Incidence of submucous fibrosis in oral cancer patients

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Abstract
Submucous fibrosis is a severely debilitating oral affliction which is most commonly seen in Indian subcontinent. The transformation of these lesions clinically into frank carcinomas has been demonstrated repeatedly in incidence of 2%-8% of all oral cancers. 288 patients with oral cancers were evaluated and we categorized that into two groups - Group A (oral cancer without submucous fibrosis) and Group B (oral cancer with submucous fibrosis). We used the clinical and histopathological parameters. Comparison between both the groups shows the oral cancer with submucous fibrosis patients always have better prognosis in comparison to group A patients because they usually have highly or moderately differentiated tumor showing superficial spread, minimum tissue thickness, low or no extra capsular spread, lympho vascular extension and peri neural invasion.

Keywords: Submucous fibrosis; oral cancer; differentiation; extra capsular spread.

Introduction
Submucous fibrosis is a severely debilitating oral affliction which is most commonly seen in Indian subcontinent. It is characterized by epithelial atrophy, progressive hyalination of the lamina propria, and later subepithelial and submucosal myofibrosis (Cox and Walker, 1996). The resultant inelasticity of the oral tissues result in often severe restriction in mouth opening, with consequences related to hygiene, nutrition, speech and swallowing. Prominent environmental causative factors appear to be areca nut chewing and capsaicin the active irritant in chilly peppers (Aziz, 1997). The transformation of these lesions clinically into frank carcinomas has been demonstrated repeatedly in incidences of 2% - 8% of all oral cancers (Murti et al., 1985).

The present study is first of its kind in the oral carcinoma literature where we studied the behavior of Oral Cancer in Submucous fibrosis patients. And we find that when we compare the final HPR (Histopathological Reports) of both the groups i.e. Group A (Oral Cancers without Submucous fibrosis) and Group B (Oral Cancers with Submucous fibrosis), it gives unique information related to progress and prognosis of the disease.

Materials and Methods
The present study was formulated on the basis of the incidence of Submucous Fibrosis in Oral Cancer patients and the histopathological behavior of the disease. The study conducted by collecting the data of 366 Oral Cancer patients. 78 patients were lost to follow up and remaining 288 patients were on regular follow up. Present study was divided into two groups - Group A (Oral Cancer without Submucous fibrosis) and Group B (Oral Cancer with Submucous fibrosis).

All the patients were treated and on regular follow up at Tata Memorial Cancer Hospital (TMCH), Mumbai between March 2010 to October 2010 (7 months), were offered participation in this prospective study. Informed consent had been taken from every patient before starting the study and they were asked to come for regular follow-up. The design and method of randomization is approved by the Ethical Committee of the TMCH.

The inclusion criteria were as follows:
1. All the age groups.
2. No prior radiotherapy.
3. No prior chemotherapy.
4. Only Maxillofacial Cancer.
5. Patient consent to participate.

The exclusion criteria were as follows:
1. Previous radio/chemotherapy.
2. Any systemic history.
3. Tumor at area other than maxillofacial area.

In group A, we collected the data of 288 Oral Cancer patients. The parameter of the data was site of Oral Cancer, TNM staging, Nodal metastasis, habits and % incidence of MAASCON-1 (Oct 23-24, 2010): “Frontiers in Life Sciences: Basic and Applied”
Submucous Fibrosis (SMF). Initially, we found that the incidence of SMF in oral cancer patients was 9%. All the resectable tumors were included in this study and after diagnosis, surgical excision was planned and final histopathological report was evaluated. We had 81 patients with final histopathology report. We assessed all the HPR data and collect the data together. The histopathological parameters were differentiation, tumor thickness, tumor free margins, extra capsular spreads (Jayson et al., 2003), lympho vascular extension (Jones et al., 2009), perineural invasion (Johannes et al., 1998). The data were collected from all the 81 patients and assessed.

In the second part of the study, we collected the data from all the group B patients i.e. Oral Cancers with Submucous Fibrosis, with the same parameters as used in group A patients. In the last part of the study, we compared the data of both the groups i.e. Group A and Group B.

Results
The result of the study presented highly interesting facts about the management and prognosis of the oral cancers. We compared both the groups of the patients under all the possible clinical as well as histological parameters i.e. incidence of age, site of cancer, tumor staging, nodal metastasis, habits, differentiation, tumor thickness, free tumor margins, extra capsular spread, lympho vascular extension, perineural invasion.

a. Incidence: The incidence of age of Group A patients was 47.78 years (range from 22 – 76 years) whereas in group B it was 44.54 years (range from 26 – 70 years). The difference was statistically significant (P = .000).

b. Site: In both cases, the buccal mucosa was the primary site for oral cancers followed by tongue and alveolus (P = .000) but in cases of group B, the % of buccal mucosa was much higher than the group A patients (P = .000) (Fig-1).

c. Tumor type: In group A patients, T3 and T4 types of tumors were predominant (P = .000), whereas in group B patients it was T1 and T2 types (P = .380). Group B shows the difference was statistically not significant (Table-1).
Table-1 shows tumor type of both the groups with respect to the number of patients.

d. **Nodal metastasis:** In group A, 70% patients were having N1 metastasis and 30% patients were having N2 metastasis whereas in group B, 86% of patients were having N1 metastasis and 14% of patients showed N2 metastasis. None of the groups claimed N3 metastasis in our study. Both the groups showed the findings were statistically significant (P = .000) (Table-2).

Table-2 shows nodal metastasis of both the groups with respect to the number of patients.

e. **Differentiation:** Most of the tumors in group A belonged to moderate to poorly differentiated tumors whereas group B had well to moderately differentiated tumors. The finding was statistically significant (P = .000) (Fig-2).

![Differentiation](image_url)

**Fig-2 shows % differentiation of both the groups.**
f. **Maximum tumor thickness:** Tumor thickness in group A patients was 1.23 cm (range from 0.1-2.8, SD: 0.65923) whereas in group B patients, it was 0.99 cm (range from 0.2-1.2 cm, SD: 0.59001) and the finding was statistically significant (Table-3).

<table>
<thead>
<tr>
<th>Maximum tumor thickness</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.1-2.8 cm</td>
<td>0.2-1.2 cm</td>
</tr>
<tr>
<td>Mean</td>
<td>1.23 cm</td>
<td>0.99 cm</td>
</tr>
</tbody>
</table>

Table-3 shows maximum tumor thickness of both the groups.

g. **Free tumor margin:** Free tumor margin in group A patients was 0.566 cm (range from 0.1-1.0 cm, SD: 0.25342) with mean whereas in group B patients it was 0.508 cm (range from 0.4-1.0 cm, SD: 0.17299) (Table-4).

<table>
<thead>
<tr>
<th>Free tumor margin</th>
<th>Group A</th>
<th>Group B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Range</td>
<td>0.1-1.0 cm</td>
<td>0.4-1.0 cm</td>
</tr>
<tr>
<td>Mean</td>
<td>0.566 cm</td>
<td>0.508 cm</td>
</tr>
</tbody>
</table>

Table-4 shows free tumor margin of both the groups.

h. **Extracapsular spreads:** Extracapsular spread of metastatic squamous cell carcinoma of the head and neck to regional lymph nodes is the most reliable predictor for poor treatment outcome. Surprisingly, it was 6% in group A whereas 8% ECS was found in group B patients (Fig-3).

<table>
<thead>
<tr>
<th>Group A (5 out of 81)</th>
<th>Group B (1 out of 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECS</td>
<td>ECS</td>
</tr>
</tbody>
</table>

Fig-3 shows % extracapsular spread of both the groups.
i. **Lymphovascular Extension (LVE):** The presence of histological evidence of lymphovascular extension in oral carcinoma surgical specimens has a significant impact on the survival outcome of the oral carcinoma patients. The LVE in group A patients was 3% whereas in group B none of the patients showed LVE. The finding was statistically significant ($P = .000$) (Fig-4).

![Fig-4 shows % lymphovascular extension of both the groups.](image)

j. **Perineural invasion:** Perineural invasion (PNI) of small nerves is associated with increased risk of local recurrence and cervical metastasis. (O'Brien et al., 1986; Daniel et al., 1993; Brown et al., 1989; Conte et al., 1989). The PNI of group A patients was 10% whereas none of the patients presented PNI in group B. The finding was statistically significant ($P = .000$) (Fig-5).

![Group A Group B](image)
Fig-5 shows % perineural invasion of both the groups.

k. Habits: Gutkha has higher concentrations of areca nut per chew and appears to cause oral submucous fibrosis more rapidly than self-prepared conventional betel quid, which contains smaller amounts of areca nut (Tilakaratne et al., 2006). In both the groups, tobacco was the predominant habit but when we compare the habits of gutkha and areca nut, in group A patients it was 23% (P = .000) whereas in group B patients the consumption of gutkha and areca nut was 36% (P = .020). The finding was statistically significant (Fig-6).

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>Type of Habits</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tobacco</td>
<td>116</td>
</tr>
<tr>
<td>2</td>
<td>Gutkha</td>
<td>46 / 16%</td>
</tr>
<tr>
<td>3</td>
<td>Beedi</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>Alcohol</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>Beetle Leave</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>Cigarettes</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>Beetle Nuts</td>
<td>19 / 6.5%</td>
</tr>
<tr>
<td>8</td>
<td>Mashery</td>
<td>15</td>
</tr>
<tr>
<td>9</td>
<td>Snuff</td>
<td>3</td>
</tr>
</tbody>
</table>

Fig-6 shows habits of both the groups with respect to the number of patients.

Statistical analysis
No statistically significant differences were found between the two groups in terms of clinical and histological findings (P=< test). While, within groups, the tumor type of group B patients is statistically insignificant (P= .380). Better prognostic results were observed in group B patients compared with group A patients (P = .000).

Discussion
The oral squamous cell carcinoma is one of the rapidly growing oral cancers in the literature of oncology and it is 6th most common cancer in the world. It is more common in south Asian countries specially India and Sri Lanka. Indian subcontinent covers 1/3rd of the world burden. Tobacco and heavy alcohol is the predominant cause of oral cancers. Tobacco alone covers 90% of all oral cancers. The five year survival rate of oral cancer is 68% in early stage and 27% in late stage.

The present study shows that the mean age of the group B patients is younger than the mean age of the group A patients and this indicates that usually SMF patients visit the hospital for complaints earlier than the routine cancer patients. The incidence of age ranges from 22 years to 76 years but the maximum cases are found within 4th-5th decade of age (Mehrotra et al., 2003; Pindborg et al., 1965).

Regarding site of the lesion, buccal mucosa is the predominant site in both the groups but in group B, buccal mucosa is much higher than in group A. This finding is similar to the earlier study by Pindborg et al. (1965). Since
the cancer is detected earlier in SMF patients in comparison to non-SMF patients, therefore, T1 and T2 type of tumors are much common in group B patients than in group A patients. Initial stage of nodal metastasis is predominant in group B in comparison to group A where advance stage of nodal metastasis was seen (Shah, 1990). Since the TNM staging is related to the prognosis of the disease, therefore it resembles the review material (Kademani et al., 2005). Poor differentiation is more common in group A patients whereas in group B highly differentiated and moderately differentiated cancers were more common due to early symptoms of the SMF. Maximum tumor thickness in group B is always less than the group A indicating early detection of SMF and early visit to the hospital in group B patients because of the symptoms of SMF. The free tumor margin is usually surgery criteria during the surgical excision and it shows that in group B, it is less than the group A patients due to healthy disease in case of group B. Extra capsular spread of the lymph nodes is interestingly higher in group B in comparison to group A. It may be because of smaller sample size. There was no lymphovascular extension in group B patients; again it indicates early detection of SMF leading to early visit to hospital of the patients. The perineural invasion is also not seen in cases of group B patients which again it gives us the same information about the early detection of the SMF. It is well-know that beetle nut chewing is the predominant cause of the submucous fibrosis. In our study, the information is statistically significant.

The result of this study is highly interesting and a landmark in the field of oral cancer because initially it was thought that oral cancer with or without submucous fibrosis will give almost same prognostic result, but present study shows that oral cancer with submucous fibrosis will give always better prognosis in terms of all the clinical and histopathological aspects.

Conclusion
Finding of the study shows oral cancer with submucous fibrosis patients always has superficial spread in comparison to oral cancer without submucous fibrosis because it usually has highly to moderately differentiated tumor, it has superficial spread of the tumor, minimum tissue thickness, low free tissue margins, low lymphovascular extension and low perineural invasion. Interestingly, the extra capsular spread is slightly higher in group B patients in comparison to group A patients. A long term randomized controlled study with larger sample size is required to validate the present findings.

Acknowledgement
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References


Murti PR, Bhonsle RB, Pindborg JJ, 1985. Malignant transformation rate in oral submucous fibrosis over a


