Original Article

Skip metastasis in mediastinal lymph node is a favorable prognostic factor in N2 lung cancer patients: a meta-analysis

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Background: Skip metastasis is a common lymph node metastatic pattern in non-small cell lung cancer (NSCLC). The relationship between skip metastasis and specific clinicopathologic factors and the prognostic value of skip metastasis are controversial.

Methods: A systematic search and analysis of skip metastasis in NSCLC was conducted in the databases of PubMed, EMBASE, and Web of Science up to Dec 2019. Summarized hazard ratio (HR), mean difference (MD), and odds ratio (OR) with associated 95% confidence intervals (CI) were evaluated to investigating the relationship between skip metastasis and overall survival (OS), disease-free survival (DFS), recurrence-free survival (RFS) and clinicopathological features in NSCLC.

Results: 29 studies with a total of 1,806 skip and 4,670 non-skip N2 patients were included. The upper lobe tumor showed a higher rate of skip metastasis compared with lower lobe one (RR =1.16, 95% CI: 1.00–1.34, P=0.044, I^2=39.8%). The presence of skip metastasis correlated with superior overall survival (HR =0.74, 95% CI: 0.66–0.83, P<0.001, I^2=48.2%) and DFS or RFS (HR =0.71, 95% CI: 0.61–0.84, P<0.001, I^2=18.2%). Further subgroup analyses indicated similar results in articles that reported intrapulmonary lymph node dissection (HR =0.67, 95% CI: 0.57–0.77, P<0.001, I^2=0).

Conclusions: The results indicate that the presence of skip metastasis is associated with a marked increase in survival of NSCLC patients compared to patients with non-skip N2 metastasis. These results suggest that skip metastasis might be a distinct subgroup for purposes of N staging of NSCLC patients, and intrapulmonary lymph node assessment is needed.

Keywords: Non-small cell lung cancer (NSCLC); prognosis; skip metastasis

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Introduction

Lung cancer is the leading cause of mortality among all malignancies. The 5-year overall survival (OS) rate of patients with lung cancer remains low because most cases are diagnosed in the advanced stage (1). Lymph node metastasis is one of the most important determinants of prognosis according to the TNM staging system (2). The prognosis decreases significantly when lymph node metastasis is observed, especially with the involvement of ipsilateral (N2) or contralateral (N3) mediastinal lymph nodes (3). Studies have shown that pathologic N2 NSCLC

exhibits heterogeneous prognosis among patients (4), and those with positive mediastinal N2 lymph nodes (approximately 20–40% of all patients with NSCLC) exhibit extremely low survival rates. Nonetheless, some selected patients with N2 disease exhibit relatively better 5-year survival (5). Skip metastasis in mediastinal lymph node is defined as positive N2 metastasis with the absence of N1 lymph node metastasis in hilar and intrapulmonary lymph nodes. With about 17.2–42.3% of all patients with resected pN2-NSCLC (6,7), the clinical significance of skip metastasis remains unclear. According to the newest proposal for TNM staging, patients with N2 metastasis are subclassified into single-station mediastinal lymph node metastasis and multi-station metastasis (N2a and N2b) (2). Single station N2 metastasis is further classified into skip metastasis and non-skip single station metastasis (N2a1 and N2a2). Many studies reported better prognosis in patients with skip metastasis compared with those with non-skip ones (8,9). However, other works showed different outcomes (10). We conducted this meta-analysis to evaluate the prognostic value of skip metastasis and clinicopathologic factors that may correlate with this phenomenon. This meta-analysis was performed according to the PRISMA statement (11), and no protocol was previously published for this review.

We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-3513).

Methods

Literature search

A literature search was conducted in PubMed, Ovid, and Web of Science from inception through December 2019 with the following terms: ((((skip N2 OR skip mediastinal lymph node) OR skip metastases)) AND (((((lung cancer) OR lung carcinoma) OR lung neoplasm) OR lung adenocarcinomas) OR NSCLC) in all fields. All references of relevant articles were reviewed.

Study selection

The results were carefully reviewed by two authors independently (Jiahan Cheng and Zihuai Wang), and any disagreement during the process was discussed and solved with a third author (Lunxu Liu). Studies focusing on the prognostic value of skip metastasis and those reporting the relationship between clinicopathologic features and skip metastasis were included in our analysis. All the included articles assessed the pathological diagnosis under surgical resection. Reviews, conference abstracts, case reports, and *in vitro* or animal studies were excluded. Articles in languages other than English or Chinese were also excluded.

Data extraction and quality assessment

The full texts of all included articles were reviewed independently by two authors (Zihuai Wang and Jiahan Cheng), and the following data were extracted: publication information, study design, grouping method, sample size in each group, length of follow-up period, relevant clinicopathological characteristics, and prognostic effect of skip metastasis.

Quality assessment was conducted using the Newcastle-Ottawa Scale (NOS) for all included studies (12). Scores of 1–9 were assigned to articles in the categories of patient selection, group comparability and outcomes ascertainment. Articles that scored greater than 7 were deemed as high quality, those with scores of 6–7 as fair quality, and those with scores less than 6 as poor quality.

Statistical analysis

Hazard ratio (HR) and relative risk (RR) were extracted from all eligible articles along with associated 95% confidential intervals (CI). HR was employed to assess the prognostic effect of skip metastasis in overall survival (OS) and disease-free survival (DFS) or recurrence-free survival (RFS). Odds ratio (OR) was determined using Mantel-Haenszel method to estimate the relationship between skip metastasis and clinic-pathological characteristics. Heterogeneity among the included studies was evaluated using Chi-square test with P value set at 0.10. I-square (I^2) test was applied to assess total variation among the studies. Mild heterogeneity was defined as I^2<50% and P > 0.1, and a standard fixed-effect model test was used to validate outcome synthesis. For studies yielding P<0.1 or I^2>50%, the random effect model was applied to pool the data (13). Compared with that in the fixed-effect model, weighting within the random-effect model assumes two sources of variability in effects, one from sampling error and the other from study level differences. A two-sided P value with <0.05 was viewed as statistically significant. All statistical analyses were conducted using Stata version 12.0 (StataCorp., College Station, TX, USA).

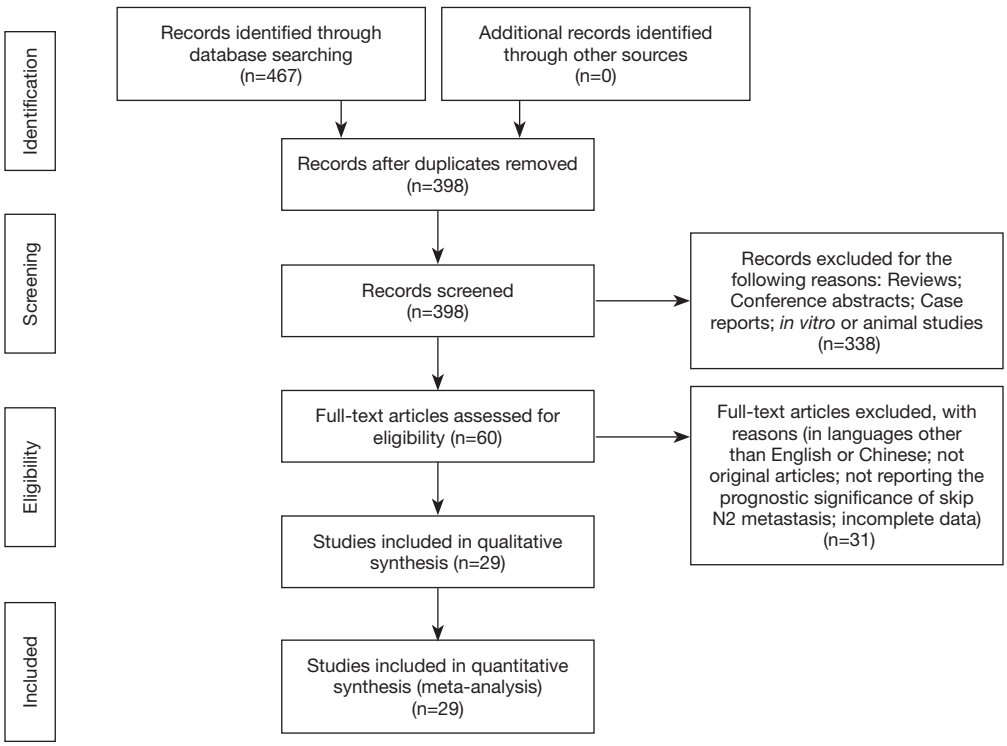

Figure 1 The flow chart of article selection.

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by sequentially retracting each study to evaluate the stability of our results. Begg's weighted regression model was applied to examine the publication bias of the studies (14).

Results

Article selection and quality assessment

A total of 398 articles were found from the initial search after discarding duplicates. Following a review of titles and abstracts, the full texts of 60 papers were assessed. All reviews, conference abstracts and case reports were excluded from our analysis, yielding 29 articles for inclusion. The selection process is depicted in *Figure 1*. The baseline characteristics of all included articles are shown in *Table 1*. The included studies were all retrospective. The articles compared the prognostic effect and clinicopathologic difference between patients with skip metastasis and non-skip N2. A total of 1,806 patients with skip N2 metastasis and 4,670 patients with N1 positive mediastinal metastasis were included in our study, while 3 articles did not report the exact number of the patients in each group (2,15,16). The publication years spanned 1996 through 2019. Only one article underwent propensity score matching to adjust the baseline characteristics between two groups (17). Quality assessment by NOS is reported in *Table 1*.

Prognostic effect of skip metastasis

The association between skip metastasis and overall survival was reported in 16 studies. Skip metastasis was found to be associated with significantly better overall survival (HR =0.74, 95% CI: 0.66–0.83, P<0.001, I^2=48.2%) compared with non-skip metastasis (*Figure 2A*). A subgroup analysis was conducted among articles that reported intrapulmonary lymph node dissection, and the result showed similar outcome with no heterogeneity (HR =0.67, 95% CI: 0.57–0.77, P<0.001, I^2=0) (*Figure 2B*). Similar results were observed in different subgroup analysis of the favorable prognosis in skip metastatic patients (*Table 2*). Additionally, skip metastasis was also correlated with better disease-free survival or recurrence-free survival compared with non-skip metastasis (HR =0.71, 95% CI: 0.61–0.84, P<0.001, I^2=18.2%) (*Table 3*).

Table 1 Characteristics of the included studies

Author	Year	Ethnicity	Sample size (skip/non-skip)	Gender (M/F)	Stage	Intrapulmonary LN detection	Analysis	Quality assessment
Asamura	2015	Mixed	NA	NA	Single level N2	NA[†]	M[‡]	8
Chen	2005	Asian	21/44	54/11	pIII	NA	M	6
Guerrera	2017	Caucasian	54/225	168/111	pN2	Yes	M	8
Hu	2016	Asian	60/288	273/75	pN2	NA	M	7
Ichinose	2014	Asian	25/42	43/24	pN2	NA	U[§]	7
Ilic	2007	Caucasian	21/64	65/20	IIIA/N2	NA	NA	6
Legras	2014	Caucasian	258/613	712/159	pN2	Yes	NA	7
Li	2012	Asian	44/212	184/72	pN2	NA	NA	6
Li	2015	Asian	45/132	96/81	N2	NA	NA	8
Liu	2009	Asian	46/246	225/67	IIIA	Yes	M	6
Luo	2007	Asian	15/45	NA	pN2	NA	NA	7
Misthos	2004	Caucasian	44/107	120/31	pIIIA/N2	NA	NA	6
Misthos	2008	Caucasian	44/107	120/31	pIIIA/N2	NA	M	6
Nakagiri	2011	Asian	43/74	79/42	pIIIA/N2	NA	M	8
Ohta	2006	Asian	50/44	52/42	Single level N2	Yes	M	8
Park	2019	Korea	131/257	NA	Single level N2	Yes	M	8
Prenzel	2003	Caucasian	17/28	32/13	pN2	NA	M	6
Riquet	2005	Caucasian	209/522	598/133	pN2	Yes	M	8
Sonobe	2013	Asian	NA	325/171	pIIIA/N2	NA	M	7
Tanaka	2004	Asian	60/67	88/39	pN2	NA	M	8
Tomita	2005	Asian	25/35	42/18	pN2	NA	M	6
Tomizawa (upper)	2015	Asian	10/22	NA	I-III	Yes	U	8
Tomizawa (lower)	2015	Asian	19/34	NA	I-III	Yes	M	8
Wang	2019	Asian	130/130	199/61	pN2	Yes	M	7
Wang	2001	Asian	53/123	122/54	IIIA	NA	NA	6
Wang	2002	Asian	21/88	64/45	pN2	NA	NA	5
Yoshino	1996	Asian	33/77	75/35	pIIIA/N2	NA	NA	6
Zhang	2010	Asian	NA	399/258	pN2	NA	M	6
Zhao	2018	Asian	137/666	541/262	pN2	Yes	NA	7
Zheng	2011	Asian	191/378	422/147	pN2	NA	M	6

[†], not applicable; [‡], multivariate analysis; [§], univariate analysis. M, male; F, female.

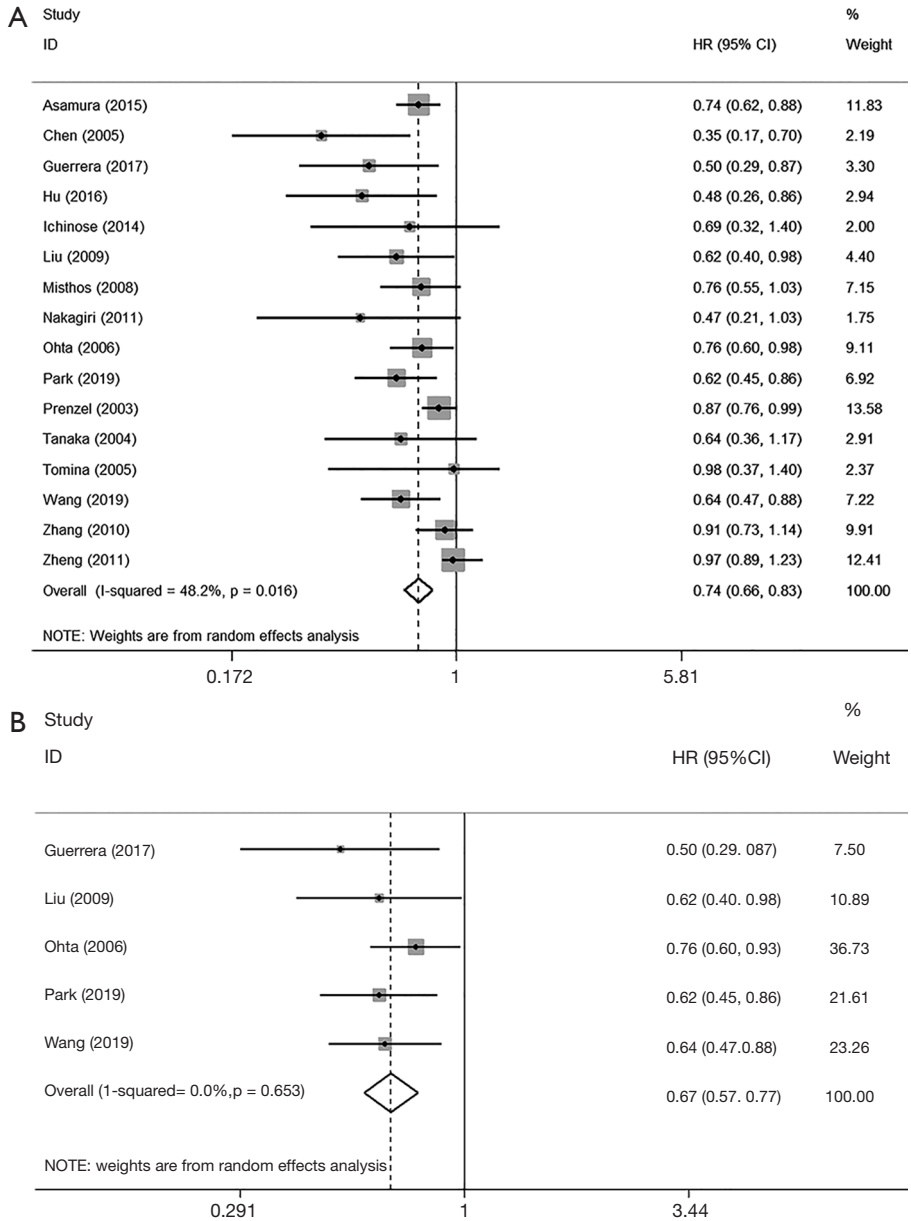

Figure 2 Comparison between skip and non-skip N2 metastatic patients in overall survival (A), and disease-free survival (B).

Relationship between skip metastasis and clinicopathologic factors

We also evaluated the correlation between clinicopathologic factors and the occurrence of skip metastasis (*Table 3*). Skip metastasis occurred more often in the upper lobe according to our result (RR =1.16, 95% CI: 1.00–1.34, P=0.044, I^2=39.8%). The histological subtype of NSCLC may correlate with skip metastasis in adenocarcinomas, which trended toward a lower rate of skip metastasis compared with squamous cell lung carcinoma (RR =0.85, 95% CI: 0.70–1.04, P=0.113, I^2=0), but the result was not significant. Other factors including tumor differentiation, smoking history, pleural invasion status, and tumor diameter showed no correlation with skip metastasis (*Table 3*).

Sensitivity analysis and publication bias

Sensitivity analysis was conducted by omitting each study

Table 2 Associations between clinicopathological features and skip metastasis

Categories	Variables	No. of studies	Pooled data			Heterogeneity	
			HR	95% CI	P	I^2 (%)	Ph
Differentiation	Well + moderate/poor	6	1.06	0.86–1.30	0.574	0	0.532
Histology	LUAD/LUSC	15	0.85	0.70–1.04	0.113	57.5	0.003
Pleural invasion	Existence/non	3	0.86	0.67–1.10	0.223	0	0.658
Smoking	Smoking/non	6	1.00	0.65–1.56	0.985	82.9	0
Diameter	<3 cm/>3 cm	5	0.96	0.80–1.15	0.645	48.8	0.099
Tumor location	Upper/lower	9	1.16	1.00–1.34	0.044	39.8	0.102

DFS, disease free survival; RFS, recurrence free survival; LUAD, lung adenocarcinoma; LUSC, lung squamous carcinoma; HR, hazard ratio; CI, confidence interval; Ph, P value for heterogeneity.

Table 3 Association between skip N2 metastasis and patient survival

Variables	OS			
	N	ES (95% CI)	P value	I^2 (%)
Overall survival (skip *vs.* non-skip N2)	16	0.74 (0.66–0.83)	<0.001	48.20
By ethnicity				
Asian	12	0.71 (0.61–0.84)	<0.001	53.6
Non-Asian	4	0.78 (0.67–0.902)	0.001	42.9
By publication year				
≥2010	9	0.72 (0.61–0.85)	<0.001	59.1
<2010	7	0.76 (0.64–0.89)	0.001	35.7
By sample size				
<300	6	0.74 (0.66–0.83)	<0.001	47.5
≥300	10	0.76 (0.66–0.88)	<0.001	55.1
By lymph node map				
Naruke	4	0.78 (0.61–1.00)	0.051	58.9
IASLC	4	0.66 (0.54–0.81)	<0.001	0.0
Mixed	1	0.74 (0.62–0.88)	0.001	56.9
Not applicable	7	0.73 (0.60–0.90)	0.003	0.0
Disease free survival (skip *vs.* non-skip N2)	3	0.71 (0.61–0.84)	<0.001	18.2

IASLC, International Association for the Study of Lung Cancer; ES, effect size; CI, confidence interval.

sequentially when assessing overall survival. A consistent result was found among all studies (*Figure 3*). Publication bias was assessed with Begg's test and a significant publication bias was observed in overall survival with Begg's weighted regression method (P=0.034).

Discussion

Overall description of our findings

The existence of skip metastasis has been reported in colorectal and breast cancer with a range of 1–3% among all

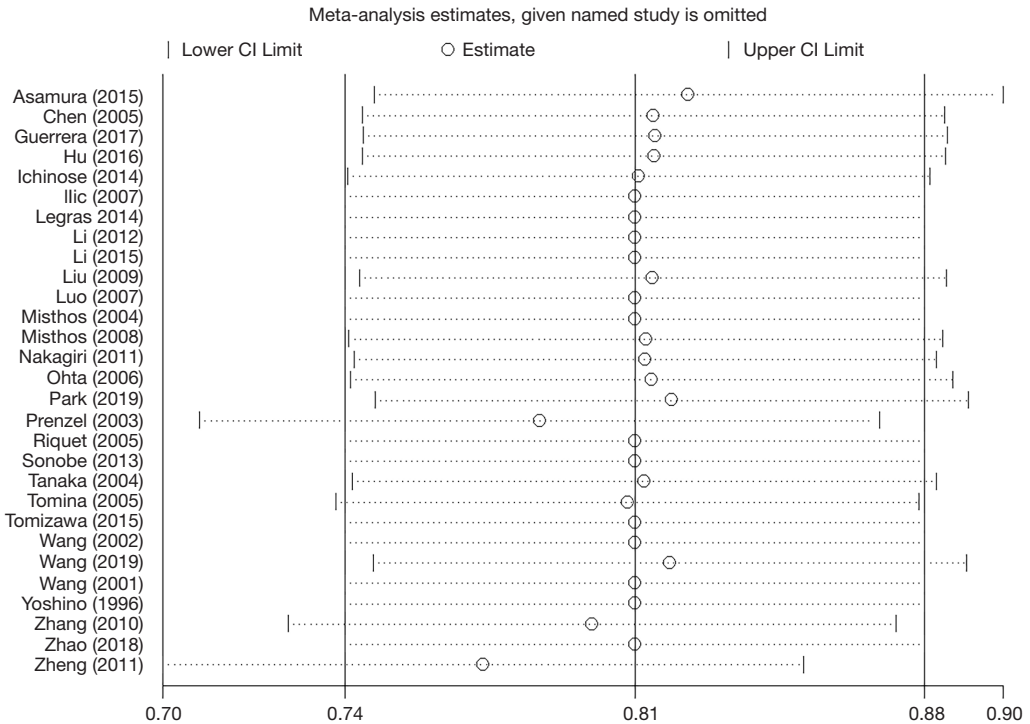

Figure 3 Sensitivity analysis in studies assessing prognostic effect of skip metastasis.

patients with lymph node metastasis (18,19). The incidence of skip metastasis in patients with N2 NSCLC ranges from 20–30% (6,10,20). Although many articles reported the association between skip metastasis and improved prognosis (6), other works demonstrated different results (10). Our comprehensive analysis showed that patients with skip N2 metastasis had superior overall survival and disease-free survival compared with patients with non-skip N2.

Possible mechanism of skip metastasis

The definition of skip metastasis was further developed, representing only one station in mediastinum without the involvement of N1. Asamura and colleagues (2) observed a significantly favorable prognosis in single-station skip metastatic patients compared with non-skip single station N2 but found no significant difference between skip metastatic and multi-stational N1 metastatic groups (2). This finding was further validated in a recent study with similar results (21).

The underlying reason for skip metastasis has not been fully unveiled. One possible explanation is the different metastatic pattern in patients with skip metastasis. Previous works proved the existence of specific subpleural lymphatic drainage pathways that can directly connect to the mediastinum (22). About 23.6% of patients with lung cancer have direct lymph node drainage pathways to the mediastinum (23). These shortcuts have higher tendency to occur in the upper lobes rather than in the lower lobes. This finding correlates with our results of the association between skip metastasis and different tumor locations (RR =1.158, P=0.044). The middle lobe was excluded in this subgroup analysis due to the limited patient number.

Based on evidence, a hypothesis was made that skip metastasis may have similar tumor burden as some N1 subgroup. The survival outcome among patients with multi-station N1, skip N2 metastasis, and non-skip single N2 also reinforced this hypothesis (2,21). In the study of Zhang *et al.*, a different response rate was observed when using post-operative radiotherapy between patients with skip and non-skip N2 (16). This finding also indicated that a different invasive stage might exist in the two groups of patients. However, further prospective and high-level evidence is warranted in this field.

Dissection of intrapulmonary lymph node

The identification of skip metastasis requires thorough intrapulmonary lymph node dissection. Few articles

reported the dissection of intrapulmonary lymph node, while the omission of intrapulmonary N1 can lead to false-positive in skip metastasis (24). In patients with N2 metastasis, the dissection of intrapulmonary lymph node is likely to be neglect because the detection of these nodes would not affect the pathologic staging. The omission of intrapulmonary lymph node may deteriorate the survival outcome in patients with "skip" metastasis and lead to a significant heterogeneity among the studies. Thus, we further analyzed the prognostic significance of skip metastasis in studies that reported intrapulmonary lymph node dissection during surgery. A subgroup analysis was conducted accordingly (8,17,21,25,26). The result is consistent with no heterogeneity (HR =0.67, 95% CI: 0.57–0.77, P<0.001, I^2=0), indicating that insufficient N1 lymph node dissection might indeed exist among the other studies and would lead to heterogeneous result.

In some centers, intrapulmonary nodes are detected by pathologists to define the disease lymphatic invasion status, which may lead to insufficient staging (6). To better define patients with skip N2 metastasis, surgeons should consider performing intrapulmonary node dissection to promote anatomic recognition of specimens and location of foci. Toward this goal, a standard intrapulmonary lymph node retrieval procedure would be a useful addition to the existing protocol (27).

Relationship between clinicopathologic factors and skip metastasis

Some studies compared the relationship between clinicopathologic factors and skip metastasis. Tanaka *et al*. reported a higher rate of skip metastasis in lung squamous carcinoma while Guerrera *et al*. observed a higher incidence of skip metastasis in patients with EGFR mutation (8,28). A previous article concluded that tumor location, histological type and tumor size were significant factors for skip metastasis (7). No significant difference was reported in patients underwent Video assisted thoracic surgery or thoracotomy in another work (29). According to our study, lung squamous carcinoma tended toward increased skip N2 metastases compared with adenocarcinoma. Factors such as differentiation, pleural invasion, smoking status or tumor diameter were not correlated with skip metastasis in our results. The occurrence of skip metastasis was also examined. Skip occurred in stations 3 [while 3A is rarely seen (30)] and 4 in right upper lobe tumor while in station 5 and 6 in left upper lobe lesion. In both lower lobe foci group, station 7 was the most frequently influenced station according to previous studies (25). The existence of metastasis in stations 4 and 7 is prevalent in patients with positive mediastinal lymph node (31). Thus, mediastinal lymph node dissection would require additional care in the above stations under the nodal station anatomy (32) even if no N1 station metastasis was found.

According to previous articles and our results, skip N2 metastasis could be a favorable prognostic indicator among patients with N2 disease. To discover the existence of skip metastasis, we recommend a thorough dissection of intra and hilar lymph nodes by trained surgeons and pathologists. The classification of N staging needs further development. Okada *et al*. proposed a different borderline between N1 and N2 in lower lobe tumors (33). Different levels of intrapulmonary lymph node metastasis were also reported to be of prognostic significance (34). However, comparison between skip and non-skip single N2 patients was not conducted in our work due to the scarcity of included studies. A further subdivision of patients with lymph node metastasis is needed. Furthermore, our work validated the subclassification of N2 based on the newest IASLC staging (2).

Our study presents some limitations as well. Some included articles did not report the exact number of mediastinal lymph node retrieved. According to the proposal for 8th edition of staging, patients with N2 disease are subclassified based on the number of metastatic station (2). A direct comparison between skip metastasis and multi-stational N1 should also be conducted in future studies. Furthermore, the publication bias among the included articles should be noticed and studies based on large-scale population should be conducted to ascertain the prognostic effect of skip metastasis.

Conclusions

Our study demonstrated a significant favorable prognostic association between skip metastasis and overall survival and disease-free survival among patients with N2 disease. Intrapulmonary lymph node retrieval should be validated more carefully. Some uncertainties regarding the significance and role of skip metastases remain unresolved, and further studies are warranted to unveil the underlying mechanism.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm-20-3513). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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