BJC

British Journal of Cancer (2018) 118, e12 | doi: 10.1038/bjc.2017.491

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

Alhadi Almangush*[,1,2,3], Ilkka Heikkinen[1,2], Antti A Mäkitie[4], Ricardo D Coletta[5], Esa Läärä[6], Ilmo Leivo[7] and Tuula Salo[2,8,9,10]

[1]Department of Pathology, University of Helsinki, Helsinki, Finland; [2]Department of Oral and Maxillofacial Diseases, University of Helsinki, Helsinki, Finland; [3]Institute of Dentistry, University of Misurata, Misurata, Libya; [4]Department of Otorhinolaryngology – Head and Neck Surgery, Helsinki University Hospital and University of Helsinki, Helsinki, Finland; [5]Department of Oral Diagnosis, School of Dentistry, State University of Campinas, Piracicaba, São Paulo, Brazil; [6]Department of Mathematical Sciences and Statistics, University of Oulu, Oulu, Finland; [7]Department of Pathology, University of Turku, Turku, Finland; [8]Helsinki University Hospital, Helsinki, Finland; [9]Research Group of Cancer Research and Translational Medicine, Medical Faculty, University of Oulu, Oulu, Finland and [10]Medical Research Center, Oulu University Hospital, Oulu, Finland

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.

REFERENCES

Almangush A, Heikkinen I, Makitie AA, Coletta RD, Laara E, Leivo I, Salo T (2017) Prognostic biomarkers for oral tongue squamous cell carcinoma: a systematic review and meta-analysis. *Br J Cancer* **117**(6): 856–866.

Dayan D, Vered M (2013) "Is immuno-expression of E-cadherin really a prognostic factor in head and neck cancer?". *Oral Oncol* **49**(3): e5.

Farsi NJ, Rousseau MC, Schlecht N, Castonguay G, Allison P, Nguyen-Tan PF, Soulieres D, Coutlee F, Hier M, Madathil S, Franco EL, Nicolau B (2017) Aetiological heterogeneity of head and neck squamous cell carcinomas: the role of human papillomavirus infections, smoking, and alcohol. *Carcinogenesis* **38**(12): 1188–1195.

Jayaraj R, Kumarasamy C (2018) Comment on 'Prognostic biomarkers for oral tongue squamous cell carcinoma: a systematic review and meta-analysis". *Br J Cancer*. e-pub ahead of print 13 February 2018: doi:10.1038/bjc.2017.482.

Kang H, Kiess A, Chung CH (2015) Emerging biomarkers in head and neck cancer in the era of genomics. *Nat Rev Clin Oncol* **12**(1): 11–26.

Liao CT, Huang SF, Chen IH, Kang CJ, Lin CY, Fan KH, Wang HM, Ng SH, Hsueh C, Lee LY, Lin CH, Yen TC (2010) Tongue and buccal mucosa carcinoma: is there a difference in outcome? *Ann Surg Oncol* **17**(11): 2984–2991.

Liu SA, Wang CC, Jiang RS, Lee FY, Lin WJ, Lin JC (2017) Pathological features and their prognostic impacts on oral cavity cancer patients among different subsites - a singe institute's experience in Taiwan. *Sci Rep* **7**(1): 7451.

Rivera C, Oliveira AK, Costa RAP, De Rossi T, Paes Leme AF (2017) Prognostic biomarkers in oral squamous cell carcinoma: a systematic review. *Oral Oncol* **72**: 38–47.

Rusthoven K, Ballonoff A, Raben D, Chen C (2008) Poor prognosis in patients with stage I and II oral tongue squamous cell carcinoma. *Cancer* **112**(2): 345–351.

Trivedi TI, Tankshali RA, Goswami JV, Shukla SN, Shah PM, Shah NG (2011) Identification of site-specific prognostic biomarkers in patients with oral squamous cell carcinoma. *Neoplasma* **58**(3): 217–226.

*Correspondence: Dr A Almangush; E-mail: alhadi.almangush@helsinki.fi
Published online 15 February 2018