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Location of stage I–III non-small cell lung cancer and survival rate: Systematic review and meta-analysis

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Abstract

Background: The association between the location of non-small cell lung cancer (NSCLC) and prognosis is a debated issue. Some studies have provided evidence of better prognosis of upper lobe tumors than lower to middle lobe tumors, while other studies have reported contrasting conclusions. The aim of this study was to further assess this association through a systematic review and meta-analysis.

Methods: Medline, Embase, and the Cochrane Central Register of Controlled Trials were searched up to 27 January 2017. Patients pathologically diagnosed with stage I–III NSCLC with three or five-year survival data were included. The main meta-analysis compared differences in survival rates according to the primary tumor location using the Mantel–Haenszel method with a random effect model. Sensitivity analysis was conducted according to lymph node metastasis, tumor node metastasis stage, staging method, and treatment modality.

Results: Ten clinical studies and 35 570 patients were recruited. Patients with tumors in the upper lobes had a higher rate of five-year survival compared to those with tumors in non-upper lobes (odds ratio [OR] 1.31, 95% confidence interval [CI] 1.15–1.49). Similarly, the three-year survival rate was high in patients with tumors in the upper lobes (OR 1.99, 95% CI 1.02–3.86) and low in those with lower lobe tumors (OR 0.31, 95% CI 0.12–0.77).

Conclusions: Stage I–III NSCLC located in the upper lobes showed higher five-year survival rates compared to other tumor locations.

Introduction

The location of primary non-small cell lung cancer (NSCLC) is reported to be associated with clinical factors. Initial clinical symptoms or signs of NSCLC have been observed to differ according to the region of the primary lesion.[1] Factors such as a history of smoking, asbestos exposure, dietary habits, and gender have been associated with the anatomical location of lung cancer.[2–5] In addition, differences in the distribution of lymph node (LN) metastasis according to the primary lung cancer location have been reported.[6,7] A previous study showed that LN evaluations were more frequently conducted in the middle lobe.[8] The incidence of upstaging after surgery has been found to be higher for NSCLC in the lower lobe compared to other lobes, mainly because of higher rates of unsuspected nodal involvement.[9] Pathologic features have been elucidated according to the location of lung cancer. Higher proportions of adenocarcinoma, especially invasive adenocarcinoma, and *EGFR* positivity have been reported in patients with lung cancer in the upper lobe than in other regions.[10,11]

The different clinicopathological features among various locations of NSCLC have focused attention on the relationship between the tumor site and prognosis.[8,12–20] However, the conclusions of previous studies have been controversial because of the use of different settings for analysis, such as histology type, targeted tumor node metastasis (TNM) stage, treatment modality, differently divided lobes, and outcomes. Although recent studies have conducted comprehensive analysis to cover variously defined cancer locations, conflicting opinions remain.[8,21] The purpose of our systematic review and meta-analysis is to establish evidence of an association between the different locations of primary lesion and the survival rate of patients with NSCLC.

Methods

We designed the study protocol following the guidelines of Meta-analysis of Observational Studies in Epidemiology (MOOSE).[22] The MOOSE checklist for our study is presented in the Supplement data 1 in Appendix S1.

Eligibility criteria

We included comparative observational studies with patients who were pathologically diagnosed with stage I–III NSCLC. Eligible groups were "upper lobe," "lower lobe," "non-upper lobe," "non-lower lobe," "left lower lobe," "right middle lobe," and "other lobes." Each group was compared to all other lobes; for example, the right middle lobe group was compared to a group including all other lobe locations. Comparative analysis was conducted among the groups to determine their eligibility for the meta-analysis. Selected literature included three or five-year survival rates of NSCLC patients with follow-up intervals of > 3 years.

Studies reporting data of three or five-year survival rates only as a Kaplan–Meier curve were excluded, because we could not clearly elucidate the number of patients with a censored event or follow-up loss. In addition, studies presenting survival rates only in terms of odds ratio (OR) or hazard ratio after multivariate analysis were excluded from because of different and heterogeneous covariates among the studies.

Information sources and search strategy

Two investigators searched Medline, Embase, and the Cochrane Central Register of Controlled Trials data registries from their inception up to 27 January 2017. Additional reference scanning was conducted. For unpublished or forthcoming papers, we contacted each corresponding author to obtain all available data. In five cases, the authors were contacted to obtain three and five-year survival rates, but none replied. Abstracts and unpublished data were included in the study if data were available for meta-analysis. We used the advanced search function in the search engine of each data registry. The search strategy for the targeted literature was drafted using medical subject headings and general text words, using the following terms: "non-small cell lung cancer," "tumor location," "upper lobe," "middle lobe," and "lower lobe." The details of the search strategy are presented in the Supplement data 2 in Appendix S1. The search process was limited to the English language and human subjects. The results from the literature search were imported into reference management software (Endnote X7, Thomson Reuters, Philadelphia, PA, USA) and shared with the authors.

Study selection and data extraction process

Two authors individually screened the titles and abstracts and selected studies that were possibly eligible. Calibration exercises targeting 10% of the collected literature were conducted at each step in the screening process to refine the screening questions and ensure mutual agreement. All reports were stored, classified, and systematized using Endnote X7 software. Initially, two authors in consensus excluded duplicate reports or overlapped data. Two reviewers independently screened the eligible articles through the title and abstract. A total of 180 titles and abstracts were randomly selected for calibration exercises to establish the standard of screening. Studies chosen as acceptable by at least one reviewer were discussed and collated for full-text review. Full-text review and assessment were conducted to decide whether those studies met the eligibility criteria. Any discrepancy in opinions between authors was discussed as a group by referring to the original articles. The selection and coding of data were conducted according to widely accepted clinical principles. The selection process was conducted following the PRISMA 2009 flow diagram.[23]

Data collection and assessment of the risk of bias

Pilot-test standardized forms were developed for data extraction. We collected the baseline data for each study, including: first author, year of publication, data source, study design or setting, number of assessed patients, geographical location, eligibility criteria, treatment modality, type of study outcome, and the lobes compared. Demographic and clinical data of participants in each study were extracted, including age, gender, country or ethnicity, histology type, American Joint Committee on Cancer (AJCC) TNM stage, LN involvement, treatment modality, and three and five-year survival rates. AJCC TNM stage and World Health Organization (WHO) classifications of lung cancer pathology were thoroughly reviewed to reduce the diagnostic differences by period. The TNM stage of each trial was restaged according to the 7th edition of the AJCC guideline and used for sensitivity analysis. Estimates or predictions of three and five-year survival rates were excluded. The survival rate had to be clearly described in the published literature to enable data extraction.

The risk of bias in each study was evaluated by two individual authors on six dimensions according to the Risk of Bias Assessment tool for Non-randomized Studies (ROBANS): (i) selection of participants, (ii) confounding variables, (iii) measurement of exposure, (iv) blinding of outcome assessment, (v) incomplete outcome data, and

(vi) selective outcome reporting. Criteria for the risk of bias were divided into high, low, and unclear according to the ROBANS assessment method. An unclear risk of bias was defined as neither a high nor a low risk of bias. The method to assess the risk of bias was individually devised depending on the study design (e.g. before-and-after or non-randomized). Discrepancies over bias were discussed and resolved.

Primary and secondary outcomes

The primary and secondary outcomes were five and three-year survival rates among the comparable pulmonary lobes, respectively. In addition, sensitivity analyses were conducted according to LN metastasis, TNM stage, staging method, and treatment modality.

Statistical analysis

The present meta-analyses were estimated with ORs and 95% confidence intervals (CIs) using the Mantel–Haenszel (M–H) method and the random effect model for incorporating qualitative heterogeneity. Quantitative heterogeneities among the pooled data were evaluated using the chi-square test. We assessed publication bias with a funnel plot. The results of each statistical method are provided with appropriate tables and graphics. P values < 0.05 were considered statistically significant. Meta-analysis, chi-square tests for heterogeneity, and funnel plots were conducted using Review Manager, version 5.3 (The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark).

Results

Included studies and data quality

The search identified 1098 studies in Medline, 1049 in Embase, and 128 in the Cochrane Library (Fig 1); 473 duplicated reports were removed. Screening by title and abstract excluded 1777 studies. Twenty-five studies were selected for the full-text review. Finally, 10 retrospectively designed studies were included as relevant to assess our hypothesis.[8,12–20] Studies excluded from full-text review

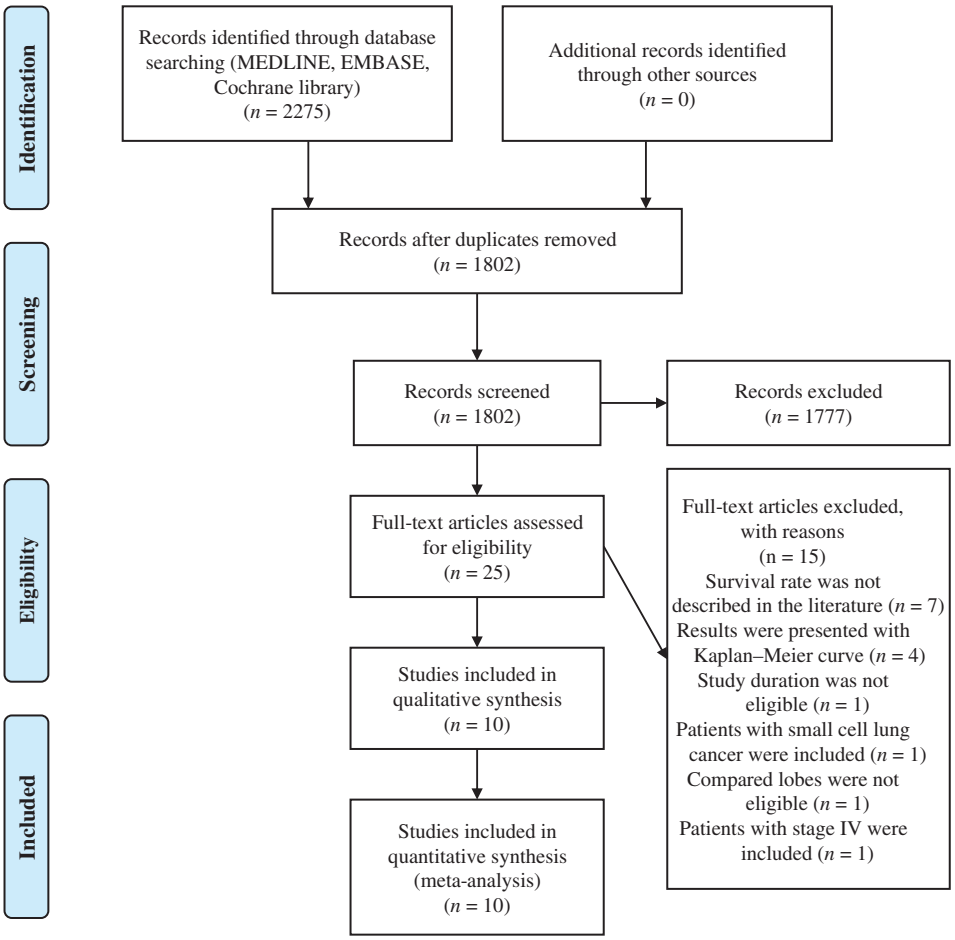

Figure 1 PRISMA flow chart of the meta-analysis.

and reasons for exclusion are described in the Supplement data 3 in Appendix S1. The risk of bias was generally high in the domains of participant selection, confounding variables, and selective outcome reporting (Supplement data 4 in Appendix S1). Data regarding five-year survival rates were available in 8 out of 10 studies,[8,12,14–19] while 3 studies were analyzed for the three-year survival rate.[13,15,20] Publication bias could not be excluded in the funnel plot for the studies including five-year survival rates (Supplement data 5 in Appendix S1).

Description of the included studies

The total number of patients in the 10 included clinical studies was 35 570 (Table 1). The included studies were published from 1996 to 2016. The median or mean age of the patients was > 60 years, and predominance in male patients was observed. The studies were conducted in Japan (6), the United States (3), and France (1). Five studies enrolled patients at stage III, three enrolled patients at stage I, and two included patients at various stages (I–III). Restaging was required for the purposes of analysis in 20 744 patients. Categories of histological diagnoses were variable but were within the range of NSCLC categories. The most frequently observed histologic types were adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Regarding treatment modality, seven studies applied curative surgery; two applied curative radiotherapy; and one study various curative therapies, such as surgery, radiotherapy, and chemotherapy. Five-year survival rate data were available in six studies for comparison between upper and non-upper lobes, three studies for comparison between lower and non-lower lobes, two studies for comparison between upper and lower lobes, two studies for comparison between left lower lobe and other lobes, and one study for comparison between right middle lobe and other lobes. Three-year survival rate data were available in two studies for comparison between lower and non-lower lobes, and in one study for comparison between upper and non-upper lobes (Supplement data 6 in Appendix S1). There appeared to be a time trend in the survival rates: higher survival rates were observed in more recent studies.

Comparison of five-year survival rates among pulmonary lobes

Eight studies were assessed to compare the five-year survival rate among pulmonary lobes. Patients with tumors in the upper lobes had better five-year survival than those with tumors in the non-upper lobes, with significant statistical heterogeneity (M–H random OR 1.31, 95% CI 1.15–1.49, I^2 = 63%) (Fig 2). The five-year survival rates in patients with lower lobe tumors were not significantly different, with significant statistical heterogeneity (M–H random OR 0.41, 95% CI 0.13–1.34, I^2 = 75%) (Fig 3). No significant result was found after direct comparison between upper and lower lobes, and no significant statistical heterogeneity (M–H random OR 1.65, 95% CI 0.49–5.48, I^2 = 46%) (Supplement data 7 in Appendix S1). There was no difference in the mortality rate in patients with left lower lobe tumors after five years of treatment, with significant statistical heterogeneity (M–H random OR 1.54; 95% CI 0.65–3.67, I^2 = 77%) (Supplement data 8 in Appendix S1). However, in sensitivity meta-analysis of the sample from a study by Kudo *et al.* there was a significantly lower survival rate in patients with positive LN metastasis in the left lower lobe compared to other lobes (data not shown).[18] There was no significant difference in the five-year survival rate between the right middle and other lobes (M–H random OR 1.12, 95% CI 0.96–1.31) (Supplement data 9 in Appendix S1).

Comparison of three-year survival rates among pulmonary lobes

Three studies were analyzed to compare three-year survival rates in the different lobes. Patients with upper lobe tumors achieved better survival compared to patients with non-upper lobe tumors (M–H random OR 1.99, 95% CI 1.02–3.86) (Fig 4). NSCLC in the lower lobe had a poor three-year survival rate compared to non-lower lobe tumors, without significant statistical heterogeneity (M–H random OR 0.31, 95% CI 0.12–0.77, I^2 = 10%) (Fig 5). Other types of comparison were not possible as data were not available.

Sensitivity analysis

Sensitivity analysis was conducted to define whether the effect of tumor location on the five-year survival rate differed according to LN involvement, TNM stage, or treatment modality. Studies including patients with or without LN metastasis showed significantly higher survival rates in upper lobe tumors than in non-upper lobe tumors (Supplement data 10 in Appendix S1). Patients with tumors in the lower lobes had poor five-year survival regardless of LN metastasis (Supplement data 11 in Appendix S1). High ORs of upper lobe tumors and low ORs of lower lobe tumors were observed in patients with LN involvement. The different editions of lung cancer staging used in the studies were unified to the AJCC 7th edition for sensitivity analysis according to TNM stage (Supplement data 12 in Appendix S1). Patients with NSCLC in the upper lobes exhibited consistently better survival compared to patients at TNM stage I/IIA or IIB/III (Supplement data 13 in Appendix S1).

Table 1 Study design and characteristics of the included non-small cell lung cancer patients

Study	Publication year	Number of patients	Age	Male (%)	Country	Inclusion criteria	AJCC edition	TNM stage (%)	Histology (%)	Treatment modality (%)	Comparison	Described outcome	Overall survival rate (%)
Hayakawa *et al*.[12]	1996	141	< 70: 74 ≥ 70: 67	84	Japan	Stage III with radiotherapy	4th	IIIA: 57 IIIB: 43	SqCC: 61, ADC: 14, LCC: 25	Definitive radiotherapy: 100	Upper vs. superior segment vs. lower vs. main or intermediate bronchus	2 and 5-year survival rates	2-year: 23, 5-year: 11
Bernard *et al*.[13]	2001	77	Mean: 60	88	France	T4 with pulmonary resection	5th	IIIA: 58 IIIB: 42	SqCC: 60, ADC: 19, LCC: 21	Lobectomy: 26, bilobectomy: 5, pneumonectomy: 69	Lower vs. non-lower	3-year survival rate	3-year: 21
Ichinose *et al*.[14]	2001	402	Mean: 63	71	Japan	Stage IIIA-N2 with complete resection (no neoadjuvant therapy)	5th	IIIA: 100	SqCC: 25, ADC: 67, Others: 8	Lobectomy: 80, bilobectomy: 8, pneumonectomy: 11	Right upper vs. right middle or lower vs. left upper vs. left lower	5-year survival rate	3-year: 42, 5-year: 31
Inoue *et al*.[15]	2004	154	Median: 62	64	Japan	Stage IIIA-N2 with complete resection	6th	IIIA: 100	SqCC: 27, ADC: 66, Others: 7	Partial resection: 2, lobectomy: 82, pneumonectomy: 16	Upper vs. non-upper	3 and 5-year survival rates	3-year: 45, 5-year: 28
Iwasaki *et al*.[16]	2005	268	Mean: 67	69	Japan	T2 with complete lobectomy and mediastinal lymphadenectomy	6th	T2N0: 65, T2N1: 10, T2N2: 25	SqCC: 37, ADC: 63	Lobectomy: 100	Left lower vs. others	5 and 7-year survival rates	5-year: 58, 7-year: 49
Ou *et al*.[17]	2007	19 702 (18838)†	< 70: 9862 ≥ 70: 9840	51	US	Stage I	6th	IA: 46 IB: 54	SqCC: 28 ADC: 42 LCC: 6 Others: 23	Wedge/ segmentectomy: 11, lobectomy: 67, pneumonectomy: 4, radiotherapy: 14, chemotherapy: 6	Upper vs. non-upper‡	5 and 10-year survival rates	5-year: 44, 10-year: 24
Kudo *et al*.[18]	2012	978 (210)§	Mean: 65	59	Japan	Stage IA-IIIA with complete resection	7th	IA: 43, IB: 29, IIA: 12, IIB: 5, IIIA: 11	SqCC: 19, ADC: 74, LCC: 5, Others: 2	Lobectomy/ bilobectomy: 98, pneumonectomy: 2	Left lower vs. others (subgroup: Right upper vs. right middle or lower vs. left upper vs. left lower¶	5-year survival rate	5-year: 74
Whitson *et al*.[8]	2012	13 650	Mean: 67	50	US	Stage I SqCC or ADC with lobectomy	7th	T1N0: 65, T2N0: 35	SqCC: 37, ADC: 63	Lobectomy: 100	Right upper vs. right middle vs. right lower vs. left upper vs. left lower	5-year survival rate	5-year: 62

Table 1 Continued

Study	Publication year	Number of patients	Age	Male (%)	Country	Inclusion criteria	AJCC edition	TNM stage (%)	Histology (%)	Treatment modality (%)	Comparison	Described outcome	Overall survival rate (%)
Shien *et al.*[19]	2015	76	Median: 60	70	Japan	Clinical stage III-N2/N3 with induction CRT followed by surgery	7th	IIIA: 58, IIIB: 42	SqCC: 39, ADC: 57, LCC: 3, Others: 1	Not pneumonectomy: 9, Pneumonectomy: 7	Lower vs. non-lower	5-year survival rate	5-year: 67
Shaverdien *et al.*[20]	2016	122	Median: 76	—	US	Stage I with SBRT	7th	IA: 77, IB: 23	SqCC: 15, ADC: 85	SBRT: 100	Lower vs. non-lower	3-year survival rate	3-year: 67

†A total of 19 702 patients were included in the study; however data of 864 patients with tumors in the bronchus, carina, hilum, and not otherwise specified (NOS) were excluded, thus 18 838 patients were evaluated in the meta-analysis. ‡Only data categorized into upper and non-upper lobes were available. §A total of 978 patients were included in the study; however survival data according to various lobes were only available for 210 patients with positive lymph nodes. ¶The left lower lobe was compared to other lobes in the analysis of total patients. In the analysis of patients with positive lymph nodes, the right upper, right middle to lower, left upper, and left lower lobes were compared to each other. SqCC, squamous cell carcinoma; ADC, adenocarcinoma; LCC, large cell carcinoma; CRT, chemoradiotherapy; SBRT, stereotactic body radiation therapy.

Subgroups of studies evaluated by either pathologic or clinical staging showed a positive association between upper lobe tumors and better prognosis (Supplement data 14 in Appendix S1). The survival rate was higher in patients with upper lobe tumors who underwent surgery, but there was no significant difference among the lobe locations in patients treated with radiotherapy (Supplement data 15 in Appendix S1). Overall, after restaging all patients using 7th edition AJCC TNM staging, upper lobe tumors had a higher rate of five-year survival than non-upper lobe tumors (Supplement data 16 in Appendix S1).

Discussion

The present study is the first systematic review and meta-analysis to reveal an association between lobar location and clinical prognosis. In meta-analysis of the five-year survival rate, better outcomes were observed in patients with upper lobe tumors, while no significant results were shown in patients with lower lobe tumors. However, considering the small proportion of middle lobe tumors, patients with lower lobe tumors are predicted to have poorer outcomes. The three-year survival rate was high in upper lobe tumors and low in lower lobe tumors. Analyses of associations between lung cancer location and three-year survival rates were uninformative, because the available data was inadequate. The differences observed in the five-year survival rates according to pulmonary lobes were not affected by nodal involvement, TNM stage, or staging method. In sensitivity analysis of treatment modality, the prognosis of upper lobe tumors was better in patients after surgical treatment, while in patients treated with radiotherapy, there was no difference in survival according to tumor location.

Several theories have been presented to explain why upper lobe tumors carry a better prognosis compared to lower or middle lobe tumors. The most frequently reported theory is the upstaging of the lower lobe tumors after surgery.[9] This theory involves the difficulties in deciding accurate T or N staging of lower lobe tumors.[24] Tumors in the lower lobes, especially those located near the chest wall, pleura, or airway, are more likely to be upstaged because of limitations in diagnostic modalities.[9] In addition, lower lobe tumors more easily spread to subcarinal, paraesophageal, or inferior pulmonary ligament LNs.[25] For these reasons, Puri *et al.* concluded that the poor prognosis associated with lower lobe tumors could be explained by the upstaging that occurs when clinical stage is migrated to pathologic stage.[26] However, our subgroup analysis revealed significant differences in the survival rates of different tumor locations in studies using both clinical and pathologic stages.

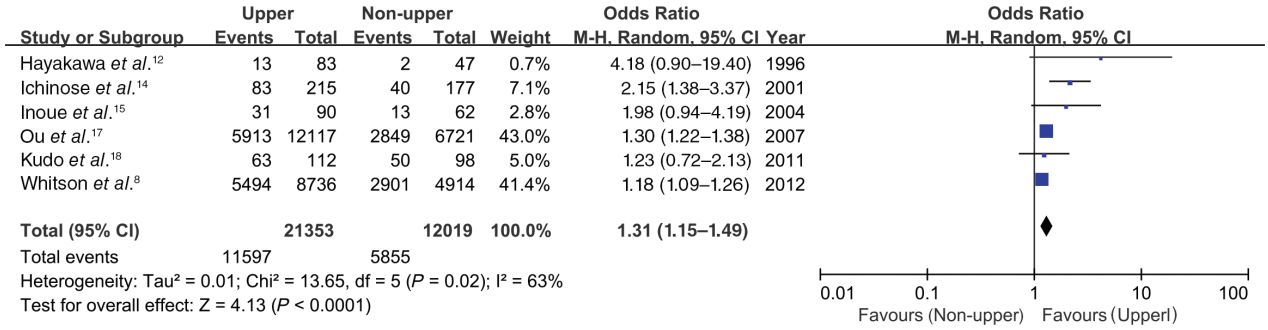

Figure 2 Comparison of five-year survival rates between upper and non-upper lobes. CI, confidence interval; M–H, Mantel–Haenszel.

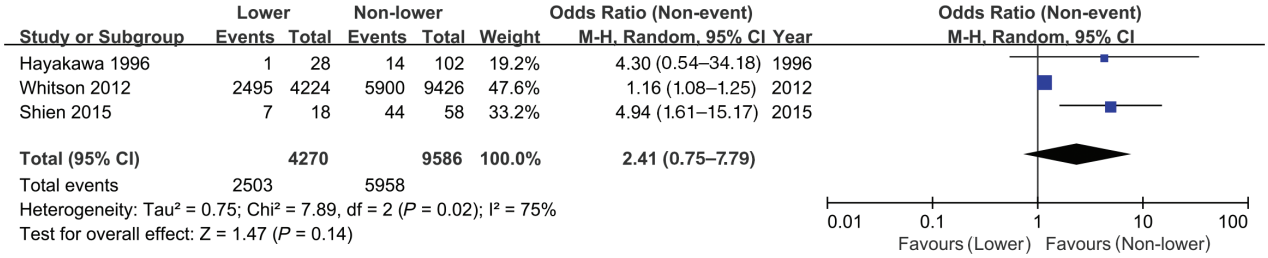

Figure 3 Comparison of five-year survival rates between lower and non-lower lobes. CI, confidence interval; M–H, Mantel–Haenszel.

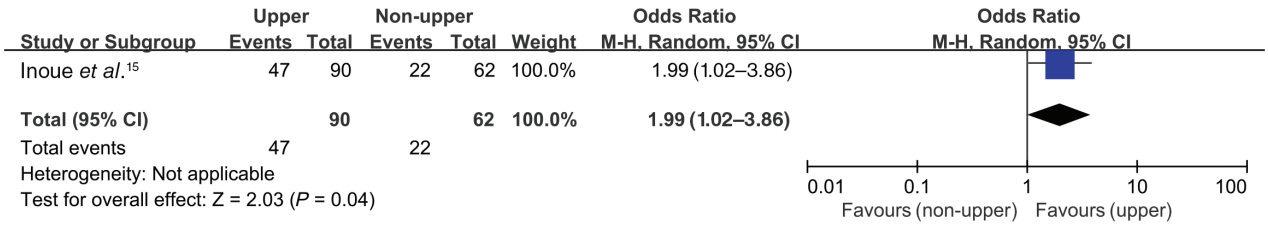

Figure 4 Comparison of three-year survival rates between upper and non-upper lobes. CI, confidence interval; M–H, Mantel–Haenszel.

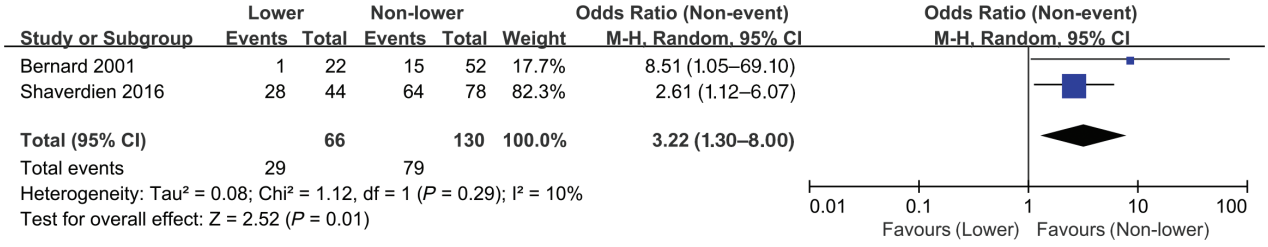

Figure 5 Comparison of three-year survival rates between lower and non-lower lobes. CI, confidence interval; M–H, Mantel–Haenszel.

Another theory is the different effectiveness of the same treatment modality according to the tumor location. Several reports have shown that operation site or side had an effect on the treatment outcome.[27] Others have shown better outcomes of complete resection in patients with upper mediastinal LN involvement.[28] Our analysis showed more favorable prognosis after surgery in patients with upper lobe tumors, consistent with previous studies. Surgical interventions are a better treatment option in patients with upper lobe tumors than in those with non-upper lobe tumors. Hayakawa *et al.* attributed the better prognosis associated with upper lobe tumors to the easier approach, as fewer obstacles are encountered during treatment of upper lobe compared to lower lobe tumors.[12] In addition, recently developed tyrosine kinase inhibitor agents are mainly used to treat adenocarcinoma or *EGFR*-positive NSCLC, both of which are more likely to manifest in the upper lobes.[10,11,29]

Other researchers have reported different patterns of metastatic spread according to tumor location that eventually affect patient prognosis. Micrometastasis and subsequent relapse rates may be higher in lung bases with overperfusion.[30] Lower lobe tumors are more likely to spread to the subcarinal station, the sentinel LN of metastasis, to contralateral hilar LNs.[31] A lower rate of contralateral mediastinal drainage is expected in upper lobe tumors as upper lobe cancers frequently involve upper mediastinal LNs.[32]

The rules of TNM staging among the studies were applied according to the published year of each study. Changes in the TNM staging system were reviewed from the AJCC 4th edition (1992) to the 7th edition (2009). In the period between the 4th and 5th editions, stages I and II were divided into IA/IB and IIA/IIB, respectively. T3N0M0 was downstaged from IIIA to IIB. No changes were found between the 5th and 6th editions. Considerable changes were made from the 6th to the 7th edition, according to the size of the cancer: T1 was divided into T1a and T1b, while T2 was divided into T2a, T2b, and T3. Some T4 tumors, with the same lobe nodule and pleural effusion, were changed to T3 or M1a, respectively. Ipsilateral lobe nodules, M1 in the 6th edition, were changed to T4 in the 7th edition. Our meta-analysis unified the different editions to a standard to avoid misclassification. We divided the patients into two groups, I/IIA and IIB/III, because it was not possible to distinguish IIA from I and IIB from III.

Pathological diagnosis has also evolved over time. The WHO classification for the pathology of lung cancer had been revised five times between 1967 and 2015. A new classification according to mucin formation was included in the 1981 edition. Several new classifications based on immunohistochemical features were added in 1999, such as bronchoalveolar carcinoma and mixed subtype in adenocarcinoma; basaloid variant in squamous cell carcinoma; and large cell neuroendocrine carcinoma and basaloid carcinoma in large cell carcinoma. Genetic or molecular diagnosis was considered significant in 2004, because the association between treatment response and genetic mutations had been elucidated. Previous classifications were considerably altered in the 2015 edition. Adenocarcinoma was regrouped as its own group. Basaloid carcinoma was moved to the squamous cell carcinoma group. The neuroendocrine tumors group was newly developed. A subgroup of the large cell carcinoma group was divided into other groups. In the present meta-analysis, it was not possible to unify the pathological diagnosis from different classification editions or to conduct sensitivity analyses by histological type. Despite the different pathological classifications of lung cancer, the results of our meta-analysis were not affected because our targeted disease was NSCLC.

Our study included the following limitations. First, the primary limitation was the low quality and heterogeneity of the included studies, which is attributed to the retrospective designs with different clinical settings. The number of comparison groups for survival analysis varied considerably between studies. In addition, the TNM stage or staging method may have possible heterogeneity given the lack of information on the rigor and techniques of staging and nodal sampling. Large prospective studies with standardized protocols will resolve these problems. Second, subgroup or sensitivity analysis could not elucidate why previous studies had presented different results or conclusions. However, we can confirm that TNM stage, staging method, and nodal status were not reasons for the different results. Third, inconclusive results attributed to heterogeneity were found. The random effect model considerably expanded the CIs in analysis of the association between lower lobe tumors and five-year survival rate. Although each study strongly suggested poorer outcomes in patients with lower lobe tumors, the pooled data showed insignificant differences.

In conclusion, better five-year survival prognosis was observed in patients with stage I–III NSCLC of the upper lobes. Higher five-year survival rates in patients with upper lobe tumors are consistently elucidated, regardless of lymph node involvement, TNM stage, or staging method. The five-year survival rate in patients with upper lobe tumors is higher in those treated with surgery.

Disclosure

No authors report any conflict of interest.

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Supporting Information

Additional Supporting Informationmay be found in the online version of this article at the publisher's website:

File S1. Detailed supplemental information for study design, risk of bias, study quality, and results of subgroup or sensitivity meta-analyses. CI, confidence interval; M–H, Mantel–Haenszel.

