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Original Research Article

Utility of Lugol's iodine in assessing the margin status of early stage oral cavity cancer-could it be a simple and effective way to achieve R0 resection?

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ABSTRACT

Background: It is often challenging to distinguish between dysplastic and normal mucosa during surgery. Use of staining agents that will identify abnormal mucosa may improve results. Because Lugol's iodine is readily available, simple to use, and cost-effective, it was chosen as the preferred staining agent. To determine the effectiveness of Lugol's iodine application in achieving R0 resection in early-stage oral cavity malignancy and thereby leading to better outcomes after treatment.
Methods: In this study we included 49 patients and randomized them into two arms. One arm we did wide excision for early-stage oral cavity cancers guided by subjective assessment of margins by surgeons and in another arm, we used Lugol's iodine to define the margin. We analysed the margin status and thereby the need for the adjuvant therapy between these two groups.
Results: In those 49 patients, two of them had microscopically positive margin. One belonged to Lugol's iodine arm and other belonged to control arm. 17 patients had close margin at mucosal site (less than 5 mm) out of which 11 belonged to control arm and 5 belonged to Lugol's iodine arm.
Conclusions: Lugol's iodine may be a simple and reliable method in achieving better resection margins and R0 resections for early-stage oral cavity cancer. By using this simple and cost-effective method we may reduce the possibility of ending up with positive or close margins and thereby avoiding the need of chemotherapy and radiation as adjuvant therapy in those patients.

Keywords: Oral cancer, Lugol's iodine, Close margin, Tongue, Buccal mucosa

INTRODUCTION

Oral cancer is a major health concern for countries going through economic change. India accounts for one-third of the global oral cancer burden.[1] It is estimated that India accounts for about one-fourth of worldwide incidences, with 52,000 deaths and 77,000 new cases recorded annually.[2]

Oral squamous cell carcinoma (OSCC) contributes significantly to oral cancer, accounting for 84-97% of all cases. It can arise from normal epithelial lining or from potentially malignant lesions. Indicators of the preclinical stage of oral cancer include potentially malignant diseases (PMDs) such as lichen planus, erythroplakia, leukoplakia, proliferative verrucous leukoplakia, and inflammatory oral submucosal fibrosis.[3]

In order to lower the death and morbidity rates associated with oral cancer patients, early identification is very crucial.[4] Visual tissue staining can aid in cancer diagnosis.[5] The staining of Lugol's iodine is dependent on the glycogen content of the normal epithelium, and this selective nature of staining aids in distinguishing

dysplatic or carcinomatous epithelium from normal epithelium where the glycogen content is low. On Lugol's iodine application normal epithelium turns into brown whereas dysplatic/malignant cells doesn't take up this stain.[6-8]

Aims and objectives

Primary objective of this study is to investigate the utility of Lugol's iodine in macroscopic assessment of margin status in early-stage oral cavity cancer, and its impact on surgical decision-making and oncological outcomes.

METHODS

Our study included 49 patients with early oral cavity cancer who got admitted in hospital during May 2021-June 2023, 25 patients were randomized into control arm and 24 patients were randomized into Lugol's iodine arm. We included all oral cavity cancer patients irrespective of age and gender with clinically T1, T2 and T3 (size less than 5 cm) disease and N0 neck.

We excluded patients with previous history of chemo radiation to head and neck cancer, patients who are all allergic to Lugol's iodine, patients with recurrent disease, patients with history of thyroid disorders and patients with grade 3 trismus.

After intubation and preparation all patients underwent through examination under anaesthesia of oral cavity followed by marking of the visible and palpable extent of tumour preferably using a cautery. Mucus secretions were removed by irrigating oral cavity with normal saline.

In control group the surgical resection with 1 cm margin is carried out by macroscopic visual examination without any other guidance. In Lugol's iodine arm after clinical examination, the entire oral cavity was irrigated with 1.25% Lugol's iodine (aqueous iodine solution containing 1.25% iodine and 2.5% potassium iodide) taken in a 10ml syringe. Excess Lugol's iodine was washed with saline and removed using suction. Irrigation with Lugol's iodine was repeated until the adjacent normal mucosa turns into brown. The malignant and dysplatic areas were identified as an unstained lesion and then wide excision was carried out.

In addition to 1 cm oncologically safe margin, areas of non-stained squamous epithelium adjacent to the tumour were identified and resected. Specimens were oriented, fixed in formalin and subject to histopathological examination as per the standard protocol. Both arms were compared for adequacy of resected margins.

Formulation of Lugol's iodine solution-Iodine 2 g, potassium iodide 4 g and distilled water 100 cc.

Chi square test used in the statistical analysis.

RESULTS

Age distribution

Mean (SD) age of the 49 study participants was 51.84 years. The median (IQR) values were found to be 51 (43-60) years. The minimum and maximum ages were 30 and 82 years respectively with a range of 52 years. The age distribution of study participants is illustrated in Figure 1.

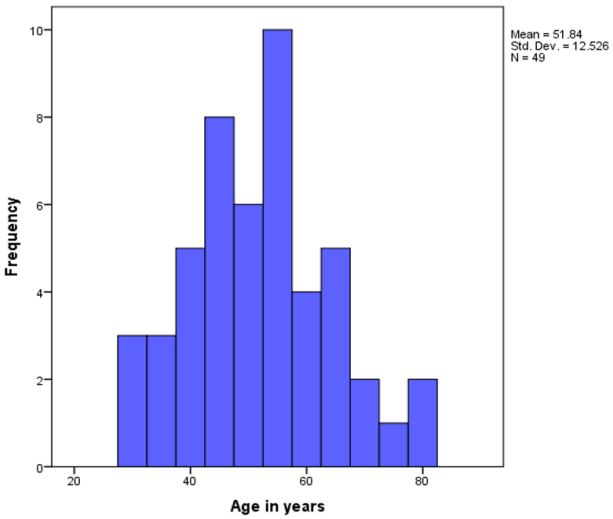

Figure 1: Age distribution of study participants.

In control group, mean (SD) age of 25 study participants was 51.12 (12.68) years. Median (IQR) values found to be 50 (41.5-58) years. Minimum and maximum ages were 30 and 78 years respectively with range of 48 years.

In Lugol's iodine arm, mean (SD) age of 24 study participants 52.58 (12.59) years. Median (IQR) values were 54 (44-61) years. Minimum and maximum ages were 30 and 82 years respectively with range of 52 years.

There were no significant differences in the distribution of age of study participants between the two groups with a p=0.522 (U=268.00).

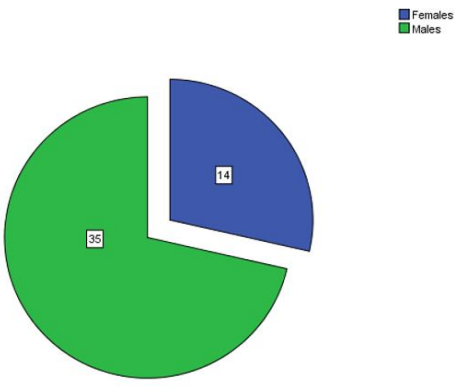

Figure 2: Sex distribution among study participants.

Sex distribution

Among 49 study participants, 35 (71.4%) were males and 14 (28.6%) were females. The sex distribution among the study participants is given in Figure 2.

Diagnosis

Among 49 study participants, 20 (40.8%) were diagnosed with carcinoma buccal mucosa, and 29 (59.2%) were diagnosed with carcinoma tongue (Figure 3).

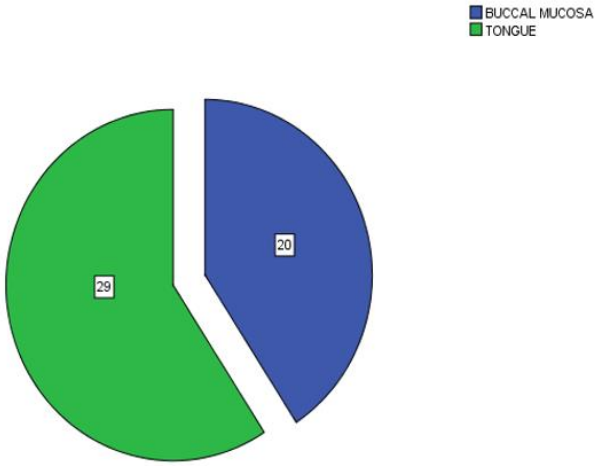

Figure 3: Diagnosis of carcinoma among study participants.

Proportion of study participants with carcinoma buccal mucosa was higher in control group, and carcinoma tongue is higher in Lugol's iodine group. But difference was not found to be significant with a p=0.296 (Table 1).

Table 1: Carcinoma diagnosis among the study participants.

Diagnosis	Control group, n (%)	Lugol's iodine group, n (%)	X^2	P value
Buccal mucosa	12 (60)	8 (40)	1.090	0.296
Tongue	13 (44.8)	16 (55.2)		

Stage of the disease

Among 20 carcinoma buccal mucosa patients, 7 are in T1 stage, 10 in T2 stage, and 3 in T3 stage. Similarly, among 29 tongue carcinoma patients, 2 are in T1 stage, 17 in T2 stage, and 10 in T3 stage. The distribution of these patients in the control and Lugol's iodine groups are illustrated in Table 2.

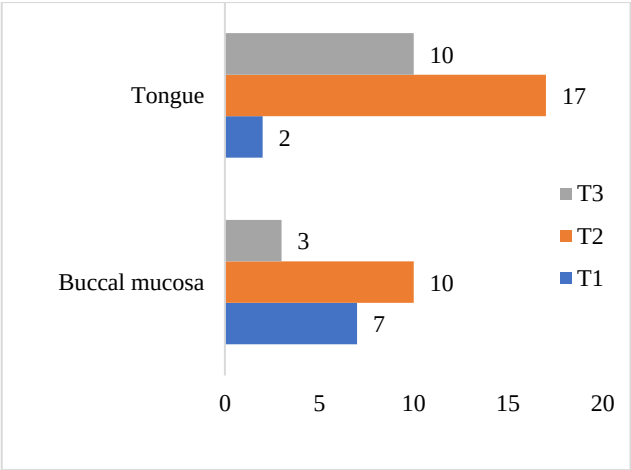

Figure 4: Distribution of study participants according to the disease stage.

Margin

Among 49 patients, margins were adequate in 31 (63.3%), close in 16 (32.7%), and involved in 2 patients (4.1%). The distribution of margin involvement in two groups are given in Table 3.The proportion of adequate margin is more in Lugol's iodine group when compared to the control group. Close margins were more in the control group, and the margin involvement were equally distributed between the two groups. But the difference is not statistically significant with a p=0.219 (Table 3).

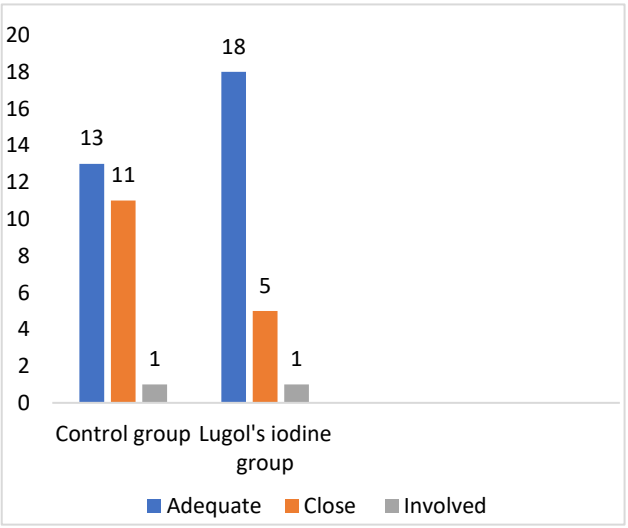

Figure 5: Distribution of study participants according to margin involvement.

Among close margins, inferior was the most common type found in 4 patients, followed by posterior and inferio-medial each having 3 patients. Superior and infero-lateral closure were found in two patients, and anterior close margin was found in two patients.

Table 2: Distribution of study participants according to the disease stage.

Carcinoma	Stage	Total	Control group, n (%)	Lugol's iodine group, n (%)	X^2	P value
Buccal mucosa	T1	7	3 (42.9)	4 (57.1)	3.413	0.182
	T2	10	8 (80)	2 (20)		
	T3	3	1 (33.3)	2 (66.7)		
Tongue	T1	2	0 (0)	2 (100)	1.767	0.413
	T2	17	8 (47.1)	9 (52.9)		
	T3	10	5 (50)	5 (50)		

Table 3: Margin involvement among the study participants.

Margin	Control group, n (%)	Lugol's iodine group, n (%)	X^2	P value
Adequate	13 (41.9)	18 (58.1)	3.307	0.219
Close	11 (68.8)	5 (31.2)		
Involved	1 (50)	1 (50)		

DISCUSSION

It is well established that both positive and close margins are linked to poor 5-year survival rates and increased likelihood of local recurrence. According to Loree et al patients with near or positive margins had a 36% local recurrence rate, but patients with adequate margin in final histopathological examination had a 18% local recurrence rate. While following up these patients, they discovered that in involved /close margins group, the 5-year survival rate was 52%, while those with sufficient margins had a 60% 5-year survival rate.[9] According to Binahmed et al patients with adequate, close, and involved margins had 5-year survival rates of 69%, 58%, and 38% respectively.[10]

Furthermore, the surgical resection margin was the sole modifiable component among all the observed poor prognostic variables. According to NCCN guidelines, if an invasive carcinoma has close margins (defined as less than or equal to 4 mm from the specimen's edge), adjuvant radiation should be added; if the carcinoma has positive margins (defined as invasive carcinoma at the edge of the resection specimen), adjuvant chemoradiation or re-excision is required.[9]

In our study there was a gross reduction of close mucosal margin in Lugol's iodine group upto 37.6%. In carcinoma tongue patients, most commonly we landed up in close margins at posterior and inferior mucosal margins and in carcinoma buccal mucosa patients, commonly we landed up in inferior or inferiomedial close margins. The close proximity to bone and floor of mouth may be the reason for the close margins in these areas. Probably much wider excision with guidance of Lugol's iodine staining would have led to better results.

According to a meta analysis, for mild to moderate dysplasia the conversion rate into malignancy is about 10.3 percent whereas in case of severe dysplasia or carcinoma in situ it is as high as 24.1 percent.[11] In our study, we had one patient with dysplasia at the margin site in control arm. None of patients in Lugol's iodine arm had a dysplatic margin. According to McMahon et al there was a reduction in the incidence of dysplasia at and around resection margins from 32% to 4% in the Lugol's iodine group.[12]

Eleven of the patients from the control arm had to undergo adjuvant radiation therapy in view of close mucosal margin. This exhausts the option of future effective radiation therapy for these patients, if they develop recurrent disease or second primary. Also, those patients experience adverse side effects of radiation therapy which can be potentially preventable.

Of the several approaches investigated to deal with the issue of close and positive resection margins, the most of them use frozen section, imprint cytology, MRI scanning, spectroscopy, which significantly increases not only the operating time but also the expenditure. Moreover, these methods are often not available in most of centres and in peripheral areas.

Lugol's iodine is especially appealing because of its widespread availability, quickness and simplicity of use, low cost, and minimal side effects. Furthermore, Lugol's iodine has been demonstrated to more accurately detect dysplasia.[13] It has additionally demonstrated a strong correlation with genetic indicators of cancer such as p53 mutations and telomerase changes.[14,15]

After using Lugol's iodine, the suggested reconstructive strategy was not changed for any of our patients. No patients had known allergy to Lugol's iodine and none had any side effects or allergic reaction related to it's use. The average additional operating time due to the use of Lugol's iodine was 8 minutes.

Limitations

In our study the sample size is small, studies with larger sample size at multi-institution level may confer more precise data. Moreover, there is no standard method for

staining Lugol's iodine, it may vary from surgeon to surgeon. The time taken for staining also varies from patient to patient. This factor may influence the staining pattern and hence the outcome.

CONCLUSION

Exploring this uncharted area, with a larger sample size study, it may be safe to conclude that Lugol's iodine may be a quick and reliable method to map the cancers and surrounding premalignant/dysplatic areas. It may guide the surgeons intraoperatively to decide about the macroscopic margins which can lead to better surgical results and oncological outcomes. Lugol's iodine may be an alternative where intraoperative frozen section is not available. Further large scale studies are needed to meet the statistical claims.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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