Oral Diseases

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LETTER TO THE EDITOR

Authors' Reply: "Surgical Treatment Compared With 'Wait and See' in Patients Affected by Oral Leukoplakia to Prevent Oral Cancer: Preliminary Data From a Multicenter Randomized Controlled Trial"

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Dear Editor,

We appreciate the interest aroused by our recent research on the surgical removal of oral leukoplakia (OL) (group A, $n=81$) compared to "wait and see" (group B, $n=80$) in the management of OL with the aim of reducing oral squamous cell carcinoma (OSCC) onset in a multi-center randomized controlled trial (RCT) (Lombardi et al. 2024). We appreciated, in particular, the letter from Liu and colleagues commenting on our RCT, which emphasizes the importance of this topic and the need for additional strong data on the management of OL (Liu, Shen, and Shi 2025).

As underlined in the study and by Liu, Shen, and Shi (2025), incisional biopsy may be associated with misdiagnosis if the selection of biopsy sites is not enough representative of the entire lesion, especially in the case of large and non-homogeneous lesions. For this reason, it is strongly recommended to perform multiple incisional biopsies in the diagnostic phase of non-homogeneous lesions (Pentenero et al. 2014).

OL associated with risk factors such as tongue localization and the presence of moderate/severe epithelial dysplasia are widely described as high-risk OL (Eccles et al. 2022; Iocca et al. 2020). Previous studies reported evidence suggesting to proceed with complete surgical excision of high-risk OL with histopathologic evidence of a clear margin (Awadallah et al. 2018; Zhang et al. 2016). However, excepting for preliminary data recently published (Lombardi et al. 2024), no RCT in the literature has still clearly established the real effectiveness of surgery in the prevention of OSSC onset (Lodi et al. 2016).

Even if "the initial data underline the increased risk of OSCC onset in case of OL of the tongue in presence of epithelial dysplasia in the 'wait and see' group compared to the surgical group" (Lombardi et al. 2024), we underline the main limitations of these preliminary results related to the small sample size and to the short follow-up period. A sample of at least 310 patients has been calculated to be needed, speculating that surgery could reduce OSCC onset from 15% in "wait and see" control group B to 5% in surgical test group A, in order to obtain solid results. Moreover, according to a recent review, a minimum follow-up of 3 years is recommended for prospective studies evaluating OSCC onset in patients affected by OL considering that the estimated malignant onset is estimated to be 3.2 ± 0.9 years (range 1.8–5.1 years) (Aguirre-Urizar, Lafuente-Ibáñez de Mendoza, and Warnakulasuriya 2021). Therefore, this RCT will continue at the same departments, to achieve more conclusive results and aim to reach 5-year follow-up for each patient enrolled.

Furthermore, the authors are also evaluating to expand this RCT including further centers of research in order to enlarge the sample size and to guarantee external validity of future definitive results.

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Author Contributions

Niccolò Lombardi: conceptualization, investigation, writing – original draft, methodology. **Paolo G. Arduino:** investigation, writing – review and editing, supervision. **Marta Lampiano:** writing – original draft, investigation. **Alessio Gambino:** investigation, supervision. **Roberto Broccoletti:** investigation, supervision. **Elena M. Varoni:** investigation, methodology, writing – review and editing. **Giovanni Lodi:** investigation, methodology, conceptualization, writing – review and editing, supervision.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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