Review paper

Iodine-125 seeds insertion with trans-arterial chemical infusion for advanced lung cancer: a meta-analysis

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Abstract

Purpose: Local treatments, including iodine-125 (^{125}I) seeds insertion (ISI) and trans-arterial chemical infusion (TAI), were used for advanced non-small-cell lung cancer (NSCLC) or small-cell lung cancer (SCLC) cases. The present meta-analysis investigated the clinical efficacy of combined TAI and ISI for advanced lung cancer (LC).

Material and methods: This meta-analysis was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. Relevant studies were searched in PubMed, Embase, Cochrane Library, CINK, Wanfang, and VIP (until October 2021) databases, using the following key words: (((((Iodine-125) OR (I125)) OR (125I)) OR (brachytherapy)) AND ((lung cancer) OR (NSCLC))) AND (chemotherapy). Outcomes included complete response rate (CRR), treatment success rate (TSR), disease control rate (DCR), 1-year survival rate, 2-year survival rate, overall survival (OS), and treatment-related toxicity. RevMan v. 5.3 and Stata v. 12.0 were applied for meta-analysis.

Results: Eight studies were included in the evaluation. Three hundred and seventy-seven patients underwent combined TAI and ISI treatment (combined group), while 397 patients underwent TAI alone (TAI alone group). The pooled CRR ($p = 0.001$), TSR ($p < 0.00001$), DCR ($p < 0.00001$), 1-year survival rate ($p < 0.00001$), OS duration ($p = 0.0002$), and gastrointestinal reaction rate ($p = 0.02$) were superior in combined group. The pooled 2-year survival rate increased in combined cohort than in TAI alone group ($p = 0.08$). The pooled myelosuppression rates were comparable between the 2 groups ($p = 0.29$). Publication bias was not found in any of endpoints.

Conclusions: ISI can enhance TAI clinical efficacy in clinical cases of advanced LC, excluding severe adverse events.

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Key words: lung cancer, ^{125}I seed, trans-arterial chemical infusion, treatment response.

Purpose

Globally, lung cancer (LC) predominates cancer-associated mortalities [1-3]. Approximately 80% of LCs are inoperable due to advanced tumor stage [2]. Systematic chemotherapy and/or radiotherapy are commonly used for inoperable LCs [1-3]. However, many patients cannot withstand such intense and systematic treatment due to older age and/or frail body conditions [4]. Moreover, traditional external radiotherapy is typically correlated with additional adverse effects. Furthermore, radiation dosing can be restricted due to distance of such tumors from neighboring normal tissue and essential organs [5].

Along with the development of interventional therapy, computed tomography (CT)-guided iodine-125 (^{125}I) seeds insertion (ISI) and trans-arterial chemical infusion (TAI) have been widely used for advanced non-small-cell LC (NSCLC) [4-10]. The advantages of interventional therapies include mini-invasive nature and lower treatment-related toxicity. However, clinical efficacy of TAI and ISI alone is limited [4,6,7]. Therefore, many researchers combined TAI and ISI to treat advanced LC cases [11-18]. However, dataset outcomes from an individual investigation could be affected by multiple parameters, thus, a meta-analysis is required to reduce bias and enhance statistical power displayed by reduced cohort size investigations.

Here, we present results of meta-analysis to evaluate the practical effectiveness of combined TAI/ISI in advanced LC.

Material and methods

This meta-analytical investigation complied with preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement [19]. Investigational protocol was submitted at INPLASY.COM (INPLASY-2021110058).

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Study research

Study selection

Relevant studies were searched in PubMed, Embase, Cochrane Library, CINK, Wanfang, and VIP (until October 2021) databases, using the following keywords: (((((Iodine-125) OR (I125)) OR (125I)) OR (brachytherapy)) AND ((lung cancer) OR (NSCLC))) AND (chemotherapy).

This meta-analysis encompassed the following reports:

1. Investigation type: comparative studies.
2. Disease: advanced LC (tumor stage ≥ III).
3. Types of interventions: TAI with ISI vs. TAI alone.
4. Languages: not limited.

The following articles were eliminated from this meta-analysis:

1. Single-arm studies, case reports, reviews, and experimental studies.
2. Studies without English titles or abstracts.

Quality assessment

Randomized controlled trials (RCTs) were evaluated using Cochrane risk of bias tool [20]. RCT bias was assessed from performance bias, attrition, detection, selection, reporting, and other sources. Non-RCTs were analyzed with a 9-point Newcastle-Ottawa scale (NOS) [21], with studies exhibiting low, intermediate, or high levels of risk, and receiving scores of ≥ 7, 4-6, and < 4, respectively. Items of NOS included designation (4 points), ability for comparison (2 points), and exposure (3 points).

Data extraction

Two authors retrieved relative data and endpoints separately, and a third researcher resolved any conflict. Baseline data from each publication included first author, publication year, countries, types of design, cancer types, tumor stage, TAI methods, sample size, age, and gender. Outcomes of each study included complete response (CR) rate (CRR), treatment success (TS) rate (TSR), disease control (DC) rate (DCR), one-year/two-year/overall survival (OS) rate, and treatment-related toxicity.

Complete response was defined as complete absence of all target lesions [4,5]. TS was identified as cases of CR and partial response [5]. DC was defined as cases of TS and stable disease [5]. OS was calculated from initial treatment to death. TSR was the primary endpoint in this meta-analysis.

Statistical analyses

RevMan v. 5.3 and Stata v. 12.0 were employed. Dichotomous variables were pooled depending upon odds ratios (ORs) with 95% confidence intervals (CIs), while continuous variables were combined depending on mean difference (MD), with 95% CI. Heterogeneity was assessed by χ^2 and I^2 tests, with $I^2 > 50\%$ suggesting significant heterogeneity. Random effects models were employed for significant heterogeneity, while fixed-effects models were employed for significant homogeneity. Heterogeneity sources were analyzed through sensitivity/sub-group assessments. Sub-group analysis was completed based on different cancer types. Funnel plots and Egger tests were utilized for evaluating publication bias risks.

Results

Study inclusion

We found 325 relevant studies using the research strategy. After reviewing the abstract and full articles, only 8 studies were included in this meta-analysis (Figure 1). There were 3 RCTs and 5 retrospective studies in the included studies (Table 1). All included studies were from Chinese researchers.

Three hundred and seventy-seven patients underwent combined TAI and ISI treatment (combined group), and 397 patients underwent TAI alone (TAI alone group). The ISI was performed under CT guidance. The results of therapeutic endpoints are shown in Table 2.

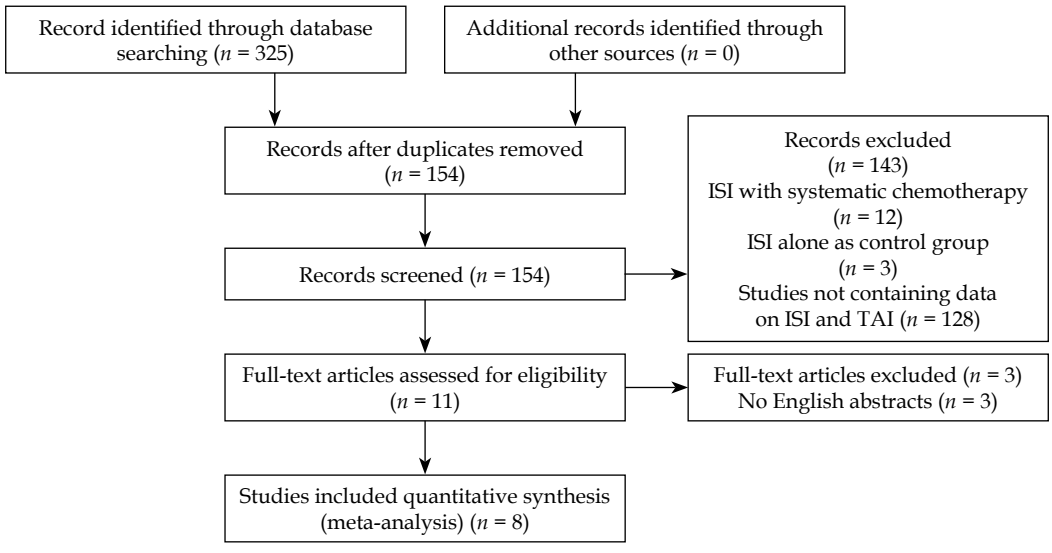


Fig. 1. Studies selection of the present meta-analysis

Table 1. Characteristics of the included studies

Study, year, country [Ref.]	Study design	Cancer type	Group	Sample size	Age (years)	M/F ratio	Stage	NOS
Guo, 2012, China [11]	RCT	NSCLC	Combined	103	63.4 ±10.1 for all	151/55 for all	III, IV for all	–
			TAI alone	103				
He, 2012, China [12]	Retrospective	NSCLC, SCLC	Combined	43	68	28/15	III: 19 IV: 24	8
			TAI alone	65	67	42/23	III: 27 IV: 38	
Li, 2007, China [13]	RCT	NSCLC	Combined	15	70.5 for all	19/11 for all	III for all	–
			TAI alone	15				
Li, 2014, China [14]	Retrospective	NSCLC	Combined	24	62	Not given	III: 1 IV: 9	7
			TAI alone	32	62	Not given	III: 16 IV: 16	
Lin, 2017, China [15]	Retrospective	NSCLC	Combined	34	45-82 for all	46/24 for all	IIIb, IV for all	7
			TAI alone	36				
Xing, 2011, China [16]	Retrospective	NSCLC, SCLC	Combined	57	59 for all	58/44 for all	III, IV for all	7
			TAI alone	45				
Zhong, 2013, China [17]	Retrospective	NSCLC, SCLC	Combined	60	56.5 for all	68/52 for all	III, IV for all	7
			TAI alone	60				
Zhu, 2020, China [18]	RCT	NSCLC	Combined	41	67.56 ±7.78	29/12	III: 24 IV: 17	–
			TAI alone	41	68.08 ±7.43	30/11	III: 21 IV: 20	

NOS – Newcastle-Ottawa scale, RCT – randomized controlled trial, NSCLC – non-small-cell lung cancer, SCLC – small-cell lung cancer, TAI – trans-arterial chemical infusion, M – male, F – female

Table 2. Characteristics of the treatments

Study	Trans-arterial treatment	Group	CRR	TSR	DCR	1-year survival rate	2-year survival rate	OS
Guo [11]	TAI	Combined	Not given	40.8%	Not given	Not given	Not given	15.1 months
		TAI alone	Not given	22.3%	Not given	Not given	Not given	10.1 months
He [12]	TAI	Combined	48.0%	84.0%	94.0%	90.7%	Not given	Not given
		TAI alone	0.0%	45.1%	78.4%	64.6%	Not given	Not given
Li [13]	TAI	Combined	60.0%	86.7%	Not given	Not given	Not given	Not given
		TAI alone	0.0%	53.3%	Not given	Not given	Not given	Not given
Li [14]	TAI	Combined	Not given	Not given	Not given	Not given	Not given	22.8 months
		TAI alone	Not given	Not given	Not given	Not given	Not given	14.2 months
Lin [15]	TAI + E	Combined	26.5%	76.5%	91.1%	Not given	Not given	Not given
		TAI alone	5.6%	50.0%	66.7%	Not given	Not given	Not given
Xing [16]	TAI	Combined	Not given	82.5%	Not given	82.5%	63.2%	Not given
		TAI alone	Not given	46.7%	Not given	33.3%	6.7%	Not given
Zhong [17]	TAI	Combined	50.0%	86.7%	96.7%	Not given	Not given	Not given
		TAI alone	23.3%	46.7%	60.0%	Not given	Not given	Not given
Zhu [18]	TAI	Combined	39.0%	82.9%	95.1%	87.8%	68.3%	Not given
		TAI alone	22.0%	61.0%	90.2%	73.2%	46.3%	Not given

TAI – trans-arterial infusion, E – embolization, CRR – complete response rate, TSR – treatment success rate, DCR – disease control rate, OS – overall survival

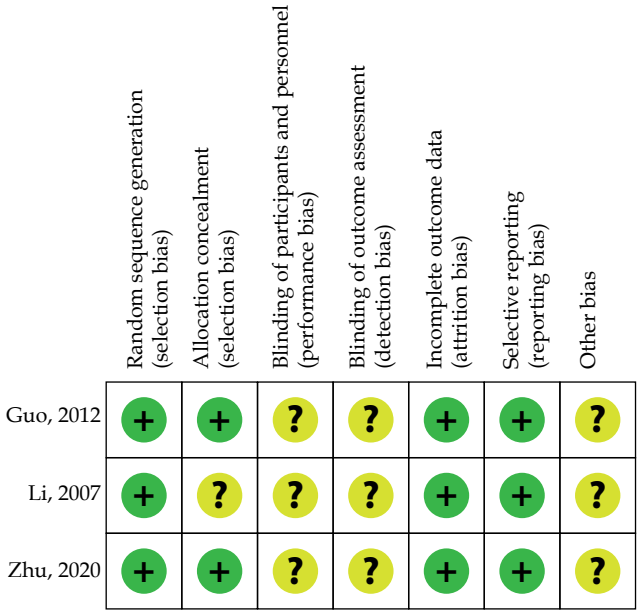


Fig. 2. Cochrane's risk of bias assessment for included RCTs

Quality evaluation

Figure 2 shows the bias risk of RCTs. All RCTs had an unclear risk of performance, detection, reporting, and other bias [11,13,18]. One RCT also had an uncertain risk for selection bias [13]. NOS concerning retrospective investigations ranged from 7 to 8 (Table 1).

Complete response rate

Five studies provided the results of CRR [12,13, 15,17,18]. The pooled result indicated that CRR was significantly increased within the combination cohort than in the TAI cohort (44.0% vs. 12.3%, $p = 0.001$; Figure 3A). The heterogeneity was significant ($I^2 = 62\%$).

The sensitivity analysis indicated that the significant heterogeneity disappeared ($I^2 = 28\%$) after removing He *et al*. study [12]. However, the CRR was still significantly increased in the combination cohort rather than in the TAI cohort (42.7% vs. 16.4%, $p = 0.004$).

Treatment success rate

Seven studies provided the results of TSR [11-13,15-18]. The pooled result indicated that TSR was significantly higher in the combined group than that in the TAI alone group (71.1% vs. 41.6%, $p < 0.00001$; Figure 3B). The heterogeneity was not significant ($I^2 = 7\%$), and sensitivity analysis was not required.

Disease control rate

Four studies provided the results of DCR [12,15,17,18]. The pooled result indicated that DCR was significantly increased within the combination cohort than in the TAI cohort (94.6% vs. 72.9%, $p < 0.00001$; Figure 3C). The heterogeneity was not significant ($I^2 = 26\%$), and sensitivity analysis was not required.

1-year survival rate

Three studies provided the results of 1-year survival rate [12,16,18]. The pooled result indicated that 1-year survival rate was significantly increased within the combination cohort than solely within the TAI cohort (86.5% vs. 57.6%, $p < 0.00001$; Figure 3D). The heterogeneity was not significant ($I^2 = 29\%$), and sensitivity analysis was not required.

2-year survival rate

Two studies provided the results of 2-year survival rate [16,18]. The pooled result indicated that 2-year survival rate was increased within the combination cohort than in the TAI cohort without significance (65.3% vs. 25.6%, $p = 0.08$; Figure 3E). The heterogeneity was significant ($I^2 = 88\%$). However, there were only 2 studies for this endpoint. Therefore, sensitivity analysis could not be performed.

Overall survival

Two studies provided the results of OS duration [11,14]. The pooled result indicated that OS duration was significantly longer within the combination cohort than in the TAI cohort ($p = 0.0002$; Figure 3F). The heterogeneity was significant ($I^2 = 98\%$). However, there were only 2 studies for this endpoint. Therefore, sensitivity analysis could not be performed.

Myelosuppression

Two studies provided the results of myelosuppression rate [12,15]. The pooled result indicated that myelosuppression rates were comparable between both the cohorts (50.0% vs. 64.4%, $p = 0.29$; Figure 3G). The heterogeneity was significant ($I^2 = 66.0\%$). However, there were only 2 studies for this endpoint. Therefore, sensitivity analysis could not be performed.

Gastrointestinal reaction

Two studies provided the results of gastrointestinal reaction rate [12,18]. The pooled result indicated that the gastrointestinal reaction rate was significantly higher in the TAI alone group than in the combined group (50.0% vs. 36.3%, $p = 0.02$; Figure 3H). The heterogeneity was not significant ($I^2 = 48\%$), and sensitivity analysis was not required.

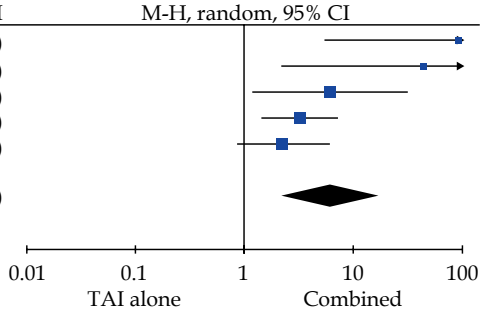
Sub-group evaluations

The sub-group evaluations were conducted depending on different cancer types (Table 3). Five studies only included NSCLC [11,13-15,18], and 3 studies included both NSCLC and small-cell LC (SCLC) [12,16,17]. When focusing on the NSCLC alone, the CRR ($p = 0.02$), TSR ($p < 0.0001$), and DCR ($p = 0.02$) were significantly elevated in the combination cohort than in the TAI cohort. When focusing on the NSCLC and SCLC, the TSR ($p < 0.0001$), DCR ($p < 0.0001$), and one-year survival rates ($p < 0.0001$) were significantly increased in the combination cohort

A

Study or sub-group	Combined Events	Total	TAI alone Events	Total	Weight	Odds ratio M-H, random, 95% CI
He 2012	24	50	0	51	10.3%	95.23 (5.57, 1628.06)
Li 2007	9	15	0	15	9.6%	45.31 (2.28, 898.87)
Lin 2017	9	34	2	36	20.2%	6.12 (1.21, 30.83)
Zhong 2013	30	60	14	60	31.2%	3.29 (1.50, 7.19)
Zhu 2020	16	41	9	41	28.6%	2.28 (0.86, 6.00)
Total (95% CI)		200		203	100.0%	6.11 (2.09, 17.89)
Total events	88		25			

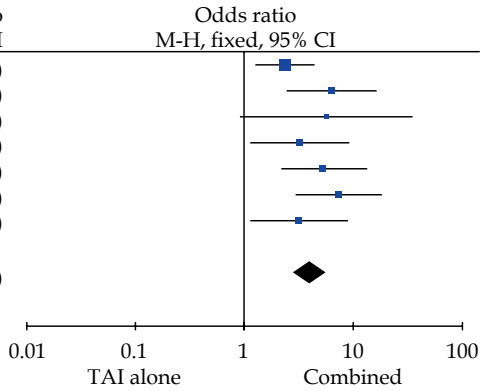
Heterogeneity: Tau^2 = 0.80, χ^2 = 10.52, df = 4 (p = 0.03), I^2 = 62%
Test for overall effect: Z = 3.30 (p = 0.0010)



B

Study or sub-group	Combined Events	Total	TAI alone Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
Guo 2012	42	103	23	103	39.4%	2.39 (1.30, 4.40)
He 2012	42	50	23	51	10.5%	6.39 (2.51, 16.29)
Li 2007	13	15	8	15	3.1%	5.69 (0.94, 34.46)
Lin 2017	26	34	18	36	11.9%	3.25 (1.16, 9.08)
Xing 2011	47	57	21	45	11.9%	5.37 (2.19, 13.20)
Zhong 2013	52	60	28	60	10.8%	7.43 (3.02, 18.28)
Zhu 2020	34	41	25	41	12.3%	3.11 (1.11, 8.68)
Total (95% CI)		360		351	100.0%	4.01 (2.86, 5.62)
Total events	256		146			

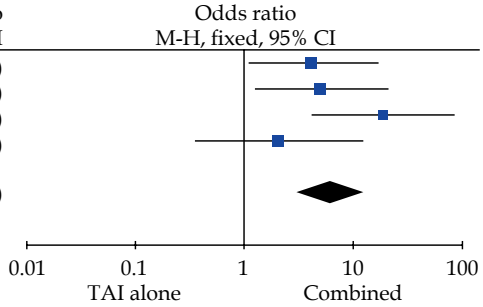
Heterogeneity: χ^2 = 6.46, df = 6 (p = 0.37), I^2 = 7%
Test for overall effect: Z = 8.04 (p < 0.00001)



C

Study or sub-group	Combined Events	Total	TAI alone Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
He 2012	47	50	40	51	31.9%	4.31 (1.12, 16.53)
Lin 2017	31	34	24	36	27.7%	5.17 (1.31, 20.39)
Zhong 2013	58	60	36	60	16.1%	19.33 (4.31, 86.75)
Zhu 2020	39	41	37	41	24.3%	2.11 (0.36, 12.20)
Total (95% CI)		185		188	100.0%	6.44 (3.17, 13.05)
Total events	175		137			

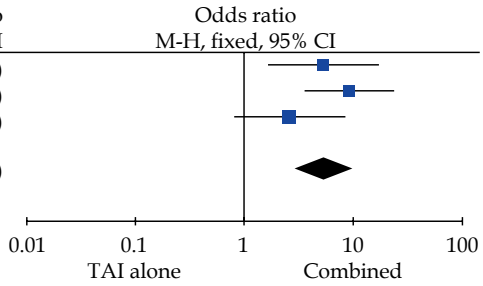
Heterogeneity: χ^2 = 4.05, df = 3 (p = 0.26), I^2 = 26%
Test for overall effect: Z = 5.16 (p < 0.00001)



D

Study or sub-group	Combined Events	Total	TAI alone Events	Total	Weight	Odds ratio M-H, fixed, 95% CI
He 2012	39	43	42	65	32.0%	5.34 (1.69, 16.82)
Xing 2011	47	57	15	45	30.3%	9.40 (3.74, 23.63)
Zhu 2020	36	41	30	41	37.7%	2.64 (0.83, 8.45)
Total (95% CI)		141		151	100.0%	5.55 (3.02, 10.21)
Total events	122		87			

Heterogeneity: χ^2 = 2.83, df = 2 (p = 0.24), I^2 = 29%
Test for overall effect: Z = 5.52 (p < 0.00001)



E

Study or sub-group	Combined Events	Total	TAI alone Events	Total	Weight	Odds ratio M-H, random, 95% CI
Xing 2011	36	57	3	45	47.9%	24.00 (6.61, 87.10)
Zhu 2020	28	41	19	41	52.1%	2.49 (1.01, 6.13)
Total (95% CI)		98		86	100.0%	7.37 (0.78, 69.44)
Total events	64		22			

Heterogeneity: Tau^2 = 2.30, χ^2 = 8.15, df = 1 (p = 0.004), I^2 = 88%
Test for overall effect: Z = 1.75 (p = 0.08)

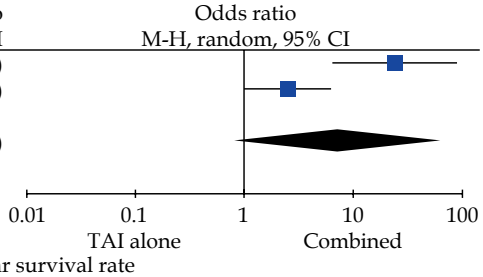


Fig. 3. Pooled results of **A**) CRR, **B**) TSR, **C**) DCR, **D**) 1-year survival rate, **E**) 2-year survival rate

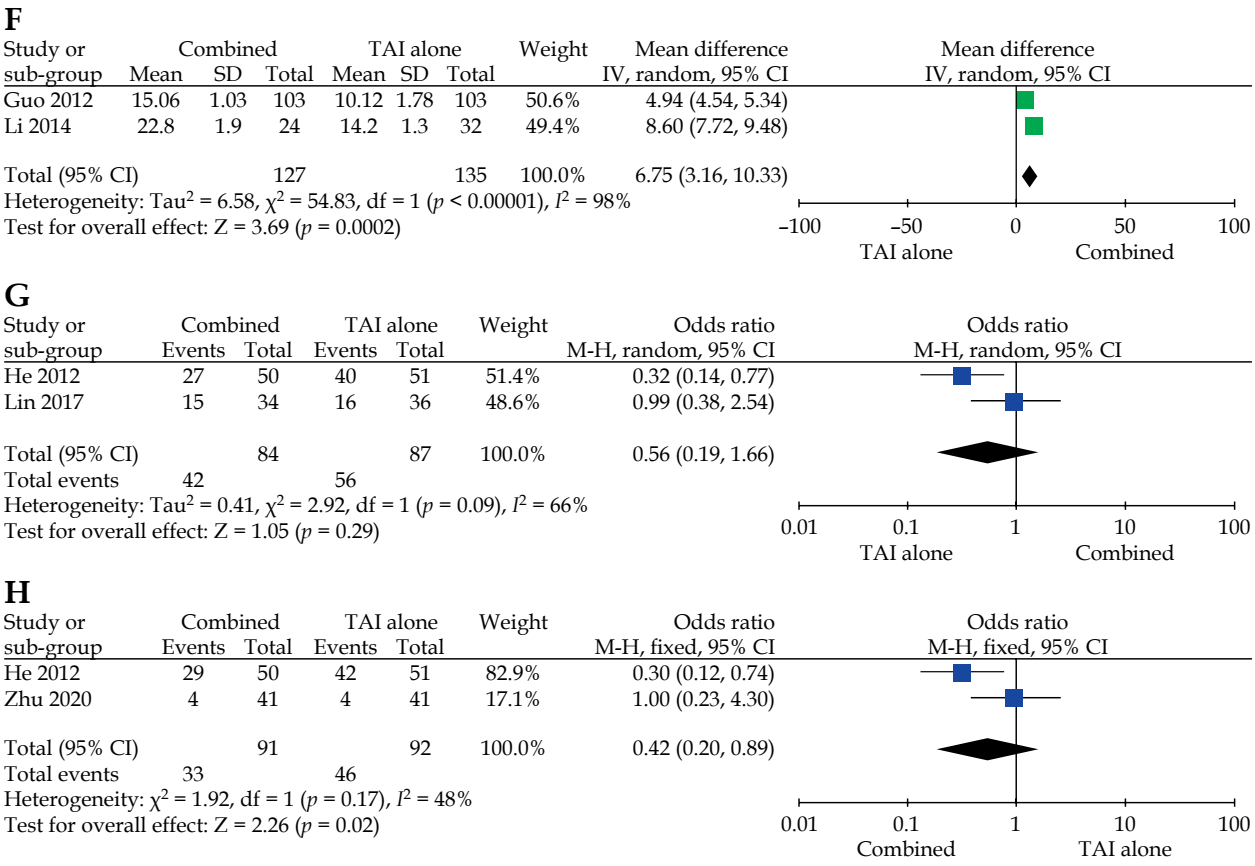


Fig. 3. Cont. **F**) OS duration, **G**) myelosuppression rate, and **H**) gastrointestinal reaction rate between the two groups

Table 3. Meta-analytic results based on the studies with different types of cancer

	Number of studies	OR or HR (95% CI)	Heterogeneity	Favor
NSCLC and SCLC				
CRR	2	14.11 (0.35, 563.88), $p = 0.16$	$I^2 = 84.0\%$	–
TSR	3	6.36 (3.76, 10.76), $p < 0.0001$	$I^2 = 0.0\%$	Combined
DCR	2	9.35 (3.55, 24.64), $p < 0.0001$	$I^2 = 54.0\%$	Combined
1-year survival rate	2	7.31 (3.53, 15.15), $p < 0.0001$	$I^2 = 0.0\%$	Combined
NSCLC alone				
CRR	3	5.22 (1.29, 21.08), $p = 0.02$	$I^2 = 53.0\%$	Combined
TSR	4	2.83 (1.81, 4.44), $p < 0.0001$	$I^2 = 0.0\%$	Combined
DCR	4	3.74 (1.28, 10.88), $p = 0.02$	$I^2 = 0.0\%$	Combined

OR – odd ratio, HR – hazard ratio, CRR – complete response rate, TSR – treatment success rate, DCR – disease control rate, NSCLC – non-small-cell lung cancer, SCLC – small-cell lung cancer

than in the TAI cohort. However, CRRs were comparable between the two groups ($p = 0.16$).

Publication bias

Egger tests showed no significant risk of publication bias on the endpoints of CRR ($p = 0.744$), TSR ($p = 0.356$), DCR ($p = 0.451$), and 1-year survival rate ($p = 0.225$). For the endpoints of two-year survival rate, OS duration, myelosuppression rate, gastrointestinal reactivity rate, and quantities of included studies were smaller than 3; therefore, Egger test could not be used, whereas funnel-plots did not show significant publication bias risks.

Discussion

The present meta-analysis provided a comprehensive evaluation of combined TAI and ISI therapy for patients with advanced LC. The clinical efficacy was mainly evaluated based on treatment response, long-term survival, and treatment-related toxicity.

For the patients with advanced LC, traditional systemic chemotherapy and radiation therapy should be initially considered [2]. However, some patients may be difficult to treat with standard chemotherapy and thoracic radiation therapy as a result of poor Eastern cooperative oncology group performance status (ECOG PS) (≥ 2),

advanced age (≥ 70 years), severe hepatic failure, severe respiratory failure, refusal of traditional chemotherapy, or failure to treat with standard therapy [4-7]. Under this condition, local treatments including ISI and TAI are usually used for patients who are difficult to treat with standard therapy [4-7].

Therapeutic consequences are vital outcomes concerning oncology therapy investigations [22-25]. However, in previous studies, the clinical efficacy of TAI and ISI alone was limited, with the CRRs ranging between 0.0-2.5% and 12.5-23.0%, respectively [4,6,7,26]. In addition, TAI alone was usually limited by multiple feeding arteries of the tumor [4,6]. On the other hand, ISI could constantly release reduced energy gamma rays and maintain tumor areas irradiated [27]. However, the clinical efficacy of ISI can be further improved using adjuvant chemotherapy [5]. Therefore, many researchers combined ISI and TAI together to achieve a better treatment effect for advanced LC.

In the present study, the pooled CRRs indicated that ISI could significantly improve the clinical efficacy of TAI for advanced LC. Furthermore, the pooled CRR of combined treatment was 44.0% higher than in previous studies [4,6,7,26]. A previous meta-analysis found a pooled CRR of 21.5% after combined ISI with systematic chemotherapy [5], which was lower than in the present study. This finding can be attributed to the first-pass effect as a mechanistic path adopted by TAI [4]. Localized potentiation of chemical medication within the designated lesion region employing TAI could obtain 2-6× fold efficacy compared to conventional systematic chemotherapeutic options [28].

The significantly improved TSR and DCR were also observed in the combined group. However, CR could not be achieved by half of the treated patients, while the pooled TSR and DCR of combined treatment could reach up to 71.1% and 94.6%, respectively. Furthermore, the low heterogeneity of these endpoints also improved the stability of pooled results. These findings indicate that combined treatment is superior to TAI alone in treatment response, while combined treatment can control the LC progression in most patients.

The survival function was assessed by the survival rates and OS duration in this meta-analysis. Previous studies reported the median OS duration for advanced LC of 9-16 months, with 28.0-31.0% one-year survival rates after TAI or ISI alone [4,6,7]. Our pooled one-year survival rate and OS duration were significantly superior within the combination cohort than within the TAI cohort. Furthermore, the 1-year survival rate after combined treatment reached 86.5%. These findings can be attributed to better TSR and DCR after combined treatment. However, the significant heterogeneity of OS duration caused the result of OS and should be further validated.

The pooled 2-year survival rates were not significantly different between the two groups, which may indicate that combined treatment has a limited effect on long-term cancer control. This phenomenon may be attributed to the fact that the activity of ^{125}I seeds reduce along with the time flowed. However, high heterogeneity indicate unstable results. Further studies are still required for conclusive results.

Myelosuppression and gastrointestinal reaction were the most common treatment-related toxicity after chemotherapy. Our meta-analysis results indicated that ISI did not aggravate TAI-related toxicity. However, the significant heterogeneity of myelosuppression should be further validated.

Most chemotherapy and/or radiotherapy studies focused on NSCLC alone [22,23,27,28]. However, this meta-analysis included both NSCLC and SCLC. Therefore, we performed sub-group evaluation depending on the variable tumor models. The results indicated that cancer types did not influence the treatment effect of combined TAI and ISI. Although the CRRs were comparable between the two groups based on the sub-groups of NSCLC and SCLC. The significant heterogeneity (I^2 = 84%) indicated that this result requires further validation.

The present study had some limitations. Firstly, some investigations were retrospective in nature, and were associated with a high-risk of bias. In addition, some articles did not provide the data regarding stage and age distribution [11,13,15-17], which further increased the risk of bias. Therefore, more comprehensive RCTs are required. Secondly, TAI is a minimally invasive treatment that establishes a route to supply the local and low-dose chemotherapy. In this meta-analysis, TAI protocols, including types of medicine, dose, and circles of treatment were not the same in the included studies. These findings may further increase the risk of bias. Thirdly, multiple LC types possibly added further selection bias within such dataset outcomes. We did not perform sub-group analysis based on different tumor stages because the included original studies did not report the results based on different tumor stages. Therefore, an individual patient data (IPD) meta-analysis is needed to provide a more comprehensive and detailed results.

Conclusions

In conclusion, the present meta-analysis demonstrated that ISI could enhance TAI clinical efficacy in clinical cases of advanced LC, excluding the introduction of severe adverse events.

Disclosure

The authors report no conflict of interest.

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