Risk Factors for Brain Metastases in Patients with Non-Small Cell Lung Cancer: A Meta-Analysis of 43 Studies

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Abstract

Background: Lung cancer is a leading cause of cancer-related mortality worldwide. The purpose of our meta-analysis was to assess the risk factors for brain metastases in patients with non-small cell lung cancer.

Methods: Multiple databases, including PubMed, EMBASE, Cochrane Library, CNKI and Wanfang were systematically searched, then the meta-analysis was performed with RevMan 5.3 software and carried out evidence quality evaluation according to the GRADE standard. The estimated odds ratio and 95% confidence intervals were set as effect measures. Moreover, funnel plots and sensitivity analysis were used to assess the publication bias and reliability of the articles, respectively.

Results: A total of 43 studies with 11415 participants were eligible. The results indicated that female, adenocarcinoma or non-squamous cell carcinoma, advanced tumor stage, node stage, lymphatic metastasis, epidermal growth factor receptor gene mutation, kirsten rat sarcoma viral oncogene gene mutation, and higher levels of carcinoembryonic antigen, carbohydrate antigen 199, cytokeratin-19 fragment, neuron-specific enolase and carbohydrate antigen 125 were significantly associated with an increased risk of brain metastases ($P<0.05$) in non-small cell lung cancer patients. Moreover, the non-small cell lung cancer with brain metastases group had a significantly lower survival rate than the non-small cell lung cancer group ($P<0.05$).

Conclusions: The meta-analysis demonstrated that non-small cell lung cancer patients with brain metastases have more aggressive clinical features and poor survival prognosis.

Introduction

Lung cancer is one of the most common malignant tumors worldwide.¹ Among lung cancer patients, non-small cell cancer (NSCLC) is the most common histology, approximately 80%~85%.² The diagnosis of NSCLC usually based on tumor markers, imaging and histopathological characteristics considering the early clinical symptoms of NSCLC are not typical. According to the statistics, around 40% of NSCLC patients have already combined with metastatic diseases when they are diagnosed,^{3,4} with the most common location for metastasis including the brain, bone and liver et al. Despite an increasing number of progress in therapy,¹ the prognosis for patients with advanced lung cancer is still mean, especially for patients combined with brain metastases (BM).⁵

According to the previous studies, BM is an important reason for morbidity and mortality for cancers, approximately 20%-40% of NSCLC patients will develop BM,⁶ and the median survival period of NSCLC patients with BM is only about 3~6 months.⁷ Although some targeted methods can play a role in controlling intracranial metastases tumor, there are little drugs can cross the blood-brain barrier effectively.⁸ Radiation therapy and surgical operation are the most effective treatment for BM now, but these two treatments may influence patients' quality of life obviously.⁹ Therefore, a greater assessment of the risk factors of NSCLC patients associated with BM becomes a rising concern, which can not only offer an earlier prevention and treatment of BM but also help patients achieve a prolonged survival. A pooled analysis of the association between BM and NSCLC has not been performed. The purpose of our meta-analysis was to summarize the risk factors, clinical characteristics and survival rates of NSCLC patients with BM.

Materials And Methods

Search strategy

Different databases, including PubMed, EMBASE, Cochrane Library, CNKI and WanFang were systematically searched for studies without language, publication and time restrictions (from incipency to December 2019). The search terms included "brain metastases", "nervous metastases" or "cerebral metastases" and "non-small cell cancer", "lung cancer" or "lung malignant disease". Finally, we sifted the references of the relevant studies to identify potentially related articles.

Eligibility/Exclusion criteria

Inclusion criteria

- i. Studies assessing the clinical features and prognosis of the NSCLC patients with BM.

- ii. The diagnostic criteria of NSCLC and BM were clear and unified, including histologically or cytologically confirmed NSCLC; imaging findings including computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET) confirmed BM.
- iii. At least one of the outcome measures of interest was provided in the study or could be calculated from the published data.
- iv. The number of cancers in the article was more than 20.

Exclusion criteria

- i. Studies based on overlapping patients.
- ii. Meta-analyses, reviews, case reports or reports based on expert experience.
- iii. No effective data could be extracted.

Data extraction and assessment of study quality

Two reviewers (Chen and Hua) independently extracted the data from all included studies, and any disagreements were resolved by discussion. The following data were retrieved from the studies: (i) basic characteristics of the included studies, including the first author's name, year of publication, country, and characteristics of the study population (gender, age, number), and study design. (ii) multivariable ORs of clinical characteristics, including age, gender, smoking history, treatment history, pathological type, Tumor (T) stage, Node (N) stage, lymphatic metastasis, distant metastasis (except outside the brain), epidermal growth factor receptor (EGFR) gene mutation, kirsten rat sarcoma viral oncogene (KRAS) gene mutation and ECOG scale. (iii) clinical laboratory parameters, including the levels of carcinoembryonic antigen (CEA), carbohydrate antigen 199 (CA199), cytokeratin-19 fragment (CYFRA21-1), neuron-specific enolase (NSE) and carbohydrate antigen 125 (CA125).

The quality of the included studies was assessed with the Newcastle-Ottawa Scale (NOS)¹⁰ and scores of 5-9 were considered fair, while scores of 1-4 indicated a high risk of bias. Cochrane Risk of Bias Tool was also used by two independent viewers, and following criteria were used to evaluate bias in each trial: random sequence generation; concealment of allocation; blinding of participants and personnel; blinding of outcome assessment; incomplete data; The risk of bias was classified as "unclear", "low" or "high".

Evaluation of evidence quality

The results of meta-analysis were evaluated using the GRADE profiler, and degradation were considered in terms of evidence quality including risk of bias, inconsistency, indirectness, imprecision and publication bias, while upgradation were decided by large effect, plausible confounding and dose-response gradie.¹¹

Statistical analysis

We utilized the RevMan 5.3 software to analyze the data in our meta-analysis. The estimated odds ratio (OR) and weighted mean difference (WMD) was used to evaluate the affiliation between the event of BM and the clinicopathologic features of NSCLC patients. All statistic values were reported with 95% confidence intervals (95%CI), and the two-sided *P* value threshold for statistical significance was set at 0.05. The Chi-square test and the I^2 statistic were used to evaluate heterogeneity among studies. In expansion, I^2 more than 50% and $P < 0.05$ for the Chi-square test suggested significant heterogeneity among the included studies. When the hypothesis of homogeneity was not rejected, a fixed-effects model was used. Otherwise, a random-effects model was used to estimate OR and 95%CI.¹² To investigate the effects of individual studies on the overall results, we also performed a sensitivity analysis by excluding each study in turn. In the end, potential publication bias was tested by a funnel plot. Because the number of included studies too small may inevitably result in publication bias, funnel plots were generated for indexes with more than 10 relevant studies.¹³

Results

Baseline study characteristics and quality assessment

We identified 14289 studies in our efficient literature search as shown in Fig. 1, and 36 studies were excluded because they were reduplicative studies. After checking the title and abstract, we retrieved 138 potential studies to review the full-text manuscript. At that point, 95 studies were avoided because they lacked an outcome of interest or since they had no compelling information and control groups. Ultimately, 43 studies met our selection criteria for the final analysis. The characteristics and demographic data of all studies included are presented in Table 1.¹⁴⁻⁵⁶ The retrieved studies were published from 2004 to 2019, and a total of 11415 patients were recruited. Of all studies, 26 were cohort studies and other 17 were case-control studies.

For quality assessment, the NOS was used for evaluation because all of the included studies were case-control studies or cohort studies. The results showed that all included studies were of fair quality (Table 1).

Meta-analysis of clinical characteristics of patients

A meta-analysis of the relevant studies suggested that the prevalence of BM was significantly higher among female patients (OR=1.18, 95%CI: 1.11-1.25, $P<0.00001$) (Fig. 2B). Nevertheless, patients with younger than 60 years old (OR=1.11, 95%CI: 0.78-1.59, $P=0.55$) (Fig. 2A), a smoking history (OR=1.06, 95%CI: 0.78-1.46, $P=0.070$) (Fig. 2C) and a treatment history (OR=0.84, 95%CI: 0.62-1.14, $P=0.27$) (Fig. 2D) did not show significant differences between BM with NSCLC group and sample NSCLC group. Obvious heterogeneity was observed among age ($I^2=99\%$, $P<0.00001$) and a smoking history ($I^2=69\%$, $P<0.00001$), thus a random-effects model was utilized. In addition, a fixed-effects model was used for the other indexes as there was no obvious heterogeneity of the above studies.

Meta-analysis of tumor-related indexes

A meta-analysis of the relevant studies suggested that NSCLC patients with adenocarcinoma (OR=2.43, 95%CI: 1.92-3.08, $P<0.00001$) (Fig. 3A) was a risk factor for BM. Conversely, squamous carcinoma was a protective factor (OR=0.39, 95%CI: 0.27-0.54, $P<0.00001$) (Fig. 3B). Meanwhile, the prevalence of BM was significantly higher among patients with higher T stage (OR=1.37, 95%CI: 1.04-1.82, $P=0.03$) (Fig. 3C), higher N stage (OR=2.01, 95%CI: 1.25-3.22, $P=0.004$) (Fig. 3D), with the number of lymphatic metastasis larger than 6 (OR=2.86, 95%CI: 1.89-4.33, $P<0.00001$) (Fig. 3E), EGFR gene mutation (OR=2.45, 95%CI: 1.65-3.65, $P<0.00001$) (Fig. 3G) and KRAS gene mutation (OR=2.88, 95%CI: 1.76-4.72, $P<0.00001$) (Fig. 3H). In contrast, patients with other distant metastasis (OR=1.34, 95%CI: 0.47-3.79, $P=0.58$) (Fig. 3F) and ECOG scale (OR=1.30, 95%CI: 0.89-1.91, $P=0.17$) (Fig. 3I) did not show significant differences between two groups. Furthermore, a fixed-effects model was utilized considering no obvious sample heterogeneity in the above studies while a random-effects model was used for studies with obvious heterogeneity.

Meta-analysis of clinical laboratory parameters

The results showed NSCLC patients had higher levels of CEA (WMD=10.94, 95%CI: 7.47-14.40, $P<0.00001$) (Fig. 4A), CA199 (WMD=20.23, 95%CI: 12.20-28.26, $P<0.00001$) (Fig. 4B), CYFRA211 (WMD=1.78, 95%CI: 0.04-3.51, $P=0.04$) (Fig. 4C), NSE (WMD=9.66, 95%CI: 6.18-13.14, $P<0.00001$) (Fig. 4D) and CA125 (WMD=22.39, 95%CI: 9.79-34.98, $P=0.0005$) (Fig. 4E). Obvious heterogeneity was observed among these five indexes ($I^2>50\%$; $P<0.05$), thus, a random-effects model was utilized.

Meta-analysis of survival rates

Eight studies assessed the survival rates. The resulted indicated that, as time goes on, the survival rates at 1-, 2-, 3-, 5-year of BM with NSCLC patients were significantly decreased compared to that of NSCLC patients ($P<0.05$) (Fig. 5).

Sensitivity analysis and risk of bias

The Newcastle-Ottawa Quality Assessment scales (Table 1) and GRADE evaluation (Fig. 6, Fig. 7) indicated that the included studies were of acceptable quality. Risk of bias was summarized and evaluated in Fig. 8 and Fig.9. A sensitivity analysis was conducted to evaluate the influence of each included study, the results showed that heterogeneity and the pooled ORs or WMDs of BM were not significantly altered by any single study, indicating that our conclusions are relatively reliable. Funnel plot were generated for the indexes and further shown in Supplementary Fig. S1.

Discussion

Our meta-analysis of individual 43 studies incorporating 11415 participants assessed the risk factors and prognosis of BM in NSCLC patients. Our findings might be important in the prevention and evaluation of NSCLC patients with BM. The results were divided into four categories: clinical characteristics, tumor-related indexes, clinical laboratory parameters and survival rates of patients.

By summarizing all relevant studies, we found female, adenocarcinoma or non-squamous cell carcinoma, advanced tumor stage, node stage, lymphatic metastasis, EGFR gene mutation, KRAS gene mutation, and higher levels of CEA, CA199, CYFRA211, NSE and CA125 were clinical risk factors which can predict BM.

Some multivariate analyses have already showed the risk of BM was reduced with age, but our meta-analysis found that age 60 years old or younger was associated with the incidence of BM. The reason why an increased risk in the younger age group remains unclear, the possible mechanism maybe due to the differential expression of some biological markers associated with BM such as Ecadherin and Caspase-3 between younger and older patients.⁵⁷ It is well known that adenocarcinoma is common in female and commonly metastasize to the brain, which may explain why female have a higher incidence of BM.²⁴ Moreover, a recent study⁵⁸ showed that the proportion of lung cancers diagnosed among smokers is increasing, the risk of developing lung cancer is 20-40 times higher in smokers compared to never-smokers, which may explain why a high proportion of smoking history in NSCLC patients with BM.

BM is closely related to tumor-related indicators. In 2015, Won et al⁵⁹ established a nomogram for predicting BM in NSCLC patients, he found histological type, T stage and N stage were closely linked to BM. Similarly, Wang et al⁶⁰ considered non-squamous cell carcinoma and multiple lymphatic metastasis were both risk factors for BM, which was also supported by our study. We found non-squamous cell carcinoma, especially adenocarcinoma was an independent risk factor for BM, which may be attributed to the invasive growth of adenocarcinoma. Previous research⁶¹ guessed if tumor spread to the lymphatic system of the chest, it will also involve the distant metastasis of other organs (including bone, liver and kidney) and if distant metastasis happened, the probability of BM will increase. Our study is consistent with these studies in identifying lymphatic metastasis as significant prognostic factor. A meta-analysis involving 22 studies has reported that patients with EGFR mutation type were more susceptible to develop into BM than those with EGFR wild type (OR=1.99, 95%CI: 1.59-2.48, $P=0.000$).⁶² The possible mechanism may involve EGFR activating MET via protein kinases and activating STAT3 via interleukin-6 to promote BM in NSCLC.^{63,64}

Besides, our study found the levels of relevant serum tumor markers were related to BM in NSCLC patients. We identified five prognostic factors: higher levels of CEA, CA199, CYFRA211, NSE and CA125. It has been reported that CEA-positive tumor cells are more easier to cross the blood-brain barrier and adhere to the cerebral vasculature, which is beneficial to the occurrence of BM.⁶⁵ Our study also found that higher level of CEA was a risk factor for BM. Meanwhile, previous studies^{45,49} demonstrated the level of serum CEA, CA199, CA125 and CYFRA211 were higher than that in the BM group than the control group, providing an important reference for early detection of BM in NSCLC.

The results of cohort studies and case-control studies have also been analyzed separately (Table 2). The statistical results based on cohort studies were consistent with the results based on case-control studies except the distant metastasis. Considering cohort studies had a more proportion and were more likely to be authentic, we think these two indexes were also probably significant risk factors for BM now. Moreover, the heterogeneity of five serum tumor markers was all significant ($P<0.05$), which may be attributable to failure to publish studies with negative results or different measuring means. And then we found there were only case-control studies for some indexes after stratified by study design, which needs more studies to confirm the conclusion.

In addition, we assessed the differences in survival rates at 1-, 2-, 3-, 5-year respectively between BM with NSCLC patients and sample NSCLC patients. The results indicated that the former group had a significantly lower survival rate ($P<0.05$). On one hand, patients with BM are more likely to combine with distant metastasis of other sites, increasing the mortality of patients. On the other hand, as the results shown in above, NSCLC patients with an advanced tumor stage were easier to combine with BM, which can also decrease the survival time of NSCLC patients.

Our study inevitably had some shortcomings and omissions. First, the studies included in our meta-analysis were all cohort or case-control studies and the quality assessment by the NOS showed that the 34 included studies had relatively low scores (5~8), indicating that the results may have been subject to selection bias. Second, potential risk factors such as cancer history, treatment approach or other biological markers could also promote the occurrence of BM and affect the prognosis of cancers, which cannot be

explored because the studies included may not be enough to provide the information required. Third, funnel plots showed there was no obvious publication bias for indexes with more than 10 relevant studies, but we considered that potential bias couldn't be completely excluded for indexes with fewer than 10 studies.

Conclusions

In summary, our meta-analysis revealed that NSCLC patients with BM have some different clinical features, including female, adenocarcinoma or non-squamous cell carcinoma, advanced tumor stage, node stage, lymphatic metastasis, EGFR gene mutation, KRAS gene mutation and higher levels of CEA, CA199, CYFRA211, NSE and CA125. Moreover, the presence of BM could significantly decrease the survival time of NSCLC patients, indicating a poor survival prognosis. The meta-analysis demonstrated that NSCLC patients with BM have more aggressive clinical features and a poor survival prognosis.

Abbreviations

BM, brain metastasis; NSCLC, non-small cell lung cancer; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; T, tumor; N, node; EGFR, epidermal growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase; CA125, carbohydrate antigen 125; NOS, Newcastle Ottawa Quality Assessment Scale; OR, odds ratio; WMD, weighted mean difference; CI, confidence interval.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Competing interest

The authors declare that they have no competing interests.

Authors' contributions

Shanshan Chen and Xin Hua designed the study; Hongming Zhang and Xiaolizhu provided substantial conception; Shuhua Han, Jinfang Jia and Lu Xu collected the data; Shuzhen Wei and Ying Wu performed the statistical analysis and wrote the first draft of the manuscript; All authors (Shanshan Chen, Xin Hua, Jinfang Jia, Ying Wu, Shuzhen Wei, Lu Xu, Shuhua Han, Hongming Zhang, Xiaoli Zhu) contributed to the interpretation of the results and critically reviewed the first draft of the manuscript. All authors gave final approval for submission of the manuscript.

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Tables

Table 1:
Basic characteristics of the retrieved studies.

Study	Year	Country	Gender(M/F)	Age	BM/total	Ad/other	BM diagnosis	Study design	NOS
Bajard et al ¹⁴	2004	France	279/26	62(33-88)	77/305	87/218	CT	Cohort	8
Carolan et al ¹⁵	2005	Canada	47/36	NM	29/83	NM	NM	Cohort	6
Arrieta et al ¹⁶	2009	Mexico	164/129	60.7±0.7	170/293	190/103	CT	Cohort	8
L Y et al ¹⁷	2010	China	132/61	58(31-77)	67/193	NM	MRI/CT	Cohort	6
H S et al ¹⁸	2010	China	74/50	59.81(40-75)	35/124	73/51	MRI/CT/PET	Case control	6
Dimitropoulos et al ¹⁹	2011	Greece	143/18	65.1±8.9	39/161	59/102	CT	Cohort	5
C J et al ²⁰	2012	China	63/47	63(38-86)	22/110	51/59	MRI/CT/PET	Case control	6
D X et al ²¹	2012	China	156/61	60(27-79)	53/217	112/105	MRI/CT	Cohort	5
L F et al ²²	2012	China	62/41	58.6±14.9	41/103	NM	MRI	Cohort	7
C X et al ²³	2012	China	94/20	NM	36/114	35/79	NM	Cohort	5
C L et al ²⁴	2013	China	95/55	60.42±11.33	100/150	61/89	NM	Case control	6
Hsiao et al ²⁵	2013	China	271/211	67.5±13.4	173/482	369/113	MRI/CT	Cohort	7
Ji Z et al ²⁶	2014	China	286/60	NM	74/346	NM	MRI/CT	Cohort	8
Iuchi et al ²⁷	2014	Japan	735/392	67(30-93)	154/1127	895/232	MRI	Cohort	6
Z WH et al ²⁸	2014	China	132/61	59.5±4.5	77/193	NM	CT	Cohort	7
L ZJ et al ²⁹	2014	China	116/68	58.43±12.68	96/184	86/98	MRI/CT/PET	Case control	7
Z WH et al ³⁰	2015	China	86/72	55(28-80)	62/158	112/46	CT	Cohort	5
Y H et al ³¹	2015	China	175/97	57(31-82)	78/272	93/179	MRI	Case control	8
Z JP et al ³³	2015	China	146/68	63(25-77)	121/214	NM	MRI/CT	Case control	6
L YP et al ³²	2015	China	72/80	55(28-80)	62/158	112/46	MRI/CT	Case control	6
X Z et al ³⁴	2015	China	78/46	63-55-80	51/124	65/59	NM	Case control	6
Z YZ et al ³⁵	2015	China	147/66	56.7±18.3	51/213	96/117	MRI/CT	Cohort	5
Z HY et al ³⁶	2015	China	129/46	55(29-76)	36/175	NM	MRI/CT	Cohort	7
Hsu et al ³⁷	2016	Canada	216/327	66-58-74	143/543	NM	MRI/CT	Cohort	6
Hendriks et al ³⁸	2016	Holland	535/303	63±10	153/838	324/514	MRI/PET	Cohort	5
Zhang et al ³⁹	2016	China	486/151	60(30-82)	NM/637	305/332	NM	Cohort	5

Koh et al ⁴⁰	2016	Korea	166/94	59.5(30-84)	94/260	194/66	MRI/CT	Cohort	8
C L et al ⁴¹	2016	China	51/16	NM	27/67	NM	MRI/CT	Case control	5
D MM et al ⁴²	2016	China	55/27	31-81	41/82	NM	NM	Case control	5
Tomasini et al ⁴³	2016	France	94/48	62 (31–88)	81/142	NM	NM	Cohort	6
L W ⁴⁴	2017	China	95/53	61.2±5.8	35/148	103/45	NM	Cohort	7
L F ⁴⁵	2017	China	84/64	NM	47/148	108/40	MRI/CT/PET	Case control	5
G QH et al ⁴⁶	2017	China	86/42	56.86±9.88	62/128	92/36	MRI/CT	Case control	7
D CY et al ⁴⁷	2017	China	40/32	49.26±10.36	15/72	NM	MRI/CT	Cohort	6
Chang et al ⁴⁸	2018	China	250/241	NM	78/491	444/47	MRI/CT	Cohort	8
Z XL et al ⁴⁹	2018	China	66/66	38-82	65/132	91/41	MRI/CT	Case control	6
L M et al ⁵⁰	2018	China	88/65	NM	41/153	123/30	MRI/CT	Case control	6
H TC et al ⁵¹	2018	China	57/103	58.21±11.73	41/160	96/41	MRI/CT	Cohort	7
Z Z et al ⁵²	2019	China	80/55	62.8±2.8	57/135	79/191	MRI/CT	Case control	6
L J et al ⁵³	2019	China	NM	51.85±13.73	51/125	NM	MRI/CT	Case control	6
L S et al ⁵⁴	2019	China	74/46	NM	40/80	NM	MRI/CT	Case control	5
C X et al ⁵⁵	2019	China	897/568	25-84	319/1465	972/493	MRI/CT	Cohort	8
H LP et al ⁵⁶	2019	China	84/26	61±17	27/110	38/72	MRI/CT	Cohort	6

Abbreviations: M/F, male/female; **BM**, brain metastasis; **TNM**, tumor node metastasis stage; **Ad**, adenocarcinoma; **NOS**, Newcastle Ottawa Quality Assessment Scale; **MRI**, magnetic resonance imaging; **CT**, computed tomography; **PET**, positron emission tomography; **NM**, not mentioned.

Table 2:
The results stratified by study design for risk factors included in the meta-analysis

Study factors	Study type	No. of studies	OR (95% CI) or	P	Heterogeneity		Model used
			WMD (95% CI)		I ² (%)	P _h	
Age	cohort studies	16	1.12(0.75-1.65)	0.59	99%	<0.00001	Random
	case-control studies	4	1.12(0.41-3.07)	0.83	90%	<0.00001	
Gender(Female)	cohort studies	15	1.37(1.20-1.55)	<0.00001	27%	0.15	Fixed
	case-control studies	9	1.12(1.05-1.21)	0.001	31%	0.17	
A smoking history	cohort studies	9	1.11(0.67-1.84)	0.67	80%	<0.00001	Random
	case-control studies	7	1.02(0.74-1.41)	0.90	25%	0.24	
A treatment history	cohort studies	2	0.94(0.60-1.48)	0.80	0%	0.56	Fixed
	case-control studies	1	0.76(0.5-1.16)	0.20	-	-	
Adenocarcinoma	cohort studies	12	2.29(1.57-3.33)	<0.00001	79%	<0.00001	Random
	case-control studies	10	2.52(1.97-3.23)	<0.00001	0%	0.87	
Squamous cell carcinoma	cohort studies	8	0.30(0.21-0.41)	<0.00001	32%	0.17	Random
	case-control studies	9	0.48(0.28-0.8)	0.001	74%	0.0002	
Tumor stage	cohort studies	10	1.24(0.89-1.73)	0.20	75%	<0.00001	Random
	case-control studies	4	1.84(1.17-2.89)	0.009	44%	0.15	
Node stage	cohort studies	7	2.31(1.51-3.53)	0.0001	73%	0.001	Random
	case-control studies	2	1.01(0.07-15.03)	0.00	92%	0.0004	
1ymphatic metastasis	cohort studies	2	3.24(1.96-5.36)	<0.00001	0%	0.89	Fixed
	case-control studies	1	2.17(1.03-4.56)	0.04	-	-	
Distant metastasis	cohort studies	2	0.87(0.12-6.39)	0.89	92%	0.0006	Random
	case-control studies	2	2.01(0.29-13.86)	0.05	94%	<0.00001	
EGFR gene mutation	cohort studies	8	1.88(1.25-2.85)	0.003	89%	<0.00001	Random
	case-control studies	3	5.87(1.87-18.43)	0.002	24%	0.008	
KRAS gene mutation	cohort studies	1	3.04(1.83-5.04)	<0.00001	-	-	Fixed
	case-control studies	1	1.00(0.11-9.42)	1.00	-	-	
ECOG scale>2	cohort studies	5	1.30(0.89-1.91)	0.17	77%	0.002	Fixed
CEA level	cohort studies	2	3.07(-10.70-16.84)	0.66	99%	<0.00001	Random

	case-control studies	9	1.68(1.04-2.31)	<0.00001	88%	<0.00001	
CA199 level	case-control studies	7	20.23(12.20-28.26)	<0.0001	94%	<0.00001	Random
CYFRA211 level	case-control studies	4	1.78(0.04-3.51)	0.04	92%	<0.00001	Random
NSE level	cohort studies	1	7.73(4.48-10.98)	<0.0001	-	-	Random
	case-control studies	2	5.42(-6.12-16.95)	0.36	97%	<0.00001	
CA125 level	cohort studies	1	7.67(4.63-10.71)	<0.0001	-	-	Random
	case-control studies	7	24.7(8.45-40.95)	0.003	98%	<0.00001	

Abbreviations: OR, odds ratio; WMD, weighted mean difference; CI, confidence interval; EGFR, epidermal growth factor receptor; KRAS, kirsten rat sarcoma viral oncogene; CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase; CA125, carbohydrate antigen 125.

Figures

Figure 1

Selection of the included studies.

Figure 2

Meta-analysis of clinical characteristics. (A) age younger than 60 years old, (B) gender is female, (C) a smoking history, (D) a treatment history.

Figure 4

Meta-analysis of clinical laboratory parameters. (A) CEA, (B) CA199, CA125, (D) CYFRA211, (E) NSE. Abbreviations: CEA, carcinoembryonic antigen; CA199, carbohydrate antigen 199; CA125, carbohydrate antigen 125; CYFRA21-1, cytokeratin-19 fragment; NSE, neuron-specific enolase.

Figure 5

Meta-analysis of survival rates. (A) 1-year survival rate; (B) 2-year survival rate; (C) 5-year survival rate.

Figure 6

GRADE evidence profile

[illegible]

 
76	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
77	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
78	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
79	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
80	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
81	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
82	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
83	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
84	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
85	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
86	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
87	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
88	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
89	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
90	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
91	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
92	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
93	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
94	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
95	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
96	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
97	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
98	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
99	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
100	Randomized trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Summary of Findings table

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Amela et al 2009	●	●	●	●	●
Bayard et al 2004	●	●	●	●	●
Carolan et al 2005	●	●	●	●	●
Chang et al 2018	●	●	●	●	●
C.J et al 2012	●	●	●	●	●
C.L et al 2013	●	●	●	●	●
C.L et al 2016	●	●	●	●	●
C.X et al 2012	●	●	●	●	●
C.X et al 2019	●	●	●	●	●
D.CY et al 2017	●	●	●	●	●
Dimitropoulos et al 2011	●	●	●	●	●
D.MM et al 2016	●	●	●	●	●
D.X et al 2012	●	●	●	●	●
G.OH et al 2017	●	●	●	●	●
Hendricks et al 2016	●	●	●	●	●
HLP et al 2019	●	●	●	●	●
H.S et al 2010	●	●	●	●	●
Hsiiao et al 2013	●	●	●	●	●
Hsu et al 2016	●	●	●	●	●
H.TC 2018	●	●	●	●	●
Iuchi et al 2014	●	●	●	●	●
Koh et al 2016	●	●	●	●	●
L.F 2017	●	●	●	●	●
L.F et al 2012	●	●	●	●	●
L.J et al 2019	●	●	●	●	●
L.M et al 2018	●	●	●	●	●
L.S et al 2019	●	●	●	●	●
L.W 2017	●	●	●	●	●
L.Y et al 2010	●	●	●	●	●
L.YP et al 2015	●	●	●	●	●
L.ZJ et al 2014	●	●	●	●	●
Tomasini et al 2016	●	●	●	●	●
X.Z et al 2015	●	●	●	●	●
Y.H et al 2015	●	●	●	●	●
Zhang et al 2016	●	●	●	●	●
Z.HY et al 2015	●	●	●	●	●
Z.J et al 2014	●	●	●	●	●
Z.JP et al 2015	●	●	●	●	●
Z.WH et al 2014	●	●	●	●	●
Z.WH et al 2015	●	●	●	●	●
Z.XL et al 2018	●	●	●	●	●
Z.YZ et al 2015	●	●	●	●	●
ZZ et al 2019	●	●	●	●	●
	Random sequence generation (selection bias)				
	Allocation concealment (selection bias)				
	Blinding of participants and personnel (performance bias)				
	Blinding of outcome assessment (detection bias)				
	Incomplete outcome data (attrition bias)				

Figure 9

Risk of bias summary

Supplementary Files

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