A histopathologic comparison between synchronous and single primary oral squamous cell carcinomas

In reply

We thank Dr. S. C. Sarode et al. for showing such interest in our article. Some of their comments are quite interesting and we also had similar concerns. However, we cannot agree with some of the comments and we hope to express our views regarding those in this reply.

The statement, “The unexpected results showed that synchronous OSCCs have more aggressive histologic features than single primary OSCC” is not correct. Synchronous OSCCs showed less aggressive histologic features compared with single primary OSCCs. We hope that it was a typing error rather than an intentional one.

We also agree that OSCCs in 2 different individuals may show a high variance depending on their biological behavior. This is one of the facts that led to this study to assess the behavior of synchronous OSCCs. According to Table 3 in our original article, it is very clear that the histologic features of synchronous OSCCs are less aggressive even though they were not compared with single primary OSCCs. We have tried our best to avoid the selection bias in the study as described in this reply.

VERRUCOUS APPEARANCE

We would like to emphasize that the synchronous OSCC group consisted of 28 cases that were reported during a period of 14 years. Therefore, this group was not a selected group out of a pool of synchronous cases. However, at the analysis of our results we found that 6 of 28 synchronous cases showed a verrucous appearance. We highlighted this finding to raise the possibility of origin of these synchronous carcinomas from proliferative verrucous leukoplakia (PVL), which is also multifocal. The carcinomas arising from PVL may show less aggressive histologic features at early stages. We did not intend to discuss verrucous carcinoma, which has a better prognosis, but the verrucous appearance of the surface of the tumor as one of the histologic features of the tumor. As the primary objective of this study was to compare histologic differences, it is not scientifically correct to look at the histology and select the control sample. In fact, that would introduce selection bias. So we cannot understand the point that “the selection bias was further exacerbated by, including only one primary OSCC showing verrucous appearance in comparison to 6 cases of synchronous OSCCs” in relation to the purpose of this study. It has proved as a finding from the study that most synchronous OSCCs have a verrucous surface histologically compared with single primary OSCC.

SITE AND SIDE

For the commenters’ interest, the expanded table is given here (Table 2). If looked at carefully, one can see there were 5 tongue synchronous cancers, which is equal to single primary OSCCs. More importantly, this table shows that it is impossible to match the number of sites in 2 groups. Regarding the side, except the 3 lip and buccal mucosa cases, all the other synchronous tumors were left and right lesions or significantly apart from each other. Even those 3 cases were identified as separate lesions according to the Warren and Gates criteria.

LYMPH NODE METASTASIS

We have stated that lymph node metastasis is one of the major determinants of prognosis in OSCCs. Further, we have correlated the lymph node metastasis with the

Table 2. Sites of synchronous and single primary OSCCs

<table>
<thead>
<tr>
<th>Synchronous OSCCs</th>
<th>n (%)</th>
<th>Single primary OSCCs</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right and left buccal mucosa</td>
<td>11 (39.3)</td>
<td>Buccal mucosa</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Lip and buccal mucosa</td>
<td>3 (10.7)</td>
<td>Alveolus</td>
<td>6 (21.4)</td>
</tr>
<tr>
<td>Palate and buccal mucosa</td>
<td>2 (7.1)</td>
<td>Tongue</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td>Right and left lateral tongue</td>
<td>2 (7.1)</td>
<td>Palate</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Commisure and retromolar</td>
<td>2 (7.1)</td>
<td>Floor of mouth</td>
<td>3 (10.7)</td>
</tr>
<tr>
<td>Lip and palate</td>
<td>1 (3.6)</td>
<td>Soft palate</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Commisure and sulcus</td>
<td>1 (3.6)</td>
<td>Buccal sulcus</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Buccal mucosa and tongue</td>
<td>1 (3.6)</td>
<td>Lip</td>
<td>1 (3.6)</td>
</tr>
<tr>
<td>Palate and tongue</td>
<td>1 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tongue and buccal mucosa</td>
<td>1 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lip and floor of mouth</td>
<td>1 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right alveolus and left retromolar</td>
<td>1 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left alveolus and symphysis</td>
<td>1 (3.6)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tumor thickness in the sentence, “In addition, all of the tumors that were positive for nodal metastasis had a depth of invasion $>4$ mm.” However, we do not see a need to go into the depth of correlating all the histologic features with the lymph node metastasis, because it is out of the scope of this study and only a single synchronous case out of 28 was positive for lymph node metastasis.

REFERENCES
The values of 5-year survival of synchronous and single primary OSCCs were based on references 1 and 4 of the article.

ARE THEY REALLY SYNCHRONOUS TUMORS?
We also agree that there is a possibility to have an underneath connection between 2 tumors of closely associated sites. However, we were meticulous in this aspect to include only lesions well apart from each other. Although commentators have proposed that “the histologic examination of normal tissue is mandatory to rule out any underneath connection between the synchronous OSCCs,” it is highly questionable whether it is ethically correct to section normal mucosa of a patient with 2 well-apart lesions with clear margins just to see whether the tumor is connected. It is automatically understood that when the excision margin is clear, there is no connection between 2 tumors. Further, most of the tumors in the study were either bilateral or from 2 different sites.

TNM, HABITS, DURATION
The clinical data such as relevant habits, TNM stage, and duration of the lesions could not be retrieved adequately as to present in the article because of the lack of access to patient records. As mentioned in the article, the lack of clinical and survival data was the major limitation of this study.

VALIDITY CONCLUSION
Because the given results cannot be explained by the prevailing knowledge, it may not be scientific to say that the results are incorrect. As we also have stated, the lack of survival data is a major limitation of this study. However, it does not negate the validity of the results, as there is a significant difference in histologic features. The question we have raised in the discussion, “whether the synchronous OSCCs behave in a different way clinically despite their less aggressive histological features or if some unknown factors affect the survival of these patients,” was just to emphasize the importance of further research in this context.

In summary, the lack of survival and clinical data to support the results of the study is a major limitation; however, this does not negate the fact that the histologic features of the synchronous lesions presented are less aggressive, because the criteria used were well defined and accepted.

We believe our explanations have answered the issues raised in the letter to editor regarding this article.

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Research and publication ethics:
What have we learned thus far?

To the Editor:

It was not surprising that Dr. Spångberg, an OOOOE editor, recently showed possible radiographic “falsification” in a submitted manuscript.1 Indeed, several research and publication ethics standards have been set up since World War II. These include the Nuremberg Code, the Declaration of Helsinki, the International Committee of Medical Journal Editors’ Uniform Requirements for Manuscripts to Biomedical Journals, and recommendations by the World Association of Medical Editors and the Committee on Publication Ethics.2-7 However, many notorious experiments have still occurred, such as Japan’s Unit (late 1930s-1940s), malaria studies and mustard gas experiments (USA, 1940s), post–World War II experimentation with radiation (USA, 1950s-1960s), the Tuskegee syphilis study (USA; 1932-72), and studies of hepatitis transmission in Willowbrook State School (USA; 1950s).2,4,6,7

Recently, fabrication of the cloning research results by Woo Suk Hwang, a Korean professor; fraudulent nutritional researches by Ram B. Singh, an Indian physician; and a Chinese clinical trial on esophageal cancer without the patient’s consent were extensively criticized.2,4-7 There is much evidence that financial conflicts of interest are found with individual researchers, departmental chairs, Ethics Committee members, and even journal editors and peer reviewers. The financial interests are continuing unabated in a large proportion of medical researches and higher rates of research citations.5

As Altman and Bland8 remind us, “Absence of evidence is not evidence of absence,” the absence of ethical documentation does not mean that the study