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Reply to 'Comment on 'Prognostic biomarkers for oral tongue squamous cell carcinoma: a systematic review and meta-analysis"

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Sir,

We thank Dr Jayaraj and Mr Kumarasamy (Jayaraj and Kumarasamy, 2017) for their comments on our meta-analysis (Almangush *et al*, 2017). Oral tongue squamous cell carcinoma (OTSCC) has a different behaviour compared with SCC of other subsites of the oral cavity. In the analysis of Surveillance, Epidemiology, and End Results (SEER) database, Rusthoven *et al* found that OTSCC is associated with worse survival compared with SCC originating in other oral cavity subsites (Rusthoven *et al*, 2008). In the analysis of a large cohort of another population, patients with OTSCC were reported to have more tendency to neck failure, one of the most consistent prognosis factors, than those with SCC of buccal mucosa (Liao *et al*, 2010). Furthermore, Trivedi *et al* have studied the prognostic value of many biomarkers using immunohistochemistry of buccal and tongue carcinomas, and they concluded that these two subsites of the oral cavity have different biological behaviours, which was reflected in their prognostic analysis (Trivedi *et al*, 2011). Variations in the prognostic significance of the histopathologic markers have also been reported between the oral SCC subsites (Liu *et al*, 2017). Therefore, it is quite common in the literature that researchers evaluate prognostic biomarkers of OTSCC separately from other subsites of the oral cavity, in order to have homogenous cohorts that provide more accurate data than mixed cohorts. Accordingly, we argue that our focus on studies of OTSCC provides a more accurate meta-analysis and more specific conclusions.

In their letter, Dr Jayaraj and Mr Kumarasamy also suggested that our review should be more flexible to include articles of OTSCC analysed as a subset of other sites of head and neck squamous cell carcinoma (HNSCC). In addition, Dr Jayaraj and Mr Kumarasamy emphasised "the histological and molecular similarities between different types of HNSCC including OTSCC". We would like to point out that HNSCCs have wide variations in clinical, histological and molecular characteristics (Kang *et al*, 2015; Farsi *et al*, 2017). In addition, squamous cell carcinomas from different areas of the head and neck typically have different etiological backgrounds (Farsi *et al*, 2017). The above aspects make them in fact different disease entities. Therefore, different treatment protocols have been confirmed for various subtypes of HNSCCs. For HPV+ oropharyngeal cancer (chemo)radiotherapy alone seems to be a feasible treatment option, while for OTSCC (which is usually HPV−), the therapeutic approach includes surgery and elective neck treatment even in T1-T2N0 tumours in case of aggressive histopathologic features (e.g. tumour invasion >4 mm). It is of note that meta-analysis of SCCs from different subsites of the head and neck has been criticised due to heterogeneity of these subsites (Dayan & Vered, 2013).

At the end of their letter, Dr Jayaraj and Mr Kumarasamy highlighted eukaryotic translation initiation factor 4E (eIF4E) and its overexpression in head and neck cancer (HNC). To the best of our knowledge, the prognostic value of eIF4E has not been studied in large cohorts of OTSCC. Moreover, eIF4E was not mentioned in a comprehensive systematic review and meta-analysis of OSCC biomarkers published recently (Rivera *et al*, 2017). Although some studies have evaluated eIF4E as mentioned by Dr Jayaraj and Mr Kumarasamy, systematic searches by us (Almangush *et al*, 2017) and others (Rivera *et al*, 2017) did not find sufficient evidence for eIF4E as an important biomarker for OSCC or OTSCC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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