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ORIGINAL ARTICLE

Evaluation of Mucociliary Activity in Maxillary Antra in Patients with Squamous Cell Carcinoma of Buccal Mucosa Undergoing Post Operative Radiotherapy

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Abstract A prospective longitudinal observational study was conducted on 24 patients of histopathologically confirmed squamous cell carcinoma of buccal mucosa upon whom bilateral 'middle meatal antrostomy was performed during the same sitting as the tumour resection with the main aim to assess the maxillary mucociliary clearance, pre-, during and post-irradiation; and compare the findings with the non-irradiated side in the same patient to avoid any confounding factors. All patients underwent methylene blue dye clearance and saccharine clearance tests before the commencement of radiation therapy, weekly during irradiation and again at first and sixth month of completion of irradiation. Pre-radiation there was statistically no difference ($P > 0.05$) in clearance times between both sides. But, there was a significant ($P < 0.001$) increase in saccharin and methylene blue clearance times on the irradiated side in comparison to contralateral non-irradiated side, during and post-radiation. It is concluded that external beam radiotherapy for oral cancers significantly affect ciliary activity in the adjacent maxillary antrum and has no effect on the opposite side. Recovery in mucociliary activity was not seen even after 6 months after radiation therapy.

Keywords Maxillary mucociliary clearance · Radiation induced sinusitis · Methylene blue transit time · Saccharin perception test · Head and neck cancer

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Introduction

30–35% of malignancies in India involve head and neck region. Oral cancer accounts for around 50% of these malignancies [1, 2]. There is a high prevalence of buccal mucosa malignancy in Kolar district due to the habit of betel nut and tobacco chewing and the use of quid.

Radiotherapy is a key component in the multidisciplinary treatment used in all head and neck cancers. It is associated with many complications and sequelae out of which sinusitis is one. It needs regular assessment as a part of followup [5–8].

The underlying cause of sinusitis in irradiated patients was proven to be decreased mucociliary clearance in the nasal cavity and paranasal sinuses [3].

Even though the field of radiation during Radiotherapy for squamous cell carcinoma buccal mucosa does not directly involve paranasal sinuses, radiation sequelae in mucociliary clearance may occur in maxillary antrum on the ipsilateral side as it is a site close to the primary tumour bed [4].

Study was designed to perform bilateral middle meatal antrostomy and study and document mucociliary clearance in patients receiving post operative radiotherapy for squamous cell carcinoma of buccal mucosa.

Materials and Methods

All patients with stages T3, T4a squamous cell carcinoma of buccal mucosa aged 18–70 years operated with a curative intent and planned for post-operative radiotherapy giving valid consent for bilateral middle meatal antrostomy at the time of cancer surgery and periodic endoscopy of bilateral maxillary antra were included in the study.

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Patients who had previously received radiotherapy, defaulters, chemoradiation, neoadjuvant chemotherapy or with known causes of mucociliary dysfunction were excluded from the study. Bilateral middle meatal antrostomy was performed using the endoscopic sinus surgery technique, using rigid 4 mm endoscopes (Karl-Storz, Tuttlingen, Germany) with deflection angles of 0° and 30° and cold instruments. Ostium was widened posteriorly and inferiorly to retain the patency of ostium wide enough to perform further periodic endoscopy and tests for mucociliary clearance.

Measurement of mucociliary clearance was performed using two tests:

1. Methylene blue transit time (MTT)
2. Saccharine transit time (STT)

Each visit of periodic nasal endoscopy was timed at before initiating radiotherapy, each week of radiation, one and 3 months intervals after completion of radiotherapy.

The patient was explained about the procedure and detailed history of other radiation-related complications was noted down in the proforma. Thorough saline nasal irrigation was given and nasal cavity on one side was packed with 4% xylocaine mixed with 1 in 10,000 adrenaline soaked cotton pledgets to achieve adequate vasoconstriction and make room for instrumentation. Rigid 4 mm endoscopes (Karl-Storz, Tuttlingen, Germany) with deflection angles of 0° and 30° were used to perform nasal endoscopy and the respective maxillary antra were visualized. Using a 26 gauge spinal needle bent at its tip which was attached to a syringe a drop of 1% methylene blue aqueous dye was instilled at the junction of medial wall and floor of maxillary antrum. During this process, care was taken not to touch nasal cavity mucosa. Using a heavily curved forceps a sodium saccharine crystal of 2 mm^3 was placed at the same site as the dye and the stopwatch is started.

The patient was immediately placed in sitting up position with quiet nasal breathing. During the test, patients were advised not to cough, blow nose, lean forward or backward. The patient was not allowed to drink any liquids, eat any foods during the test period.

A 30° rigid 4 mm endoscope (Karl-Storz, Tuttlingen, Germany) attached to a camera, monitor and light source was used to examine the movement of dye in the maxillary antrum in 10-min intervals. The time taken for methylene blue dye to reach the posteroinferior edge of antrostomy window is noted as MTT (Fig. 1). 60 min is taken as cut off for MTT. STT is measured depending on the subjective feel of taste sensation (sweet) by the patient and recorded on the stopwatch. 120 min was considered as a cut off for STT. The test was repeated on the opposite side after 6 h for determining MTT and STT.

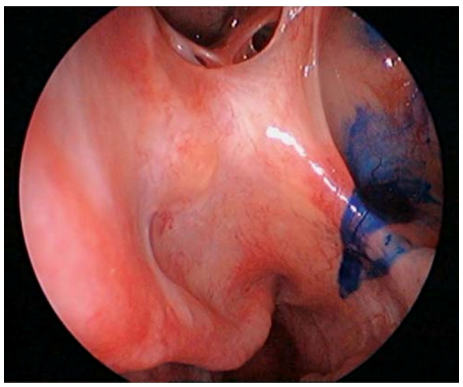

Fig. 1 Clearance of methylene blue dye from the maxillary antrum

Results

Mean age of study population 47.58 years and median was 46.5 years. Sex ratio male to female was 0.411. Majority of study population 66.6% presented with advanced disease. Statistically significant transit times ($P < 0.001$) were seen during and after radiation therapy on the irradiated side (Tables 1, 2). Comparison of maxillary antral mucociliary

Table 1 Trend of saccharine transit time on ipsilateral antrum

Parameter	Mean ± SD	*P* value
Pre radiotherapy	45.17 ± 13.26	(Base line)
Week 1	63.92 ± 21.95	**< 0.001**
Week 2	92.33 ± 21.8	**< 0.001**
Week 3	101.08 ± 18.67	**< 0.001**
Week 4	106.04 ± 14.72	**< 0.001**
Week 5	108.46 ± 12.56	**< 0.001**
Week 6	106.67 ± 15.73	**< 0.001**
1 month post RT	100.92 ± 21.14	**< 0.001**
3 month post RT	96.17 ± 22.02	**< 0.001**

P value of < 0.05 being significant. All the results on the treatment side are specified in bold

Table 2 Trend of methylene blue transit time on ipsilateral antrum

Parameter	Mean ± SD	*P* value
Pre radiotherapy	45.17 ± 13.26	(Base line)
Week 1	63.92 ± 21.95	**< 0.001**
Week 2	92.33 ± 21.8	**< 0.001**
Week 3	101.08 ± 18.67	**< 0.001**
Week 4	106.04 ± 14.72	**< 0.001**
Week 5	108.46 ± 12.56	**< 0.001**
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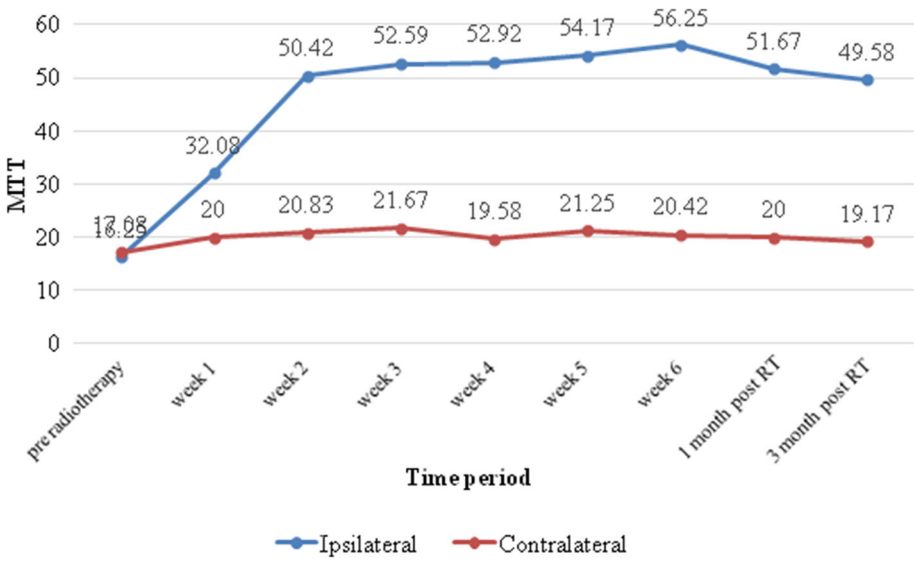

Fig. 2 Trend diagram of comparison of STT between Ipsilateral and Contralateral before and after radiotherapy

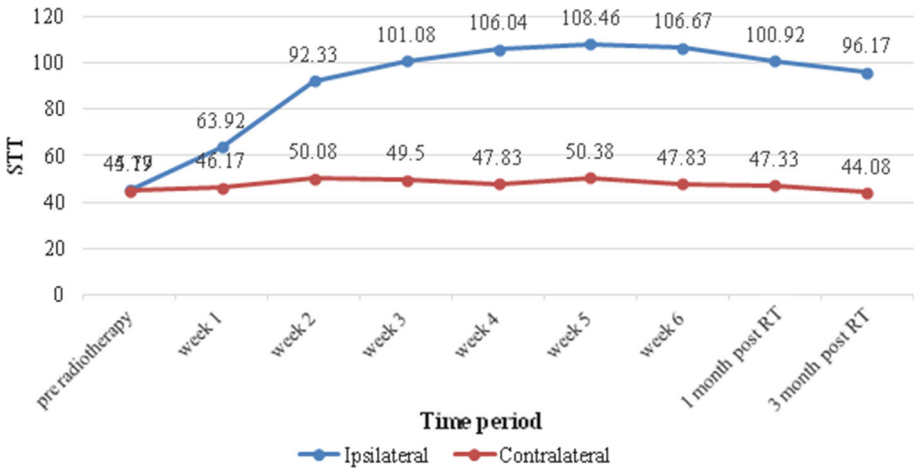

Fig. 3 Trend diagram of comparison of MTT between Ipsilateral and Contralateral before and after radiotherapy

clearance between irradiated and non irradiated sides are portrayed through trend diagrams (Figs. 2, 3), shows that opposite side antral mucociliary clearance is not affected.

Discussion

Results of our study demonstrate a female preponderance in the study subjects (male to female sex ratio was 0.411), which may be attributed to the quid chewing habit and demographic characteristics of Kolar district population. A case–control study conducted in three areas of southern India (Bangalore, Chennai, Trivandrum) regarding the incidence of oral cavity cancer has demonstrated that male to female sex ratio in Bangalore area was the least accounting to 0.5 when compared to other areas of south India. This study has also evaluated the reason for such high incidences in women of this area and attributed it to quid chewing habit of rural women [9].

The median age group of our study population was 46.5 years and mean age group is 47.5 years. In a paper published by Ministry of health and family welfare, Government of India, it has been stated that the majority of oral cancer burden is in the age group of 35–50 years [10].

66.6% of our study population presented with advanced disease (T4a) and 33.3% of subjects were stage T3 tumours. A study performed in a regional cancer centre also showed similar findings where 60% of OSCC patients presented with T4a tumours while 30% presented with T3 tumours [11]. This late presentation to speciality surgical centre may be attributed to lack of medical education, negligence and low literacy rates among a majority of study population [10, 12].

It has already been proven by many studies that direct exposure of irradiation to nasal mucosa (nasopharyngeal carcinoma, nasal and paranasal sinus carcinoma) where the field of irradiation includes a majority of the nasal cavity and paranasal sinuses, hampers mucociliary clearance and

subsequently leads to the development of chronic rhinosinusitis in these patients [5–8]. A Chinese study showed that the occurrence rates of paranasal sinusitis at first month, third month, sixth month and 1 year after radiotherapy were 21.0, 33.7, 41.5 and 29.3% respectively [13].

Our study was designed to evaluate MCC in maxillary antrum which lies adjacent to the field of radiation in postoperative patients with squamous cell carcinoma of buccal mucosa. There is paucity in the literature regarding studies which evaluated maxillary antral mucociliary clearance during radiotherapy to the adjacent area over the head and neck region.

Studies showed a reduction in nasal clearance times in patients receiving radiation where nasal mucosa was in close proximity to the field of radiation but not included in it. A Turkish study showed elevated nasal STT in patients who received radiotherapy for laryngeal cancers [14] and an Indian study showed similar results for hypopharyngeal, laryngeal and buccal cancer subjects [3].

In our study STT in ipsilateral antra on the side of radiation shows significant elevation beginning from the second week of radiotherapy following which throughout the treatment period STT values were above the 100-min mark, suggesting severe diminution in ciliary clearance. A similar trend was shown in MTT values rising from the second week of radiation and persistently remained over 50 min throughout the treatment period. The maximum residual delay in STT during radiation was 63.29 min which was recorded during the 5th week of treatment. The maximum residual delay in MTT was 40 min observed during the 6th week of treatment. These findings suggest that maximum deterioration of mucociliary clearance was occurring towards the completion of radiotherapy.

A Japanese study demonstrated that on an ultrastructural level there is a significant loss of ciliary epithelium when STT is above 100 min [15]. An Egyptian study shows that there is a steep elevation of nasal STT from a mean of 25–35 min along the course of radiotherapy for nasopharyngeal carcinoma. It also demonstrated that the maximum deterioration in MCC was occurring towards the end of the treatment course [16].

In our study on the contralateral side i.e., non-irradiated maxillary antra, pre-radiotherapy mean STT and mean MTT were 44.79 and 17.08 min respectively, Maximum elevation of these recordings were 50.38 and 21.67 respectively towards the end of the radiotherapy treatment course and 3rd-month post-RT values were 44.08 and 19.17 min. Even though there are slightly reduced clearance times during radiotherapy there is no statistically significant establishment of such findings.

When contralateral antral clearance in patients receiving radiotherapy for squamous cell carcinoma of buccal mucosa is considered, as the contralateral antral mucosa was not included in the field of radiation there were no findings of statistically significant decrease in mucociliary clearance recorded.

Conclusion

It is the responsibility of the surgeon to improve the long term quality of life of head and neck cancer patients. Radiation induced sinusitis is a well established complication in patients who have direct radiation exposure to nasal and para nasal sinus mucosa.

When considering surgical drainage procedures for radiation induced sinusitis it is to be kept in mind that the concept of successful FESS is not applicable to radiation induced rhinosinusitis as its based on healthy and normal Mucociliary clearance. Taking into account that reversal of radiation induced changes takes much longer or might not revert back at all, dependant drainage procedures should be considered in such symptomatic individuals.

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