

Computed tomography-guided localization for multiple pulmonary nodules: a meta-analysis

Xia Tang¹, Hong-Mei Jian¹, Yi Guan², Jie Miao³, Xin Liang¹

¹Department of Oncology, Fengjie People's Hospital, Chongqing, China

²Department of Endocrine, Fengjie People's Hospital, Chongqing, China

³Department of Second Surgery, Fengjie People's Hospital, Chongqing, China

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Abstract

Introduction: Preoperative computed tomography (CT)-guided localization is commonly employed to facilitate video-assisted thoracoscopic surgery (VATS)-guided diagnostic wedge resection of pulmonary nodules (PNs).

Aim: The present meta-analysis was conducted with the goal of better evaluating the feasibility, safety, and clinical efficacy of preoperative CT-guided localization for multiple PNs (MPNs).

Material and methods: PubMed, Embase, and the Cochrane Library databases were reviewed in order to identify all relevant studies published as of June 2020. Random effects modeling was then used to evaluate the pooled data. The meta-analysis was conducted using Stata v12.0 software.

Results: Eight relevant studies were identified for inclusion in the present meta-analysis. In total, 345 patients with 799 PNs were treated with preoperative CT-guided localization and subsequent wedge resection. The overall pooled technical success rate based on the nodules and patients was calculated to be 97% (95% confidence interval (CI): 0.94–0.99) and 92% (95% CI: 0.86–0.97), respectively. The overall pooled incidence rate of complications was calculated to be 40% (95% CI: 0.16–0.63). Significant heterogeneity was observed among the studies for all the parameters described above ($I^2 = 74.5\%$, 77.7% , and 96.3% , respectively). No significant differences were detected in the technical success of localization and incidence of complications between coil and hook-wire groups. The risk of publication bias in the reporting of technical success rate of localization based on both nodules and patients was found to be high ($p < 0.001$ and < 0.001 , respectively).

Conclusions: Preoperative CT-guided localization may be effective in guiding VATS-guided wedge resection in patients with MPNs.

Key words: computed tomography, lung nodule, multiple, localization.

Introduction

Preoperative computed tomography (CT)-guided localization is commonly employed to facilitate video-assisted thoracoscopic surgery (VATS)-guided diagnostic wedge resection of pulmonary nodules (PNs), achieving high rates of successful localization (89.6–100%) and wedge resection (97–100%), with an acceptable

rate of complications (8.8–12.6%) [1–3]. Localization methods usually involve methylene-blue, hook-wire, coils, and radio-labeling agents [1–7]. Relative to cases without localization, preoperative localization can significantly decrease the need for thoracotomy or VATS anatomical resection when diagnosing PNs [4].

Preoperative CT-guided localization of PNs has a number of advantages over other methods and is

Address for correspondence

Xin Liang, Department of Oncology, Fengjie People's Hospital, Chongqing, China, e-mail: lx18581301026@163.com

widely used for patients with multiple PNs (MPNs) [8–15]. Several groups have reported their experiences of one-stage localization for MPNs [12, 14, 15]. However, variability in the technical success of such localization has been reported, with studies employing different localization methods (methylene blue, hook-wire, or coils) reporting success rates of anywhere between 88% and 100% [8–15]. There is a similar degree of variability in the reported complication rates (13–90%) [8–15]. As such, there is a clear need for other large-scale studies with large datasets to more accurately evaluate the feasibility and safety of preoperative CT-guided localization for MPNs.

Aim

The present meta-analysis was conducted with the goal of better evaluating the feasibility, safety, and clinical efficacy of preoperative CT-guided localization for MPNs.

Material and methods

Study selection

PubMed, Embase, and the Cochrane Library databases were searched for all relevant articles published up to June 2020, using the following search strategy: ((localization[Title/Abstract]) AND (nodule[Title/Abstract])) AND (multiple[Title/Abstract]).

Only studies that satisfied the following criteria were included in the review: (a) studies specifically focused on preoperative CT-guided localization (including staining materials, hook-wire, coil, and radio-label localization) for PNs; (b) patients with MPNs; (c) the diameter of each PN \leq 30 mm; and (d) studies should report the technical success of CT-guided localization.

Studies were excluded if they were: (a) case reports (only 1–3 cases); (b) conference abstracts; (c) non-human studies; or (d) reviews.

Data extraction

Two investigators independently extracted data from all studies; the corresponding author asked to resolve any discrepancies that arose. Baseline data, demographic information, and treatment-related data were extracted from all studies.

Quality assessment

All studies identified for inclusion in the present meta-analysis had a non-randomized design. Their

quality was evaluated using the Newcastle–Ottawa scale [16]. Any study with a score \geq 5 was deemed to be of high quality [16].

Endpoints

The endpoints of this meta-analysis included the technical success of localization, technical success of wedge resection, and localization-related complications.

MPNs were defined as the number of PNs $>$ 1. Technical failure of localization was defined as the surgeon being unable to visualize the localized materials [9]. When the localization device was dislodged it was also considered a technical failure. Wedge resection was considered to be successful if the target nodule was identified in the wedge-shaped lung tissue [15].

Meta-analysis

Stata v12.0 software was used to conduct the present meta-analysis. Owing to presumed heterogeneity, a random-effects model was used to calculate the pooled results, with weighting applied according to the inverse variance of the included studies, where heterogeneity was assumed. Heterogeneity of the studies was evaluated using the *Q* test and measured using the *I*² statistic, with *I*² $>$ 50% indicative of substantial heterogeneity. Subgroup analysis was used to investigate sources of heterogeneity. *P*-value $<$ 0.05 was the threshold of significance. Egger's regression asymmetry test was used to evaluate the risk of publication bias.

Results

Study characteristics

In the initial literature search, 231 studies that were potentially relevant to the present analysis were identified. Of these, 8 were ultimately included in the final meta-analysis. Full details of the study selection process are presented in Figure 1.

The overall characteristics of the studies included in the present meta-analysis are shown in Table I. All studies included in the review were retrospective, with scores on the Newcastle-Ottawa scale in the range 6–8. In total, 345 patients with 799 PNs were treated with preoperative CT-guided localization and subsequent wedge resection. In four studies, coil localization was used [11, 12, 14, 15],

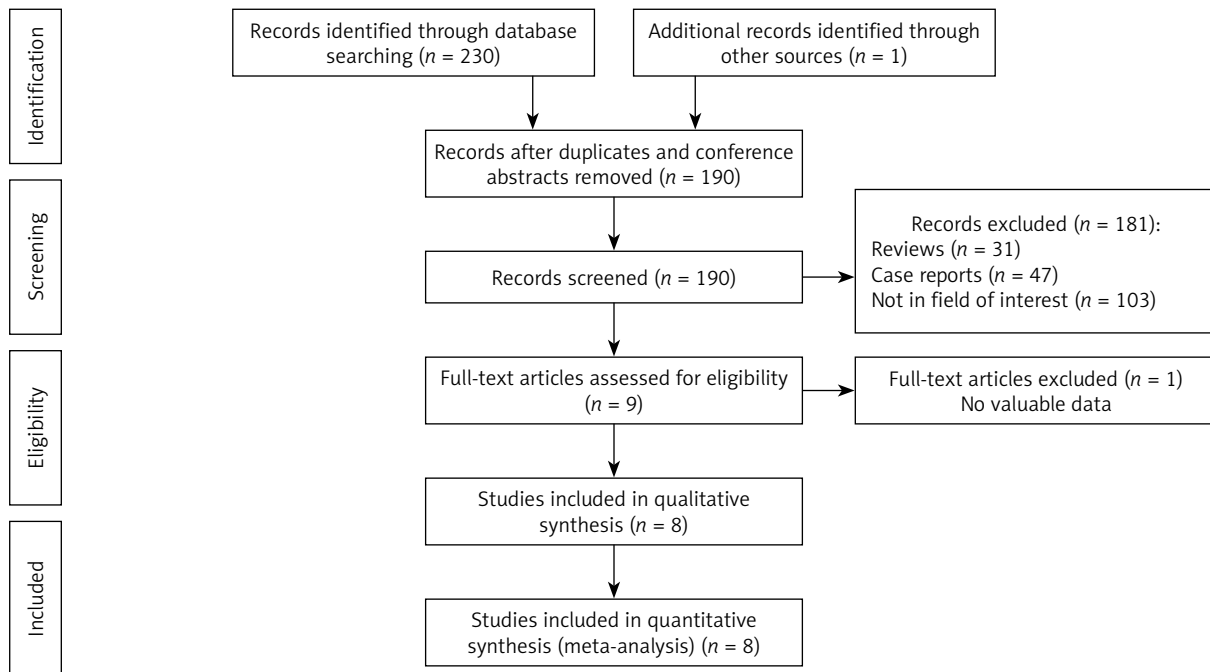


Figure 1. Flowchart of the meta-analysis

Table I. Characteristics of studies included in the meta-analysis

Study	Year	Country	Number of patients	Number of nodules	Mean age [years]	Newcastle–Ottawa score
Iguchi [8]	2015	Japan	35	80	59.9	8
Tseng [9]	2016	Taiwan	100	217	59.9	6
Kadeer [10]	2018	China	76	194	55	8
Li [11]	2018	China	51	126	58.9	8
Fu [12]	2019	China	19	43	56.3	6
Sun [13]	2019	China	16	34	47	6
Teng [14]	2020	China	31	68	55	8
Yang [15]	2020	China	17	37	Not given	6

hook-wire localization was used in 3 [8, 10, 13], and one used methylene-blue localization [9]. The characteristics of the procedures are presented in Table II.

Technical success of localization

Data pertaining to the technical success of localization were reported in all studies, and calculated in relation to both nodules and patients. The overall pooled technical success rate based on nodules was calculated to be 97% (95% confidence interval (CI): 0.94–0.99, Figure 2 A). Significant heterogeneity

was detected among these studies ($I^2 = 74.5%$, $p = 0.001$). The overall pooled technical success rate based on patients was calculated to be 92% (95% CI: 0.86–0.97, Figure 2 B), also with significant heterogeneity among the studies ($I^2 = 77.7%$, $p = 0.000$).

Technical success of wedge resection

The technical success of wedge resection was reported in 6 studies [9, 10, 12–15]. However, because 5 of those studies reported a technical success rate for wedge resection of 100% [9, 12–15], it was not possible to pool the results.

Table II. Characteristics of procedures

Study	Mean lesion size	Localized materials	TS of localization (per nodule)	TS of localization (per patient)	TS of wedge resection (per nodule)	TS of wedge resection (per patient)	Complication rate
Iguchi [8]	0.8 cm	Hook-wire	96%	91%	Not given	Not given	90%
Tseng [9]	0.8 cm	Methylene blue	99%	98%	100%	100%	55%
Kadeer [10]	0.7 cm	Hook-wire	88%	72%	96%	85%	64%
Li [11]	0.8 cm	Coil	96%	90%	Not given	Not given	24%
Fu [12]	0.7 cm	Coil	98%	95%	100%	100%	16%
Sun [13]	0.7 cm	Hook-wire	100%	100%	100%	100%	13%
Teng [14]	0.7 cm	Coil	99%	97%	100%	100%	13%
Yang [15]	0.9 cm	Coil	97%	94%	100%	100%	Not given

TS – technical success.

Complications

The complication rate was reported in 7 studies [8–14]. The overall pooled complication rate was calculated to be 40% (95% CI: 0.16–0.63, Figure 2 C). Significant heterogeneity was detected among the studies ($I^2 = 96.3\%$, $p < 0.001$).

Subgroup analysis

Subgroup analysis was then conducted for each endpoint variable for the different localization tech-

niques (Table III). Only one study used methylene blue localization [9] and so it was excluded from the subgroup analysis. No significant differences were found in the technical success of localization and the incidence of complications between coil and hook-wire groups.

Publication bias

Publication bias analysis suggested that the risk of such bias relating to the reported complication

A

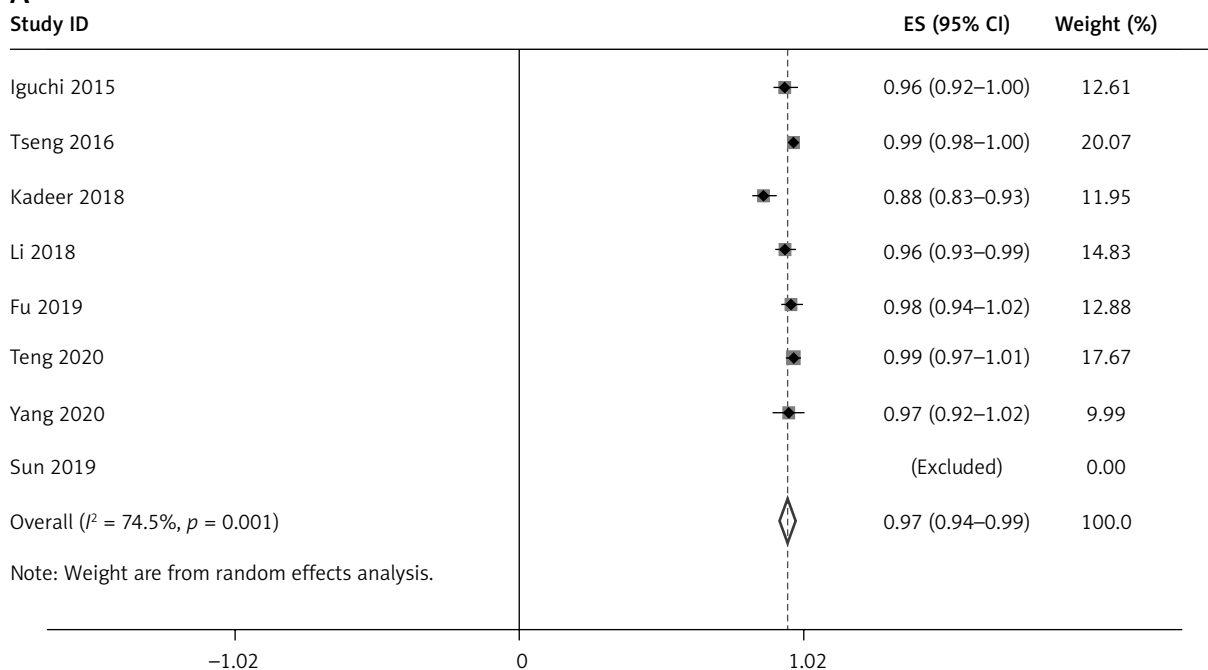


Figure 2. Forest plots of the technical success rate of localization (based on PNs) (A)

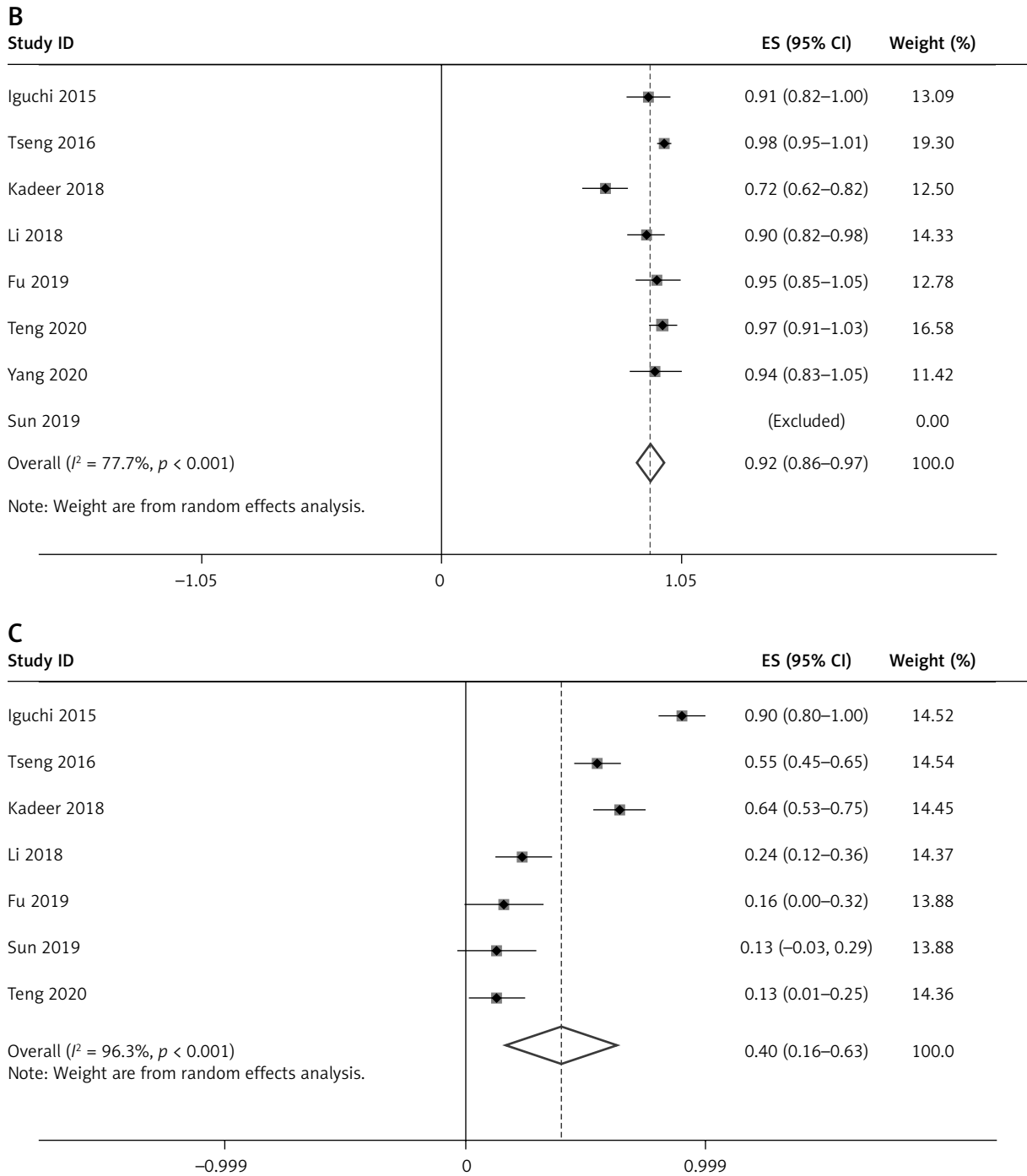


Figure 2. Cont. Technical success rate of localization (based on patients) (B) and complication rate (C)

rate was low ($p = 0.351$). In contrast, the risk of publication bias pertaining to the reported technical success rate of localization based on both nodules and patients was found to be high ($p < 0.001$ and 0.001 , respectively).

Discussion

In the present meta-analysis, the feasibility, safety, and clinical efficacy of preoperative CT-guided localization for MPNs were evaluated. The overall results of our analysis were relatively positive, with a pooled

Table III. Subgroup analyses

Variable	TS of localization (per nodule)	TS of localization (per patient)	Complication rate
Total	97%	92%	40%
Localized materials:			
Coil	98%	95%	18%
Hook-wire	92%	82%	56%
P-value	0.104	0.117	0.163

TS – technical success.

technical success rate of 97% and 92%, respectively, for localization in PN- and patient-based analyses. These results may indicate that it is feasible to simultaneously localize MPNs in a single-stage procedure. However, significant heterogeneity was also detected and it might decrease the reliability of the conclusion. The source of heterogeneity may come from the following factors: (a) all included studies are retrospective in nature; and (b) the included studies used different localized materials. Subgroup analysis demonstrated that the technical success rate for localization was not significantly different for coil and hook-wire groups. These results possibly indicate that the preoperative technical success of localization was not influenced by localization method. Although the study of Tseng *et al.* [9] was not included in the subgroup analysis due to the use of methylene blue, the technical success rates of localization in PN- and patient-based analyses were 99% and 98%, respectively. Nevertheless, further meta-analysis which focuses on one unique localized material is still required.

The reasons for technical failure using the different localization methods differ. The failure of methylene blue localization was due principally to its diffusive nature [2, 9]. The failure of hook-wire localization was due to it becoming dislodged while coils were occasionally inserted into the lung parenchyma causing the loss of intra-operative localization function [1]. Recently, Zhang *et al.* [17] reported their clinical experience of computed tomography in combination with intraoperative noninvasive percutaneous ultrasonic localization of PNs with a high technical success rate of 95.6%. Intraoperative ultrasound can provide real-time localization. However, this technique may not localize the MPNs simultaneously.

Although the pooled localization technical success rate was more than 90%, the raw data of the

studies included in the review indicated that the majority of studies had a 100% technical success for wedge resection [9, 12–15]. VATS-guided wedge resection was usually initially performed following preoperative localization [18]. If localization failed, wedge resection could be performed on tissue identified by palpation of the nodule or coil [1, 9, 12, 14, 15]. Therefore, wedge resection was possible even if preoperative localization failed, although this resulted in wasted surgical time. Fu *et al.* [12] and Teng *et al.* [14] found that preoperative CT-guided multiple coil localization could be used to guide single-stage VATS diagnostic wedge resection in patients with MPNs.

Some researchers also performed simultaneous VATS for PNs and synchronous mediastinal/esophageal lesions [1, 19]. Under this condition, if the PNs were metastatic lesions or presented with ground-glass PNs, only wedge resection was enough [1, 18]. Therefore, preoperative CT-guided localization should be performed for such patients to increase the technical success rate of wedge resection.

In the meta-analysis, the pooled complication rate was 40%. This rate is higher than that reported in previous studies (24–29%) regarding preoperative localization for a single PN [11, 20]. It seems reasonable that localization-related complications occurred more frequently in patients with MPNs. However, the significant heterogeneity still requires further trials to confirm this conclusion. Subgroup analysis revealed that the complication rate in the coil group was lower than in the hook-wire group, although not significantly so (18% vs. 56%, $p = 0.163$). This may be as a result of the limited number of studies. A previous study of coil vs. hook-wire localization for PNs indicated that the total complication rate was lower in the coil group (25% vs. 54%, $p = 0.04$) [21]. Further meta-analysis which compares the clinical effectiveness between different localized materials is required. Although the pooled complication rate was high in this meta-analysis, the majority of studies reported that most localization-related complications did not influence the subsequent VATS-guided resection procedure [1, 9, 12, 14, 15].

There are a number of limitations to the present meta-analysis. Firstly, all studies included in the analysis were retrospective. In addition, we detected significant heterogeneity in the pooled results. Some variability may be attributable to the many potential confounding variables or covariates not reported in the manuscripts, such as operator experience, the direc-

tion of approach, or needle tract depth. Furthermore, the meta-analysis included a variety of different localization methods, thus potentially biasing the results of technical success and complication rate analysis.

Conclusions

The results of the present meta-analysis suggest that preoperative CT-guided localization may be used effectively to guide VATS wedge resection in patients with MPNs. The use of a coil may decrease localization-related complications. Further meta-analysis which focuses on one unique localized material is still required.

Conflict of interest

The authors declare no conflict of interest.

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