A meta-analysis of prognostic roles of molecular markers in papillary thyroid carcinoma

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Abstract

The prognostic role of molecular markers in papillary thyroid carcinoma (PTC) is a matter of ongoing debate. The aim of our study is to investigate the impact of RAS, BRAF, TERT promoter mutations and RET/PTC rearrangements on the prognosis of PTC patients. We performed a search in four electronic databases: PubMed, Scopus, Web of Science and Virtual Health Library (VHL). Data of hazard ratio (HR) and its 95% confidence interval (CI) for disease-specific survival (DSS) and disease-free survival (DFS) were directly obtained from original papers or indirectly estimated from Kaplan–Meier curve (KMC). Pooled HRs were calculated using random-effect model weighted by inverse variance method. Publication bias was assessed by using Egger’s regression test and visual inspection of funnel plots. From 2630 studies, we finally included 35 studies with 17,732 patients for meta-analyses. TERT promoter mutation was significantly associated with unfavorable DSS (HR = 7.64; 95% CI = 4.00–14.61) and DFS (HR = 2.98; 95% CI = 2.27–3.92). BRAF mutations significantly increased the risk for recurrence (HR = 1.63; 95% CI = 1.27–2.10) but not for cancer mortality (HR = 1.41; 95% CI = 0.90–2.23). In subgroup analyses, BRAF mutation only showed its prognostic value in short-/medium-term follow-up. Data regarding RAS mutations and RET/PTC fusions were insufficient for meta-analyses. TERT promoter mutation can be used as an independent and reliable marker for risk stratification and predicting patient’s outcomes. The use of BRAF mutation to assess patient prognosis should be carefully considered.

Introduction

PTC is the most common histologic type of thyroid cancer, and its incidence has been increasing over the years (1). PTCs rarely behave as aggressive tumors clinically, with a cancer-specific mortality rate less than 5% (2). However, there is a small proportion of cases with aggressive features at presentation that develop early distant metastasis or relapse and are associated with adverse outcomes. Various clinicopathological factors have been investigated as prognostic factors in PTCs, and some of them have been reported to associate with poor outcomes such as old age, large tumor size or distant metastasis (2, 3).
Recent progress in molecular analyses has improved our understanding of tumorigenesis and pathogenesis in PTC. Several genetic alterations have been described in PTC (4). Among them, BRAF mutation, especially BRAF V600E, is the most common mutation in PTC; however, its prognostic role in PTC is still debated (5, 6, 7). Another recently described genetic marker, TERT promoter mutations, has shown promise in predicting patient’s outcomes (8, 9). The prognostic implications of RAS mutations and RET/PTC rearrangements in PTC are still controversial.

In the present study, we performed a comprehensive systematic review and meta-analysis of observational studies to examine the prognostic impact of molecular markers on tumor recurrence and cancer-related mortality in PTC.

Materials and methods

Literature search

Four electronic databases, including PubMed, Web of Science, Scopus and VHL were searched for relevant articles from inception to September 2016. We used the following search term: (BRAF OR TERT OR RAS OR RET/PTC) AND (papillary thyroid) AND (carcinoma OR cancer). We also searched for potential studies by reviewing the citations within the included studies and reviews. Our study protocol strictly followed the recommendation of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement (10).

Selection criteria and abstract screening

We imported all search results from each electronic database into Endnote (Thompson Reuters, PA, USA) and deleted duplicates. Titles and abstracts of included studies were independently screened by two reviewers. Studies were included if they reported the association between at least one of the following molecular markers (BRAF, TERT promoter, RAS mutations or RET/PTC rearrangements) and PTC patient outcomes (tumor recurrence or cancer-related mortality). We excluded studies if they were (i) studies on other thyroid cancer subtype other than PTC, (ii) case reports, (iii) reviews, (iv) posters, conference papers, theses or books, and (v) duplicated articles. Discordant results between two reviewers were solved by discussion and consensus.

Full-text screening and data extraction

Full-text of all relevant studies were consecutively downloaded and screened independently by two reviewers. Available data were extracted into a predefined extraction form. The following data were extracted from full-text papers: authors, institution, city, country, publication year, surgical period, study design, number of patients, mutational detection method, follow-up periods, data of HR and its 95% CI on DFS and DSS and adjusted variables if available. Data of HR and its 95% CI were directly obtained from full-text papers or indirectly estimated from KMC using the methods by Tierney and coworkers (11). Any disagreements between two reviewers, if present, were resolved again by discussion and consensus. In cases of insufficient data in the original papers or unpublished data, we tried to obtain potential further data by contacting the authors via email. Studies in which data of HR and KMC on DFS or DSS were not provided in original paper or via email were further excluded from the final analyses.

Quality assessment and risk of bias analysis

We used the Newcastle-Ottawa Scale (NOS) to evaluate the quality of included studies in our meta-analyses (12). Two reviewers independently awarded stars for cohort or case-control studies (maximum nine stars) based on a developed checklist (12). In the second domain of outcome category, we awarded one star if the study had a median time of follow-up longer than five years, which was considered long enough for tumor recurrence and mortality to occur. In the last domain of outcome category, studies with the follow-up rate ≥80% or description of those lost suggesting no difference from those followed were awarded one star. Studies awarded at least six stars were considered moderate-to-high-quality studies and those with a NOS value of less than six were regarded low-quality studies.

Meta-analysis

Review Manager 5.3 (Cochrane Collaborative, Oxford, UK) was used for statistical analysis. Pooled HR for DSS and DFS was calculated using the random-model effect weighted by inverse variance method. An HR >1 indicated a compromised prognosis in PTC patients with mutations. If the authors provided various data of HR in the same study, we selected the most powerful one for primary outcome analysis (adjusted HR was superior to
unadjusted HR and unadjusted HR was superior to HR estimated from KMC).

Among-study heterogeneity was assessed by the $I^2$ statistic, which shows the total variation across studies that is not a result of chance (13). An $I^2$ statistic <25% indicates a low amount of heterogeneity and >50% indicates a high amount of heterogeneity (14). We examined the sources of heterogeneity by using (i) subgroup analyses and (ii) sensitivity analysis. Egger’s regression test and funnel plot were carried out to further assess the presence of publication bias and calculated by Meta-Essentials: Workbook for meta-analysis (15). A $P$ value less than 0.05 was considered statistically significant publication bias.

Results

We found total 6444 articles after initial search and 2630 articles after deleting duplicates. Three additional studies were found by reading citations within included studies. After title and abstract screening step, 84 potential studies were identified to read full-text. By reading full-texts, we further excluded 49 articles that did not meet the inclusion criteria. Finally, 35 articles with a total of 17,732 PTC patients were included for final analysis (Fig. 1).

We contacted all corresponding authors of the included studies via email requesting unreported HR and its 95% CI for effects of mutations on DSS and DFS. We received responses from authors of six studies in Korea, Italy, Poland and Turkey to provide their unpublished data (16, 17, 18, 19, 20, 21).

Study characteristics

Characteristics of included studies were described in Supplementary Table 1 (see section on supplementary data given at the end of this article). We found data of HR for effects of RAS, TERT promoter and BRAF mutations on DSS in one, six and eight studies, respectively. For DFS, survival data are available for RAS, TERT promoter and BRAF mutations in two, six and 26 studies, respectively. No survival data were found for effect of RET/PTC rearrangements on DSS or DFS. In cases of duplicated study population from same institutions, we selected data of higher statistical power as described previously or studies with higher number of cases. Because of insufficient data, we did not perform meta-analyses for effects of RAS mutations and RET/PTC rearrangements in this study.

Impact of TERT promoter and BRAF mutations on DSS

We found eligible data to pool HR for TERT promoter mutations in six studies and for BRAF mutations in eight studies, including 1396 and 6659 patients with PTC, respectively. The effect estimate for TERT mutations demonstrated that upon comparing patients without mutations, PTCs harboring mutations showed a significantly poor DSS (HR=6.81; 95% CI=3.63–12.80) (Fig. 2A). Among-study heterogeneity was not present ($I^2=0\%$).

The pooled result for BRAF mutations showed an insignificant association of patients possessing mutations
with compromised DSS (HR = 1.41; 95% CI = 0.90–2.23) (Fig. 2B). A high amount of heterogeneity between included studies was found ($I^2 = 54\%$). Excluding the study by Xing and coworkers (22) considerably decreased the heterogeneity among studies, but the overall effect remained insignificant (HR = 1.14; 95% CI = 0.80–1.63; $I^2 = 22\%$).

**Impact of TERT promoter and BRAF mutations on DFS**

Six and 26 studies, including 1589 and 13,213 patients with PTC contained relevant data to pool HR for TERT promoter and BRAF mutations, respectively. PTCs from the studies by Alzahrani and coworkers (23), Fraser and coworkers (24), Czarnecka and coworkers (17), Xing and coworkers (8, 25), Kim and coworkers (26), Fernandez and coworkers (27), and Lee and coworkers (28) possibly overlapped with the multicenter study by Xing and coworkers (5) and the study by Kim and coworkers (29) in the meta-analysis of HR for BRAF mutations and were, therefore, excluded from the pooled estimate of HR for BRAF mutations.

The overall estimates showed a significant impact for both TERT promoter and BRAF mutations on DFS (HR = 3.08; 95% CI = 2.40–3.96 and HR = 1.63; 95% CI = 1.27–2.10, respectively) (Fig. 3). No heterogeneity among studies was found in the meta-analysis of TERT promoter mutations ($I^2 = 0\%$). A high amount of heterogeneity was
found among included studies for pooled estimate of BRAF mutations ($I^2 = 76\%$). Excluding the study by Costa and coworkers (30), resulted in a significant decrease of the heterogeneity among included studies ($I^2 = 17\%$), and the overall effect remained statistically significant (HR = 1.69; 95% CI = 1.41–2.02).

**Subgroup analyses**

Subgroup analyses were conducted according to HR calculation method (unadjusted and adjusted), study origin (Caucasian and Asian), follow-up duration (short/medium term and long term) and detection method (direct sequencing and other methods). We classified studies with median value (or mean value in case of no median value) of follow-up duration more than five years as long-term duration and studies with median value of five or less than five years as short-/medium-term follow-up duration.

TERT promoter mutations were significantly associated with unfavorable DFS and DSS in all subgroup analyses. We also found that BRAF mutations were significantly associated with poor DFS and DSS in subgroup of short-/medium-term follow-up but not in long-term follow-up. After subgroup analyses, the source of heterogeneity in the effects of BRAF mutations on DFS and DSS might be attributed to the follow-up duration (Table 1). All results of subgroup analyses are presented in Table 1.

**Impact of coexisting TERT promoter and BRAF mutations on DSS**

We carried out a meta-analysis to further compare the effects of coexisting TERT and BRAF mutations with effects of TERT mutation only and BRAF mutation only. In 35 included studies, six studies reported the prevalence of each genetic subgroup when combining BRAF and TERT promoter mutations (Supplementary Table 2).

PTCs wild type for both mutations harboring BRAF mutation only were the most prevalent subgroups (48.4% and 41.2%, respectively). PTCs with concomitant BRAF and TERT comprised 6.2% of cases and the subgroup of PTCs with only TERT promoter mutation was the least common genotype (4.2%). We could directly or

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**Table 1** Results of subgroup analyses for DSS and DFS.

| Subgroup | DSS | | | DFS | | |
| --- | --- | --- | --- | --- | --- |
| | No. of studies | No. of patients | HR | 95% CI | $I^2$ (%) | No. of studies | No. of patients | HR | 95% CI | $I^2$ (%) |
| **HR calculation method** | | | | | | | | | | |
| TERT promoter mutations | | | | | | | | | |
| Unadjusted HR | 6 | 1396 | 14.30$^a$ | 5.31–38.53 | 58 | 6 | 1589 | 3.22$^a$ | 2.52–4.13 | 0 |
| Adjusted HR | 4 | 1177 | 13.60$^a$ | 5.22–35.44 | 0 | 3 | 1146 | 3.27$^a$ | 2.22–4.82 | 0 |
| **BRAF mutations** | | | | | | | | | |
| Unadjusted HR | 8 | 6659 | 1.72 | 0.91–3.26 | 78 | 15 | 10,327 | 1.68$^a$ | 1.30–2.17 | 80 |
| Adjusted HR | 2 | 4450 | 2.69$^a$ | 1.34–5.39 | 0 | 4 | 5972 | 1.65$^a$ | 1.28–2.12 | 7 |
| **Study origin** | | | | | | | | | |
| TERT promoter mutations | | | | | | | | | |
| Caucasian | 4 | 556 | 5.03$^a$ | 2.35–10.73 | 0 | 4 | 950 | 3.04$^a$ | 2.32–3.97 | 0 |
| Asian | 2 | 841 | 13.42$^a$ | 4.32–41.65 | 0 | 2 | 639 | 3.42$^a$ | 1.67–7.01 | 0 |
| **BRAF mutations** | | | | | | | | | |
| Caucasian | 5 | 2860 | 1.58 | 0.94–2.46 | 64 | 14 | 7234 | 1.94$^a$ | 1.33–2.82 | 80 |
| Asian | 3 | 3799 | 1.14 | 0.25–5.08 | 46 | 7 | 6591 | 1.31 | 0.93–1.84 | 71 |
| **Follow-up duration** | | | | | | | | | |
| TERT promoter mutations | | | | | | | | | |
| Short-term (≤5 years) | 1 | 432 | 20.47$^a$ | 2.95–142.22 | NA | 3 | 1146 | 3.27$^a$ | 2.22–4.82 | 0 |
| Long-term (>5 years) | 5 | 965 | 5.98$^a$ | 3.07–11.65 | 0 | 3 | 445 | 2.95$^a$ | 2.12–4.11 | 0 |
| **BRAF mutations** | | | | | | | | | |
| Short/medium-term (≤5 years) | 3 | 4730 | 2.52$^a$ | 1.45–4.37 | 9 | 7746 | 2.35$^a$ | 1.81–3.07 | 0 |
| Long-term (>5 years) | 5 | 1929 | 1.05 | 0.71–1.54 | 25 | 11 | 1922 | 1.09 | 0.96–1.23 | 0 |
| **Detection method** | | | | | | | | | |
| BRAF mutations | | | | | | | | | |
| Direct sequencing | 4 | 3122 | 1.33 | 0.55–3.22 | 67 | 14 | 6183 | 1.7 | 1.22–2.35$^a$ | 57 |
| Other methods | 4 | 3537 | 1.32 | 0.81–2.17 | 24 | 7 | 4283 | 1.68 | 1.04–2.71$^a$ | 82 |

*Statistically significant.

CI, confidence interval; DFS, disease-free survival; DSS, disease-specific survival; HR, hazard ratio; NA, not available.
indirectly obtain HR data from two studies (31, 32) and received unpublished data via email from one additional study (19). The group with concomitant TERT and BRAF mutations exhibited a worse but statistically insignificant effect on DSS as compared with the group harboring TERT mutations only (HR = 1.69; 95% CI = 0.42–6.90; $I^2 = 57\%$). On the other hand, a significant effect was found when comparing the dual mutations group and the group of BRAF mutations only (HR = 30.08; 95% CI = 3.14–287.98; $I^2 = 88\%$).

Risk of bias assessment and quality of studies

The NOS tool was used to assess the quality of included studies. The majority of included studies were retrospective studies. The number of stars awarded to each study ranged from four to seven stars. Details of given stars within each domain of NOS were described in Supplementary Table 3.

Publication bias

Funnel plot observation did not show strong evidence of publication bias among the set of studies. In addition, Egger’s regression test of all effects did not suggest any evidence of publication bias (Supplementary Figs 1, 2, 3 and 4).

Discussion

A number of clinicopathological factors have been assessed as prognostic factors in PTC, and several potential factors have been identified such as old age, large tumor size, the presence of nodal and distant metastasis or extrathyroidal extension (33, 34, 35). The understanding of pathogenesis and genetic profiles in thyroid cancer has been much improved in recent years with the rapid growth of translational medicine. The majority of thyroid cancer cases are driven by the activation of RAS–mitogen-activated protein kinase (MAPK) signaling pathway via BRAF or RAS point mutations (36) or chromosomal fusions (RET/PTC or TRK) (37, 38). Therefore, it is very essential to investigate the usefulness of genetic events as trustworthy prognostic markers for risk stratification and patient management.

The BRAF mutations are the most common genetic events in PTCs, and the BRAF V600E is the most common mutation in BRAF mutation family (4). In the past two decades, the significance of BRAF V600E in tumor aggressiveness and its usefulness as prognostic marker have been extensively studied. The BRAF V600E has been reported to associate with aggressive behaviors in PTC patients (39, 40, 41). However, there were remarkable inconsistencies regarding its prognostic role among various studies (7, 18, 22, 42). It is most likely that the heterogeneities in patient selections, follow-up periods and statistical analyses are the major factors responsible for these discrepancies. Hence, meta-analysis, the most powerful statistical method of pooling results from multiple studies, is required to solve the controversial result. In our meta-analyses, we identify a significant effect of BRAF mutations on patient DFS but not on patient DSS. This significant effect, however, should be interpreted with caution as there is a considerable amount of heterogeneity among included studies. Although the meta-analysis for multivariate HR on DFS remains significant, the result is dominated by studies with short-/medium-term follow-up (5, 21). Interestingly, we only find a significant association of BRAF mutations with unfavorable DFS and DSS in subgroup of studies with short-/medium-term follow-up, and this significant result completely disappears in long-term follow-up subgroup (Table 1). Thus, BRAF mutation should only be used very cautiously as a prognostic marker in PTC patients, given that it only differentiates outcomes in short-/medium-term follow-up and does not show good predictive value in long-term prognosis. However, it is important to note that the majority of PTC recurrence occurs in the first five years of follow-up (43), and the use of BRAF mutations as a prognostic factor in PTC, therefore, can be considered.

TERT promoter mutations, the more recently discovered mutations in thyroid cancer, have been found to correlate with aggressive clinicopathological features and poor outcomes in PTCs (8, 19, 44). Our pooled analyses show a promising value of these mutations as a prognostic marker in PTCs. TERT promoter mutations are significantly associated with worse patient DFS and DSS in primary and all subgroup analyses. Although the number of included studies with survival data of TERT promoter mutations is relatively small, there are no inconsistencies among the included studies. In addition, subgroup analyses of multivariate HR on DFS and DSS both demonstrate an independent and significant association of TERT promoter mutations with poor survival outcomes. TERT promoter mutations are not prevalent in PTCs but are more frequently detected in poorly differentiated and anaplastic thyroid carcinoma (45, 46). On the other hand, Landa and coworkers reported that TERT promoter mutations are subclonal in a small subset of PTCs but are
clonal in poorly differentiated and anaplastic cancer (46). Furthermore, the survival of anaplastic thyroid carcinoma patients harboring TERT promoter mutations was significantly worse in comparison with patients without these mutations (46), thus supporting the association of TERT promoter mutations with aggressive clinical course and poor outcome in thyroid cancer.

The presence and roles of RAS mutations and RET/PTC rearrangements in thyroid cancer have been established since a long time. RAS mutations have been shown to be associated with aggressive tumor phenotypes, distant metastasis and poor prognosis in thyroid cancer (47). However, their association with clinical course in PTC is controversial. We could find data for RAS mutation is controversial. We could find data for RAS mutation in only two studies (30, 48). In the study by Hara and coworkers, the authors reported that the presence of RAS mutations was a significant and independent predictor of both death and recurrence of PTC (48). However, these results should be carefully scrutinized as the authors selected a high number of cases with distant metastasis in which the majority of RAS mutations were detected (48). Additionally, TERT promoter mutations were found to be associated with distant metastasis in PTCs (19, 49, 50), and these mutations could be coexisting in those cases harboring RAS mutations and thus have enhanced the significant effect on patient’s outcomes. In addition, Song and coworkers (50), Musa and coworkers (51) and Shen and coworkers (52) reported that concomitant RAS and TERT promoter mutations enhanced the risk prediction in differentiated thyroid cancer. These findings support a hypothesis that differentiated thyroid cancer will most likely lack aggressiveness when harboring RAS mutations alone but will be associated with adverse outcome when harboring concomitant RAS and TERT promoter mutations (53). RET/PTC rearrangements may seem to play an unimportant prognostic role in PTCs as there were no published data on this topic, but further investigation may be needed to affirm this view.

At an earlier period, genetic alterations in thyroid cancer were thought to be mutually exclusive (54). With the improvements of detection methods and discoveries of novel genetic events, concomitant mutations have been reported in a number of cases and studies (8, 50, 55, 56). Concomitant mutations in thyroid cancer were proposed to enhance tumor aggressiveness and worsen patients’ survival, especially coexisting TERT promoter and BRAF mutations in PTC (31, 56, 57). TERT promoter mutations are not common events in PTCs, but they are prevalent in aggressive tumors (58). Interestingly, these mutations have been found to frequently occur in coexistence with BRAF mutations in PTCs (8, 32, 50). Our pooled results show that PTCs with concomitant BRAF and TERT mutations showed a significantly worse DSS as compared to PTCs with BRAF mutations only. We find an insignificant result in the comparison of PTCs with concomitant BRAF and TERT mutations and PTCs with TERT mutations only, and it further supports the fact that TERT promoter mutations have an independent prognostic value, irrespective of BRAF status. There are several published papers (8, 19, 31, 32, 50, 59, 60) reporting the impact of BRAF and TERT interaction on clinical significance, but we could only find available HR data to analyze the interaction between BRAF and TERT on patient prognosis in only three studies including one provided via email request (19, 31, 32). Therefore, additional studies are needed to confirm the results from the large cohort study in the United States in which the authors demonstrated PTCs with coexisting BRAF and TERT mutations to have the highest risk for mortality (31).

This is the first meta-analysis to investigate the prognostic impact of various genetic events on PTC, and we included a high number of studies, 35 studies with nearly 18,000 PTC patients from 15 countries for meta-analyses. We also conducted detailed subgroup analyses on different statistical and clinicopathological features to systematically evaluate the prognostic effect of genetic alterations in PTC and to identify the potential source of heterogeneity, the follow-up duration. Our subgroup analyses further emphasize the prognostic values of TERT promoter mutations and prompt reconsideration of the usefulness of BRAF mutations to predict patient prognosis. However, our present study might have limitations that need to be addressed. First, most of included studies are retrospective studies so selection biases are unavoidable such as treatment models or mutational detection methods. Secondly, several data of HRs were estimated from KMC and the results, therefore, sometimes lack precision (11). To minimize this bias, we have made all efforts to contact the authors to provide unreported HR and 95% CI, and we received responses from authors of six studies. PTCs harboring BRAF V600E have been reported to represent a diverse group of tumors, consisting at least four molecular subtypes, with variable degrees of thyroid differentiation and these tumors, therefore, should not be considered a homogenous group in clinical studies (36). However, the majority of our included studies only provided unadjusted hazard ratio of BRAF mutation on patient outcomes and did not take into account other genetic alterations. Additional studies should include
other genetic events designed to capture the extent of genetic diversity in PTCs.

In conclusion, our present study indicates strong evidence that TERT promoter mutation is an independent and reliable molecular marker to predict recurrence and mortality in PTCs. TERT should be used for risk stratification in PTC patients, especially in high-risk patients, in preference to other molecular markers. The use of BRAF mutation to assess patient prognosis should be considered carefully as it can only be shown to have prognostic value in short/medium-term follow-up.

Supplementary data
This is linked to the online version of the paper at http://dx.doi.org/10.1530/EC-17-0010.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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