Loss of Expression of PTEN is Associated with Worse Prognosis in Patients with Cancer

Zhi-Xin Qiu¹&, Shuang Zhao¹&, Lei Li¹, Wei-Min Li¹*

Abstract

Background: The tumor suppressor phosphatase and tensin homolog (PTEN) is an important negative regulator of cell-survival signaling. However, available results for the prognostic value of PTEN expression in patients with cancer remain controversial. Therefore, a meta-analysis of published studies investigating this issue was performed. Materials and Methods: A literature search via PubMed and EMBASE databases was conducted. Statistical analysis was performed by using the STATA 12.0 (STATA Corp., College, TX). Data from eligible studies were extracted and included into the meta-analysis using a random effects model. Results: A total of 3,810 patients from 27 studies were included in the meta-analysis, 22 investigating the relationship between PTEN expression and overall survival (OS) using univariate analysis, and nine with multivariate analysis. The pooled hazard ratio (HR) for OS was 1.64 (95% confidence interval (CI): 1.32-2.05) by univariate analysis and 1.56 (95% CI: 1.20-2.03) by multivariate analysis. In addition, eight papers including two disease-free-survival analyses (DFSs), four relapse-free-survival analyses (RFSs), three progression-free-survival analyses (PFSs) and one metastasis-free-survival analysis (MFS) reported the effect of PTEN on survival. The results showed that loss of PTEN expression was significant correlated with poor prognosis, with a combined HR of 1.74 (95% CI: 1.24-2.44). Furthermore, in the stratified analysis by the year of publication, ethnicity, cancer type, method, cut-off value, median follow-up time and neoadjuvant therapy in which the study was conducted, we found that the ethnicity, cancer type, method, median follow-up time and neoadjuvant therapy are associated with prognosis. Conclusions: Our study shows that negative or loss of expression of PTEN is associated with worse prognosis in patients with cancer. However, adequately designed prospective studies need to be performed for confirmation.

Keywords: Cancer - PTEN - overall survival - meta-analysis

Introduction

The global burden of cancer continues to increase dramatically with approximately 12.7 million new cancer cases and 7.6 million cancer-related deaths every year worldwide (Jemal et al., 2011). Due to a major part of patients diagnosed with advanced stage and die as a result of cancer metastases resistant to conventional therapy, the overall survival for patients with cancers is still with a very low proportion.

Tumor occurrence and development is a multi-step and complex process that influenced by various environment and genetic factors. Nowadays, several biological markers have been recognized as prognosticators, as well as indicator of potential therapeutic targets for different types of human cancers. Owing to the complicated molecular biology, multiple factors including the cell growth, cell cycle control, angiogenesis, morphogenesis, apoptosis, and metastatic adhesion have been researched with the aim of creating biological risk assessment and biological staging models for cancers (Al-Saad et al., 2008). The tumor suppressor phosphatase and tensin homolog (PTEN) is an important negative regulator of cell-survival signaling (Sawai et al., 2008), it’s involved in the regulation of cell growth, proliferation, and apoptosis in signal transduction pathways and participates in the control of cell cycle (Yin et al., 2008; Ortega-Molina et al., 2013). Recently, some evidences to suggest that loss of expression of PTEN have adverse association with prognostic value, but some other researches showed no correlation. Additionally, underexpression of PTEN confers resistance to cetuximab-induced apoptosis (Loupakis et al., 2009). Therefore, investigate the relationship between the expression of PTEN and the prognosis of patients with cancers is important, as this will be helpful for adopting appropriate targeted therapy.

However, the relationship of PTEN expression levels to cancer patients’ survival remains to be controversial. Therefore, based on the discordant results obtained by numbers of studies, we conducted this meta-analysis to quantify the role of PTEN as prognostic marker among patients with cancer.
Zhi-Xin Qiu et al

Materials and Methods

Literature search

A literature search via PubMed and EMBase databases was conducted to find articles that evaluated the role of PTEN in cancer (Last search was updated on Jan 13, 2015) using the following keywords and text words: i) Phosphatase and tensin homolog or PTEN, and ii) cancer, and iii) survival analysis or prognostic, and iv) expression, and v) tissue.

Selection criteria

The language in which the articles were written was not restricted, and all eligible studies that examined the association between the expression of PTEN and overall survival (OS) or any other survival analysis were gathered. However, the papers which only have abstracts were excluded because of insufficient data for meta-analysis. Therefore, we first carefully read the titles and abstracts of the publications to find exactly those studies that indeed examined the relationship between the expression of PTEN and OS or other survival analysis in patients with cancer. After the abstracts met these conditions, the full texts were analyzed and included into our meta-analysis according to the following criteria: i) articles were written as full paper; ii) expression levels of PTEN were compared to patient’s OS or other survival analysis; iii) expression of the proteins were evaluated in tumor tissues by immunohistochemistry (IHC) or reverse transcription and polymerase chain reaction (RT-PCR) analysis; iv) Hazard ratios (HR) and 95%CI for survival were provided or could be calculated from the sufficient data; v) if the same group of patients were used to analyze more than once, the most complete research was selected for our study.

Data extraction

Two investigators (Zhi-Xin Qiu and Shuang Zhao) checked all potentially relevant articles and extracted data in separate databases. In case of disagreement, a third author (Lei Li) would assess these articles. The following information were collected from each study: first author’s name, year of publication, ethnicity, number of patients, laboratory methodology, median follow-up time, cut-off value, information about neoadjuvant therapy, histological type, lymph node metastasis, clinical stage and HR with 95%CI.

Statistical analysis

The intensity of relationship between the expression levels of PTEN and survival were described as HRs. Negative expression of PTEN indicated poor prognosis in patients with cancer if HR>1 with the 95%CI did not overlap 1. From some published researches, HR and 95%CI could be directly obtained by using univariate or multivariate survival analysis. Otherwise, HR and 95%CI were calculated by Kaplan-Meier survival curves using the software Engauge Digitizer Version 4.1 (http://digitizer.sourceforge.net/) and the method presented by Parmar et al. before (Parmar et al., 1997; Higgins et al., 2002). If there was no obvious heterogeneity, the fixed-effects model ( Mantel-Haenszel method) was used to estimate the pooled HR; otherwise, the random-effects model (DerSimonian and Laird method) was used. Funnel plot and Begg’s rank correlation method were designed for assessing risk of publication bias. STATA 12.0 ( STATA Corp., College, TX) was used to perform statistical analysis. A P-value less than 0.05 was consider to be statistically significant.

Results

Study Selection and Characteristics

164 and 78 articles were retrieved from PubMed and EMBase electronic database according to our defined keywords and text words, respectively (Figure 1). Then, via careful reading the abstracts, 51 researches that focused on the association between the expression of PTEN and survival were included in our full-text review process. After reading the full-text researches, 24 papers had to be excluded because data were not extractable or could not provide enough information about survival. Finally 27 studies including 3810 cases were available for our meta-analysis. All the included studies were in English. The individual characteristic of the eligible researches are summarized in Table 1. 11 studies included patients from Asia, nine from America, two from United Kingdom, two from Germany, one from Portland, one from Australia and one from Australia respectively. Among all the included studies, three papers about breast cancer, six papers about colorectal cancer, three papers about gastric carcinoma, four papers about prostate cancer, two papers about lung cancer and nine papers about other cancer types. Expressions of PTEN were detected via IHC, Taqman, TMA or RT-PCR. 23 articles evaluated the relationship between PTEN expression and OS, 10 articles evaluated the relationship between PTEN expression and other survival analysis that including DFS, PFS, MFS.

The pooled HR corresponding to the 95%CI was used to assess the prognostic value of PTEN in patients. Statistical heterogeneity was tested by Cochrane’s Q test (Chi-squared test; Chi2) and inconsistency (I2) (Lau et al., 1997; Higgins et al., 2002). If there was no obvious heterogeneity, the fixed-effects model ( Mantel-Haenszel method) was used to estimate the pooled HR; otherwise, the random-effects model (DerSimonian and Laird method) was used. Funnel plot and Begg’s rank correlation method were designed for assessing risk of publication bias. STATA 12.0 ( STATA Corp., College, TX) was used to perform statistical analysis. A P-value less than 0.05 was consider to be statistically significant.

Figure 1. Flow Chart Summarizing the Literature Search and Study Selection
Table 1. Main Characteristics and Results of Eligible Studies

| First Author       | Year     | Ethnicity | Cancer type       | Cases | P/N | Method      | Median Follow-up Time | Neoadjuvant Therapy | Histological Type     | Lymph Node Metastasis (Yes/No) | Diff (Well and moderate/poor) |
|--------------------|----------|-----------|-------------------|-------|-----|-------------|-----------------------|---------------------|-----------------------|-------------------------------|-------------------------------|
| Femaleschi         | 2015     | British   | Prostate cancer   | 144   | 87/57| IHC, score>0| 55M                   | Yes                 | NA                    | NA                            | NA                            |
| Kessler            | 2015     | German    | Glioblastoma      | 79    | 37/42| IHC, >1% cell| 15M                   | Yes                 | NA                    | NA                            | NA                            |
| Martins            | 2014     | British   | Ovarian cancer    | 228   | 117/111| IHC         | 200M                  | NA                   | High-grade serous       | NA                            | NA                            |
| Barnett            | 2014     | Portland  | Prostate cancer   | 48    | 31/17| IHC         | 109M                  | NA                   | 9/39                  | NA                            | NA                            |
| Wu                 | 2013     | American  | Breast cancer     | 65    | 35/30| IHC, >5% cell| 60M                   | NA                   | IDC/ILC (SCC)           | NA                            | NA                            |
| Atienza            | 2013     | American  | Colorectal cancer | 30    | 43/7 | IHC, >90% cell| 24M                   | Yes                 | NA                    | NA                            | NA                            |
| Yin Li             | 2013     | Chinese   | Gastric carcinoma| 114   | 47/87| IHC, score>4| 60M                   | Yes                 | NA                    | 74/40                        | 67/47                         |
| Hong Yan Zhang     | 2013     | Chinese   | Breast cancer     | 146   | 84/82| IHC, >0% cell| 103M                  | NA                   | 99/47                 | NA                            | NA                            |
| Timothy J. Price   | 2013     | Australian| Colorectal cancer | 302   | 185/117| Taqman     | 30.6M                 | Yes                 | NA                    | NA                            | NA                            |
| Limin Song         | 2013     | Chinese   | Colorectal cancer | 404   | 365/39| IHC, qRT-PCR| NA                   | 60M                  | NA                    | NA                            | NA                            |
| Fu-ning Xing       | 2013     | Chinese   | Prostate cancer   | 112   | 36/66| IHC         | 100M                  | NO                   | NA                    | 28/84                         | NA                            |
| Xinhua Zhu         | 2013     | Chinese   | Gastric carcinoma| 159   | 61/98| TMA, IHC>0 | 36M                   | NO                   | NA                    | 123/36                       | NA                            |
| S Boeck            | 2013     | German    | Pancreatic cancer | 171   | 141/30| IHC, score>4| 30M                   | NA                   | NA                    | NA                            | NA                            |
| Nilda D. Gonzalez-Rubio | 2013 | American | Urothelial cancer | 19    | 14/5 | IHC, H score | 242D                 | NA                   | NA                    | 2/4                           | NA                            |
| Yu-Mei Liang       | 2012     | Chinese   | Breast cancer     | 104   | 61/45| TMA, %>10% cell| 33M                   | NA                   | NA                    | 15/89                         | NA                            |
| Arjan Sood         | 2012     | American  | Colorectal cancer | 76    | 32/44| IHC, >50% cell| 62.5M                 | Yes                 | NA                    | NA                            | NA                            |
| Nokitaka Setou     | 2012     | Japanese  | Soft tissue       | 111   | 89/22| IHC         | 150M                  | Yes                  | NA                    | NA                            | NA                            |
| Akihiko Yoshizawa  | 2010     | American  | Non-small cell lung cancer | 267 | 250/17| IHC, >TS2 | 60M                   | NO                   | 137/128 (ADC/SCC)       | NA                            | NA                            |
| Jeon-Yong Chang    | 2009     | Korean    | Extrathoracic     | 134   | 117/17| TMA         | 60M                   | NA                   | 74/147               | NA                            | NA                            |
| Hirozumi Sawai     | 2008     | Japanese  | Colorectal cancer | 69    | 52/17| IHC, Group W| 60M                   | Yes                  | NA                    | 67/2                          | NA                            |
| Evangelia Ruirz    | 2008     | Greek     | Colorectal cancer | 72    | 62/10| IHC, >10% cell| 53M                   | Yes                 | NA                    | NA                            | NA                            |
| Hallidour K.       | 2008     | American  | Gliomas           | 85    | 56/29| IHC, score>2 | 48M                   | NO                   | 63/22 (LG/HGG)          | NA                            | NA                            |
| Robie Bedolla      | 2007     | American  | Prostate cancer   | 65    | 51/14| IHC, score>0| NA                   | Yes                  | NA                    | NA                            | NA                            |
| Allan J. Pantuck    | 2007     | American  | Renal cell carcinoma | 375  | 360/15| IHC, score>3| 56.9M                 | NA                   | 323/40 (clear cell/papillary/other) | 52/232                       | NA v                          |
| Huachuan Zheng     | 2007     | Japanese  | Lung carcinoma    | 155   | 82/73| IHC         | 20.6M                 | NA                   | 37/36 (14/18 SCC/ADC/LCC/SQ) | 53/102                       | NA                            |
| Tsing-Hui Hu       | 2007     | Chinese   | Breast cancer     | 105   | 43/82| IHC, score>0| 147M                 | NA                   | NA                    | 78/27                         | NA                            |
| Peter L. Depowski  | 2001     | American  | Breast cancer     | 151   | 93/58| IHC         | 59M                   | NA                   | 104/47 (ductal/lobular)   | 74/63                         | 25/75                         |

*P/N, positive expression/negative expression; IHC, immunohistochemistry; TMA, tissue microassay; qRT-PCR, quantitative reverse transcription; IDC, Infiltrating ductal; ILC, Lobular carcinoma; DCIS, Ductal lobular carcinoma situ; LGG, Low-grade gliomas; HGG, High-grade gliomas; SCC, Small cell carcinoma; ADC, Adenocarcinoma; LCC, Large cell carcinoma; SQ, Squamous cell carcinoma; M, month; NA, no available or no applicable.
and RFS. According to univariate analysis in OS, 10 studies provided the HR with 95%CI directly, 12 studies showed survival curves that available to calculate the HR. Additionally, nine studies provided the HR with 95%CI directly, the other 14 papers had no data available by multivariate analysis (Table 2).

Meta-analysis
First of all, we evaluated whether PTEN expression levels were associated with the OS in patients with cancer.

Of the 23 trials evaluable for systematic review, 14 articles could not be included in meta-analysis by multivariate analysis due to insufficient data to estimate the HR and 95%CI.

A total of 22 studies, including 3212 patients, reported the effect of PTEN on OS using analyses unadjusted for other factors (Depowski et al., 2001; Hu et al., 2003; Zheng et al., 2007; Pantuck et al., 2007; Bedolla et al., 2007; Sawai et al., 2008; Thorarinsdottir et al., 2008; Razis et al., 2008; Sawai et al., 2008; Chung et al., 2009; Yoshizawa et al., 2010; Sood et al., 2012; Liang et al., 2012; Gonzalez-Robon et al., 2013; Boeck et al., 2013; Zhu et al., 2013; Jiang et al., 2013; Song et al., 2013; Price et al., 2013; Li et al., 2013; Atreya et al., 2013; Ferraldeschi et al., 2015; Kessler et al., 2015). As shown in Figure 2A, negative expression of PTEN was significantly correlated with worse OS according to univariate analysis, with a combined HR of 1.64 (95%CI: 1.32-2.05). The random-effects model (the DerSimonian and Laird method) was used because of significant heterogeneity was observed among these researches (p=0.000, I²=75.3%). Nine studies, demonstrated the effect of PTEN on OS using analyses adjusted for other factors, including 1581 patients (Hu et al., 2003; Pantuck et al., 2007; Liang et al., 2012; Zhu et al., 2013; Price et al., 2013; Li et al., 2013; Atreya et al., 2013; Ferraldeschi et al., 2015; Martins et al., 2014). As shown in Figure 2B, statistically significant was observed between the expression of PTEN levels and OS, with a combined HR of 1.56 (95%CI: 1.20-2.03). The random-effects model (the DerSimonian and Laird method) was used because of significant heterogeneity was observed among these researches (p=0.008, I²=61.4%). Furthermore, eight papers reported the effect of PTEN

Figure 2. A) Forest Plot Showing the Combined relative HR from the Random-Effects Model for Overall Survival By Univariate Analysis. (B) Forest plot showing the combined relative HR from the random-effects model for overall survival by multivariate analysis. (C) Forest plot showing the combined relative HR from the random-effects model for overall survival by other survival analysis

Figure 3. Funnel Blot was Designed to Visualize a Potential Publication Bias. A, univariate analysis; B, multivariate analysis
Loss of Expression of PTEN is Associated with Worse Prognosis in Patients with Cancer

Table 2. Relationship between PTEN Expression and Survival

| First Author | Ethnicity      | Overall Survival | Other Survival Analysis |
|--------------|----------------|------------------|-------------------------|
|              | Univariate     | Multivariate     | Univariate             | Multivariate           |
| Ferralde-schi| British HR 95% CI | 1.75 1.19-2.25  | HR 95% CI 1.6 1.02-2.04 | NA NA NA NA            |
|              | HR 95% CI      | NA NA NA NA     | NA NA                   | NA NA NA NA            |
| Kessler      | German HR 95% CI | 2.17 1.49-7.69  | NA NA NA NA (RFS)HR 95% CI | 2.63 2.17-11.11 NA NA |
| Martins      | British NA NA NA | 1.8 1.2-2.6     | NA NA NA NA             | NA NA NA NA            |
| Barnett      | Portland NA NA NA | NA NA NA NA | NA NA HR 95% CI 2.47 1.18-5.21 NA NA |
| Wu           | African American | NA NA NA NA | NA NA (DFS)Surv. Curve 2.17 1.08-4.38 NA NA |
|              | Hispanic/Latin NA NA NA | NA NA NA | NA NA Sur. Curve 0.91 0.40-2.07 NA NA |
| Atreya       | American HR 95% CI | 6.25 1.98-15.42 | HR 95% CI 6.3 2.03-17.93 | NA NA NA NA          |
| Li           | Chinese Sur. Curve 1.28 1.00-2.19 | HR 95% CI 0.773-10.610 | NA NA NA NA | NA NA NA NA |
| Zhang        | Chinese NA NA NA | NA NA NA NA | NA NA (RFS)Sur. Curve 2.3 1.52-3.47 0.786 0.595 1.037 |
| Price        | Australia Sur. Curve 0.95 0.70-1.29 | HR 95% CI 1.04 0.79-1.38 | NA NA (PFS) Sur. Curve 0.92 0.73-1.17 0.9 0.7-1.16 |
| Song         | Chinese Sur. Curve 1.05 0.72-1.55 | NA NA NA | NA NA (MFS) Sur. Curve 0.74 0.41-1.33 NA NA |
| Jiang        | Chinese Sur. Curve 0.5 0.22-1.14 | NA NA NA | NA NA (RFS) HR 95% CI 2.5 1.15-5.26 1.32 0.40-4.29 |
| Zhu          | Chinese HR 95% CI | 0.522-1.310 | HR 95% CI 0.626-1.435 | NA NA NA NA |
| Boeck        | German HR 95% CI | 0.77 0.51-1.17 | NA NA NA NA | NA NA NA NA |
| Gonzalez-Roibon | American Sur. Curve 1.46 1.13-16.10 | NA NA NA NA | NA NA NA NA |
| Liang        | Chinese HR 95% CI | 4.35 1.35-14.29 | HR 95% CI 2.86 0.83-10 | NA NA NA NA |
| Sood         | USA Sur. Curve 2.71 1.91-3.86 | NA NA NA | NA NA (PFS) HR 95% CI 1.53 1.06-2.22 NA NA |
| Setsu        | Japanese NA NA NA | NA NA NA NA | (DFS)Sur. Curve 2.77 1.58-4.85 NA NA |
| Yoshizawa    | USA HR 95% CI | 1.11 0.63-2.20 | NA NA NA NA | NA NA NA NA |
| Chung        | Korean Sur. Curve 2.43 1.62-3.63 | NA NA NA NA | NA NA NA NA |
| Sawai        | Japanese Sur. Curve 2.10-7.51 | NA NA NA NA | NA NA NA NA |
| Razis        | Greek Sur. Curve 1.44-4.78 | NA NA NA | NA NA NA NA |
| Thorarinsdottir | USA Sur. Curve 1.47-19.75 | NA NA NA | (PFS) Sur. Curve 1.62 0.58-4.56 NA NA |
| Bedolla      | USA HR 95% CI | 0.72-1.79 | NA NA NA NA | NA NA NA NA |
| Pantuck      | American Sur. Curve 1.19-3.80 | HR 1.49 1.05-2.13 | NA NA NA NA |
| Zheng        | Japanese Sur. Curve 1.23-2.70 | NA NA NA NA | NA NA NA NA |
| Hu           | Chinese HR 95% CI | 1.37-3.78 | HR 1.85 1.10-3.09 | NA NA NA NA |
| Depowskii    | American HR 95% CI | 1.08-2.67 | NA NA NA NA | NA NA NA NA |

*HR, hazard ratio; CI, confidence interval; sur., survival; DFS, disease-free-survival; PFS, progression-free-survival; MFS, metastasis-free-survival; RFS, relapse-free-survival; NA, no available or no applicable
on other survival analysis using analyses unadjusted for other factors including four RFSs, three PFSs, two DFSs and one MFS (Barnett et al., 2014). As shown in Figure 2C, the results showed that loss of PTEN expression was significant correlated with poor prognostic, with a combined HR of 1.74 (95%CI: 1.24-2.44). The random-effects model (the DerSimonian and Laird method) was used because of significant heterogeneity was observed among these researches (p=0.000, I²=75.3%).

Next, we performed subgroup analyses to investigate if there were differences in results with respect to the year of publication, ethnicity, cancer type, method, cut-off value, median follow-up time and neoadjuvant therapy in which the study was conducted. Despite the limited number of studies that were eligible for this meta-analysis, in the stratified analysis by ethnicity, increased risks were found for American (HR: 1.92, 95%CI: 1.35-2.74, p=0.0013) and Japanese (HR: 2.58, 95%CI: 1.21-5.51, p=0.041). Moreover, subgroup analyses regarding the cancer type and method of the study revealed that articles about colorectal cancer and IHC method showed a worse prognostic value for survival in patients with cancer (HR: 2.18, 95%CI: 1.25-3.78, p=0.000; HR: 1.75, 95%CI: 1.38-2.23, p=0.000 respectively). Additionally, subgroup analysis by median follow-up time of 60 months and neoadjuvant therapy with yes also showed loss of PTEN expression with poor prognostic (HR: 1.67, 95%CI: 1.06-2.63, p=0.001; HR: 1.95, 95%CI: 1.37-2.78, p=0.000). However, we couldn’t get the statistically significant results from the other factors (Supporting Information Figure 1-5). Because inadequate of researches, the stratified analysis on other survival analysis showed a trend that negative expression of PTEN with worse prognostic by DFS (HR: 2.52, 95%CI: 1.63-3.90, p=0.594) and RFS (HR: 2.40, 95%CI: 1.77-3.90, p=0.991). Thus, more studies should be conducted in the future.

Publication bias statistics were determined using the method of Begg’s test. No publication biases were found in the 22 OS studies used for univariate analysis and nine OS studies used for multivariate analysis (p >0.05) (Figure 3). Sensitivity analysis was performed to investigate the effect of every study on the overall meta-analysis by omitting one study each time, and the omission of any study made no significant difference, demonstrating that our results were statistically reliable.

However, we didn’t investigated the relation of PTEN expression with clinicopathological variables because of insufficient clinicopathological information.

Discussion

There is a trend towards individualized treatment in tumor therapy. As we all known, immortalization and invasiveness are important characteristics for cancer tissues, and postoperative recurrence and metastasis are the principal causes for treatment failure and death in patients with cancers. Therefore, identifying the specific molecular markers to distinguish the high risk of disease recurrence and mortality in cancer patients is critical to monitor patients and select appropriate adjunctive therapies in clinical practice. However, several biological effectors related to cell growth, differentiation and adhesions have been studied in individuals who develop cancers. In previous studies, various kinds of genetic alterations have been identified as prognostic factors such as EGFR gene in NSCLC and HER-2 in breast carcinoma (Qiu et al., 2013). But, most other clinically useful molecular markers which have predictive value of the therapeutic response and prognostic value failed to demonstrate usefulness in subsequent investigations.

PTEN, a tumor suppressor has been firmly established. It is mapped to chromosome 10q23.3 (Song et al., 2012). The role of PTEN is to antagonizes the phosphoinositid-3-kinase (PI3K)/PTEN/AKT signaling pathway and suppresses cell survival and proliferation, thereby safeguard important cellular machineries against carcinogenesis (Wang et al., 2008; Sun et al., 2014). In addition, PTEN regulates a variety of biological processes including cell proliferation, growth, migration and death (Wang et al., 2008). Based on these reasons, we undertook a meta-analysis to determine whether PTEN can serve as a prognostic marker for patients with cancers.

Our meta-analysis focuses on the relationship between PTEN expression and survival of patients with cancer. This meta-analysis with accumulated data suggested that negative or loss of E-cadherin expression was associated with shorter survival time and predicted worse prognosis in patients with cancer. The pooled HR for OS was 1.64 (95%CI: 1.32-2.05) by univariate analysis and 1.56 (95%CI: 1.20-2.03) by multivariate analysis. Furthermore, small number of studies investigated the association between PTEN expression and other survival analyses including DFS, PFS, MFS and RFS, and also found that loss of PTEN expression was significant correlated with poor prognostic, with a combined HR of 1.74 (95%CI: 1.24-2.44). Interesting, after we did the stratified analysis, we found that increased risks were found for American (HR: 1.92, 95%CI: 1.35-2.74, p=0.0013) and Japanese (HR: 2.58, 95%CI: 1.21-5.51, p=0.041). Moreover, subgroup analyses regarding the colorectal cancer showed a worse prognostic value for survival in patients with cancer (HR: 2.18, 95%CI: 1.25-3.78, p=0.000).

Our meta-analysis is based on published data and was performed using univariate analysis followed by further multivariate analysis, which is the first time to evaluate the effect of PTEN on survival in different kinds of cancers. However, some limitations exist in our study. We did not include unpublished papers and abstracts into meta-analysis because the required data was available only in full publications. Additionally, the risks calculated in our meta-analysis may be an overestimate due to publication and reporting bias. Positive results tend to be accepted by journals, whereas negative results often are rejected or even not be submitted. Another potential source of bias is related to the method used to extrapolate the HR. HR was extracted from the data included in the article directly or calculated from the survival curves. Actually, the method of extrapolating HR from survival curves seems to be less reliable because this strategy did not completely eliminate inaccuracy in the extracted survival rates. Furthermore, we included studies with detection method by using IHC. As we known, prognostic markers based
on IHC can provide inconsistent or contradictory results, owing to the use of different antibodies and processing methods, as well as different scoring and categorization systems (Kase et al., 2000). It would be desirable to have IHC findings reported carefully and in detail. Moreover, we also think that different therapy strategies on patients after surgery in these studies have different impact on OS, thus this factor should be taken into consideration. Unfortunately, none of these studies has described the details of therapy strategy after the patients have diagnosed the cancer. Therefore, more meticulous research should be conducted. Nevertheless, no publication bias was detected using Begg's test (p>0.05), indicating that the statistics obtained approximate the actual results. Sensitivity analysis was also conducted to investigate the influence of a single study on the overall meta-analysis by omitting one study at a time, and the omission of any study made no significant difference, suggesting that our results were statistically reliable.

In summary, loss of E-cadherin expression was associated with worse OS in patients with cancers. Undoubtedly, these results should be confirmed by more prospective and randomized clinical studies, however, we provide new insights that support PTEN as a potential prognostic biomarker and biological target for anticancer therapies.

Acknowledgements

This work was supported by grants from the Nature Science Foundation of China (30771227, 81241068), Technology Support Program of Science and Technology Department of Sichuan Province (2011SZ0194) and Project 863 (2014AA022202). No conflict of interest exits in the submission of this manuscript.

References

Jemal A, Bray F, Center MM, et al (2011). Global cancer statistics. CA Cancer J Clin, 61, 69-90.
Al-Saad S, Al-Shibli K, Donnem T, et al (2008). The prognostic impact of NF-kappaB p105, vimentin, E-cadherin and Par6 expression in epithelial and stromal compartment in non-small-cell lung cancer. Br J Cancer, 99, 1476-83.
Sawai H, Yasuda A, Ochi N, et al (2008). Loss of PTEN expression is associated with colorectal cancer liver metastasis and poor patient survival. BMC Gastroenterol, 8, 56.
Ortega-Molina A, Serrano M (2013). PTEN in cancer, metabolism, and aging. Trends Endocrinol Metab, 24, 184-9.
Loupakis F, Pollina L, Stasi I, et al (2009). PTEN expression and KRAS mutations on primary tumors and metastases in the prediction of benefit from cetuximab plus irinotecan for patients with metastatic colorectal cancer. J Clin Oncol 27, 2622-9.
Yin Y, Shen WH (2008). PTEN: a new guardian of the genome. Oncogene, 27, 5443-53.
Parmar MK, Torri V, Stewart L (1998). Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med, 17, 2815-34.
Lau J, Ioannidis JP, Schmid CH (1997). Quantitative synthesis in systematic reviews. Ann Intern Med, 127, 820-6.
Higgins JP, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. Stat Med, 21, 1539-58.
Depowski PL, Rosenthal SI, Ross JS (2001). Loss of expression of the PTEN gene protein product is associated with poor outcome in breast cancer. Mod Pathol, 14, 672-6.
Hu TH, Huang CC, Lin PR, et al (2003). Expression and prognostic role of tumor suppressor gene PTEN/MMAC1/TEPI in hepatocellular carcinoma. Cancer, 97, 1929-40.
Zheng H, Tsuneyama K, Takahashi H, et al (2007). Expression of PTEN and FHIT is involved in regulating the balance between apoptosis and proliferation in lung carcinomas. Anticancer Res, 27, 575-81.
Pantuck AJ, Seligson DB, Klatte T, et al (2007). Prognostic relevance of the mTOR pathway in renal cell carcinoma: implications for molecular patient selection for targeted therapy. Cancer, 109, 2257-67.
Bedolla R, Prihoda TJ, Kreisberg JI, et al (2007). Determining risk of biochemical recurrence in prostate cancer by immunohistochemical detection of PTEN expression and Akt activation. Clin Cancer Res, 13, 3860-7.
Thorarinsdottir HK, Santi M, McCarter R, et al (2008). Protein expression of platelet-derived growth factor receptor correlates with malignant histology and PTEN with survival in childhood gliomas. Clin Cancer Res, 14, 3386-94.
Razis E, Briasoulis E, Vrettou E, et al (2008) Potential value of PTEN in predicting cetuximab response in colorectal cancer: an exploratory study. BMC Cancer, 8, 234.
Chung JY, Hong SM, Choi BY, et al (2009) The expression of phospho-AKT, phospho-mTOR, and PTEN in extrathoracic cholangiocarcinoma. Clin Cancer Res, 15, 660-7.
Yoshizawa A, Fukuoka J, Shimizu S, et al (2010). Overexpression of phospho-eIF4E is associated with survival through AKT pathway in non-small cell lung cancer. Clin Cancer Res, 16, 240-248.
Sood A, McClain D, Maitra R, et al (2012). PTEN gene expression and mutations in the PIK3CA gene as predictors of clinical benefit to anti-epidermal growth factor receptor antibody therapy in patients with KRAS wild-type metastatic colorectal cancer. Clin Colorectal Cancer, 11, 143-50.
Liang YM, Li XH, Li WM, et al (2012) Prognostic significance of PTEN, Ki-67 and CD44s expression patterns in gastrointestinal stromal tumors. World J Gastroenterol, 18, 1664-71.
Gonzalez-Roibon ND, Chaux A, Al-Hussain T, et al (2013). Disregulation of mammalian target of rapamycin pathway in plasmacytoid variant of urothelial carcinoma of the urinary bladder. Hum Pathol, 44, 612-622.
Boeck S, Jung A, Laubender RP, et al (2013). EGFR pathway biomarkers in erlotinib-treated patients with advanced pancreatic cancer: translational results from the randomised, crossover phase 3 trial AIO-PK0104. Br J Cancer, 108, 469-76.
Zhu X, Qin X, Fei M, et al (2013). Loss and reduced expression of PTEN correlate with advanced-stage gastric carcinoma. Exp Ther Med, 5, 57-64.
Jiang FN, He HC, Zhang YQ, et al (2013) An integrative proteomics and interaction network-based classifier for prostate cancer diagnosis. PLoS One, 8, 63941.
Song M, Chen D, Lu B, et al (2013) PTEN loss increases PD-L1 protein expression and affects the correlation between PD-L1 expression and clinical parameters in colorectal cancer. PLoS One, 8, 65821.
Price TJ, Hardingham JE, Lee CK, et al (2013). Prognostic impact and the relevance of PTEN copy number alterations in patients with advanced colorectal cancer (CRC) receiving bevacizumab. Cancer Med, 2, 277-85.
Li Y, Cui J, Zhang CH, Yang DJ, et al (2013) High-expression of DJ-1 and loss of PTEN associated with tumor metastasis.
and correlated with poor prognosis of gastric carcinoma. *Int J Med Sci*, 10, 1689-97.

Atreya CE, Sangale Z, Xu N, et al (2013) PTEN expression is consistent in colorectal cancer primaries and metastases and associates with patient survival. *Cancer Med* 2, 496-506.

Ferraldeschi R, Nava Rodrigues D, Riisma R, et al (2015) PTEN protein loss and clinical outcome from castration-resistant prostate cancer treated with abiraterone acetate. *Eur Urol*, 67, 795-802.

Kessler T, Sahm F, Blaes J, et al (2015) Glioma cell VEGFR-2 confers resistance to chemotherapeutic and antiangiogenic treatments in PTEN-deficient glioblastoma. *Oncotarget*.

Martins FC, Santiago I, Trinh A, et al (2014) Combined image and genomic analysis of high-grade serous ovarian cancer reveals PTEN loss as a common driver event and prognostic classifier. *Genome Biol*, 15, 526.

Qiu ZX, Zhang K, Qiu XS, et al (2013) The prognostic value of phosphorylated AKT expression in non-small cell lung cancer: a meta-analysis. *PLoS One*, 8, e81451.

Song MS, Salmena L, Pandolfo PP (2012) The functions and regulation of the PTEN tumour suppressor. *Nat Rev Mol Cell Biol*, 13, 283-96.

Wang X, Jiang X (2008) PTEN: a default gate-keeping tumor suppressor with a versatile tail. *Cell Res*, 18, 807-16.

Sun L, Liu J, Yuan Q, et al (2014) Association between PTEN Gene IVS4 polymorphism and risk of cancer: a meta-analysis. *PLoS One*, 9, e98851.

Kase S, Sugio K, Yamazaki K, et al (2000) Expression of E-cadherin and beta-catenin in human non-small cell lung cancer and the clinical significance. *Clin Cancer Res*, 6, 4789-96.

Barnett CM, Heinrich MC, Lim J, et al (2014) Genetic profiling to determine risk of relapse-free survival in high-risk localized prostate cancer. *Clin Cancer Res*, 20, 1306-1312.