# Visceral Pleural Invasion Remains a Size-Independent Prognostic Factor in Stage I Non-Small Cell Lung Cancer

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*Background.* **The prognostic effect of visceral pleural invasion remains controversial when a tumor is less than 3 cm in stage I non-small cell lung cancer patients. We conducted this meta-analysis to evaluate the prognostic impact of visceral pleural invasion in these early patients.**

*Methods.* **We searched PubMed, EMBASE, Cochrane Library, and China National Knowledge Infrastructure and included published studies on the prognostic significance of visceral pleural invasion in stage I non-small cell lung cancer. Meta-analysis was performed and heterogeneity and publication bias were also evaluated.**

*Results.* **Twenty-two studies were included in the meta-analysis. In all stage I patients, visceral pleural invasion was associated with death (hazard ratio1.427; $p = 0.000$) and recurrence (hazard ratio1.600; $p = 0.000$). In subgroup analyses, visceral pleural invasions were consistently associated with death in each tumor size subgroup and recurrence in tumor less than 3 cm subgroup. Publication bias was not found.**

*Conclusions.* **Visceral pleural invasion is a size-independent poor prognostic factor in stage I non-small cell lung cancer patients. We suggest adjuvant treatment should be considered in stage I patients with visceral pleural invasion.**

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Visceral pleural invasion (VPI) in non-small cell lung cancer (NSCLC) has been known to be an adverse prognostic factor and increases the T classification from T1 to T2 [1, 2]. Since the 1970s, VPI has been adopted as a T descriptor in the TNM classification of the International Union Against Cancer (UICC) staging system and remained unchanged until today [3].

However, in the 7th edition of the TNM staging system of lung cancer [1], VPI was not included into the analysis of the cohort with the tumor size because of insufficient data and inconsistent pathologic methods. Some recent studies suggested that VPI was not a poor prognostic factor when a tumor is less than 3 cm in size; especially tumors less than 2 cm in stage I NSCLC patients [4–10]. The studies with negative results suggested the tumors less than 3 cm, especially 2 cm, with VPI should not be upstaged to T2a. These results were contrary to those of former studies which demonstrated significant adverse impact of VPI on survival and recurrence [11–21]. The prognostic effect of VPI in early patients remains controversial. We therefore conducted this meta-analysis to answer the question whether VPI represents an adverse prognostic factor for stage I NSCLC and which patients should be considered to receive aggressive adjuvant treatment.

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## Material and Methods

### *Eligibility Criteria*

This meta-analysis was performed according to the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] statement [22]. The study participants had been pathologically diagnosed stage I NSCLC after resection according to the 7th edition of the TNM staging system for lung cancer [2]. The eligible cohort studies would compare either overall survival (OS) or recurrence free survival (RFS) between resected stage I NSCLC patients with or without VPI. Patients who received neoadjuvant chemotherapy or radiotherapy were excluded.

### *Search Strategy*

An electronic search in PubMed, EMBASE, The Cochrane Library, and China National Knowledge Infrastructure (CNKI) were performed from 1966 to August 10, 2014. The following key words in combination as medical subject heading terms and text words were used: "visceral pleural" and "lung cancer." Potentially relevant articles were identified by reading titles and abstracts. The full texts of the relevant articles were read to determine whether they met the inclusion criteria. We also searched the references to identify relevant studies.

### *Quality Assessment*

For cohort studies, the 9-star Newcastle-Ottawa Quality Assessment Scale was used to assess the risk of bias [23].



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**Abbreviations and Acronyms**

CI = confidence interval
CNKI = China National Knowledge Infrastructure
HR = hazard ratio
NSCLC = non-small cell lung cancer
OS = overall survival
PL = pleural invasion
RFS = recurrence free survival
UICC = International Union Against Cancer
VPI = visceral pleural invasion

This scale is an 8-item instrument that allows for assessment of patient population and selection, study comparability, follow-up, and outcome of interest. Interpretation of the scale is performed by awarding points or stars for high-quality elements. Studies with 5 or more stars were defined as high-quality studies and were included.

### *Statistical Analyses*

Data were extracted using a unified form. Study information including author name, study year, study area, sample size, tumor size, pathologic type, staining method, adjuvant therapy, and hazard ratio (HR) of OS or RFS were collected. If the original HR was not reported, it was calculated from reported data or survival curves according to the methods described by Tierney and colleagues in 2007 [24]. Statistical heterogeneity between studies was examined using the Cochrane Q test by calculating the $I^2$ value [25]. An $I^2$ value greater than 50% or $p$ value less than 0.05 were considered to represent significant heterogeneity. The pooled HR and the 95% confidence interval (CI) were calculated using the Mantel-Haenszel formula (fixed-effect model) when heterogeneity was not detected ($p > 0.05$), or using the DerSimonian-Laird formula (random-effect model) when heterogeneity was significant ($p < 0.05$) [26]. When studies reported the outcomes by subgroups, the data for each subgroup were pooled as from individual study. In order to reduce the confounding effect, subgroup analysis was performed by different tumor size subgroups. Publication bias was evaluated using the funnel plot and the Begg test [27]. An influence analysis was conducted to describe how robust the pooled estimator was by removing individual studies. An individual study was suspected of excessive influence if the point estimate of its omitted analysis was outside the 95% CI of the combined analysis. Statistical analysis was performed with Comprehensive Meta Analysis professional version 2.2 (Biostat Inc, Englewood NJ, www.meta-analysis.com).

## Results

### *Study Selection*

Electronic search identified 416 potentially relevant references. An additional 8 references were further identified by checking the reference list. One hundred twenty-three duplicates and 257 clearly irrelevant references were excluded through reading the abstracts. Thirty-six references were read in full and 14 references were excluded for lack of data either on survival outcomes or on stage I patients. Finally, 22 references [4–12, 14–20, 28–33] fulfilled the inclusion criteria and provided data for the meta-analysis. Figure 1 shows the flowchart of the search results.

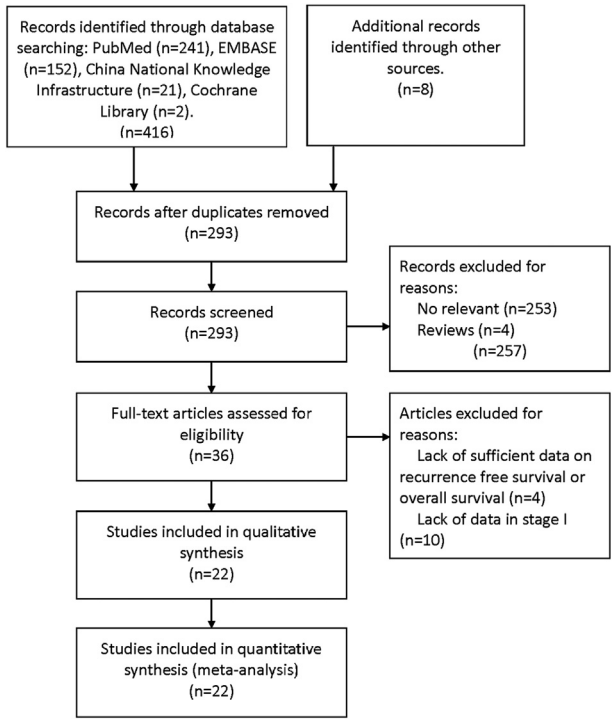


*Fig 1. Flow chart of study selection of meta-analysis.*

### *Characteristics of Included Studies*

All 22 included articles were cohort studies published from 1995 to 2014. This study, including 25,280 patients, contained 15 studies from Asia (Japan, Taiwan, and China), 5 studies from North America (United States, Canada) and 2 studies from Europe (Spain). Potential confounders, such as tumor size, age, gender, history of smoking, tumor differentiation, and type of operation were reported and adjusted in most of them. The quality score of included studies ranged from 5 to 8 stars. Characteristics of the included studies are listed in Table 1.

### *Effect of VPI on OS for All Stage I Patients*

Twenty-one HRs [4–12, 15, 19, 20, 28, 30, 33] were available from 15 included studies. Significant heterogeneity was found among studies ($I^2 = 64.9\%$, $p = 0.000$; Table 2). Random-effect model was used. The pooled HR estimate was 1.427 (95% CI, 1.221 to 1.669; $p = 0.000$; Fig 2), which means VPI is significantly associated with the risk of death in resected stage I NSCLC.