ORIGINAL RESEARCH

Oral Mucosa Sparing Adjuvant Radiotherapy in Patients of Squamous Cell Carcinoma of Oral Tongue: A Prospective Randomised Study

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ABSTRACT

Background: A major limitation of Radiotherapy (RT) in an adjuvant setting for oral tongue cancer is the development of acute oral mucositis. By employing intensity-modulated radiotherapy (IMRT), it is possible to minimize the RT dose to the mucosa and potentially reduce the incidence and severity of acute mucositis. Therefore, we conducted a randomized trial to evaluate the efficacy of oral mucosa-sparing radiotherapy (OMSRT) compared to oral mucosa-non-sparing radiotherapy (OMNSRT) in patients with oral tongue cancer. **Methods:** A prospective randomized study was conducted, including patients diagnosed with oral tongue squamous cell carcinoma (SCC), who underwent upfront surgery and were eligible for adjuvant radiotherapy. Patients were randomized into OMSRT and OMNSRT groups. IMRT was employed for the treatment of all the cases. In the OMSRT arm, the dose to the oral mucosa was restricted to a D mean of 32Gy. Patients were followed up regularly to assess treatment response, and toxicities. Statistical analysis was performed using appropriate tests. **Results:** The study included 32 patients, with 16 patients in each group. The dose to the oral mucosa was significantly lower in the OMSRT group compared to the OMNSRT group (Dmean: 29.16 Gy vs. 32.14 Gy, $p = 0.00$). The OMNSRT arm had a significantly higher number of patients suffering from higher-grade mucositis (grades 2 and 3) ($p = 0.032$). Additionally, these toxicities were delayed in the mucosa-sparing arm. Even though a higher percentage of patients had to use analgesics in the OMSRT arm, this difference was not statistically significant. **Conclusion:** OMSRT using IMRT effectively reduced the dose to the oral mucosa in patients with oral tongue SCC, thereby addressing one of the major limitations of RT in this setting - acute oral mucositis.

Keywords: Oral Mucosa Sparing Radiotherapy (OMSRT), Oral Tongue Cancer, Squamous Cell Carcinoma (SCC), Intensity Modulated Radiotherapy (IMRT).

INTRODUCTION

Radiotherapy (RT) plays a crucial role in the management of oral tongue canceras an adjuvant therapy following surgery [1-3]. One of the major limitations of RT in this setting is the development of acute oral mucositis, which significantly affects patients' treatment and quality of life [4]. The severity of mucositis can vary from mild discomfort to debilitating pain, with potential implications for treatment interruptions, nutritional compromises, and the need for supportive care.

Strategies aimed at sparing the oral mucosa from high radiation doses have been explored. By employing intensity-modulated radiotherapy (IMRT), it is possible to minimize the RT dose to the mucosa and potentially reduce the incidence and severity of acute mucositis [5-7].However, the specific impact of sparing the oral mucosa with IMRT remains to be fully elucidated. Therefore, we conducted a randomized trial to evaluate the efficacyof oral mucosa-sparing radiotherapy (OMSRT) compared to oral mucosa-non-sparing radiotherapy (OMSRT) in patients with oral tongue cancer. This study aimed to assess the incidence, severity, and duration of acute mucositis among patients treated withOMSRTas opposed to OMSRT. Furthermore, it aimed to evaluate the oncological outcomes and long-term complications associated with OMSRT.

MATERIALS AND METHODS

Patients diagnosed with oral tongue squamous cell carcinoma (SCC) who had undergone upfront surgery and were eligible for adjuvant radiotherapy were included.Informed consent was obtained from all participating patients beforetheir enrolment in the study.

Inclusion criteria: Patients with histologically confirmed oral tongue SCC, age ≥18 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and adequate organ function following surgery.

Exclusion criteria: Patients with contraindications for radiotherapy, previous radiotherapy to the head and neck region, or significant comorbidities that could impact treatment or follow-up.

Radiotherapy Planning and Treatment

All patients underwent computed tomography (CT) simulation for treatment planning. CT images were acquired with patients immobilized in the treatment position. Target volumes, including the postoperative tumor bed, clinical target volume (CTV), and planning target volume (PTV) along with the organs at risk (OARs) were delineated according to DAHANCA guidelines [8].

Distinctive contouring of oral mucosa was performed based on the individual patient's anatomy and tumor location. It mainly encompassed the bilateral buccal mucosa, alveolar mucosa and the superior and inferior labial mucosa. Its craniocaudal boundaries were the hard palate superiorly and the level of the floor of the mouth, inferiorly. Anteriorly, it followed the mucosa around the teeth up to the lips, and posteriorly up to the soft palate.Figure 1 illustrates the delineation of oral mucosa in one of the patients as described.

The patients were randomly assigned by a lottery system to one of the two groups: OMSRT or OMSRT. In the OMSRT group, IMRT was employed to spare the oral mucosa while delivering an effective dose to the postoperative tumor bed by limiting the Dmean to oral mucosa to less than 32 Gy wherever possible. In the OMSRT group, IMRT was used without specific efforts to spare the oral mucosa, targeting the postoperative tumor bed and regional lymph nodes.

The prescribed radiation dose, fractionation, and treatment duration were determined by the treating radiation oncologist based on individual patient factors and institutional protocols. All the patients were treated on a 6 MV photon linear accelerator with conventional RT schedules.

Toxicity Monitoring

Acute oral mucositis during treatment was monitored using acute RTOG toxicity criteria, considering erythema and ulceration at defined oral sites, including the postoperative tumor bed and adjacent mucosa. Pain control and management of mucositis-related symptoms were recorded, including the use of analgesics and antibiotics. Toxicities related to acute mucositis, such as the need for nasogastric tube insertion and treatment interruptions were monitored and documented.

Follow-up

Patients were followed up regularly to assess treatment response, acute toxicities, and long-term outcomes. Follow-up visits were scheduled according to institutional protocol. During the treatment, the patient was followed up weekly with clinical examination, toxicity grading, and blood counts. Symptomatic treatment was given for the management of acute toxicities whenever needed. Following treatment completion, the patients were clinically examined for treatment response and toxicities at monthly intervals for the first three months.

STATISTICAL ANALYSIS

Data was tabulated and analyzed using SPSS software version 25. Descriptive statistics were used to summarize patient characteristics, treatment details, and acute mucositis outcomes in the two study groups. The incidence of toxicities was compared between the OMSRT and OMSRT groups using appropriate statistical tests (Fisher's exact test). Test for normality was done for all the parameters to be compared using the Shapiro-Wilk test and the Wilcoxon signed-rank test was applied to compare the parameters having non-normal distribution. Statistical significance was set at a predetermined level (e.g., $p < 0.05$).

RESULTS AND OBSERVATIONS

A total of 32 patients were included in the study with 16 patients in each arm. The patients and treatment characteristics are enumerated in Table 1. The oral mucosa dose was compared between the two arms and Dmean to oral mucosa was significantly higher in the OMSRT group (29.16 Gy in the OMSRT arm and 32.14 Gy in the OMSRT arm, $p = 0.001$). Additionally, the number of patients suffering higher grades of mucositis i.e., grades 2 and 3, were significantly higher in the OMSRT arm ($p=0.032$) [Figure 2]. Also, these toxicities were delayed in the OMSRT arm. Even though a higher percentage of patients had to use analgesics in the OMSRT arm, this difference was not statistically significant. At 1 month of treatment completion, a significantly higher number of patients had grade 1 or higher mucositis in the OMSRT arm ($p=0.009$) and this difference was maintained even at three months of treatment completion ($p=0.043$).

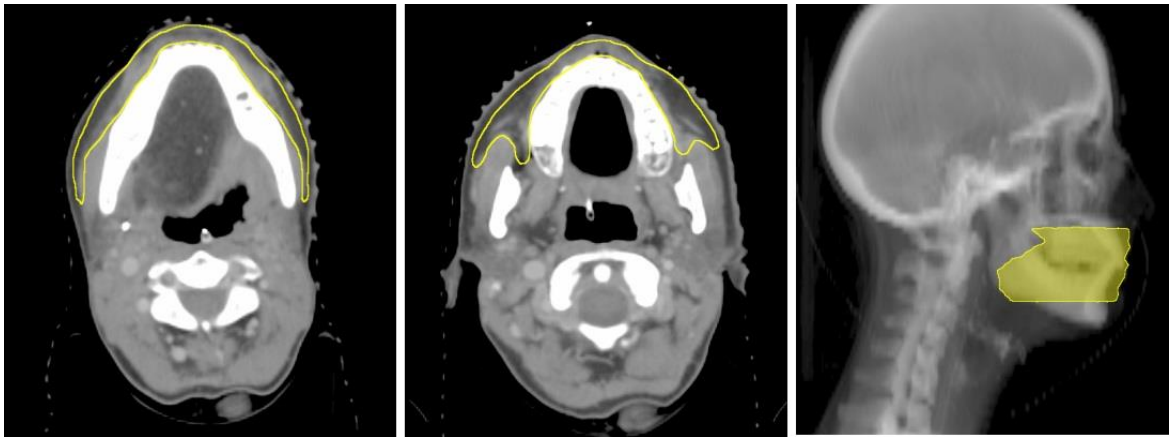

Figure 1: Delineation of Oral Mucosa as an OAR in RT of Oral Tongue Cancer extending from the level of the floor of mouth inferiorly to the hard palate, superiorly. Anteriorly, it follows the gingival mucosa to the labial mucosa, and posteriorly up to the soft palate.

Table 1: Patient and Treatment Characteristics

Characteristics	OMSRT N (%)	OMSRT N (%)	P-Value
Median Age	51 Years (Range 21-62)	47 years (Range 31-68)	0.567
Stage			1.00
Stage I-II	2	3	
Stage III-IV	14	13	
Concurrent Chemotherapy	5	4	1.00
RT Interruption (>5 days)	4	6	0.704
Oral Mucosa Dmean	29.16	32.14	0.001
Oral Mucositis during RT			0.032
Grade 0-1	12	5	
Grade 2-3	4	11	
Use of Analgesics during RT	4	8	0.273
Oral Mucositis at 1 month			0.009
No toxicity	10	2	
Grade 1 or more	6	14	
Oral Mucositis at 3 months			0.043
No toxicity	16	11	
Grade 1 or more	0	5	

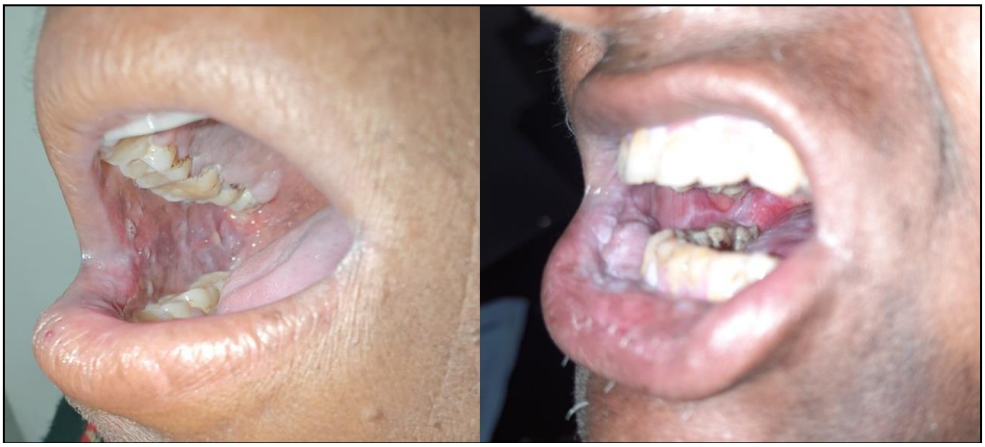

Figure 2: Grades of oral mucositis- Higher grades of oral mucositis were observed in the OMNSRT arm (Right) as compared to the OMSRT arm (Left).

DISCUSSION

The integration of RT as an adjuvant treatment modality following surgical resection in oral tongue cancer patients significantly contributes to disease control and improved survival rates. Nonetheless, the emergence of acute oral mucositis as a common and distressing side effect presents a considerable challenge, impeding treatment continuation and detrimentally affecting patients' quality of life. Our study aimed to address this critical concern by evaluating the potential benefits and clinical outcomes associated with OMSRT compared to OMSRT in patients with SCC of the oral tongue.

The occurrence of acute oral mucositis is extensively documented in the context of head and neck cancer patients undergoing RT. A systematic literature review by Trotti et al. established that acute oral mucositis manifests in approximately 80% of patients, with grades 3–4 mucositis occurring in approximately one-third of cases treated with conventional RT [9]. This finding underscores the clinical significance of investigating strategies to mitigate mucositis severity. Furthermore, the specific challenges posed by oral cavity cancer are evident from the studies by Gomez et al. and Elting et al., which highlight that patients with this type of cancer are predisposed to more severe and prolonged mucositis due to the broad radiation coverage of the oral mucosa [10,11]. These insights emphasize the importance of interventions aimed at reducing mucositis-related morbidity in patients with oral tongue cancer.

The advent of IMRT has ushered in a new era of precision in radiation delivery. In this context, the concept of OMSRT, as introduced by Wang et al., offers a novel approach to address mucositis-associated challenges [12]. Our study builds upon this foundation and adopts a prospective randomized design to comprehensively evaluate the clinical utility of OMSRT in oral tongue SCC patients.

The results of the present study substantiate the potential benefits of OMSRT in reducing the severity of acute mucositis. Patients in the OMSRT group experienced a significantly lower radiation dose to the oral mucosa, a direct result of the meticulously tailored contouring of the oral mucosa. This finding aligned with the study by Wang et al., where the total mean dose in the united oral site was considerably lower in the OMSRT group compared to the non-spared group.Similarly, in the study by Giuseppe et al., it was demonstrated that IMRT plans, particularly when formulated with a focus on mucosal sparing, have the potential to substantially reduce radiation exposure to the oral mucosa, as evidenced by lower dose values delivered to this critical structure [13]. This consistent dosimetric benefit indicates the reproducibility of OMSRT's ability to reduce radiation exposure to the oral mucosa.

The dosimetric advantage observed in the present study translated into a tangible clinical benefit, as evidenced by the substantially reduced incidence of grade 2 and 3 mucositis in the OMSRT group. The trend towards increased analgesic use in the OMSRT group further underscores the efficacy of OMSRT in mitigating mucositis-associated pain and discomfort. Additionally, the appearance of mucositis was delayed in the OMSRT arm where the highest grade of mucositis was observed in the fourth week of RT or later in 81.25% (n=13) of the cases as opposed to the OMSRT arm where 68.75% of the cases(n=11) had the highest grade of mucositis by the third week of RT. These findings parallel Wang et al.'s results in highlighting the clinical significance of OMSRT in reducing the severity of acute mucositis where the incidence of grade 3 mucositis in the united oral site was considerably higher in the non-spared group compared to the OMSRT group. Both studies elucidate the temporal patterns of mucositis, indicating that mucositis-associated toxicities were delayed in the OMSRT arm. These studies reveal that these toxicities were more frequent and severe in the OMSRT arm, reinforcing the concept that OMSRT can delay and mitigate the impact of mucositis.

The clinical implications of our study's findings are substantial and warrant careful consideration. By mitigating mucositis-associated toxicities, OMSRT has the potential to transform the treatment experience for patients. The significantly reduced rates of grade 1 or higher mucositis at both 1 month and 3 months post-treatment in the OMSRT group reflect a sustained clinical advantage and highlight the long-term benefit of sparing the oral mucosa from high radiation doses.

Nevertheless, it is important to acknowledge the limitations of our study. The relatively modest sample size and single-center nature of the study may temper the generalizability of our findings. Larger multicenter studies are imperative to corroborate our observations and to establish the broader clinical applicability of OMSRT. As the field continues to evolve, larger-scale studies encompassing diverse patient populations are essential to validate and refine the clinical utility of oral mucosa-sparing strategies in the comprehensive management of oral tongue cancer. Ultimately, these efforts have the potential to revolutionize the landscape of RT in oral tongue SCC, improving treatment tolerability and ultimately patient outcomes.

CONCLUSION

In conclusion, our prospective randomized study offers valuable insights into the potential advantages of OMSRT in ameliorating the severity of acute mucositis and enhancing patients' quality of life during RT for oral tongue SCC. The personalized approach of sparing the oral mucosa yields substantial reductions in mucositis-related toxicities, underscoring the importance of tailored treatment planning.

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