Response to Asgari (Letter)

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Title: Response to Commentary "Utility and Limitations of Large Population-Based Data for Skin Cancer Outcomes"

Short title: Response to Commentary by Asgari

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Abbreviations: IACR = International Association of Cancer Registries; SEER = Surveillance, Epidemiology, and End Results Program (National Cancer Institute).

To the Editor,

We wish to clarify key points raised in a recent commentary (Asgari, 2016) about our paper on survival outcomes following multiple primary invasive melanomas (Youlden et al., 2016) published in the November 2016 issue of JID.

In this work we noted that most prior studies on multiple melanomas have calculated survival from the time of diagnosis of the first melanoma (Method A in Fig 1). However, this technique introduces "survival bias", as patients who remain alive longer generally have an increased chance to be diagnosed with additional melanomas. A second approach is to calculate survival from the time of diagnosis of the last melanoma (Method B in Fig 1), but this causes bias in the opposite direction by disregarding the survival time between the first and last melanoma.

As stated in our paper (Youlden et al., 2016), we used an approach known as "delayed entry" or "left truncation" specifically to avoid survival bias for those individuals with more than one primary invasive melanoma (Method C in Fig 1). Using the delayed entry method, survival time was calculated from the date of diagnosis of the first primary invasive melanoma for all patients in the study. However, patients who were diagnosed with multiple melanomas did not contribute survival time to the analysis until the date of last diagnosis. This is *not* the same as calculating survival time from the date of diagnosis of their last melanoma. Thus, in asserting that we "…chose a survival time that began with the last melanoma" (Asgari, 2016), the Commentator has misinterpreted our method. Indeed, we believe that the method we used is a strength that distinguishes our analysis from previous publications on this issue.

To demonstrate the biases that occur when calculating survival using Methods A and B, we presented the results obtained from these two methods, along with our preferred method C, using the study cohort (Youlden et al., 2016). We found that the respective excess hazard

ratios for 10-year melanoma-specific mortality for patients with two invasive melanomas compared to those with a single melanoma was underestimated at 1.17 (95% confidence interval = 0.98-1.39; p = 0.078) using Method A (calculating survival from time of diagnosis of first melanoma) and overestimated at 2.35 (95% CI = 2.02-2.72; p < 0.001) using Method B (calculating survival from time of diagnosis of last melanoma), compared to our excess HR estimate of 2.01 (95% CI = 1.57-2.59; p < 0.001) using the delayed entry method that corrects for these biases (Method C in Figure 1).

In addition, we specifically included "entry time" (date of last diagnosis) as a covariate in our multivariate modelling, as recommended (Matsuura and Eguchi, 2005), to directly address the issue of introducing late entry bias for patients with multiple melanomas. Therefore, we strongly reject the Commentator's suggestion that our approach could lead to systematic bias in calculating survival for those individuals with more than one primary melanoma (Asgari, 2016).

It should also be clarified that we used all melanomas in the analysis, not just those considered as "incident" for reporting purposes under IACR rules. Accordingly, issues relating to differential definitions by SEER and IACR are not relevant to our results or subsequent interpretation.

We stand by our findings that survival for patients diagnosed with multiple primary invasive melanomas is significantly worse compared to those with a single primary invasive melanoma. Clearly, this is an important public health concern.

Conflict of Interest

The authors state no conflict of interest.

References

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Figure Legend

Figure 1: Comparison of methods used to calculate survival time for patients with multiple melanomas