47.26±4.72			
MMO_1	Group I: PORT	40.78±5.62	-1.586	35	.122
	Group II: Control	43.53± 4.91			
MMO_3	Group I: PORT	39.11±5.22	-3.883	35	< .001
	Group II: Control	45.42± 4.66			
MMO_6	Group I: PORT	35.56±4.81	-6.605	35	< .001
	Group II: Control	45.58±4.41			
MMO_9	Group I: PORT	33.44±4.64	-8.909	35	< .001
	Group II: Control	46.37± 4.18			
MMO_{12}	Group I: PORT	32.56±4.29	-9.385	35	< .001
	Group II: Control	46.37±4.65			
Significant at the .05 level					

Table-5: Comparison of MMO at different months between the groups

groups pectoralis major myocutaneous (PMMC) flap was used in maximum number of patients. Postoperative complications at the site of reconstruction developed in 06 patients (33%) of PORT group and 04 patients (21%) of control group. In both the groups complications were minor except in 02 patients of PORT group where major complications developed which required some form of intervention.

Result of repeated measures ANOVA with Greenhouse-Geisser correction (Table-3) at alpha level .05, shows within subject effect was significant in both group I (PORT) and group II. There was significant difference of MMO between the groups and significant interaction effect between the variable of month and radiation.

Figure-1 shows mean MMO vs month plot in group I and group II. In group I (PORT), MMO gradually decreases over time, however in group II, MMO decreases in 1st month (MMO_1) then gradually it increases towards pre-operative MMO over time. Table-4 shows, whether within group difference was significant at different months. Bonferroni adjusted post-hoc-analysis for pairwise comparison of means within the group for MMO at different time point was done and p-value was calculated at alpha level .05.

Table-5 shows result of *t*-test of between group difference of mean MMO at different months. Between group difference of MMO_0, MMO_1 were not significant, however at 3rd (MMO_3), 6th (MMO_6), 9th (MMO_9) and 12th month (MMO_{12}) differences were significant p<.001 (alpha level .05).

Figure-2 A & B shows preoperative trismus in a patient of PORT group and Figure-2 C &D shows MMO_{12} in patient of Gr- II(Control) and Gr- I (PORT) respectively.

Figure-2: Images of patients and radiograph. (A) Pre-op trismus in a case of carcinoma of retromolar trigone of PORT group (B) CT scan showing involvement of the mandible of the same patient (C) MMO_{12} in a patient of control group (D) MMO_{12} in a patient of PORT group.

DISCUSSION

The word trismus, derived from Greek word 'trismos' means grinding of teeth, was initially associated with tetanus or lockjaw since the experiment of Nicolaier in 1884.[8] However at present, the term broadly includes all conditions of limited mouth opening. In head neck cancer patients, trismus can be the result of cancer invasion, result of surgery or long-term sequelae of radiotherapy.[9] During the time of diagnosis trismus can be present in 2% - 55% of patients.[1,10] It can result from tumour growth or invasion in masticator space or reflex spasm of the elevator group of muscles. In our study, MMO_0 of Group I (PORT) and Group II was 43.22 ±10.5mm and 47.26±4.72mm respectively and only 3 patients (16.7%) of Group I presented with trismus (≤35mm).

Surgical excision of a tumour located in the buccal mucosa, retromolar trigone area and tonsillar fossa might lead to trismus due to fibrosis or scarring of pterygoid muscles or pterygomandibular ligament.[5] In cases of tumours of posterior portion of maxilla, surgical extension might extend up to infratemporal fossa, leading to post-operative hematoma and subsequent fibrosis.[11] In the study of Ichimura et al[5] 7 patients (3%) developed postoperative trismus among 212 patients. Agarwal et al[1] showed 86.7% of the patients developed trismus, in study with 30 patients. However, in those studies, same group of patients received radiation also. In our study the effect of surgery can be assessed without any confounding factors from the observation in Group II, where no radiation was given. MMO_1 in group I (before radiation) was 40.78±5.62 mm and in Group II was 43.53± 4.91mm and in comparison to the MMO_0 the difference was significant in Group II (p=.04) but not in Group I (p=.74). Mouth opening gradually became normal in Group II and the difference with MMO_0 was insignificant in 3rd, 6th, 9th and 12th month. Same trend is also depicted in figure 1, where top line shows change of mean MMO vs time in group II.

Radiation effect on mouth opening can be largely unpredictable. It usually manifests after 3 to 6 months of therapy and remains permanently.[12] Goldstein et al[13] states that the effect of radiation depends on multiple factors like source of radiation, configuration of the field, dose and tissue in the irradiated field. Ichimura et al[5] opines that trismus develops above greater than 50 Gy radiation dose to temporomandibular joint (TMJ) capsule and masticatory muscle area. However, Goldstein et al[13] states functional impairment can happen even in as low dose as 1493 cGy in pterygoid muscle and TMJ area and the most critical factor seems to be the pterygoid muscles in the field of radiation. Teghu et al[14] studied dose-effect relationship in masticator space and found significant correlation between trismus with dose in masseter and pterygoid muscle. The probability of trismus increases 24% with each 10 Gy increase of radiation.[14] Wang et al in their study of time-course assessment, found absence of significant change of maximum interincisal distance during the course of radiotherapy, however rapid decrease happened within 1-9 months at the rate of 2.4% per month.

In our study, mean MMO of Group I at 3rd, 6th, 9th and 12th month was significantly different than preoperative MMO_0 and the figure-1 also reflects the gradual decrease of bottom line. The increasing difference between the lines of group I and group II, can be explained from t-test (table-5), where 3rd month onward difference of MMO between the groups became significant ($p < .05$) and value of t at successive month also increased.

Literature reports a wide range of prevalence of trismus, after head neck cancer treatment. Dijkstra et al, 2004, in a systematic review, states that prevalence ranges from 5% to 38% after cancer treatment.[15] The wide variation of prevalence exists due to the absence of uniform criteria for trismus and a cut-off point of 35 mm was established by Dijkstra et al in 2006, according to a study in Dutch population, among 89 patients.[10] However there might be variation in normal mouth opening due to age, sex, build and population.[16] Kent et al reports 45% trismus in patients after radiation and there was no difference in prevalence between conventional radiotherapy (RT) vs intensity modulated radiotherapy (IMRT). Benasdron et al, 2010 reports in a systematic review, 25.4% trismus in RT and 5% in IMRT. Agarwal et al 2016 reports 65.4% of trismus at the end of 6 months. In our study where Group I patients have undergone conventional radiotherapy and at the end of 01-year MMO_{12} was 32.56±4.29mm and 12 patients (66.67%) developed trismus, which corroborates with the findings of previous studies.

Several studies have shown that radiation induced trismus can largely be prevented by doing regular mouth opening exercise, however the benefit is guarded in non-compliant patients.[6,17–20] In our studies high rate of trismus might be due to use of conventional radiotherapy and non-compliance to the advice of exercise by the patients. One of the factors in this regard was the fact that most of the patients were

from the lower socioeconomic group and hence obtaining compliance and multiple follow-ups was a challenge. This may be seen less in patients who are more motivated or have the support of more educated caregivers to assist them in this regard.

CONCLUSION

Trismus following cancer surgery has been well documented and this has also been shown to have been aggravated when associated with subsequent radiotherapy.[3–5] The effect of radiation on mouth opening may not be evident immediately but the effect is seen over a subsequent period of 1-9 months and is quite alarming. Intensity modulated radiotherapy (IMRT) has been reported to have better outcomes on MMO as compared to conventional radiotherapy. Wherever the facilities exist, IMRT or 3D conformational radiotherapy should be considered to reduce the side-effects on MMO. Strict protocols on mouth opening exercises should also be advised to the patients, and close monitoring of the patients is necessary to have measurable effect. We cannot prevent what has happened, but we can surely mitigate the side effects of the patients entrusted to our care.

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