Original Article

Should primary tumor be resected for non-small cell lung cancer with malignant pleural disease unexpectedly found during operation?—a systemic review and meta-analysis

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Background: Non-small cell lung cancer (NSCLC) with malignant pleural disease (MPD) was considered to be contraindication for surgery, but sometimes MPD was unexpectedly found intraoperatively. There was no consensus on the role of surgical intervention on the primary tumor in patients with MPD. The object of this research was to assess whether exairesis of primary tumor could prolong survival time.

Methods: A systemic research of literature was performed on the databases of PubMed, Embase and Web of Science. Literatures examining surgical benefit or other prognostic factors among NSCLC patients with MPD unexpectedly found during operations were included. Hazard ratio (HR) with 95% confidence interval (95% CI) as well as P value is applied for prognostic role of surgical removal or other potential factors.

Results: Nine articles with a total number of 861 patients fulfilled the eligibility criteria, five of them compared the survival benefit between exploration and resection among NSCLC patients with unexpected MPD, and other studies also investigated the prognostic factors in these patients. There was a significant survival benefit in patients with primary tumor resection (HR =0.443; 95% CI: 0.344–0.571; P<0.001). This role was further detected when stratified by analysis method and ethnicity. Female was an independent favorable predicted factor (HR =0.788; 95% CI: 0.648–0.959; P=0.017) while higher N-stage was a risk factor (HR =1.879; 95% CI: 1.307–2.701; P=0.001). Among patients who received primary tumor resection, higher N-stage was also a risk factor for poorer survival (HR =2.021; 95% CI: 1.496–2.730; P<0.001).

Conclusions: Resection of primary tumor, female and lower-N stage were suggested to be beneficial prognostic factor among NSCLC patients who were detected with MPD for the first time in the operating room. And among these people who received surgical removal of primary tumor, lower N-stage also indicated a better survival.

Keywords: Surgery; non-small cell lung cancer (NSCLC); malignant pleural disease (MPD)

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Introduction

Non-small cell lung cancer (NSCLC) with malignant pleural disease (MPD) including malignant pleural effusion (MPE) and malignant pleural nodules (MPN) is considered to have poor outcomes, which happens on 1–7% of NSCLC patients (1-4). According to The International Association for the Study of Lung Cancer (IASLC) staging project, the median survival time (MST) and the 5-year survival rate of patients with malignant pleural disease were 8 months and 2%, respectively (2). Thus, in the seventh edition of the Union for International Cancer Control (UICC) lung cancer staging system, NSCLC with malignant pleural disease was clarified as stage IV (M1a) (5). Due to its poor prognosis, NSCLC with MPD is generally regarded as a contraindication for surgery, and this part of patients are usually treated by systemic chemotherapy (3,6).

However, in clinical practice, despite advances in diagnostic imaging techniques in recent years (7), malignant pleural disease cannot always be detected before surgery and are sometimes found during operation. Among them, whether to undergo surgical resection of the primary tumor or not is still controversial. A few studies have been published while their findings were inconclusive (8-12). Yet no randomized controlled trial has been performed to assess the role of primary tumor resection in NSCLC patients with MPD first detected during surgery.

Therefore, the purpose of this meta-analysis was to clarify whether or not the surgical removal of the primary tumor should be taken and further investigate the other prognostic factors among NSCLC patients with MPD first detected during surgery and those who undertook primary tumor resection.

Methods

Search strategy

We searched articles published in the PubMed, Embase and Web of Science update to May. 11, 2016 by using the following search terms: lung cancer, lung carcinoma or lung neoplasm, pleural, pleural dissemination, pleural seeding, pleural spread or pleural carcinomatosis, and surgical resection, pulmonary resection or primary tumor resection. References of related studies were identified manually for potential eligible studies.

Inclusion and exclusion criteria

Studies met the following criteria were included in our meta-analysis: (I) studies recruited NSCLC patients with MPD first detected during surgery; (II) investigated the surgical benefits of pulmonary resection and/or assessed other prognostic factors of NSCLC patients with MPD first detected during surgery; (III) hazard ratio (HR) with 95% confidence interval (95% CI) was available in univariate or multivariate analyses with Cox proportional hazards model or could be estimated by Parmar's method (13) for primary tumor resection or other prognostic factors. Articles were excluded from the present study if they: (I) were conference literatures; (II) recruited patients with contralateral lung metastasis or distant metastasis; (III) included patients who were diagnosed as NSCLC with MPD before operation. Two trained reviewers browsed abstracts and selected articles based on the inclusion and exclusion criteria, and any disagreement was solved by discussion.

Data extraction

Data were extracted independently by the two reviewers with standard extraction table. The two reviewers got coherent conclusion after discussion, and information are extracted as follows: the first author, publication year, ethnicity, source of patients, type of studies, number of patients included, HR with 95% CI for primary tumor resection or other prognostic factors.

Statistical analysis

HR and 95% CI were applied to evaluate the survival influence of primary tumor resection and prognostic role of potential factors, and the P value <0.05 meant that the results had statistical significance. It should be noted that when the author did both univariate and multivariate analysis on prognostic factors, we included the outcomes carried out by multivariate analysis in our meta-analysis. We further conducted subgroup analysis stratified by analysis method and ethnicity. All statistical analyses were calculated on Stata 12.0 (STATA Corporation, College Station, TX, USA).

Results

Studies characteristics

There were mostly 2,406 citations from the PubMed, Embase and Web of Science. The majority of the articles were excluded after screening the titles and abstracts. Seventeen papers in total were left, the full texts of which

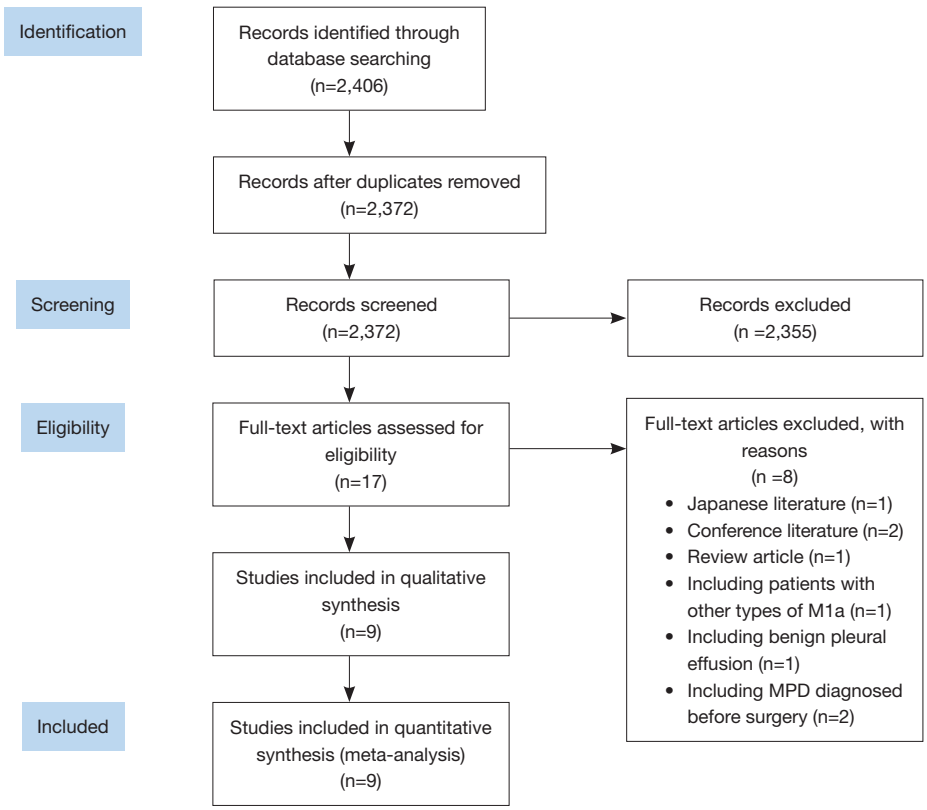

Figure 1 PRISMA flow chart of literature selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were further studied in detail. Finally, nine papers met the inclusion and exclusion criteria and were included in the present study (*Figure 1*). All of the nine included original articles published between 2001 and 2015 were retrospective analyses. Eight researches studied on Asian and five of them came from Japanese research institutions. Only one research from Georges Pompidou European Hospital and Cedre Surgical Center was about Caucasian. Further information of the studies is shown in *Table 1*.

Pooled results

Five studies with totally 376 patients performed the comparison of resection group with exploration group. When compared to exploration group, resection of primary tumor was significantly associated with better survival (HR =0.443; 95% CI: 0.344–0.571; P<0.001) (*Figure 2*).

In subgroup analysis, the survival benefit of primary tumor resection was proved by both univariate and multivariate analysis, especially multivariate analysis (HR =0.359; 95% CI: 0.262–0.493; P<0.001). In addition, when stratified by ethnicity, resection group showed an advantage over exploration group on overall survival among Asian (HR =0.404; 95% CI: 0.304–0.538; P<0.001) (*Table 2*). The detailed extracted data were presented in *Table 3*.

As for other prognostic factors for NSCLC patients with MPD first found during operation (all cohort), female (HR =0.788; 95% CI: 0.648–0.959; P=0.017) and higher N stage (HR =1.879; 95% CI: 1.307–2.701; P=0.001) (*Figure 3*) were significantly associated with survival. However, we did not indicate any association between survival and histological type, size of primary tumor, T stage, postoperative treatment and location of primary tumor (*Table 2*).

Besides, we further investigated the prognostic factors for NSCLC patients with MPD first found during operation which performed primary tumor resection (resection cohort) (*Table 4*). Higher N-stage suggested poorer survival after primary tumor resection (HR =2.021; 95% CI: 1.496–2.730; P<0.001) (*Figure 3*) while no statistical difference was detected between male and female patients (HR =0.767;

Table 1 Baseline information of included articles

First author	Publication year	Study period	Source	Ethnicity	Type of study	Number of patients	Average age (if reported)	Significant prognostic factors
Ichinose	2001	1985–1994	The JCOG, Japan	Asian	Retrospective case note review	100	63.0	N factor; gender
Fukuse	2001	1981–1997	Otsu Red-Cross Hospital, Japan	Asian	Retrospective case note review	49	62.3	T factor
Ichinose	2000	1985–1994	The JCOG, Japan	Asian	Retrospective case note review	227	61.7	Histology; N factor
Mordant	2011	1983–2006	Georges Pompidou European Hospital and Cedre Surgical Center, France	Caucasian	Retrospective case note review	70	NR	Resection of primary tumor
Okamoto	2011	1990–2007	Chiba University Hospital, Japan	Asian	Retrospective case note review	73	NR	N factor
Ren	2015	2005–2013	Shanghai Pulmonary Hospital, China	Asian	Retrospective case note review	83	57.0	Resection of primary tumor; histology; N factor
Sawabata	2002	1980–1994	14 Japanese national referral hospitals, Japan	Asian	Retrospective case note review	43	61.1	NA
Yun	2015	20001–2011	Asan Medical Center, South Korea	Asian	Retrospective case note review	78	NR	Resection of primary tumor
Wang	2011	1990–2008	Taipei Veterans General Hospital, China	Asian	Retrospective case note review	138	NR	Resection of primary tumor; N factor

NR, not reported; NA, not available.

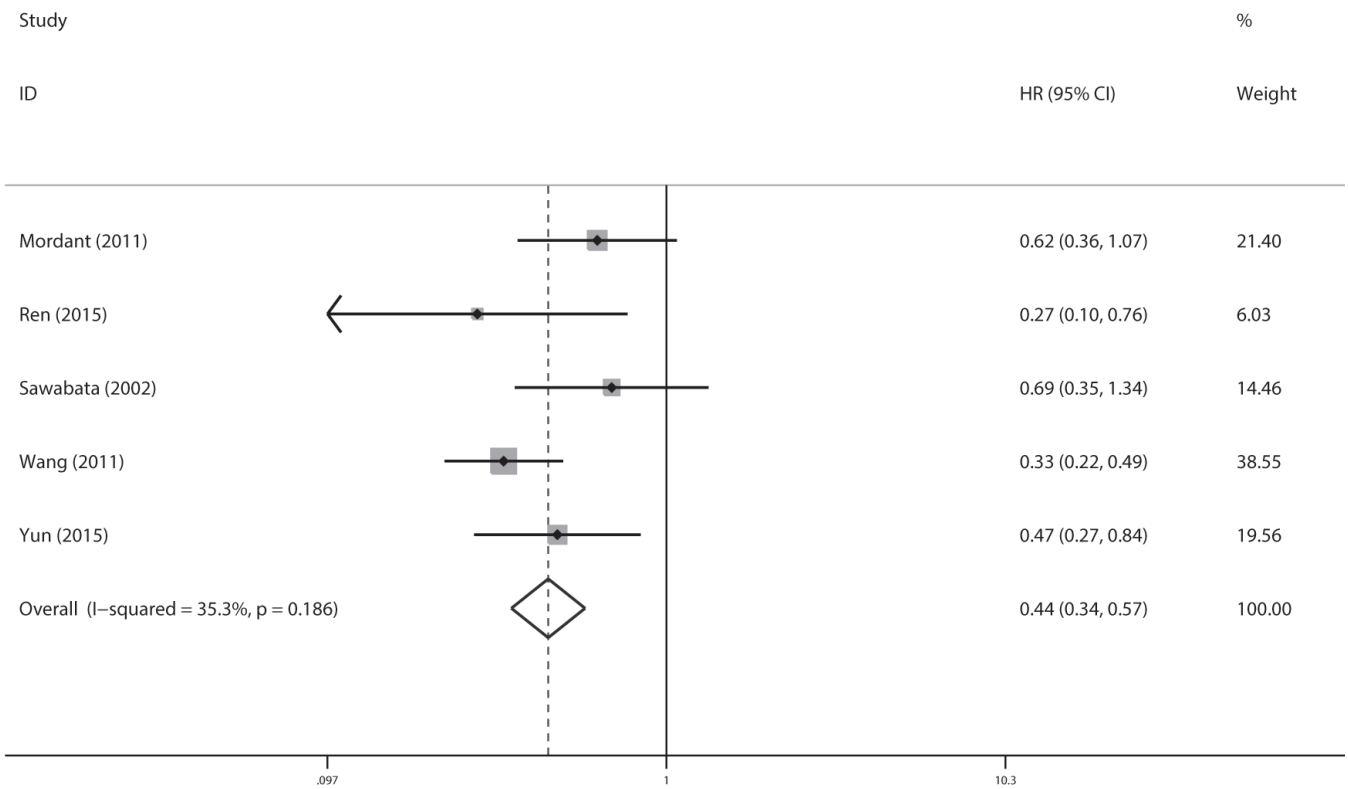

Figure 2 Forest plot of role of surgical resection of primary tumor on survival in NSCLC patients with MPD first detected during surgery. NSCLC, non-small cell lung cancer; MPD, malignant pleural disease.

95%: 0.530–1.709; P=0.158) (*Table 2*).

Discussion

We did the present systemic review and meta-analysis to evaluate whether surgical resection of primary tumor was beneficial to NSCLC patients with MPD that were first detected during operation, as well as other factors which affected prognosis. After statistical analysis, we found that surgical removal of primary tumor had a lower risk of death compared to exploration only among these participants with the HR of 0.443 according to meta-analysis.

Moreover, as reported by Ichinose *et al*. (14), the HR (95% CI) on N1–3 versus N0 was 0.541 (0.343–0.853; P=0.008), which demonstrated that no lymph node metastases was a beneficial prognostic factor. While based on studies of Wang *et al*. (15) as well as Iida *et al*. (16), MPD patients without mediastinal nodal metastases had a better survival. In this meta-analysis, we got an outcome that higher N-stage suffered a higher risk in NSCLC patients with MPD first detected during surgery. More importantly, we achieved the same conclusion in the resection group.

With rapid development in diagnostic imaging techniques, such as brain magnetic resonance imaging (MRI), computed tomography (CT), bone scan and especially application for positron emission tomography-CT (PET-CT), it became more effective and accurate to detect malignant pleural disease preoperatively (17). Therefore, patients from recent studies were likely to be at better condition than previous ones, who might have less MPE or/and less pleural disseminations. On the other hand, patients in 1980s or 1990s probably be misdiagnosed as without MPD before surgery because of lack of imaging protocols (18).

Meanwhile, it has changed constantly both in therapeutic management and operative procedures of NSCLC. More than decade ago, thoracic surgeon undertaken thoracotomy including lobectomy, pneumonectomy and pleuropneumonectomy on MPD patients, while limited resection was barely adopted. Reyes *et al*. reported profitable results of pleuropneumonectomy

Table 2 Pooled results of role of surgical resection and prognostic factors

Variable	HR	95% CI	P value
Resection versus exploration			
Total (n=5)			
Exploration	1	Reference	
Resection	0.443	0.344–0.571	<0.001
Univariate analysis subgroup (n=2)			
Exploration	1	Reference	
Resection	0.646	0.424–0.987	0.043
Multivariate analysis subgroup (n=3)			
Exploration	1	Reference	
Resection	0.356	0.262–0.493	<0.001
Asian patients subgroup (n=4)			
Exploration	1	Reference	
Resection	0.404	0.304-0.538	<0.001
Prognostic factors in all cohort			
Gender (n=6)			
Male	1	Reference	
Female	0.788	0.648–0.959	0.017
Histological type (n=4)			
Adenocarcinoma	1	Reference	
Others	1.634	0.756–2.792	0.073
Tumor size (cm) (n=4)			
≤3	1	Reference	
>3	1.079	0.851–1.368	0.531
T stage (n=3)			
T1	1	Reference	
T2–T4	1.07	0.843–1.359	0.576
N stage (n=5)			
Lower N	1	Reference	
Higher N	1.879	1.307–2.701	0.001
Postoperative treatment (n=2)			
Yes	1	Reference	
No	1.701	0.946–3.056	0.076

Table 2 *(continued)*

Variable	HR	95% CI	P value
Location of main tumor (n=2)			
Left	1	Reference	
Right	0.086	0.643–1.222	0.461
Prognostic factors in resection cohort			
Gender (n=2)			
Male	1	Reference	
Female	0.767	0.530–1.709	0.158
N-stage (n=4)			
Lower N	1	Reference	
Higher N	2.021	1.496–2.730	<0.001

N, number of included studies; HR, hazard ratio; 95% CI, 95% confidence interval.

Table 3 Extracted data for surgical resection and prognostic factors from included articles

Study	Analysis method	Survival analysis		
		HR	95% CI	P value
Surgical resection of primary tumor (exploration *vs*. resection)				
Mordant	UV	0.621	0.359–1.074	0.088
Ren	MV	0.272	0.097–0.765	0.014
Sawabata	UV	0.686	0.352–1.335	0.256
Yun	MV	0.472	0.266–0.837	0.010
Wang	MV	0.326	0.217–0.491	<0.001
Gender (male *vs*. female)				
Fukuse	MV	0.770	0.550–2.240	0.770
Ichinose [2000]	MV	0.760	0.542–1.065	0.111
Okamoto	MV	1.100	0.590–2.050	0.770
Ren	UV	0.649	0.366–1.150	0.139
Yun	MV	0.621	0.362–1.064	0.083
Wang	UV	1.095	0.734–1.632	0.657
Histological type (adenocarcinoma *vs*. others)				
Fukuse	MV	1.250	0.660–2.390	0.490
Ichinose [2000]	MV	1.598	1.051–2.431	0.028
Okamoto	UV	0.960	0.430–2.150	0.930
Ren	MV	5.481	1.910–15.725	0.002

Table 3 *(continued)*

Table 3 *(continued)*

Study	Analysis method	Survival analysis		
		HR	95% CI	P value
Tumor size (cm) (≤3 *vs*. >3)				
Ichinose [2000]	MV	0.964	0.643–1.446	0.859
Okamoto	UV	1.160	0.660–2.030	0.610
Yun	MV	0.786	0.365–1.694	0.539
Wang	MV	1.248	0.851–1.832	0.256
T-stage (T1 *vs*. T2–T4)				
Fukuse	MV	1.790	1.010–3.160	0.046
Ichinose [2000]	MV	0.964	0.734–1.267	0.795
Yun	MV	0.904	0.338–2.418	0.841
N-stage (lower N *vs*. higher N)				
Ichinose [2000]	MV	1.321	1.082–1.612	0.006
Okamoto	MV	2.390	1.210–4.740	0.010
Ren	MV	5.937	1.882–18.733	0.002
Yun	MV	1.668	0.925–3.010	0.089
Wang	MV	1.955	1.279–2.988	0.002
Postoperative treatment (yes *vs*. no)				
Ichinose [2000]	MV	1.262	0.909–1.750	0.164
Ren	UV	2.295	1.558–3.032	0.260
Location of main tumor (left *vs*. right)				
Ren	UV	1.128	0.622–2.046	0.692
Wang	UV	0.803	0.549–1.176	0.260

HR, hazard ratio; 95% CI, 95% confidence interval; UV, univariate analysis; MV, multivariate analysis.

in ten patients with MPE diagnosed initially for the first time in 1991 (19). Even if Sugarbaker *et al*. (20) proved that pleuropneumonectomy to be a safe choice for cancers involves an ipsilateral pleura, it was still relevant to a perioperative mortality of 4.6%. Until the first application of video-assisted thoracic surgery (VATS) lobectomy in early 1990s (21,22), more and more evidence demonstrated that VATS lobectomy might be an alternative approach, which concerning with less intraoperative bleeding, less trauma, reduced postoperative pain, shorter hospitalization days (23-29), and these aspects all improved survival indirectly. Consequently, the survival outcomes of VATS were still to be explored. In addition, Ichinose and his colleagues (30) did another study in 2000 and gathered data on 227 MPD patients treated surgically from 21 institutions registered in the Japan Clinical Oncology Group (the JCOG), and they suggested that no macroscopic residual tumors were prognostic factors for better outcomes. However, since there was few data about it, we didn't get any conclusion about the optimal surgical approach and excision range in the meta-analysis.

On the other hand, Go *et al*. found that postoperative chemotherapy might improve prognosis (31), but the present study indicated no statistical significance of it. The possible reason might be insufficient data. And as different chemotherapy regimens were applied in the various studies with different results, further researches might be needed to clarify the association between different chemotherapy regimens and survival of MPD unexpectedly found during surgery. Besides, since the sensibility of tyrosine kinase inhibitors (TKIs) to epithelial growth factor receptor (EGFR) mutations was discovered, the clinical strategies of NSCLC have changed a lot (32-34). It is an independent predictor of overall survival and progression-free survival in patients with NSCLC with EGFR mutations who are treated with TKIs (32).

Furthermore, Kim and his colleagues showed a longer MST in MPD patients if no pleural effusion was found (38 *vs*. 13 months; P<0.001) (35). However, Okamoto *et al*. considered that there was no benefit in MPE patients without nodules compared to MPN patients with or without effusion (11). Moreover, a review from Fiorelli A and Santini M in 2013 considered that there was no evidence strong enough to support surgery over conservative therapy in lung cancer patients with MPE found at operation (36). As mentioned above, the grouping situation of MPD was different in various studies, it was hard for us to draw a unified conclusion that what kind of MPD suffered a higher risk and in what situation should surgical treatment be contraindicated. So it could be an issue in future research.

Our study also had some limitations. It should be mentioned that there were no randomized controlled trials in our study, and all articles included in were retrospective studies. Thus, because of the distinct inclusion and exclusion criteria of variant original studies, there were possibly some selection biases. The long periods of follow-up were different among included studies and some follow-up data were derived from description of patient, and it probably led to information bias. All these bias may cause deviation to the results. As described before, Asian were put as the

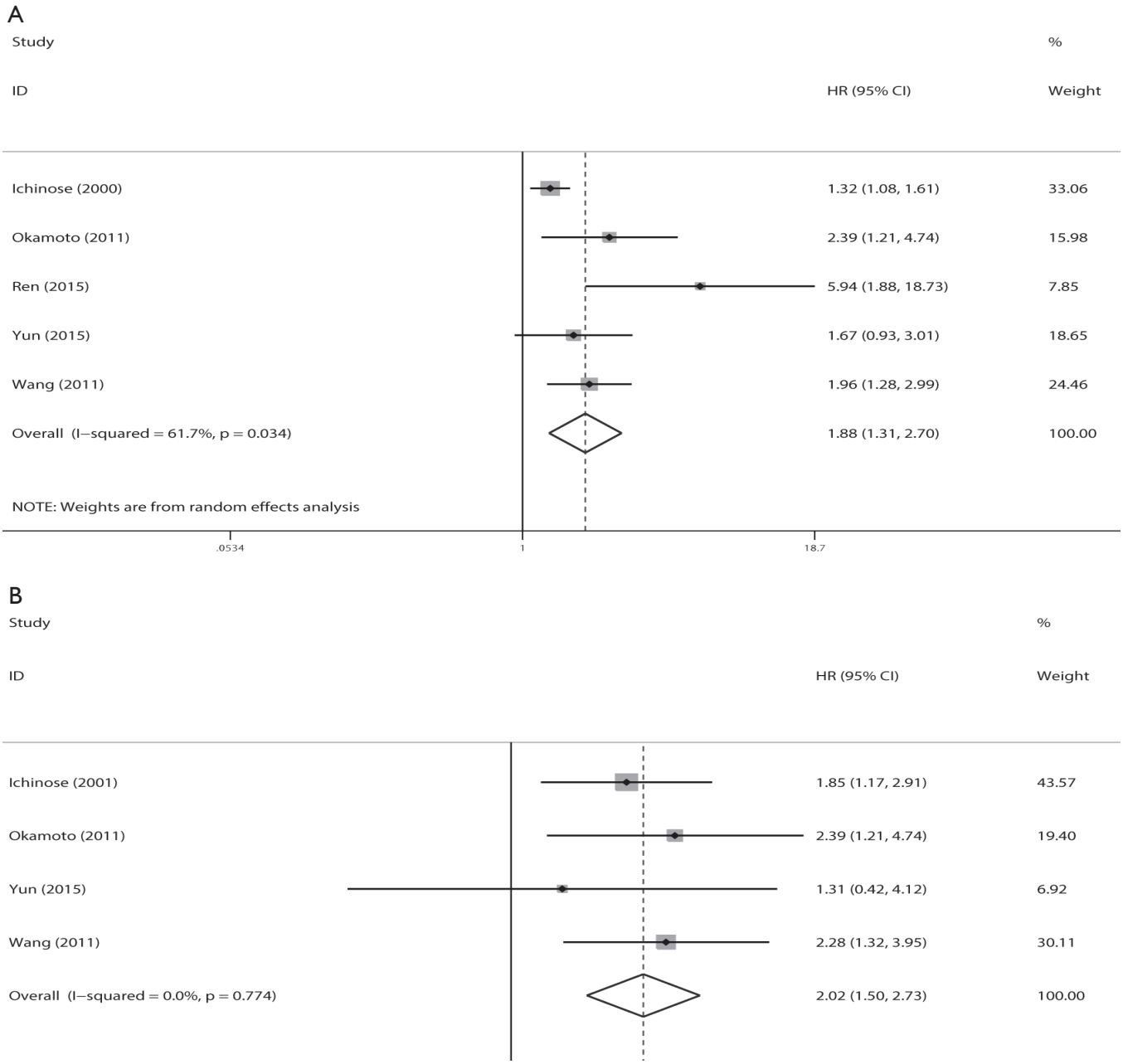

Figure 3 Forest plot of prognostic role of N-stage in NSCLC patients with MPD first detected during surgery (A) and resection cohort (B). NSCLC, non-small cell lung cancer; MPD, malignant pleural disease.

object of study in 8 of 9 researches, so the outcomes of our meta-analysis might be more applied to Asians. In addition, we put forward a general conception of lower N-stage and higher N-stage, which was a relative conception like N0 versus N1/2 or N0/1 versus N2. Still more prospective analysis should be done to discuss the relationship between N-staging and survival in resected NSCLC patients with no evidence of MPD preoperatively.

Conclusions

The present systemic review and meta-analysis showed that surgical resection of primary tumor was appropriate for NSCLC patients with malignant pleural disease first

Table 4 Extracted data for prognostic factors in resection cohort

Source	Analysis method	Multivariate analysis		
		HR	95% CI	P value
Gender (male *vs*. female)				
Ichinose [2001]	MV	0.631	0.399–0.997	0.049
Okamoto	MV	1.100	0.590–2.050	0.770
N-stage (lower N *vs*. higher N)				
Ichinose [2001]	MV	0.541	0.343–0.853	0.008
Okamoto	MV	2.390	1.210–4.740	0.010
Yun	MV	1.313	0.419–4.119	0.641
Wang	UV	2.280	1.320–3.950	NA

HR. hazard ratio; 95% CI, 95% confidence interval; MV, multivariate analysis; UV, univariate analysis; NA, not available.

detected during surgery. Among this group of patients, female and lower N-stage were independent favorable prognostic factors. And for patients who were treated surgically, lower N-stage also showed a better survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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