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Corresponding Author
M. Aspin Nivya,
Department of Radiation Oncology, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamil Nadu, India
nivyaaspin950@gmail.com

Author Designation
[1]Professor and HOD
[2]Junior Resident

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Objective Evaluation of Trismus in Patients Receiving Intensity-Modulated Radiation Therapy (IMRT) for Oral Cavity and Oropharyngeal Carcinoma

[1]K.L. Jayakumar and [2]M. Aspin Nivya
[1,2]Department of Radiation Oncology, Sree Mookambika Institute of Medical Sciences, Kanyakumari, Tamil Nadu, India

ABSTRACT
The aim of this study was to determine the role of risk factors in the development of trismus in patients with oral and oropharyngeal cancer (OOPC) receiving intensity-modulated radiation therapy (IMRT) and to estimate the incidence of trismus in this population. A retrospective cohort study was conducted at our institution involving patients treated for Oral Cavity and Oropharyngeal Carcinoma with IMRT. Inclusion criteria consisted of patients with pre-RT maximal inter-incisor opening (MIO) ≥36 mm, who received high-dose radiation therapy (≥60 Gy) and had MIO measurements before and 6-48 months post-RT. Trismus was defined as MIO ≤35 mm. The study used Fisher's exact test to assess the association of risk factors (age, gender, tumor site, tumor size, tumor stage, pre-RT MIO and radiation dose to the masticatory muscles) with trismus development. Wilcoxon Signed Rank test was applied to compare radiation doses to the ipsilateral muscles of mastication between patients with and without trismus. The cohort comprised 30 patients with a median age of 58 years, 60% of whom were male. The median follow-up period was 10 months. The trismus incidence rate was 26.6%. Pre-RT MIO measurements were significantly associated with the development of trismus (P<0.001). While the mean radiation doses to the masseter and medial pterygoid muscles were numerically higher in patients who developed trismus, no statistically significant differences were observed (P=0.06, P=0.21, respectively). Other factors such as age, sex, tumor site, tumor size (T) and tumor stage were not significantly associated with trismus. Pre-RT MIO measurement emerged as a significant risk factor for the development of trismus, though it is an unchangeable factor. To mitigate this complication, limiting radiation exposure to the masticator muscles may be a key preventive strategy.

INTRODUCTION

Oral and oropharyngeal cancers are tumors with high heterogeneity. They are presumably representing genetically similar tumours by virtue of the common anatomy as well as their challenging location in close proximity to vital structures which overlap in such tumours. The human papilloma virus-positive squamous cell carcinoma, which is becoming more common, is one of this group of RT-sensitive malignancies[1]. Over the last twenty years, developments in radiotherapy have progressed from standard/2D radiotherapy to three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiation therapy (IMRT). RT is also associated with late complications including dermatitis, fibrosis, soft tissue atrophy, osteoradionecrosis, mucositis, dysphagia, Trismus and loss of salivary function. IMRT represents a major advance in both improving the dose distribution to be more conformal to the tumour, involved neck and high-risk areas while reducing doses from the best previous technique to critical normal structures[2]. As a result, initial toxicity and locoregional control rates with IMRT have been encouraging and have translated into lower rates and severity of radiation-associated toxicity[3-6]. Intensity modulated radiation therapy (IMRT) has become standard of care for oral and oropharyngeal cancer in the past years. Trismus, the inability to open the mouth or difficulty with mouth opening secondary to spasm of the muscles of mastication, is a well -documented complication[7]. Normal values for maximal inter-incisor opening (MIO) range from 36-55 mm with ≤35 mm classified as trismus. It may result from a tumour infiltrating the muscle of mastication, their nerves and the temporomandibular joint, or as a result of surgery or radiation therapy[8]. Trismus can lead to difficulty in achieving healing, as speech, feeding, most importantly oral hygiene becomes hard[9]. In oral and oropharyngeal cancer patients treated with IMRT, the literature has reported incidences of trismus ranging from 4-77.3%[9]. Such variability is likely related to different inclusion criteria, subjective or objective assessments of trismus, cut-off values for trismus and follow-up periods. On the other hand, we have only limited data directly comparing the questionnaires. The development of trismus and the risks associated with it stem from a multitude of variations, including patient age and sex, location of the tumour, maximum inter incisor opening (MIO) values prior to the onset of radiation therapy (RT), radiation dose to the primary tumour and radiation dose to the masticatory muscles. The study aims to assess the incidence of trismus in oropharyngeal tongue cancer (OOPC) managed with intensity modulated radiotherapy (IMRT). To evaluate risk factors: Age, sex, site, T, stage, pre-treatment MIO, radiation dose to primary tumour and radiation dose to ipsilateral muscles of mastication in patients with trismus after IMRT Patients determined to develop trismus should have lower pre-RT MIO measurements and receive higher RT doses to the muscles of mastication.

MATERIALS AND METHODS

This was a prospective observational study conducted in our centre After getting Institutional ethical committee approval, In order to obtain information to answer our research questions, we designed the present study as a retrospective cohort study and specifically targeted patients who received IMRT for their oral/oropharyngeal cancer. The subjects of the study were patients who came to pre-and post-RT evaluation. Study sample inclusion criteria were the availability of pre-RT and post-RT MIO measurements ≥6 months post RT, high-dose radiation (≥60 Gy) and a pre-RT MIO ≥36 mm. Trismus has been characterized as mouth opening of <35 mm in previously published studies and its peak incidence occurred at 6 months following RT. A review and analysis of risk factors including gender, tumour site and tumour size (T), overall tumour stage, pre-RT MIO measurements and ipsilateral muscles of mastication radiation doses in patients who developed trismus was performed. The mean radiation dose to the ipsilateral muscles of mastication (medial pterygoid and masseter) was compared between patients who developed trismus and matched control (nontrismus) patients matched for tumour site, tumour size and radiation dose to the primary tumour. In this study we evaluated the following predictor variables., Age, Gender, Tumour site, Tumour size (T), overall tumour stage, pre -treatment (pre-RT) MIO measurements, the dose of radiation to the primary tumour and the radiation doses to the muscles of mastication on the ipsilateral side. Patients were classified into 2 groups based on maximum interincisal opening (MIO) with a cut-off value of 40 mm before RT. The main outcome variables were the presence or absence of any trismus. Trismus was defined as post-RT MIO measurements of ≥35 mm. Based on measurements trismus was classified as mild/grade I (35-26 mm), moderate/grade II (25-16 mm) and severe/grade III (15-0 mm). In patients with complete anterior dentition, mouth opening measurements were recorded as the maximum separation between the tips of the upper and lower incisors., for edentulous patients, the denture teeth were used as reference points. Pre-RT measurements were taken. An RT completion date is established and post-RT measurements occur at least 6 months after finishing RT. Ipsilateral muscles of mastication [masseter and medial pterygoid] mean radiation dose). Incidence of trismus and patient/tumour characteristics were analyzed descriptively. Were utilized Fisher exact test for assessing roles of age,

gender, primary tumour location, size (T), total tumour stage (AJCC 8th edition tumor classification) and pre-RT MIO measurements 9, as well as radiation doses to the primary tumour and matched control (non-trismus) patients A P-value <0.05 was considered as statistically significant.

RESULTS AND DISCUSSIONS

At a median follow-up time of 10 months, 30 patients fulfilled the inclusion criteria. The median age was 58 years (range 31-75 years), with 18 males and 12 females. The histology of the patients was squamous cell carcinoma (27), adenoid cystic carcinoma (2) and mucoepidermoid carcinoma (1). Tumour sites included: anterior 2/3rd of tongue, buccal mucosa. Of the 30 patients with known stage, 24 were Stage IV, 3 were Stage III, 2 Stage II and 1 Stage I. Primary tumour total radiation dose ranged from 66Gy in 30 Fr-75Gy in 35Fr with a maximum of 2Gy per fraction and 5 fractions per week and a mean of 68.9 Gy (27 of 30 patients received ≥66 Gy). MIO measurement mean 45.14 mm, (PRE-RT MIO: 36-58 mm).

Table 1: Patient Parameters

Parameters	Number	Percentages
Age		
>50 years	12	40%
<50 years	18	60%
Median range	58 (31-75 years)	-
Gender		
Male	18	60%
Female	12	40%
Tumour site:		
anterior 2/3rd of tongue	20	66.6%
buccal mucosa	10	33.3%
Pathological diagnosis:		
Squamous cell carcinoma	27	90%
Adenoid cystic carcinoma	2	6.67%
Mucoepidermoid carcinoma	1	3.33%
Tumour stage		
I	1	3.33%
II	2	6.67%
III	3	10%
IV	24	80%
Trismus status		
Trismus	8	26.66%
No trismus	22	73.34%

Trismus occurred in 8 (26.6%, 6 male and 2 female., P=0.34) patients with ages between 45-70years (5 patients ≤50 years and 3 patients >50 years., P=0.84) after IMRT with MIO measurements ≤35 mm at a median of 10 months. At a minimum of 6 months post-RT, their MIO measurements ranged from 10-35 mm (mean 26 mm)., the radiation doses to the primary tumour were 66-70 Gy. Trismus was grade I/mild (n=5), grade II/moderate (n=2) and grade III/severe (n=1). The sites of the primary tumours in patients with trismus were anterior 2/3rd of tongue (n=20) and buccal mucosa (n=10) (P=0.51) and tumour stages were Stage IV (7) and Stage II (1) (P=0.56). The tumour sizes were T1 and T2 (five), T3 and T4 (three) (P=0.68). In patients without trismus, the pre-RT MIO values varied from 36-66 ongoingmm (mean: 59.25 mm., P 40mm., P<0.001).

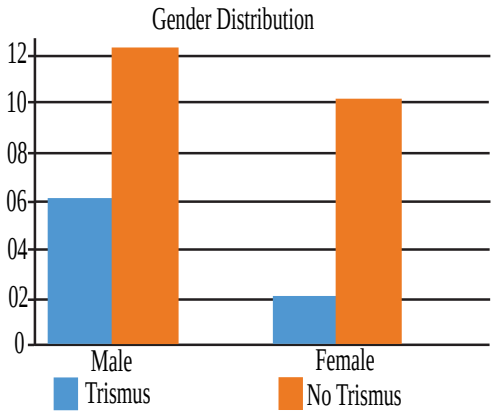

Fig. 1: Gender Distribution Among Study Group

Trismus was assessed using the Gothenburg trismus questionnaire and significant changes in quality of life were reported in 5 of 8 patients. Both feeding and jaw opening are directly influenced by the most relevant functional changes for patients with a greater impact on quality of life, all of which scored moderate to very difficult. In trismus patients, post-RT MIO measurements between 33 and 35 mm indicated no clinically important changes in quality of life.

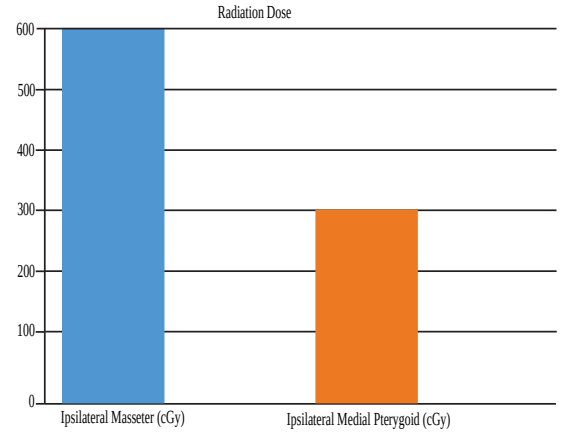

Fig. 2: Radiation Dose to Ipsilateral Muscles of Mastication

To determine the contribution of radiation dose to the masticatory muscles, a matched, paired comparison of mean radiation dose to the masticatory muscles (masseter and medial pterygoid) of 7 patients developing trismus was made with radiation dose in 4 patients matched with trismus patients by similar tumour site, tumour size (T) and radiation dose to the primary tumor. Mean radiation doses to the medial pterygoid were significantly higher than to the masseter in all patients dosimetrically contoured. Among the trismus patients, the mean radiation doses for the masseter and medial pterygoid muscles were numerically but not significantly higher than those delivered to muscle among control (non-trismus) patients (masseter, P=0.06, medial pterygoid, p=0.21). Its trismus is a well-established complication in

patients receiving radiation therapy either as a radical or adjuvant therapy in conjunction with surgery or chemotherapy. The aim of this study was to determine the incidence of trismus in patients with Oral cavity and Oropharyngeal Carcinoma treated with IMRT and to test the association of risk factors (age, gender, tumour site, T, stage, pre-RT measurements, dose to the primary tumour and dose to the ipsilateral muscles of mastication) with trismus status. We hypothesized that lower baseline (pre-RT) measurements of maximum interincisor opening (MIO) and higher radiation dose to the muscles of mastication would predict which patients would be at higher risk for developing trismus (≥20% loss of MIO). They were followed up for a median of 10 months. The incidence of trismus which we found is 26.6%. Trismus was highly prevalent in patients with pre-RT MIO measurements ≤40 mm. The mean radiation dose to the ipsilateral muscles of mastication (masseter, medial pterygoid) was higher in matched patients that did develop trismus compared to control (non-trismus) patients, although not significantly different. None of the other parameters, such as age, gender, radiation dose to the primary tumour, tumour site and tumour size (T) and tumour stage were statistically significant either. In head and neck cancer treatment, IMRT has been shown to provide superior target coverage and reduced complication rates compared to older techniques in study by Kraaijenga *et al.,* 2015, Lohia *et al.,* 2014., Vergeer *et al.,* 2009 and Setton *et al.,* 2012. A study by Chen *et al.* Incidences of 0.22-5.7% have been reported during treatment of nasopharyngeal carcinoma with IMRT[4]. Rao *et al.* The annual percentage of chronic trismus development after IMRT for oropharyngeal cancer has been 14.1% of patients[11]. In a different population of 3D-CRT or IMRT treated head and neck cancer patients, the trismus rate was 28.3%[12]. Hsieh *et al.* IMRT used to treat oral cancer is associated with a relatively high incidence of trismus 2 years post-treatment[8], with 77.3% of patients reportedly suffering from this adverse effect 2 years after the initiation of treatment[8]. In this study, the sample size of the 22 patients and the cut off value for trismus were not defined and the time gap after radiation to obtain the measure of maximum inter incisor opening was not specified so the result of the study has been probably enhanced. Patients most often present with trismus due to the early complication of RT (mucositis) and not as a late sequelae of radiation. Trismus was evaluated more than 6 months after RT in this study conducted by Pauli[13], by which time the acute side effect of RT (mucositis) should have resolved and the peak incidence of trismus could be measured. This specific distribution of radiation enables radiation, which can reduce toxicity to tissues surrounding the tumour. Yet it remains difficult not to irradiate the high-risk structures when these structures are adjacent to those tumours, particularly in specific patients with tumours adjacent to the muscles of mastication or temporomandibular joint (TMJ), without compromising locoregional cancer control. The use of a newer radiation technique, intensity-modulated proton therapy, which offers better conformal delivery and thus minimization of radiation to nearby organs at risk, may be preferable in the treatment of oral and oropharyngeal cancer. As trismus can be complex to manage it must be prevented instead of treated. In certain patients, prophylactic and immediate conservative management of trismus has been proved to be effective[14,5]. Exercise therapy and jaw opening devices such as stacked tongue depressors, corkscrews, TheraBite and Dynasplint devices are used as a routine. One of these is pre-RT MIO measurement, which is a fixed variable. Hence, reduction of IMRT dose to the muscles of mastication and temporomandibular joint complex would likely reduce trismus in the oral and oropharyngeal cancer population.

CONCLUSION

Trismus still persists as a sequelae of IMRT in the treatment of patients with oral and oropharyngeal cancers as this study demonstrates. Trismus is seen in patients with natural small mouth opening or those who undergo surgery or have tumour infiltrating the muscle of mastication, their nerves, or temporomandibular joint. Such patients should be carefully monitored and jaw exercise therapy should be started as early as possible at the beginning of radiotherapy.

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