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 (125I) 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, 125I 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 (125I) 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 $\chi^2$ and $I^2$ tests, with $P > 50\%$ 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 analyses. 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](Image)
### 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 | 151/55    | 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, year, country [Ref.] | 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
The heterogeneity was not significant ($I^2 = 29\%$), 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 | TAI alone | Weight | Odds ratio | Odds ratio
Events | Total | Events | Total | M-H, random, 95% CI | 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 | TAI alone | Weight | Odds ratio | Odds ratio
Events | Total | Events | Total | M-H, fixed, 95% CI | 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)
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 | TAI alone | Weight | Odds ratio | Odds ratio
Events | Total | Events | Total | M-H, fixed, 95% CI | 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  | 36  | 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 | TAI alone | Weight | Odds ratio | Odds ratio
Events | Total | Events | Total | M-H, fixed, 95% CI | M-H, fixed, 95% CI
He 2012  | 39  | 43  | 42  | 65  | 32.0% | 5.34 (1.69, 16.82)
Xing 2011 | 39  | 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 | TAI alone | Weight | Odds ratio | Odds ratio
Events | Total | Events | Total | M-H, random, 95% CI | 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
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 irradiation 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 ($\chi^2 = 84\%$) 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.

References

1. Sun L, Ma JT, Zhang SL et al. Efficacy and safety of chemotherapy or tyrosine kinase inhibitors combined with bevacizumab versus chemotherapy or tyrosine kinase inhibitors alone in the treatment of non-small cell lung cancer: a systematic review and meta-analysis. Med Oncol 2015; 32: 473.
2. Puri S, Saltos A, Perez B et al. Locally advanced, unresectable non-small cell lung cancer. Curr Oncol Rep 2020; 22: 31.
3. Yuan M, Zhai Y, Men Y et al. Endostar (rh-endostatin) improves efficacy of concurrent chemoradiotherapy for locally advanced non-small cell lung cancer: A systematic review and meta-analysis. Thorac Cancer 2021; 12: 3208-3215.
4. Fu YF, Li Y, Wei N et al. Transcatheter arterial chemical infu-

sion for advanced non-small cell lung cancer: long-term out-

come and predictor of survival. Radiol Med 2016; 121: 605-610.

5. Wu H, Li L, Yang J et al. Radioactive seeds insertion with 

chemotherapy for advanced non-small-cell lung cancer: 

A meta-analysis. Clin Respir J 2021; 15: 187-195.

6. Yuan Z, Li WT, Ye XD et al. Intra-arterial infusion chem-

otherapy for advanced non-small-cell lung cancer: prelimi-

nary experience on the safety, efficacy, and clinical outcomes. 

J Vasc Interv Radiol 2013; 24: 1521-1528.e4.

7. Li W, Guan J, Yang L et al. Iodine-125 brachytherapy im-

proved overall survival of patients with inoperable stage III/

IV non-small cell lung cancer versus the conventional radio-

therapy. Med Oncol 2015; 32: 395.

8. Wei S, Li C, Li M et al. Radioactive iodine-125 in tumor ther-

apy: advances and future directions. Front Oncol 2021; 11: 

717180.

9. Tian LJ, Liu HZ, Zhang Q et al. Efficacy and safety aiming 

at the combined-modality therapy of external beam radio-

therapy (40 Gy) and iodine-125 seed implantation for locally 

advanced NSCLC in the elderly. Cancer Manag Res 2021; 13: 

5457-5466.

10. He Y, Li L, Liu J et al. Iodine-125 seed brachytherapy inhibits 

non-small cell lung cancer by suppressing epithelial-mesen-

chymal transition. Brachytherapy 2018; 17: 696-701.

11. Guo GH. The clinical effect of 125I radioactive particles in 

the transplantation within lungen of advanced non-small cell 

lung cancer in combination with gemcitabine and cisplatin 

bronchial arterial infusion. China Modern Doctor 2012; 50: 

152-153.

12. He KW, Gao B, Qin HL et al. CT-guided percutaneous 125I 

seed implantation combined with bronchial arterial infusion 

chemotherapy for lung cancers: observation of therapeutic 

efficacy. J Intervent Radiol 2012; 21: 554-558.

13. Li YL, Wang YZ, Zhang FJ. Effect of curing central broncho-

genic cancer by percutaneous interstitial 125I particle implant-

ing under CT guided in old patients. Chin J Cancer Prev Treat 

2007; 14: 1818-1820.

14. Li RF, Wang YD, Yan Y et al. Implantation of 125I seeds for 

the treatment of non-small cell lung cancer: evaluation of short-

term effect. J Intervent Radiol 2014; 23: 65-68.

15. Lin H, Su XH. Effect observation of CT guided 125I particle 

implantation combined with bronchial artery infusion chemother-

apy and embolization in the treatment of advanced non-small 

cell lung cancer. China Med Mod 2017; 24: 51-54.

16. Xing H, Cao GW, Ning HF et al. The clinical application of 

bronchial artery infusion with 125I radioactive seeds implanta-

tion for the treatment of advanced lung cancer. J Med Imag-

ing 2011; 21: 1685-1688.

17. Zhong L. Clinical analysis of bronchial artery infusion com-

bined with 125I seed implantation in the treatment of 

advanced lung cancer. Medical Innovation of China 2013; 10: 

118-119.

18. Zhu JF, Zhu HJ, Song XL. Curative effect and survival anal-

ysis of CT-guided 125I interstitial implantation for the treat-

ment of 41 cases of middle-aged and elderly patients with 

squamous cell carcinoma of the lung. Mod Oncol 2020; 28: 

3911-3915.

19. Moher D, Shamseer L, Clarke M et al. Preferred reporting 

items for systematic review and meta-analysis protocols 

(PRISMA-P) 2015 statement. Syst Rev 2015; 4: 1.

20. Higgins JP, Altman DG, Gotzsche PC et al. The Cochrane 

Collaboration’s tool for assessing risk of bias in randomised 

trials. BMJ 2011; 343: d5928.

21. Cook DA, Reed DA. Appraising the quality of medical educa-

tion research methods: the medical education research study 

quality instrument and the Newcastle-Ottawa scale-educa-

tion. Acad Med 2015; 90: 1067-1076.

22. Nakanishi M, Demura Y, Umeda Y et al. Multi-arterial infu-

sion chemotherapy for non-small cell lung carcinoma—signif-

icance of detecting feeding arteries and tumor staining. Lung 

Cancer 2008; 61: 227-234.

23. Nakanishi M, Yoshida Y, Natsuzaka T. Prospective study of 

transarterial infusion of docetaxel and cisplatin to treat non-

small-cell lung cancer in patients contraindicated for stan-

dard chemotherapy. Lung Cancer 2012; 77: 353-358.

24. Sumie S, Yamashita F, Ando E et al. Interventional radio-

therapy for advanced hepatocellular carcinoma: comparison of 

hepatic artery infusion chemotherapy and transcatheter arterial 

lipiodol chemoembolization. AJR Am J Roentgenol 2003; 181: 

1327-1334.

25. Qiu B, Zhang X, Tsuo J et al. Transcatheter arterial infusion 

for pancreatic cancer: a 10-year National Cancer Center ex-

perience in 115 patients and literature review. Abdom Radiol 

(NT) 2019; 44: 2801-2808.

26. Kou F, Gao S, Liu S et al. Preliminary clinical efficacy of io-

dine-125 seed implantation for the treatment of advanced 

malignant lung tumors. J Cancer Res Ther 2019; 15: 1567-1573.

27. Chen C, Wang W, Yu Z et al. Combination of computed to-

mography-guided iodine-125 brachytherapy and bronchial 

arterial chemoembolization for locally advanced stage III 

non-small cell lung cancer after failure of concurrent chemor-

adiotherapy. Lung Cancer 2020; 146: 290-296.

28. Zhao G, Huang Y, Ye L et al. Therapeutic efficacy of tradi-

tional vein chemotherapy and bronchial arterial infusion com-

bining with CIKs on III stage non-small cell lung cancer. 

Zhongguo Fei Ai Za Zhi 2009; 12: 1000-1004.