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An attempt to reduce close and positive margins in oral cancer using Lugol's Iodine

General Surgery

KEYWORDS : Surgical margins, Oral Cancer, Lugol's iodine, vital staining

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ABSTRACT

Introduction: *Conventionally, all operable oral cancers are excised with 1-1.5 cms margins. The presence of invasive tumour or dysplasia within 5 mm of the surgical margins can leads to local recurrence. The use of Lugol's iodine, a vital stain, has shown promising results to improve intraoperative identification of the extent of the tumour and dysplasia at the margins to reduce recurrence.*

Materials and methods: *Consecutive patients with resectable primary tumours of the oral cavity were enrolled in the Lugol's iodine study, between 01.01.12 and 31.10.13 (group II). The extent of the tumour on clinical examination was marked. The margins of the malignancy prior to, and following the application of Lugols iodine were compared.*

The institutional records of all patients who underwent curative resection of squamous cell carcinoma of the oral cavity from 01.03.10 – 31.12.11 (group I) were reviewed. The incidence of close and positive margins was studied, retrospectively in group I and prospectively in group II, and compared.

Results: *Overall, tongue cancers were the most common and approximately 80% percent of patients were within the 40 -60 years age group. The incidence of close margins (invasive carcinoma < 4cm from the margin) had decreased from 39% in group I to 32% in group II. The incidence of involved margins (invasive carcinoma at the margin) had decreased from 25% in the group I to 8% in group II (p=0.000).*

Conclusion: *The use of Lugol's iodine helped us define the tumour circumference better, thereby improving the incidence of tumour free surgical margins.*

Introduction:

The presence of invasive carcinoma or dysplasia, either at or within 5mm of the surgical margins, following resection of carcinoma of the head and neck region has been proven to be a high risk factor for local recurrence (1), (2). The ability to completely resect an oral carcinoma with clear margins weighs heavily on the surgeon's decision to use surgery as the primary modality to eradicate cancer (22). Batasakis et al notes that 5-10% of all carcinomas resist the surgical goal of clear margins, regardless of tumour stage (3). Various factors have been considered to account for the presence of positive and close mucosal margins. These include advanced stage at presentation, shrinkage of tissue in formalin, unquantifiable submucosal disease and field cancerization. Among these, submucosal spread can be predicted by imaging - pre-operative and intra-operative- and field cancerization, using staining or fluorescence imaging (4), (5), (6).

In a recent audit of our unit's performance, we found that of 50 patients with oral cancer operated in over a year, 34 % had positive margins and 44% had close margins, which was unacceptably high. These numbers generally vary between institutions, based on the volume of work, surgeon's experience and spectrum of advanced disease (7), (8), (9).

Literature shows that vital staining (with Lugol's iodine) of the area to be resected has a long and well established place in the identification of non-visible, non-palpable malignant areas including dysplasia, thereby reducing the presence of tumour at the margins. Many authors have examined its use as an aid to identify areas of malignancy and dysplasia of the cervix, oesophagus, oral cavity and oro-pharynx (10), (11). McMahon et al showed that the presence of dysplasia or tumour at the margins was reduced from 32% to 4%, with the help of Lugol's iodine staining (12).

We report our experience of using Lugol's iodine as an aid in the resection of oral squamous cell cancers, as a prospective audit.

Materials and methods:

We analyzed our patients in two groups, before and after intervention with Lugol's iodine, in two different time periods. We studied all the oral cancer patients who were operated between 01.03.10 and 31.12.11 (group I) at our Head and Neck Unit, Department of General Surgery. All patients were staged as per the existing protocol, discussed at the MDT conference and underwent resection of the tumour. During resection, we followed the standard guidelines of excision of visible or palpable tumour, with a 1cm circumferential margin.

Following approval by the institutional review board, contingent on informed consent, consecutive patients with resectable primary tumours of the oral cavity were enrolled in the Lugol's iodine study, between 01.01.12 and 31.10.13 (group II). Patients with severe preoperative trismus and known iodine allergy were excluded. The choice of lymphadenectomy and reconstruction was left to the surgeon's discretion and did not vary significantly during the two time periods.

The visible and palpable extent of the tumour as per examination under anesthesia was marked using the pen and cautery respectively. Mucus secretions were removed by irrigating the oral cavity with 30ml of 5% carbocisteine syrup, left for 1 minute. The entire oral cavity was irrigated with 1.25% Lugol's iodine (aqeuous iodine solution BP

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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 mucosa distant to the tumour stained dark brown or black. The malignant area was identified as an unstained lesion. The margins of the malignancy following the application of Lugol's iodine were compared to the tumour margins on clinical examination. In addition to the 1 cm oncologically safe margin, areas of non-stained squamous epithelium adjacent to the tumour were identifed and resected where feasible. Where the extent of the non-staining area was very extensive (as an on-table surprise), the clinical judgement of the surgeon directed resection. The specimen was oriented, fixed in formalin and subject to histopathological examination with eosin and hematoxylin staining as per the standard protocol.

The institutional records of all patients who underwent curative resection of squamous cell carcinoma of the oral cavity from 01.03.10 – 31.12.11 (group I) were reviewed. The incidence of close and positive margins was studied, retrospectively in group I and prospectively in group II, and compared. The results were tabulated and subject to statistical analysis. Pearson's chi square test was used to identify significant association.

Fig. 1 – Extent of the tumour under anesthesia marked with blue pen, with the diathermy mark indicating the proposed resection margin

Fig 2 – Difference in the extent of the tumour prior to (blue line) and following (white line) the application of Lugol's iodine

Results:
The distribution of patients between the two groups was comparable, except for 17 additional patients and fewer primary closures of the surgical defect in group II (Lugol's iodine group). Overall, tongue cancers were the most common and approximately 80% percent of patients were within the 40 -60 years age group (ref. table 1). Though T2 disease was the most common, considering the overall clinical TNM stage, most patients presented with stage IV disease (40%), with advanced disease (stages III and IV) accounting for 63% of patients (ref. table 1). This was likely due to the fact that nearly 50% of them had node positive disease at presentation.

On comparison between the two groups regarding the status of the surgical margins, there was a pronounced difference (ref. table 2):
- The incidence of adequate, tumour free margins had increased from 36% in group I to 60% in group II.
- The incidence of close margins (invasive carcinoma < 4cm from the margin) had decreased from 39% in group I to 32% in gp II.
- The incidence of involved margins (invasive carcinoma at the margin) had decreased from 25% in the group I to 8% in gp II

On applying the chi square test to the numerical values, p value of 0.000 was obtained, indicating that this difference was statistically significant.

Discussion:
Among the risk factors for local recurrence in oral cancers, surgical margins have been studied extensively. Both close and involved tumour margins of the specimen were found to be associated with higher rates of local recurrence and poorer 5 year survival rates (1), (13). Recently, a study from Tata Memorial Hospital (TMH), Mumbai including a series of 306 patients, reported that 42 (22.2%) cases with negative margins developed recurrence, as compared to 31 (30.4%) cases with close margins and 6 (42.8%) cases with positive margins (p= 0.01). The average time to recurrence was 34.8 months in patients with negative margins, compared to 33.9 months and 10.18 months for patients with close and positive margins respectively (p= 0.002). Close and positive margins were also found to be significantly associated with increased local recurrence (p=0.01 and 0.03, respectively) and increased overall recurrence (p= 0.003 and 0.003, respectively) (14). It has also been noted that though recurrence rates decreased following adjuvant radiation therapy, it still did not compare with those who had adequate margins initially. Additionally, there was no significant improvement in 5 year survival following adjuvant radiotherapy for these patients (1).

Our institutional records of 50 consecutive patients undergoing curative resection for malignancies of the oral cavity prior to June 2011 were reviewed. It was found that 34% of our patients had involved margins, comparable to 32% in Glasgow, 22% in Manitoba and 11% in New York (12),(4), (1). The incidence of close margins was 44%, compared to a similar figure from Manitoba and 21% from NewYork . Our high numbers can be explained in part due to the advanced stage of disease at presentation (ref. table 1), and to submucosal spread of the disease in tongue and buccal mucosa cancers, leading to difficulty in providing adequate margin clearance, particularly for tongue malignancies (tongue cancer being more common in our cohort).
Various options have been explored to reduce this high incidence, including preoperative MR imaging for better visualization of the extent of the tumour, intra-operative use of vital stains (Lugol's iodine, toludine blue), optical spectroscopy, frozen section examination of the margins and increasing the margin clearance.

A retrospective study comparing the distance of clear surgical margins with 5 year survival by Nason et al, noted significantly improved 5 year survival rates as the distance

of normal tissue increased. They concluded that each additional millimeter of tumour free tissue contributed to increased five year survival (15). This was corroborated by McMahon et al, who also noted that beyond 1cm macroscopic margin, there was no additional survival benefit. They suggested that inadequate histopathological margins and recurrence in these patients was a consequence of poor tumour biology, rather than inadequate resection (16). Shrinkage of tumour in formalin has also been a contributing factor for close margins. Beaumont and Haines noted a 46% reduction in longitudinal diameter of the specimen with a mean reduction of 4.82 mm (21). They also concluded that shrinkage occurred predominantly after resection, with formalin fixation contributing to 30% or less of the overall shrinkage. Current NCCN guidelines recommend excision of 1-1.5 cm of normal tissue circumferentially around the visible and palpable extent of the tumour.

Lugol's iodine has been widely evaluated as an aid in resection of oral cancers and appears to help reduce the incidence of close and positive margins (12). It has also been shown to identify areas of dyplasia at the margins. Currently, a UK multi-centre randomized control trial, evaluating the efficacy of Lugol's iodine to assist excision of dysplasia and carcinoma in situ at the resection margins is underway. The oral cavity and oro-pharynx are covered by para-keratinized stratified squamous epithelium. Normal cells in the intermediate and superficial layers contain glycogen in their cytoplasm, as opposed to tumour cells which lack glycogen as a result of increased cell turnover rates. Iodine is glycophilic, hence application of Lugol's iodine results in uptake of iodine by normal glycogen rich areas, turning them a black or brown colour. Areas of invasive carcinoma and dysplasia do not change colour and are thereby highlighted. This difference in colour between normal and abnormal tissue has been well correlated to the histological margins of the specimen (17).

There are, however, certain limitations to the use of Lugol's iodine. Mucosa lined by columnar epithelium, areas of erosive (shredded) mucosa, benign conditions, area of hyperkeratosis and ortho-keratinized epithelium (like gingivae, hard palate), do not take up iodine to change colour.

Intra-operative frozen section was found to have a very high accuracy in the assessment of margin as well nodal status. Chaturvedi et al showed, using intraoperative frozen section, that 2% of patients had positive margins and 21% had close margins. Following intra-operative revision, final pathology showed 1.2% patients had positive margins and 11% had close margins. Frozen section nearly halves the rates of positive and close margins, which certainly translates into clinical benefits (18). Whether this revision of margins based on intraoperative frozen section helps improve local control is debatable. Guillemaud et al showed that in patients receiving primary surgery for oral squamous cell carcinoma, microscopic tumour cut-through on intraoperative frozen section independently portended a poorer oncologic prognosis, regardless of the ultimate tumour margin pathology (19).
Optical spectroscopy (using VEL Scope), use of toludine blue, analysis of various molecular markers (P-53 and eif4E) and gene expression alteration including hypermethylation of tumour related genes at the margins, are all being tested in research settings. They have not yet been adequately proven for everyday practice.

The steep increase in clear margins and fall in positive margins noted in our study can also be attributed to other factors, apart from the use of Lugol's iodine. We recently started ordering MR imaging for all tongue cancers, despite the cost, which may have helped improve our understanding of the extent of the tumour. It can, however, be argued that this would influence the deep margin alone, not the mucosal margins. A change in the trend of reconstruction of the surgical defect was noted in group II. Rotational flaps were used more commonly than primary closure, which may have allowed the surgeon greater freedom to achieve adequate surgical clearance, without concern regarding closure of the defect. Hanasono et al noted that after the introduction of free flaps in their unit, the rate of positive pathologic margins decreased significantly, contributing to improved oncological outcome (20).

Our series contained a greater proportion of patients with tongue cancer, which has been shown in other studies to harbour a higher level of dysplasia at the cut margins, compared to other anatomical sites within the oral cavity. It is likely that the use of Lugol's iodine has helped us define the tumour circumference better, thereby improving the incidence of clear surgical margins.

Regrettably, we do not have concise data concerning all cases where revision of margins was undertaken based on Lugols' iodine, hence long term follow up to see whether this translates to improved local control is not possible.

The wide availability, ease of use, rare occurrence of side effects and modest cost of Lugol's iodine makes it a promising option to employ, in a bid to reduce the incidence of close or positive surgical resection margins in oral cancer.

Conclusion:
Staining with Lugol's iodine is a simple, inexpensive and reproducible method that has a potential to reduce the incidence of positive margins in oral cancer.

Table 1 - Comparison of the demographic profile between the two

Variable	Group I (01.03.10 –31.13.11)	Group II (01.01.12 – 31.10.13)	
Number	122	139	
Age	<40 years	15 (12%)	21 (15%)
	40 – 60 years	77 (64%)	77 (55%)
	>60 years	30 (24%)	41 (30%)
Gender	Male	80 (66%)	97 (70%)
	Female	42 (34%)	42 (30%)
Site	Alveolus	14 (11%)	21 (15%)
	Buccal mucosa	42 (34%)	42 (30%)
	Tongue	52 (44%)	65 (47%)
	Others	14 (11%)	11 (8%)
Clinical T stage	T1	22 (18%)	26 (19%)
	T2	42 (35%)	52 (37%)
	T3	21 (17%)	13 (9%)
	T4	32 (26%)	45 (33%)
	Tx	5 (4%)	3 (2%)
TNM stage	I	19 (16%)	16 (12%)
	II	21 (17%)	36 (26%)
	III	32 (26%)	27 (19%)
	IV	45 (37%)	58 (42%)
	Indeterminate	5 (4%)	2 (1%)
Reconstruction	Primary closure	47 (39%)	42 (30%)
	Minor reconstructive procedure	14 (11%)	7 (3%)
	Major rotational flap	40 (33%)	65 (49%)
	Free tissue transfer	21 (17%)	25 (18%)

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Groups:

Table 2 - Comparison of the margin status between the two study groups

	Group I (01.03.10-31.12.11)	Group II (01.01.12 – 31.10.13)
Free	45 (36%)	83 (60%)
Close	47 (39%)	45 (32%)
Involved	30 (25%)	11 (8%)

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