Original Article

Prognostic factors of oligometastatic non-small cell lung cancer: a meta-analysis

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Background: The prognostic factors of oligometastatic non-small cell lung cancer (NSCLC) are uncertain. We performed a meta-analysis to assess the prognostic factors of oligometastatic NSCLC patients who are most likely to achieve long-term survival.

Methods: We searched PubMed, EMBASE, the Cochrane to identify eligible articles and performed the meta-analysis of all randomized controlled trials (RCTs) and retrospective comparative studies revealing the prognostic factors of oligometastatic NSCLC. The primary endpoint of interest was overall survival (OS).

Results: We analyzed data from twenty-four eligible studies, including data from 1,935 patients with oligometastatic NSCLC. In the univariate analysis, we found no significant difference in OS of prognostic factors including age [hazard ratios (HRs) 1.02, 95% CI: 0.80–1.31, P=0.86], smoking status (HR 1.08, 95% CI: 0.80–1.46, P=0.62), type of metastases (HR 1.61, 95% CI: 0.86–3.03, P=0.14), but significantly positive prognoses containing female (HR 1.21, 95% CI: 1.02–1.45, P=0.03), (y)pN0 stage (HR 1.82, 95% CI: 1.40–2.36, P<0.00001), adenocarcinoma (HR 1.44, 95% CI: 1.10–1.88, P=0.008). In the multivariate analysis, patients with (y)pN0 stage had an obvious survival benefit compared with (y)pN1 (HR 1.63, 95% CI: 1.27–2.10, P=0.001), but no significant survival in contrast with (y)pN2 (HR 2.01, 95% CI: 0.80–5.03, P=0.14). In subgroup analyses, neither thoracic stage (HR 2.06, 95% CI: 1.52–2.78, P=0.55), (y)pT-stage of primary lung cancer (HR 1.38, 95% CI: 0.86–2.21, P=0.14) nor tumorous histology (HR 2.99, 95% CI: 2.10–4.28, P=0.91) and oligometastatic number (HR 1.25, 95% CI: 0.97–1.62, P=0.98) were significantly different in OS. However, patients with aggressive thoracic treatment (ATT) had improved survival (HR 0.56, 95% CI: 0.37–0.83, P=0.001), and notably, different strategies of ATT received by oligometastatic NSCLC patients might significantly influence survival (HR 0.54, 95% CI: 0.36–0.82, P<0.00001).

Conclusions: Overall, factors including age, smoking status, type of metastasis were not associated with long-term survival of oligometastatic NSCLC patients. However, our finding suggests that aggressive therapies in the primary lung cancer, as well as female, (y)pT-stage, absence of nodal diseases, adenocarcinoma histology have been clarified as positive prognosis. Further studies of prospective study for these patients are warranted.

Keywords: Prognostic factor; oligometastasis; non-small cell lung cancer (NSCLC); meta-analysis

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Introduction

Non-small cell lung cancer (NSCLC) is the leading cause of cancer mortality in man and women worldwide (1). Approximately half of all patients diagnosed with NSCLC, at the same time, present metastatic diseases. Despite the improved surgical techniques and advanced therapeutic regimens, its 5-year overall survival (OS) is still only about 18% (2). Unfortunately, more than 70% of cases are diagnosed at an advanced stage of the disease, and loss optimal opportunity for therapies (1).

The inspiration for this review depends on the strength of the rationale about cancer spread proposed by Hellman and Weichselbaum. Among the spectrum of locally identified to widely metastatic cancer, there exists an intermediate "oligometastatic state" where metastases are limited in number and location (3). It had hypothesized that in selected oligometastatic patients, locally aggressive therapies given with the intent of eradicating all sites of known metastatic sites could result in long-term survival, or even cure (4). Though multiple retrospective case series have reported long-term survival in oligometastatic NSCLC patients treated with curative intent (5), however, some scholars have suggested that the long-term survival outcomes observed in such studies may be more reflective for patient's selection, rather than treatment effect (5,6). Thus, there is a great need for clearly defined parameters to identify which patients might have a benefit survival of oligometastatic NSCLC.

A prognostic factor explaining part of the population heterogeneity is a variable measured in individual patients and is at the time of diagnosis able to provide information on clinical guide and select patient (7). Some independent prognostic factors have been identified in order to predict survival and to help in the management of patients with resectable NSCLC (8), such as performance status, age, TNM stage, and TNM stage, age, sex, weight loss with advanced NSCLC (9). Since several emerging reports in the articles describing the prognostic factors of NSCLC, and the available studies permitting the delineation of factors predictive of long-term survival of oligometastatic NSCLC were rare. Therefore, we performed a meta-analysis to identify more benefit factors for long-term OS of oligometastatic NSCLC.

Methods

Search strategy and selection criteria

In cooperation with a trained librarian, we identified articles by searching PubMed, EMBASE and the Cochrane from inception to Mar 1, 2017 to ensure that all possible studies were found. The search strategy included the following terms combined of "non-small cell lung cancer OR non-small cell lung carcinoma OR non-small cell lung neoplasm OR non-small cell lung tumor OR NSCLC OR pulmonary adenocarcinoma OR lung adenocarcinoma OR adenocarcinoma of the lung OR lung squamous carcinoma OR pulmonary squamous carcinoma OR squamous cell lung carcinoma" AND "metast* OR oligomet* OR stage IV OR late stage OR advanced stage" AND "risk* OR prognos* OR epidemiology OR etiology". We restricted our searches to reports published in English.

Two reviewers independently screened the titles and abstracts of retrieved articles. This systematic review incorporated studies that reported populations meeting the following inclusion criteria: (I) NSCLC confirmed histologically; (II) NSCLC patients with 1–5 synchronous or metachronous metastases. (A synchronous metastasis was defined as being diagnosed at the same time or within 2 months of the primary lung and metachronous as ≥2 months after the histological diagnosis of primary lung); (III) a controlled primary tumor (defined as previous or current treatment of the primary tumor with radiation, primary surgery, or combination, with or without systematic chemotherapy); (IV) a uncontrolled primary tumor (defined as palliative treatment or without any primary treatment); (V) reported outcome of interest (i.e., OS); (VI) from an original study (i.e., retrospective study). Articles were excluded based on the following criteria: (I) not oligometastatic NSCLC; (II) duplicate articles; (III) the outcomes of interest [OS, hazard ratios (HRs)] of oligometastatic NSCLC patients could not be ascertained or separately analyzed; and (IV) data was insufficiently provided or was not extractable. The full text article of any study that appeared to meet the inclusion criteria was retrieved for further examination. Disagreements between reviewers regarding data abstraction were resolved through discussion.

Data extraction and study quality

For the review, the same reviewers extracted the data independently using standard data collection forms. The following information retrieved from all original reports: primary author, year of publication, number of eligible patients, age, gender, type of study, follow-up time, (y)pT and N-stage of the primary lung cancer (AJCC 7th edition),

histology of primary lung cancer, thoracic stage [Union for International Cancer Control (UICC) 7th edition], treatment of primary lung cancer or both sites (primary and metastatic sites), OS and prognostic factors (univariate and multivariate). Preferred index for evaluating the risk of prognostic factors was HR. The primary endpoint of interest was OS which was defined as time to death from any cause, or to end of follow-up (censored).

The quality of eligible articles was evaluated by a modification of the Newcastle-Ottawa Scale (NOS). Full-length articles were all available for review. Among the included studies, matching criteria were variable, and little matching information was identified from the conference abstracts.

Statistical analysis

We analyzed data from all included patients, as well as the following baseline characteristics: sex, age (<65 *vs.* ≥65 years), smoking status (never or former *vs.* current), (y)pN stage (N0 *vs.* N1–3), tumorous histology (adenocarcinoma *vs.* others).

We did further exploratory analyses in the subgroups for the following factors: (y)pTNM stage [(y)pT1 *vs.* (y)pT2 *vs.* (y)pT3, (y)pN0 *vs.* (y)pN1 *vs.* (y)pN2], thoracic stage (I *vs.* II *vs.* III), tumorous histology (adenocarcinoma *vs.* squamous carcinoma *vs.* large cell carcinoma), oligometastatic number (n=1 *vs.* n=2 *vs.* n=3–5), aggressive therapy (AT) (AT to primary lung site *vs.* AT *vs.* AT to both sites), in order to describe possible heterogeneity of prognosis.

We calculated HR and 95% CIs for OS with Cox proportional hazards regression. We did an integration test of prognostic factors efficacy for each subgroup for all outcome index. We also analyzed the primary endpoint by trail, with all patients who were originally included in the eligible articles. These HRs and CIs slightly differ from the original articles whose definite follow-up information was not provided.

We calculated I^2 and Q to assess whether significant heterogeneity existed between the included studies and did statistical analyses with Review Manager (version 5.3.0). P value of 0.05 or less was considered as statistically significant.

Results

Our initial search identified 7,787 potentially eligible articles and excluded 7,617 citations by title that did not meet eligibility criteria. Finally, we ensured 24 eligible publications according to study the abstracts of the remaining 170 articles (*Figure 1*). All of these full eligible articles were retrospective trials. We were able to extract prognostic factors for each article. *Table 1* shows the main characteristics of included studies.

Included trials were published between 1989 and 2014. The selected trials were conducted in United States [6], France [4], Italy [3], Germany [2], Canada [2], China [2], Japan [1], Turkey [1], Spain [1], Korea [1], and Netherland [1]. Of the twenty-four articles, there were four literatures reporting synchronous and metachronous metastasis, twenty studies exclusively involving synchronous metastasis. A total of 1,935 eligible participants were included and the sample size ranged from 28 to 219 patients. *Table 2* describes the main characteristics of the selective patients in the meta-analysis.

Univariate analysis

Firstly, we compared the effects on the prognosis of oligometastatic NSCLC between synchronous and metachronous metastasis. According to the quantitative synthesis, we detected no significant differences in OS (HR 1.61, 95% CI: 0.86–3.03; P=0.14) (*Figure 2*).

Then, we further explored prognostic factors of synchronous oligometastasis in NSCLC patients. Among these patients, the results showed that factors have no prognostic value among patients between younger and older than 65 years old (HR 1.02, 95% CI: 0.80–1.31; P=0.86, I^2=0%) (*Figure S1*), as well as smoking status (HR 1.08, 95% CI: 0.80–1.46; P=0.62, I^2=0%) (*Figure S2*). Female had slightly better prognosis (HR 1.21, 95% CI: 1.02–1.45; P=0.03, I^2=22%) (*Figure 3A*). (y)pN0 existence might be significant benefit prognosis compared with (y)pN + (N1–3) (HR 1.82, 95% CI: 1.40–2.36; P<0.00001, I^2=19%) (*Figure 3B*). Similarly, the result of tumorous histology demonstrated adenocarcinoma was favorite prognostic factor in the cohort (HR 1.44, 95% CI: 1.10–1.88; P=0.008, I^2=49%) (*Figure 3C*).

Multivariate analysis

In multivariable analysis, we also extracted data from 2 studies including 122 synchronous metastases in NSCLC patients, and found a survival benefit with (y)pN0 stage compared with (y)pN1 stage (HR 1.63, 95% CI: 1.27–2.10; P=0.001, I^2=0%), but no significant difference between (y)pN0 stage and (y)pN2 stage (HR 2.01, 95% CI: 0.80–5.03;

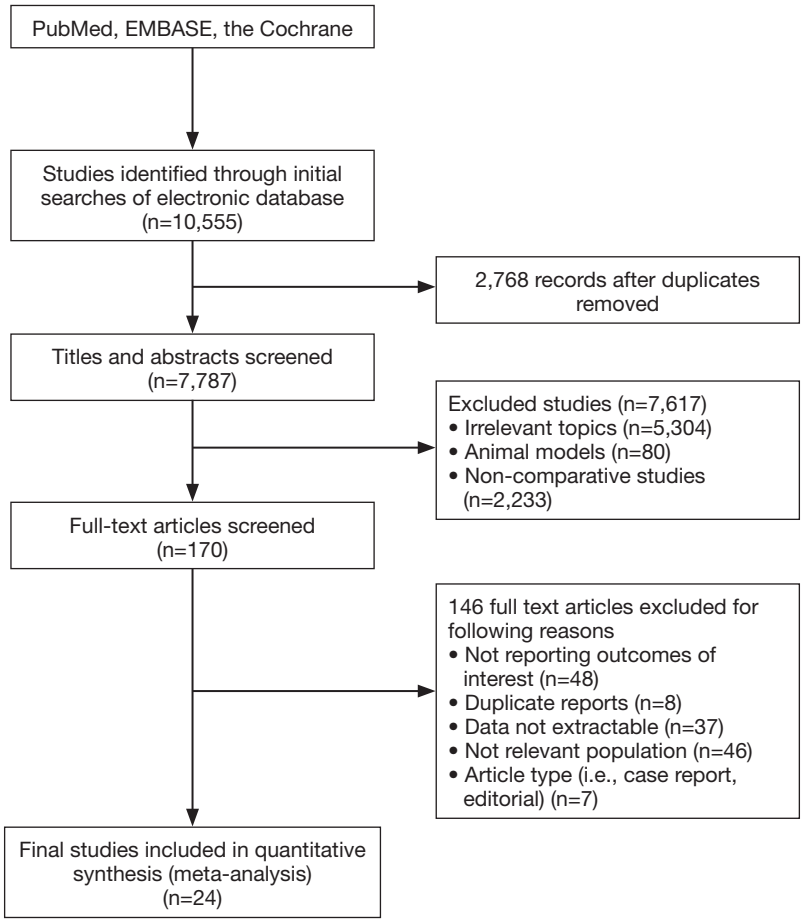

Figure 1 Flow diagram of studies identification and selection.

P=0.14, I^2=52%) (*Figure S3*).

Subgroup analysis

In subgroup analyses among prognostic factors, we recorded significant differences in OS of prognostic factors including tumorous histology, oligometastatic number, (y)pT-stage, Thoracic stage of synchronous oligometastasis from NSCLC (*Figures 4*,*S4*). And, patients with synchronous metastasis from NSCLC had a survival benefit with thoracic stage T1 compared with stage T3 (HR 2.07, 95% CI: 1.14–3.76; P=0.02) (*Figure S5*). Similarly, *Figure 4A* shows that patients diagnosed with thoracic stage I had a better prognosis in OS in contrast with either stage II (HR 1.69, 95% CI: 1.06–2.69; P=0.03) or stage III (HR 2.39, 95% CI: 1.52–3.75; P=0.0002). In contrast with patients whose progress was stage III of synchronous metastasis in NSCLC, patients diagnosed stage I or II had a positive prognosis in OS (HR 2.33, 95% CI: 1.01–5.38; P=0.05). In this review, we detected obvious benefit of patients with adenocarcinoma diagnosed pathologically in OS compared with squamous carcinoma or large cell carcinoma (HR 2.89, 95% CI: 1.41–5.92; P=0.004; HR 3.03, 95% CI: 2.01–4.57; P<0.00001, respectively) (*Figure 4B*). We also found that patients had a significant survival benefit with AT to primary sites, but no significant difference with AT to primary and metastatic sites (HR 0.43, 95% CI: 0.32–0.57; P<0.00001; HR 1.12, 95% CI: 0.67–1.88; P=0.67, respectively) (*Figure 5*). Furthermore, we observed that neither aggressive thoracic treatment [ATT, defined as thoracic surgery ± chemoradiotherapy (CRT)] (HR 0.43, 95% CI: 0.32–0.57; P<0.00001), nor ATT compared with CRT alone (HR 0.4, 95% CI: 0.16–1.01; P=0.05) were significantly associated with improved survival. But interestingly, upfront addition of radiotherapy (RT) to aggressive treatment (AT) to primary sites shows its negative prognosis in OS (HR

Table 1 Characteristics of the twenty-four articles included in the meta-analysis

Series	Year	Sample size	Inclusion period	Country	Follow-up (months)	Quality score
Tonnies *et al.* (10)	2014	99	1997–2009	Germany	36 [1–157]	★★★★★
Flannery *et al.* (11)	2003	72	1992–1999	United States	15.7 (0.5–107)	★★★★★
Louie *et al.* (12)	2009	35	1999–2006	Canada	7.8	★★★★★
Flannery *et al.* (13)	2008	42	1993–2006	United States	64.5 [9–150]	★★★★★
Griffioen *et al.* (14)	2013	61	1999–2012	Netherland	26.1	★★★★★
Parikh *et al.* (15)	2014	186	2002–2012	United States	24	★★★★★★
Mussi *et al.* (16)	1996	52	1975–1992	Italy	NR	★★★★
Granone *et al.* (17)	2001	30	1989–1999	Italy	[6–128]	★★★★★
Mordant *et al.* (18)	2012	94	1983–2006	France	11 [0–131]	★★★★★★
Demange *et al.* (19)	1989	54	1980–1985	France	NR	★★★★
Bonnette *et al.* (20)	2001	103	1985–1998	France	17.3	★★★★★★
Yuksel *et al.* (21)	2014	28	2004–2010	Turkey	23.6 [4–69]	★★★★
Melloni *et al.* (22)	2011	31	1992–2008	Italy	16 [2–123]	★★★★
Plones *et al.* (23)	2015	56	1987–2011	Germany	24.3	★★★★★
Kanou *et al.* (24)	2014	29	1980–2008	Japan	9.6 [3–107]	★★★★★
Xu *et al.* (25)	2013	213	2002–2010	China	15.6 [5–78]	★★★★★★
Kong *et al.* (26)	2006	35	2001–2004	Korea	12.5 (0.75–43)	★★★★★
Gray *et al.* (27)	2014	66	2000–2011	United States	31.9	★★★★
Lopez Guerra *et al.* (28)	2012	78	2000–2011	Spain	35 [2–109]	★★★★★★
Chidel *et al.* (29)	1999	219	1982–1996	United States	NR	★★★★★
Guo *et al.* (30)	2014	53	2005–2012	Canada	17.2 (3.6–73)	★★★★★
Girard *et al.* (31)	2006	51	1992–2004	France	NR	★★★★★
Sahqal *et al.* (32)	2015	214	1980–2014	United States	NR	★★★★★
Hu *et al.* (33)	2006	84	1993–2004	China	9.7 [1–86]	★★★★★

1.89, 95% CI: 1.08–3.31; P=0.03) (*Figure 6*). We found no heterogeneity among positive prognostic factors including (y)pT stage of primary sites, tumorous histology, thoracic stage, ATT.

Table 3 shows the exploratory analysis in OS of synchronous brain metastasis from NSCLC by treatment arms. The pooled HR with Gamma knife radiosurgery (GKRS) plus whole brain radiation therapy (WBRT) was 0.37; systemic chemotherapy was 0.96; complete lung resection was 0.17. Because of limited analysis of retrospective studies, the result showed no significant difference in treatment arms of GKRS plus WBRT compared with WBRT alone (P=0.21), but an obvious survival benefit between WBRT plus ATT and ATT alone (HR 0.22, P=0.002) in OS.

Discussion

Since Martini and Melamed (34) firstly published a literature to clarify the definition of multiple primary NSCLC and solitary metastases, and later Hellmann and Weichselbaum (3) described the term "oligometastases" as a restricted loco-regional tumor load in 1995. Based on the UICC 8th edition, the stage of M1b was correspondence

with concept of oligometastases. And despite the treatment for isolated distant metastases is gaining more and more momentum in the oncologic literature, some scholars found that the long-term survival outcomes observed might be more reflective for patient selection, rather than treatment effect (6). Moreover, the available studies assessing factors for long-term survival of oligometastatic NSCLC were rare. Thus, performing a meta-analysis on prognosis of oligometastases in NSCLC shows its great need.

Firstly, our finding shows that no significant benefit of metachronous metastases compared with synchronous metastases (HR 1.61, P=0.14). Several studies have evaluated the prognostic significance of synchronous versus metachronous metastases, and although none have reported significance in multivariable analyses, some previous studies' experiences suggested that the synchronous metastases presentation of lung cancer results in a negative prognostic factor (18,35,36). According to this meta-analysis, overall, the result that synchronous metastases presented as a negative prognostic factor is basically consistent with previous reports.

NSCLC is a heterogeneous disease (37). Patients in NSCLC with advanced stage are also full of heterogeneity. Synchronous solitary metastasis is assumed to be stage IV, as is widely distributed metastatic disease. Furthermore, patients categorized as stage IV with symptoms or not, usually receive systemic treatments (18). Although these systemic therapies are appropriate for the majority of patients with stage IV NSCLC, patients with synchronous solitary metastasis with positive prognosis may get more benefit from this strategy than those with negative

Table 2 Main characteristics of patients in the meta-analysis

Prognostic factors	With data available, n (%)
Univariate analysis	
Gender	567
Female	258 (45.5)
Male	309 (54.5)
Age, Years	360
<65	229 (63.6)
≥65	131 (36.4)
Smoking status	324
Never or former	196 (60.5)
Current	128 (39.5)
Type of metastases	201
Synchronous	108 (53.7)
Metachronous	93 (46.3)
N stage	382
N0	181 (47.4)
N1–3	201 (52.6)
Histology	142
Adenocarcinoma	83 (58.5)
Others	59 (41.5)
Multivariate analysis	
N stage	122
N0	67 (54.9)
N1	20 (16.4)
N2	35 (28.7)
Subgroup analysis	
T stage	156
T1	32 (20.5)
T2	103 (66)
T3	21 (13.5)
Oligometastatic number	384
N=1	188 (49)
N=2	196 (51)
Thoracic stage	358
I	52 (14.5)
II	87 (24.3)
III	219 (61.2)
Histology	223
Adenocarcinoma	172 (77.1)
Squamous carcinoma	20 (9)
Large cell carcinoma	31 (13.9)
Aggressive treatment	488
To primary sites	358 (73.4)
To primary and metastatic sites	130 (26.6)

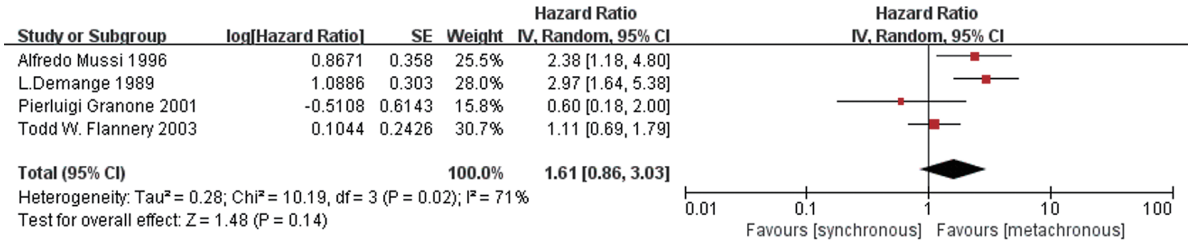

Figure 2 Forest plot for synchronous and metachronous oligometastasis in NSCLC patients. NSCLC, non-small cell lung cancer.

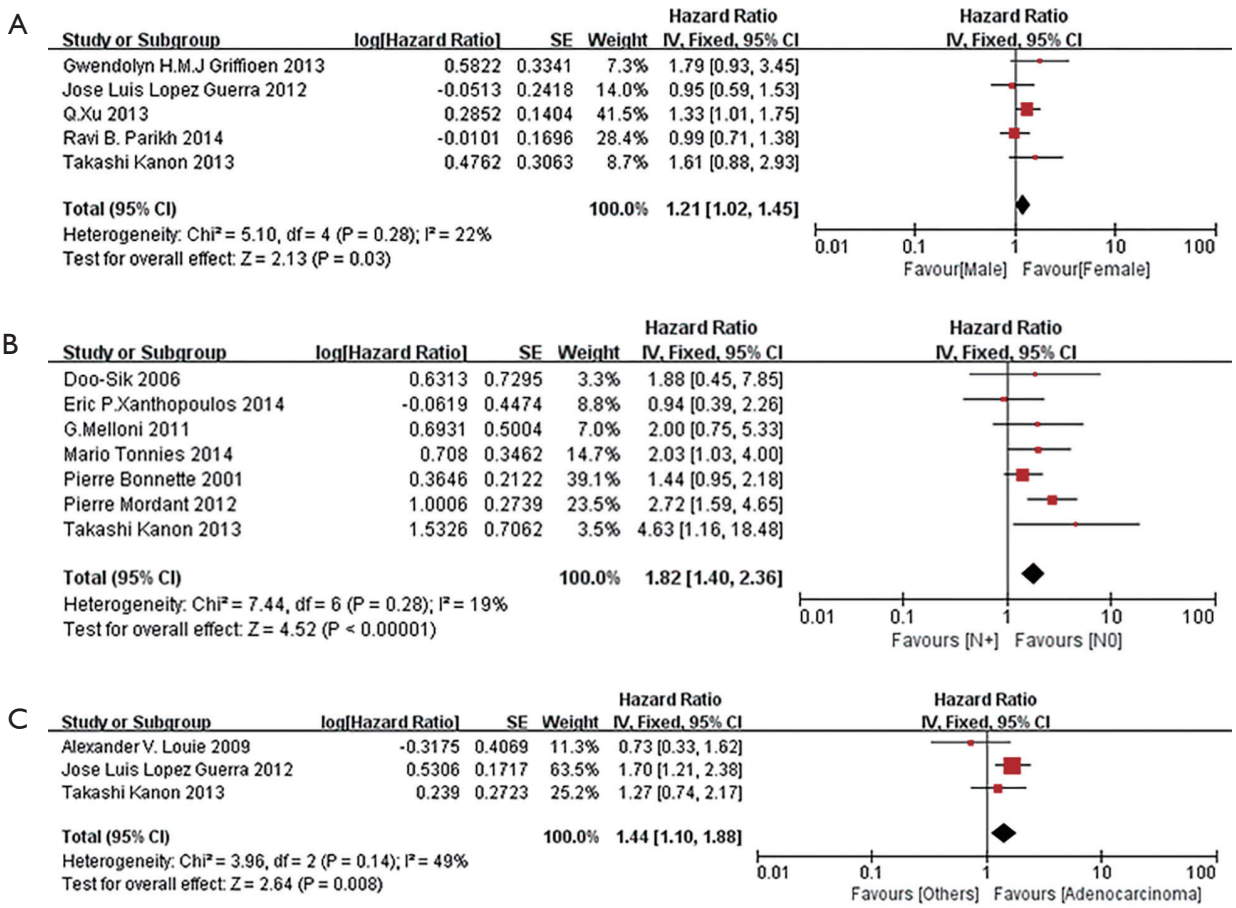

Figure 3 Forest plots of univariate analysis for prognostic factors of synchronous oligometastasis in NSCLC patients. (A) Gender; (B) lymph node; (C) tumor type. NSCLC, non-small cell lung cancer.

prognosis. For these patients, more aggressive local therapies may be advantageous (38,39). However, to our knowledge, there are relatively few reports concerning prognostic factors for patients with primary NSCLC and synchronous solitary metastasis, which could distinguish the distinct subset as a group that requires more ATs.

Therefore, we further comprehensively explored the prognostic factors of synchronous oligometastases NSCLC patients. On univariate analyses, we found that neither age (P=0.86, I^2=0%), nor smoking status (P=0.62, I^2=0%) had significant difference in OS. However, prognoses such as female (P=0.03, I^2=22%), absence of nodal disease

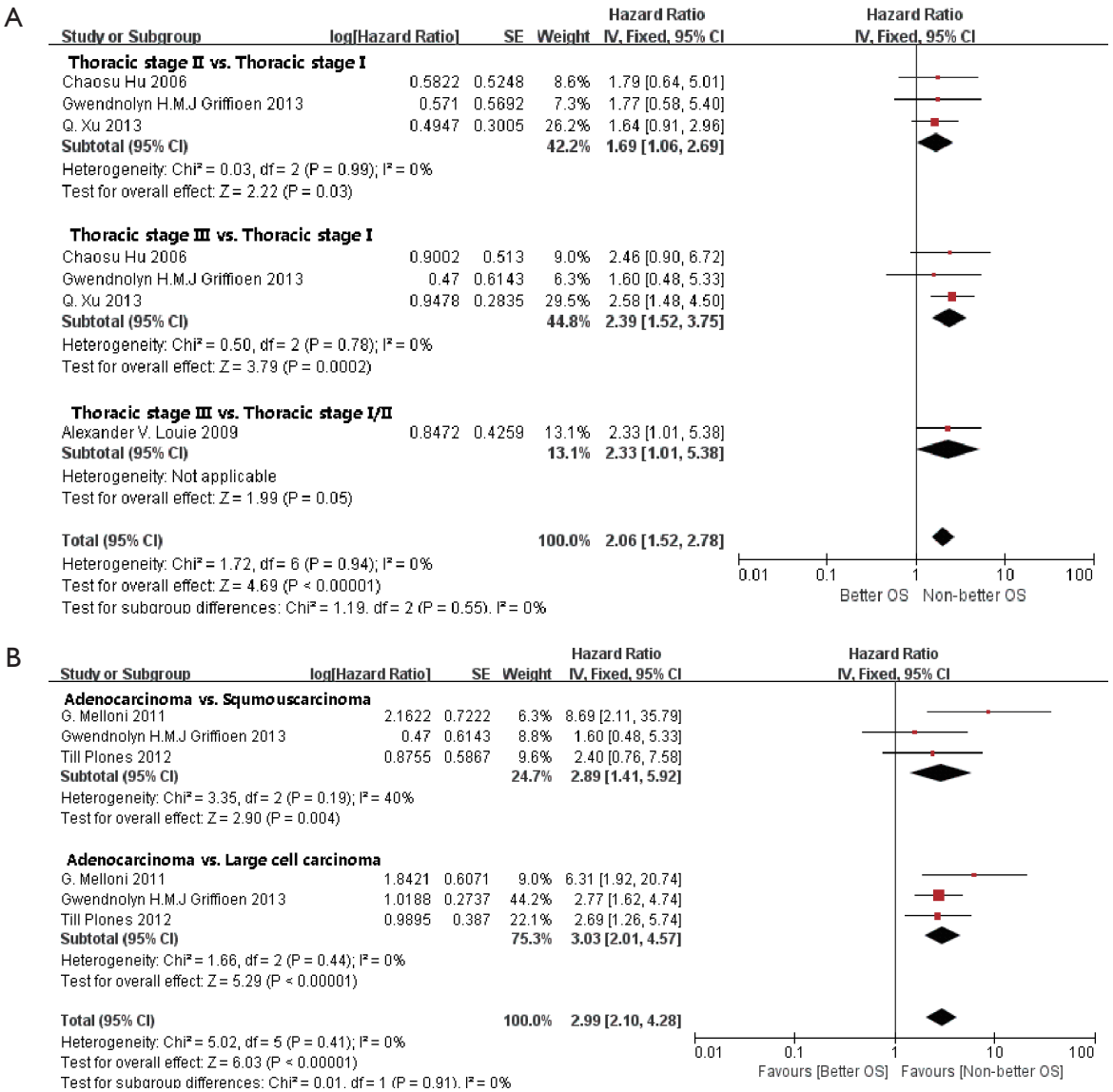

Figure 4 Forest plots of subgroup analysis for prognostic factors of synchronous oligometastasis in NSCLC patients. (A) Thoracic stage; (B) tumor type. NSCLC, non-small cell lung cancer.

(P<0.00001, I^2=19%), adenocarcinoma histology (P=0.008, I^2=49%) were clarified as positive factors. In subgroup analyses, comparisons among the studies were limited by small sample sizes, heterogeneity in patient populations, and types of treatments delivered. Moreover, the primary tumor N-stage was found to be a significant prognostic factor for survival in multivariable analyses, and we further reflected the absence of nodal disease could achieve a survival benefit in oligometastatic NSCLC. By examining survival results across studies, this review also suggested that the thoracic T stage of synchronous oligometastases in NSCLC might also be prognosis for survival. However, survival outcomes in studies that included patients with T1 stage diagnosed pathologically might have a better survival benefit than those of patients with T3 stage (P=0.02, I^2=0%), but no significant difference compared with patients with T2 stage (P=0.83, I^2=44%). Interestingly, low number of metastatic lesions, which had been associated with favorable

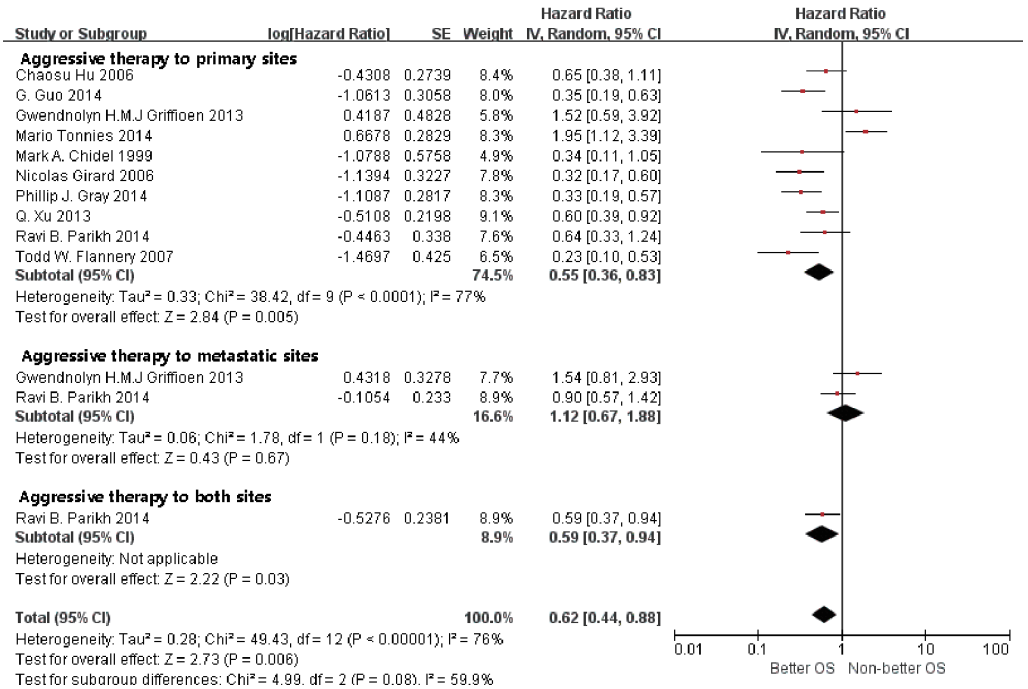

Figure 5 Forest plots of subgroup analysis for ATT to primary sites and ATT to metastatic sites and ATT to both sites in synchronous oligometastatic NSCLC patients. ATT, aggressive thoracic treatment; NSCLC, non-small cell lung cancer.

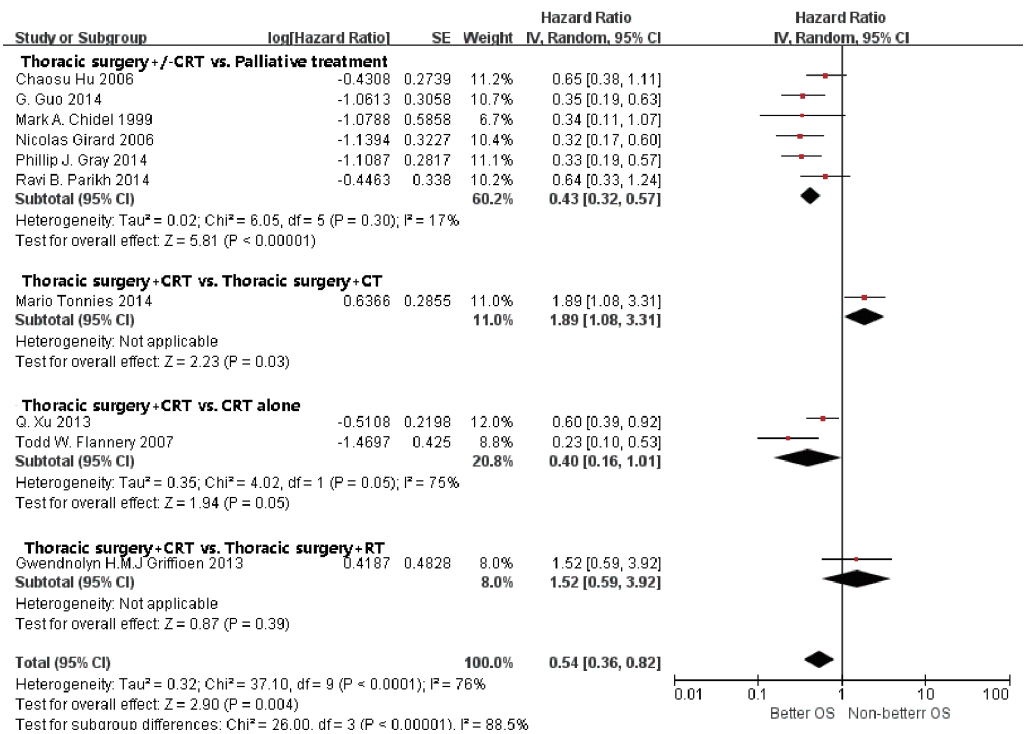

Figure 6 Forest plot of therapeutic approaches of ATT in synchronous oligometastatic NSCLC patients. ATT, aggressive thoracic treatment; NSCLC, non-small cell lung cancer.

Table 3 Results of synchronous brain metastases with NSCLC by treatment arms

Series	Therapeutic strategies		5-years OS		
	Intervention	Control	HR	95% CI	P value
Sahqal *et al.*	SRS + WBRT	WBRT	0.67	0.55–1.05	0.1
Chidel *et al.*	ATT + WBRT	ATT	0.22	0.08–0.63	0.002
Doo-Sik *et al.*	SRS + WBRT	SRS	0.16	0.06–0.43	0.0002
Sahqal *et al.*			0.76	0.55–1.05	0.096
Synthesize			0.37	0.08–1.71	0.21
Louie *et al.*	Systemic chemotherapy	Non-systemic chemotherapy	0.956	0.4–2.31	0.92
Doo-Sik *et al.*			2.12	0.68–6.61	0.2
Kanon *et al.*			0.82	0.54–1.25	0.36
Synthesize			0.96	0.62–1.49	0.87
Melloni *et al.*	CPR	Non-CPR	0.06	0.01–0.36	0.002
Bonnette *et al.*			0.29	0.16–0.53	<0.0001
Synthesize			0.17	0.04–0.73	0.02

NSCLC, non-small cell lung cancer; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy; ATT, aggressive thoracic treatment; HR, hazard ratio; CI, confidence interval; OS, overall survival; CPR, complete pulmonary resection.

progression-free survival (PFS) in other case series (39-41), but were not significantly associated with longer OS in our cohort. The discrepancy between the findings of other studies and ours may be explained by the cause that previous trials included only patients with definitive treatment to metastases, whereas our study screened all NSCLC patients with oligometastatic disease, regardless of treatment received.

Subsequent to these findings, several prognostic factors influencing survival in patients suffering from NSCLC with synchronous metastases have been described in the medical literature (16,42,43), and ATT in the form of lung resection, as well as absence of nodal disease (44), adenocarcinoma histology, and stage I/II disease have commonly been described as playing positive role in survival. However, the prognosis of ATT and various treatment strategies for synchronous metastases in NSCLC remains unclear. Therefore, in the cohort, we further assessed the benefit of aggressive therapies, and investigated the role of different ATs for synchronous metastases in NSCLC. Our finding suggested that neither ATT (HR 0.43, P<0.00001) nor ATT compared with CRT alone (HR 0.4, P=0.05) were significantly associated with improved survival. But observingly, upfront addition of RT to AT showed its negative prognosis (HR 1.89, P=0.03), and chemotherapy to AT had no significant difference in OS (P=0.39). However, owning to the limitation of retrospective studies and the number of articles included, more prospective studies are need to be further verified.

In the review, approximately two-third of the patients was diagnosed as synchronous metastases, especially synchronous brain metastases (SBM). Thus, we further investigated risk of variously therapeutic methods among the SBM. Despite the integrated results showed no significant difference, we fund differently combinative strategies presented a better survival than one treatment received separately.

In the meantime, several limitations to this review should be cautiously observed. Firstly, a retrospective analysis cannot replace randomized controlled trials (RCTs). Thus, these results should be interpreted with caution. Secondly, it is possible that patients receiving definitive local therapy to the primary tumor were more likely to have additional favorable characteristics which we could not control, and due to the different time of publication of included literatures, the data on RT use and in general on therapeutic approach are surely biased by baseline different characteristics. Thirdly, we were not able to assess prognosis in PFS, local recurrence (LC) and the toxicity of treatment because of relatively insufficient data. Finally, more than two-third of metastatic sites involved in the cohort was

synchronous brain metastasis. Therefore, establishing the benefit in other oligometastatic location in NSCLC is extremely necessary. However, except for the absence of randomized trials, retrospective analysis can play a positive role in clinical guild and provide the basis for future randomized comparisons.

Conclusions

Among patients with oligometastatic disease, defined as 5 or fewer lesions, we identified several factors associated with improved survival and they were consistently found to be significant in the literature. Key determinants of long-term survival of oligometastases in NSCLC patients include female, lower nodal stage, adenocarcinoma histology, thoracic stage, as well as AT to the primary tumor. We propose that these factors be used in future prognostic models to identify those oligometastatic NSCLC patients who are most likely to be long-term survivors, and be utilized to guide clinical selection making and the design of future prospective randomized studies.

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Footnote

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

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Supplementary

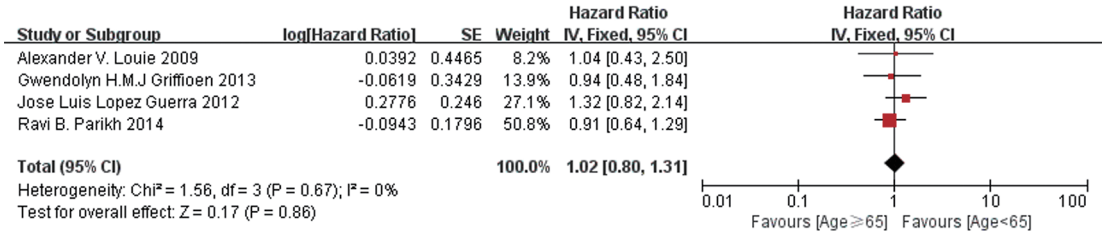

Figure S1 Forest plots of age ≥65 and <65 years old in synchronous oligometastasis in NSCLC patients. NSCLC, non-small cell lung cancer.

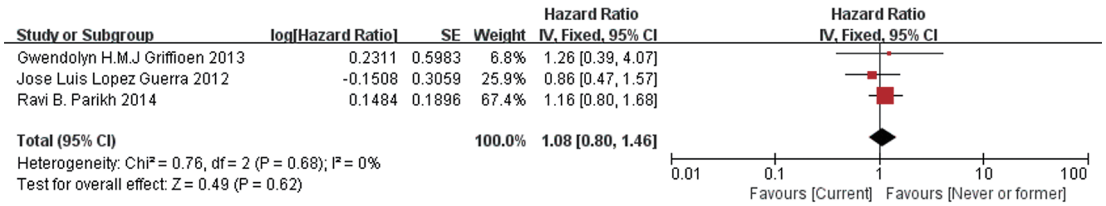

Figure S2 Forest plots of current smoking and never or former smoking in synchronous oligometastasis in NSCLC patients. NSCLC, non-small cell lung cancer.

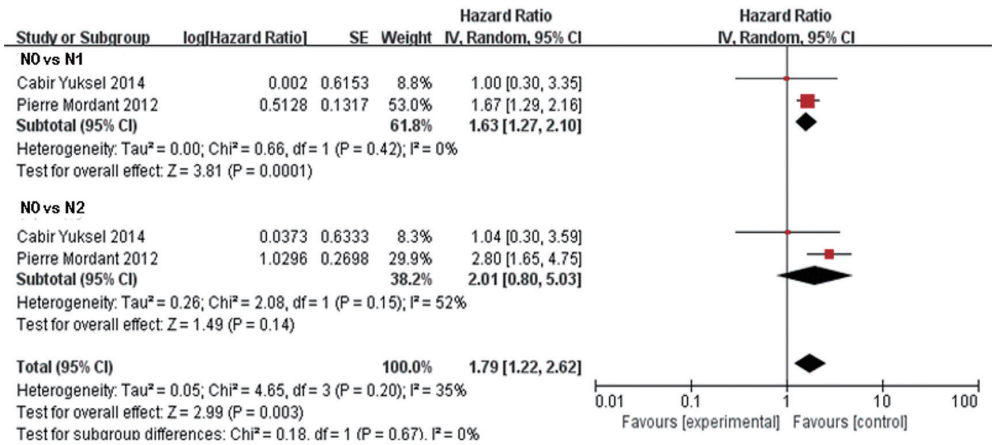

Figure S3 Forest plots of subgroup analysis of multivariate analysis for N-stage in synchronous oligometastasis in NSCLC patients. NSCLC, non-small cell lung cancer.

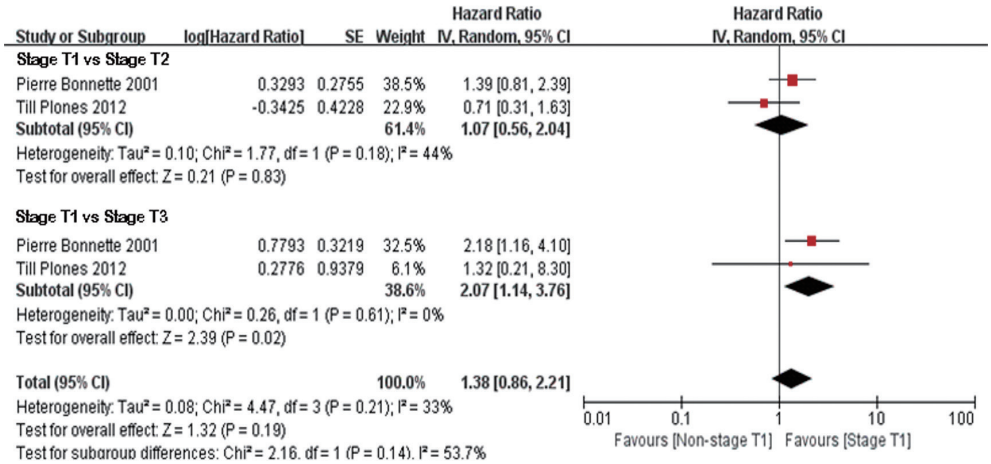

Figure S4 Forest plots of subgroup analysis of univariate analysis for T-stage in synchronous oligometastasis in NSCLC patients. NSCLC, non-small cell lung cancer.

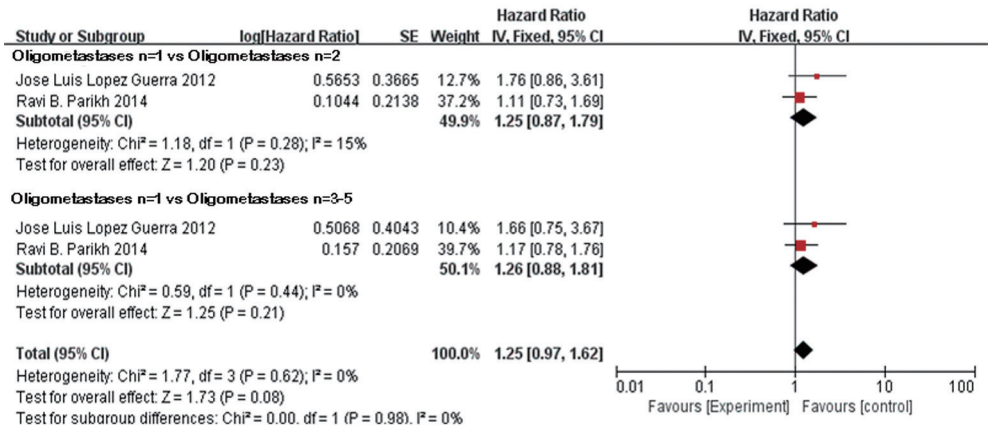

Figure S5 Forest plots of subgroup analysis oligometastatic number in synchronous oligometastasis in NSCLC patients. NSCLC, non-small cell lung cancer.