Peer Review File

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REVIEWER #1

Comment 1: In the title, the authors mentioned "the prevalence of BRAFV600E" but in the manuscript, it is not clear that the authors only included cases with BRAFV600E and excluded other BRAF mutations (for example: codon 601).

Reply:

We stated explicitly in the Data Extraction section that BRAF nonV600E mutations were not included in this analysis.

Comment 2: Background: "PTC development is closely linked to somatic point mutations….". This sentence requires reference(s).

Reply:

The reference has been added.

Comment 3: Methods: it is not clear to me in studies using multiple methods to detect BRAF mutation, how the authors extracted the data for those studies?

Reply:

Our selection criteria were as follows:

1) if multiple techniques were used in study but only one definite result was shown in abstract, we provided data from the abstract;

2) if discordant cases were rendered by additional genotyping, we provided data after adjustment;

3) if above is not applicable, we relied on BRAF rate detected by the most sensitive technique, ex. Sanger > gel PCR, qPCR > Sanger, NGS > IHC.

Comment 4: Methods: the BRAF prevalence may be strongly affected by the proportion of PTC subtypes. What about studies only included a specific subtype of PTC other than classical PTC; for example: follicular variant PTC or tall cell PTC. These study results may underestimate or overestimate the true prevalence of BRAF mutation.

Reply:

We agree with the reviewer that PTC histotype is largely determined by mutation. It should be noted that vast majority of the studies enrolled consecutive/unselected cohorts of PTC, likely representative of real-life scenario in the particular country.

Furthermore, we found that only 10/138 studies were focused on specific subtypes of PTC (9 on CV-PTC and 1 on FV-PTC). Upon comparison with BRAF rate in the corresponding countries, we found no remarkable differences: 68% in CV-PTC vs. 71% in PTC-all (China) and 81% in CV-PTC vs. 76% in PTC-all (Korea). We believe that detailed analysis of the issue could be a scope of another study.

Comment 5: Results: the authors need to specify the reason why they separated studies from Japan, China, and Saudi Arabia in a subgroup.

Reply:

We have not separated those countries in a subgroup. Due to the high number of reports, results from Japan, Korea, China, and India were presented in separate tables. Otherwise, we followed distribution of countries by geography.

Comment 6: Results: The authors mentioned that tissue types (frozen, aspirate) may affect the

BRAF prevalence. The detection methods have long been known as the main reason for causing heterogeneities in mutation prevalence. Sanger sequencing is the most common method for BRAF detection, I guess. I suggest performing a subgroup analysis for studies only using Sanger sequencing so it can help reduce the heterogeneities and reflect a more correct estimate of BRAF prevalence across Asian countries.

Reply:

Indeed, Sanger sequencing has been widely acknowledged as a gold standard. However, own extensive experience with BRAF detection by different techniques made us confident that such assumption is overestimated (addressed in detail in PMID 32150939). We also afraid that additional subgroup analysis in the frame of this project will be too much consuming, which is likely not balanced by the added value.

Comment 7: There are a number of factors that can affect the BRAF prevalence such as PTC histotypes, rate of nodal and distant metastasis, study period, etc. One way to control the among-study heterogeneities is that the authors should limit studies providing BRAF prevalence for classical PTC. However, based on the inclusion criteria, it is impossible for the authors to do so. In table 1, I think the authors should at least mention (i) patient selection is random, consecutive, or any inclusion criteria for PTC; (ii) the proportion of classical PTC and follicular variant PTC.

Reply:

Thank you for this suggestion.

The issue of histotypes is explained above (see rebuttal to Q4).

Re. limiting cases only to CV-PTC: 1) about half of the studies did not provide details on histologic subtypes; and 2) excluding specific subtype is automatically deflecting our findings from real-life scenario.

Re. adding footnote to Table 1: all inclusion and exclusion criteria are listed in Methods.

Comment 8: Discussion: it is useful if the authors can write 1-2 sentences about the effect of concomitant TERT and BRAF mutations on the patient outcomes. It is one of the most important characteristics of BRAF mutation.

Reply:

Has been added, as requested.

Comment 9: Discussion: it would be great if the authors can give some explanations why the prevalence of BRAF mutation in Europe and America is lower than that in Asia.

Reply:

Has been added.

Comment 10: There are certain limitations of this study that need to be discussed in the Discussion.

Reply:

The sentence about limitations of this study was added in the discussion.

REVIEWER #2

Comment 1: The prevalence of BRAFV600E mutation was 61.7%, and those of RAS genes were found 12.9% of 402 PTCs by the TCGA study (Cell 159:676-690, 2014.). Therefore the reported prevalence (45-50%, Xing M et al. JAMA 309:1493-1501, 2013) in Western PTC patients also suffer technical issues and might not reach the real incidence (about 61.7%) accurately.

Reply:
Thank you for this reminder. We added the TCGA paper in the references the text was changed accordingly (Abstract, Background, Discussion).

Comment 2: RAS driver mutations have been reported in PTCs, particularly in Western series. However, RAS mutated (follicular variant) PTCs are rare in Asian series, and the majority of them are classified in benign follicular adenomas or follicular carcinoma (Hirokawa M et al. Am J Surg Pathol 26:1508-1514, 2002.). Thus the prevalence of BRAFV600E mutation in PTCs becomes high in Asian series. Please add this interpretation in the discussion.
Reply :
We agree with the reviewer. The interpretation above was added in the discussion.

Minor comments:
Comment 1: Some words or symbols were garbled in this PDF. Please fix them.
Reply :
Distorted characters were fixed when recognizable.

Comment 2: Overall survival rates should be measured with time, such as at 10 years or 20-years. Please supply it.
Reply:
10-year survival rate was specified.

Comment 3: A statement in the discussion on page 11, "Thyroid cancer was estimated to be the third most common malignant tumor in women in the USA (157)," should be replaced with the incidence in the Asian population, if available.
Reply:
Provided both.