



CLINICAL UTILITY OF LUGOL'S IODINE IN MALIGNANT AND PREMALIGNANT ORAL LESIONS

Oncology

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ABSTRACT

Introduction Head and neck malignancies are the sixth most common of all malignancies worldwide but is most common cancer in Indian subcontinent. Among various risk factors, inadequate (close /involved) surgical margin is an important risk factor determining recurrence. We used lugol's iodine staining for early detection of suspicious lesions, proper delineation of margin and achieve margin negative resection in malignant lesions. **Methods** This prospective observational study was conducted in Indraprastha Apollo hospital, New Delhi, between July 2018 to June 2020 and included 55 patients with oral lesions including malignant and suspected lesions. Intra-operatively the extent of the tumour on clinical examination was determined and marked and then 5% lugol's iodine was applied. The extent of the tumour following the application of lugol's iodine was compared for any discordance and the resection boundary was revised when deemed appropriate. **Results** 55 patients were included, 37(67.37%) had cancer (squamous cell carcinoma) and 18(32.73%) had suspicious lesions. Male: female ratio was 4.5:1. Mean age was 51.82±7.25 years. 8 additional lesions detected after the application of the Lugol's iodine resulting in additional 14.55% increase in the detection. Out of these 8, six (75%) were with dysplastic changes and 2(25%) were malignant (SCC). 7(87.5%) of these additional lesions were detected in ulcerative type lesion and 1(12.5%) was detected in proliferative type lesion. 28(75.68%) out of 37 malignant lesions were visually well demarcated before staining and 9(24.32%) were not well demarcated visually, but after the staining all 37 (100%) were visually well demarcated. And among suspicious lesions, 15(83.33%) were visually well demarcated before the staining and 3(16.67%) were not well demarcated visually, but after the staining, all 18 (100%) were visually well demarcated. No allergic reaction was noted. **Conclusion** Lugol's iodine can play a major role in demarcating the margins of suspicious and cancerous lesions and thus obtaining tumour free resection margins in carcinoma of the oral cavity.

KEYWORDS

Oral cancer, lugol's iodine, Premalignant lesions.

INTRODUCTION

Head and neck malignancies are the sixth most common of all malignancies worldwide, and squamous cell carcinoma accounts for 95% of them. In the Indian subcontinent, it is most common cancer and ranks first among the male population and third among the female population. This can be attributed to the habit of chewing tobacco, khaini and other forms of smokeless tobacco, which in addition to alcohol and smoking, has been identified as one of the major risk factors for oral malignancies.¹

Risk of recurrence in these malignancies are related to tumour biology, stage of the disease and final histopathology following excision. The presence of close (invasive carcinoma < 4mm from the resection margin) or involved margins (invasive carcinoma at the resection margin), has been reported to have a significant association with increased local recurrence rates and decreased 5year survival. The avoidance of close or positive margin, of all the identified adverse risk features, is within the direct control of the surgeon and thereby amenable to modification by variation in treatment strategies.^{2,3}

Adjuvant radiotherapy in cases with close or involved resection margins has resulted in decreased local recurrence rate but it fails to match the local recurrence rates of those with adequate margins in the first instance and also did not significantly impact five-year survival.^{2,3}

Various methods to decrease the incidence of inadequate surgical resection margin are described including preoperative imaging modalities, frozen sections and optical spectroscopy for better visualization of malignant tissue. Of particular interest is the use of vital dyes including toluidine blue and Lugol's iodine for staining. These dyes stain malignant tissue and normal tissue with different colour. And so can be used as an adjunct to clinical examination in identifying the presence and extent of malignant tissue intra-operatively and to better delineate lesions unclear on clinical examination, thereby improving completeness of resection.

Oral carcinoma is usually diagnosed when it becomes symptomatic and approximately two-thirds of the patients, present with advanced disease, regional metastasis and so has poor prognosis. A number of diagnostic techniques have been developed to support clinical examination and improve the diagnosis at early stage. These include – Toluidine blue staining test¹, Lugol's iodine, Methylene blue, Rose Bengal, Oral exfoliative cytology, Brush biopsy. Oral squamous cell carcinoma is frequently associated with field cancerization leading to

frequent margin positive resection. Margin positivity can be reduced if accurate delineation or mapping of carcinoma in situ and suspected lesions is done with iodine staining. The Schiller iodine test⁴, was first performed to detect early cervical cancer in the 1930s, and technique is routinely used immediately before endoscopic mucosal resection as a useful and minimally invasive test to determine the area and margin of resection for early esophageal cancer in Japan.^{4,5} Many studies have also reported the usefulness of iodine staining of oral lesions using current detection techniques such as narrow band imaging (NBI) and magnifying endoscopy, which are routinely used by clinicians⁶⁻⁸.

Literature exists regarding lugol's iodine staining, includes aid to the identification of neoplasia of the squamous epithelium of the esophagus. The mucosal surfaces of mouth and oropharynx are very similar to the proximal esophagus and the risk factors for neoplastic transformation at these sites are similar. Lugol's iodine visualization of dysplastic mucosa is employed in management of esophageal disease.^{4,8} However, there is limited literature describing the use of lugol's iodine in the head and neck neoplasm.

Lugol's iodine Solution- consists 5g iodine and 10g Potassium iodide mixed with 85 ml distilled water to make a brown solution. It is cheap, widely available and easy to use and require about 5 minutes to perform the staining procedure. Iodine is glycoliphilic and forms tri-iodide molecules within the glycogen polymer spiral. This results in chocolate brown staining of normal non keratinized mucosa. Areas of dysplasia and invasive cancer do not take up iodine as they lack glycogen and appear pale coloured areas. This is thought to be due to the Warburg effect of increased cytosol glycolysis consequent to the genomic chaos seen in the cancer cell.^{9,10} Limitation of lugol's iodine is heavily keratinized areas of the mouth such as the attached gingivae and hard palate do not avidly take up lugol's iodine. Respiratory mucosa also does not contain glycogen and does not stain.

Incidence rates reported worldwide for close margins were 20- 43 % and 11-32% for involved margins.^{2,4,6} For this, we decided to use Lugol's iodine to stain the lesion in a bid to better visualize abnormal tissue and thereby decrease the incidence of close and inadequate resection margins. Also, for delineation of biopsy site in premalignant or suspicious oral lesions, Lugol's iodine was preferred due to the wide availability, simple procedure, reproducibility, low cost, few side effects and minimal additional time required.

One study showed that different shades of discolouration after

application of Lugol's iodine was associated with the varying degrees of dysplasia. So it was hypothesized that a colorimetric scale correlating with histopathology might be developed which would enable macroscopic discrimination of the various degrees of dysplasia by comparing the shade of the unstained lesion with a colour scale.¹¹ Genotypical studies involving measurement of p53, PCNA (proliferating cell nuclear antigen) levels and telomerase activity, also revealed good correlation between Lugol's unstained areas and the presence of malignancy.^{12,13} Later studies were directed towards the use of Lugol's iodine to better identify margins. Kurita et al compared the distance between the boundaries of the tumour noted following the application of Lugol's iodine, with the location of the proliferative tumour front on final histopathology. They noted a mean difference of 0.81 mm + 0.64 mm (mean + standard deviation), showing that the margin of the lesion on examination with Lugol's iodine correlated well with the histopathological tumour front.¹⁴ Other methods including brush cytology, improved imaging with MRI for better determination of the extent of the lesion preoperatively have also been used with varying success.

AIM:

To study clinical utility of lugol's iodine in malignant and suspicious oral lesions.

OBJECTIVES:

1. To study effectiveness of lugol's iodine staining in diagnosis of suspicious oral lesions.
2. To study lugol's iodine usefulness intra operatively for accurate delineation/demarcation of extent and mapping of oral lesions for margin negative resection (safe margin).
3. Observe any limitations and any reactions if occurred.

MATERIALS AND METHODS

This is a hospital based prospective observational study carried out in department of surgical oncology at Indraprastha Apollo Hospital New Delhi. In this study malignant and suspicious oral lesions were included as per inclusion and exclusion criteria. Data were processed and analyzed with SPSS-20. The test statistics used to analyze the data were descriptive statistics. The quantitative data were presented as mean and standard deviation from the mean.

Study area:

Department of surgical oncology. Indraprastha Apollo hospital, NewDelhi.

Study population:

A total of 55 patients with malignant, premalignant and suspicious oral lesions between July 2018 and June 2020 at our institute were included as per inclusion and exclusion criteria.

Inclusion Criteria:

1. All malignant, premalignant and suspicious oral lesions.
2. Age > 18 years.
3. Resectable tumor.

Exclusion Criteria:

1. Those unwilling, uncooperative and had not given written informed consent for the participation in the study.
2. Those with known allergy to iodine.

After the selection, patients were interviewed with the help study proforma and subjected to undergo clinical investigations and oral and other examinations. Intra-operatively, on examination under anaesthesia, the extent of the tumour on clinical examination was determined and marked. The proposed boundary of resection including a 1 cm circumferential margin of normal tissue was marked using diathermy. Oral cavity was irrigated with 5% lugol's iodine until the mucosa distant to the lesion stained dark brown.

The extent of the tumour following the application of lugol's iodine was compared for any discordance and the resection boundary was revised where deemed appropriate. The resected specimen was oriented and sent for histopathological examination. All information will be collected as per the data collection form designed for the study.

RESULTS

Total cases	55
Male: Female	4.5:1

Mean Age	51.82±7.25 years
Primary Diagnosis	Carcinoma - 37 (67.27%) suspicious lesion- 18 (32.73%)
Subsites in carcinoma	Tongue - 20 (36.36%) Buccal Mucosa -16 (29.09%) Hard Palate - 1 (1.82%)
Subsites in suspicious lesion	Tongue -9 (16.36%) Buccal mucosa - 9 (16.36%)
Histopathology of Suspicious Lesion in tongue	Carcinoma - 8 (44.44%) Dysplasia - 1 (5.56%)
Histopathology of Suspicious Lesion in BM	Carcinoma - 7 (38.86%) Dysplasia- 1 (5.56%) Normal - 1 (5.56%)
Type of lesion	Ulcerative - 45 (81.82%) Proliferative - 10 (18.18%)
Treatment	Composite resection and MND (buccal mucosal cancer) - 16 (29.09%) Examination and biopsy - 18 (32.73%) Hemiglossectomy with MND - 1 (1.82%) Partial glossectomy with MND - 19 (34.55%) Partial maxillectomy with tracheostomy- 1 (1.82%)
Total Additional lesions after the staining by Lugols iodine	8
HPE of additional lesion	Dysplasia - 6 (75%) Malignant- 2 (25%)
Morphological type of lesion having additional lesion on staining	Ulcerative type -7 (87.5%) Proliferative type - 1 (12.5%)

Margin demarcation in the study subjects

Diagnosis	Visually well demarcated	
	Before staining (%)	After staining (%)
Malignancy(n=37)	28(75.68%)	37(100%)
Other suspicious lesions (n=18)	15(83.33%)	18(100%)



Fig1- lugol's iodine staining



Fig 2 – final resected specimen

DISCUSSION

In this study total 55cases of malignant and suspected lesions in oral cavity were included for lugol's iodine staining. There was male predominance with 81.82% of patients were males. Male: female ratio was 4.5:1 in our study.

Mean age of participants was 51.82±7.25 years. In males it was 52.13±7.16 and in female it was 50.40±7.88 years. Most common age group of presentation was 51-60 years with 25(45.45%) patients, followed by 22(40%) in the age group of 41-50years. There were only 3(5.45%) patients with age above 60years.

Among 37 cancer patients, 20 had carcinoma tongue (SCC), 16 had carcinoma (SCC) buccal mucosa and 1 patient of carcinoma (SCC) hard palate.

Out of 18 suspicious lesions 9 each were found in tongue and buccal mucosa. Of tongue lesions 8 were malignant (SCC), 1 was dysplastic and among 9 buccal lesions 7 were malignant (SCC), 1 each was found to be normal and dysplastic as confirmed by histopathological examination. We found most lesion were ulcerative 45(81.82%) and only 10(18.18%) were proliferative.

Patients with confirmed malignancy underwent standard surgical

resection with lugol's iodine staining for proper delineation of mucosal margin. Rest 18 (32.73%) with suspicious lesions underwent examination and biopsy after lugol's iodine staining.

There were 8 additional lesions detected after the application of the lugol's iodine. This means that additional 14.55% increase in the detection attributed to the Lugol's iodine. Out of these 8, six (75%) were with dysplastic changes and 2(25%) were malignant (SCC). Out of the 8 lesions additionally detected, 7(87.5%) were detected in ulcerative type lesion and 1(12.5%) was detected in proliferative type lesion.

28(75.68%) of malignant lesion were visually well demarcated before the staining by lugol's iodine but rest 9(24.32%) malignant lesion were not well demarcated visually but after the staining, all 37 (100%) were visually well demarcated.

Among suspicious lesions, 15(83.33%) were visually well demarcated before the staining and 3(16.67%) were not well demarcated but after the staining, all 18 (100%) were visually well demarcated. We achieved safe mucosal (superficial) margins as well as for safe deep margins i.e. margin negative for tumour after lugol's iodine staining and standard surgical procedure in all. None of the 55 patients had any allergic response towards the lugol's iodine.

CONCLUSION

Lugol's iodine is a simple cost effective, non-invasive technique with good diagnostic accuracy, it may be performed as a routine diagnostic adjunct to enhance margin negative resection. Lugol's iodine can play a major role in demarcating the margins in suspicious and cancerous lesions. It also enables the clinician to estimate the correct size and extent of the suspicious lesion for proper biopsy site selection leading to early diagnosis and better management of the patient.

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