PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Can Oral Cancer Screening Reduce Late-Stage Diagnosis, Treatment Delay, and Mortality? A Population-Based Study in Taiwan

Authors

Tsai, Ethan; Walker, Brigham; Wu, Shiao-Chi

VERSION 1 - REVIEW

Reviewer	**1**
Name	**Bowrey, David**
Affiliation	**University Hospitals of Leicester NHS Trust, Surgery**
Date	**11-Apr-2024**
COI	**None declared**

This is an interesting study addressing an important topic. There are however some areas of ambiguity in the manuscript. Please can the authors address these:

1. The results have been displayed very briefly. It feels as though there should be a lot more information available that has been omitted/truncated. Can the authors elaborate in more detail eg. it would be helpful to see Table 1 comparing the characteristics of the screeened and unscreened population.

2. The authors have combined stages 1 and 2 into early, and stages 3 and 4 into late stage. They may be missing some subtle differences/nuances of stage difference. It would be better to report individual UICC/AJCC stages.

3. Again, some of the characteristics have been reported as binary variables - present or absent, rather than trying to quantify exposure (alcohol, smoking, etc)

4. The discussion is very short and needs elaboration. The conclusions are not supported by the data. The expense of a national screening programme has yielded a 2% absolute improvement in earlier stage disease and a similar improvement in 5 year survival. A counter argument could be made that screening has made virtually no impact of the survival of oral cancer in Taiwan? The authors should defend their stance or adjust their conclusions. Can

the authors include in the discussion a section on the cost of screening and what the cost per cancer detected/life saved was?

5. The authors reported a delay of 30 days or greater as being a significant treatment delay. Why? Can they justify why this definition was used?

6. The way the multi-variate analysis has been presented is confusing. Please can the authors reword this in a more user friendly manner?

Reviewer	**2**
Name	**do Amaral, Regiane**
Affiliation	**Universidade Federal de Sergipe, Odontologia**
Date	**13-Apr-2024**
COI	**no, competing interests**

The manuscript “The Impact of Oral Cancer Screening on Late-stage Diagnosis, Treatment Delay, and Survival” has the objective evaluates the effectiveness of the Taiwanese nationwide oral cancer screening program in reducing late-stage diagnosis and treatment delays, and improving survival among oral cancer patients.

The manuscript provides an interesting approach to the cancer screening model in Taiwan, and constructive criticism of the model, such as mortality and delay in treatment.

I consider the manuscript important.

Methodology

In the summary it is written that the analysis period was from 2010 -2018 and in the methodology it is from 2010 to 2013?

Results

However, patients undergoing screening had a higher rate of treatment

delay (19.2%) compared to those without screening (17.8%) (Table 2). Prior to adjusting for control variables, patients with screening were more likely to experience treatment delays (COR=1.10, 95% CI: 1.01 to 1.19, p=0.02) (Table 3). This finding aligns with multivariate analysis, indicating that patients with screening were 1.09 times more likely to experience treatment delays (95% CI: 1.00 to 1.19, p = 0.0496) (Table 4).

Screening populations have slightly lower mortality rates than the un-screened population: 32.3% versus 34.1% (Table 2). Before controlling covariates, OCC patients undergoing screening exposed to a lower risk of death (CHR = 0.93, 95% CI: 0.88 to 0.98,

p<0.01) (Table 3). This trend persisted in the controlled regression model, OCC patients undergoing screening had a 0.94 times hazard of death (95% CI: 0.89 to 0.99, p=0.01) (Table 4). The adjusted model further indicated that treatment delay in general was associated with a

1.13 times higher hazard of death (95% CI: 1.06 to 1.21, p<0.01) (Table 4)

the results are interesting, as a constructive criticism of the health model (screening).

VERSION 1 - AUTHOR RESPONSE

Reviewers' comments:

Reviewer #1:

1. The results have been displayed very briefly. It feels as though there should be a lot more information available that has been omitted/truncated. Can the authors elaborate in more detail eg. it would be helpful to see Table 1 comparing the characteristics of the screeened and unscreened population.

   Thank you for your suggestions regarding the results. We have addressed your concerns by providing a detailed comparison of the characteristics of the screened and unscreened populations. Specifically, we have combined our previous Table 1 and Table 2 into an updated table that includes these characteristics. The key characteristics among the screened and unscreened populations include betel chewing, cigarette smoking, and alcohol consumption, which are important due to their relevance to eligibility for oral cancer screening.

   We have also discussed the potential selection bias associated with these characteristics, acknowledging that the screened population might be less healthy overall. To mitigate this bias, we have controlled for these characteristics in our analysis. While this bias could potentially attenuate the effect of oral cancer screening toward the null, our findings still demonstrate a significant benefit in terms of reducing late-stage diagnosis and improving mortality outcomes.

2. The authors have combined stages 1 and 2 into early, and stages 3 and 4 into late stage. They may be missing some subtle differences/nuances of stage difference. It would be better to report individual UICC/AJCC stages.

   Unfortunately, due to government policy, we do not have access to the original dataset used in this study, limiting our ability to perform a multinomial regression analysis on individual AJCC stages.

   In case it is helpful context, we chose to categorize stages 1 and 2 as early-stage and stages 3 and 4 as late-stage because stages 1 and 2 are associated with significantly lower mortality compared to stages 3 and 4. Additionally, patients diagnosed at a late stage may reflect a diagnostic delay, which the oral cancer screening program aims to mitigate.

3. Again, some of the characteristics have been reported as binary variables - present or absent, rather than trying to quantify exposure (alcohol, smoking, etc)

Unfortunately, due to government policy, we do not have access to the original dataset used in this study, limiting our ability to update the control variables into continuous versus binary variables.

4. The discussion is very short and needs elaboration. The conclusions are not supported by the data. The expense of a national screening programme has yielded a 2% absolute improvement in earlier stage disease and a similar improvement in 5 year survival. A counter argument could be made that screening has made virtually no impact of the survival of oral cancer in Taiwan? The authors should defend their stance or adjust their conclusions. Can the authors include in the discussion a section on the cost of screening and what the cost per cancer detected/life saved was?

   Thank you for the suggestions, we have elaborated our discussion including expanding a discussion of oral cancer screening costs and cost effectiveness. Also, we agree that even if we had measured the effectiveness of screening on late-stage diagnosis and mortality, the magnitude of this benefit still needs to be improved. Our findings suggest that one of the potential ways that this could occur is to reduce the treatment delay on screening populations.

5. The authors reported a delay of 30 days or greater as being a significant treatment delay. Why? Can they justify why this definition was used?

   Thank you for raising this question. We have clarified the rationale for defining treatment delay as 30 days in the Methods section. Previous studies have shown that the typical time to initiation of treatment for oral cancer is around 21-30 days [1-4]. Moreover, a prior study conducted in Taiwan demonstrated that a diagnosis-to-treatment interval exceeding 30 days is associated with increased mortality [4, 5]. Therefore, we adopted the 30-day threshold as an indicator of treatment delay.

   References:

   1. Fujiwara, R.J., et al., *Treatment delays in oral cavity squamous cell carcinoma and association with survival.* Head Neck, 2017. **39**(4): p. 639-646.
   2. Chiou, S.J., W. Lin, and C.J. Hsieh, *Assessment of duration until initial treatment and its determining factors among newly diagnosed oral cancer patients: A population-based retrospective cohort study.* Medicine (Baltimore), 2016. **95**(50): p. e5632.
   3. Su, W.W., et al., *Impact of treatment delay on survival of oral/oropharyngeal cancers: Results of a nationwide screening program.* Head Neck, 2021. **43**(2): p. 473-484.
   4. Tsai, W.C., et al., *Influence of time interval from diagnosis to treatment on survival for oral cavity cancer: A nationwide cohort study.* PLoS One, 2017. **12**(4): p. e0175148.
   5. Liao, C.T., et al., *Association between the diagnosis-to-treatment interval and overall survival in Taiwanese patients with oral cavity squamous cell carcinoma.* Eur J Cancer, 2017. **72**: p. 226-234.

6. The way the multi-variate analysis has been presented is confusing. Please can the authors reword this in a more user friendly manner?

Thank you for your suggestion. We have updated the multivariate analysis table to improve clarity and make it easier to read and understand.

Reviewer #2:

1. In the summary it is written that the analysis period was from 2010 -2018 and in the methodology it is from 2010 to 2013?

   Thank you for pointing out this inconsistency. To clarify, we included patients diagnosed from 2010 to 2013, and they were followed up until 2018. We have updated the text to ensure this distinction is clear.

2. However, patients undergoing screening had a higher rate of treatment delay (19.2%) compared to those without screening (17.8%) (Table 2). Prior to adjusting for control variables, patients with screening were more likely to experience treatment delays (COR=1.10, 95% CI: 1.01 to 1.19, p=0.02) (Table 3). This finding aligns with multivariate analysis, indicating that patients with screening were 1.09 times more likely to experience treatment delays (95% CI: 1.00 to 1.19, p = 0.0496) (Table 4). Screening populations have slightly lower mortality rates than the un-screened population: 32.3% versus 34.1% (Table 2). Before controlling covariates, OCC patients undergoing screening exposed to a lower risk of death (CHR = 0.93, 95% CI: 0.88 to 0.98, p<0.01) (Table 3). This trend persisted in the controlled regression model, OCC patients undergoing screening had a 0.94 times hazard of death (95% CI: 0.89 to 0.99, p=0.01) (Table 4). The adjusted model further indicated that treatment delay in general was associated with a 1.13 times higher hazard of death (95% CI: 1.06 to 1.21, p<0.01) (Table 4) the results are interesting, as a constructive criticism of the health model (screening)

   Thank you for your comments.