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Meta-analysis

Complication Following CT-guided Transthoracic Lung Biopsy: A Systematic Review and Meta-analysis

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ABSTRACT

Background: CT-guided transthoracic lung biopsy is a minimally invasive diagnostic technique for tissue detection of peripheral lung nodules. This can alternatively be carried out by surgery, but CT-guided transthoracic lung biopsy is proposed to be less invasive and correlated with lower costs. Therefore, in this study we aimed to evaluate complication rate of computed tomography (CT)-guided transthoracic lung biopsy.

Methods: Five databases were searched from inception to December 2020 to identify investigations reporting complications in CT-guided lung biopsy. The extracted data of overall and major complication rates were pooled by the random-effects model. Risk factors for complications of FNA were evaluated by meta-regression analysis.

Results: Seventeen studies of complication rate of FNA were included in our meta-analysis. The pooled rate of major complication of FNA was 4.4 % (95 % CI: 2.7–7 %). The pooled rate of pneumothorax was 5 % (95 % CI: 3.1-8 %). Increased traversed lung parenchyma and smaller lesion size were risk factors for major complications.

Conclusions: In CT-guided lung biopsy, major complication rate was low. Our study showed that in patients who underwent FNA, smaller nodule diameter, larger needle diameter and increased traversed lung parenchyma were associated with higher risk of complications.

Keywords: Lung neoplasms, Meta-analysis, Biopsy, Pneumothorax, Computed tomography, X-Ray.

Introduction

In the United States, lung cancer screening by low-dose computed tomography (CT) is suggested for subjects at high risk (1), and the European Society of Radiology and the European Respiratory Society have recently suggested lung cancer screening within clinical trial setting or in common clinical practice at approved medical centers (2). This development will lead to an increase in CT-detected lung nodules. Nodules >10 mm and most likely even smaller nodules with high growth rate will be candidate for medical assessment, including CT-guided lung biopsy (2). CT-guided transthoracic lung biopsy is a minimally invasive diagnostic method for tissue diagnosis of peripheral lung nodules. This can also be carried out by surgery, but CT-guided transthoracic lung biopsy is less invasive and correlated with lower costs. CT-guided transthoracic lung biopsy is a widely approved technique (3, 4), although the findings of previous

studies regarding its complication rate varies greatly. Where some studies show a higher complication rate for core needle biopsy in comparison with fine needle aspiration (FNA), other investigations do not (5, 6). Yao et al. (7) reported in a systematic review comparing FNA with core biopsy that there is no significant difference in complication rate between these techniques. These authors also showed that core biopsy is commonly suggested to have a somewhat higher diagnostic efficacy compared to FNA, especially in detecting histological subtypes; the evidence is not convincing to approve a difference. Complication rate and diagnostic efficacy are the two important factors in indicating a diagnostic method. To find the importance of CT-guided transthoracic lung biopsy in the work-up of screen-detected lung nodules, it is necessary to determine the safety of the method. Therefore, in this study we aimed to evaluate complication rate of computed tomography (CT)-guided transthoracic lung biopsy.

Methods

Search Strategy

A systematic literature research was carried out from inception to June 2020, on MEDLINE, EBSCO, CINAHL, Web of Science, and Cochrane using different combinations of the following keywords: (biopsy OR FNA) AND (transthoracic OR CT-guided) AND (lung cancer) AND CT. After evaluation of title and abstract, two reviewers (M.KH., B.Y.) assessed the full text of the remaining papers, with disagreements resolved by consensus and third reviewer. Inclusion criteria were: (a) having results of complications of at least 50 intervention; (b); the investigation was not a subset of cases from other included researches; (c) appropriate complication assessment. Complication monitoring was determined appropriate if directly following the intervention a CT scan was performed, plus a CT scan or chest radiograph 2 to 4 h after the intervention. Investigations were excluded during screening if they clearly reported a different topic, were case reports, conference abstracts, reviews or editorials, or if they were not written in English. A designed extraction form was used to extract the details of the study with respect to cases, nodules, interventions and complications, and how complication assessment was conducted. Two authors (M.KH., B.Y.) independently collected these variables, with disagreement resolved by consensus and third reviewer.

Two authors (M.KH., B.Y.) independently evaluated the studies, with disagreement resolved by consensus. Complications were considered as minor or major based on the guidelines of the Society of Interventional Radiology (SIR). Minor complications included pneumothorax without requirement of intervention, ground glass opacity around the target detected as pulmonary hemorrhage, and transient hemoptysis. Major complications included pneumothorax requiring intervention, hemothorax, air embolism, needle tract seeding, and death. Intervention was considered as treatment consequences (manual aspiration, chest tube placement, or pain control) or hospital admission. For each investigation the number of (major) complications was calculated as the sum of all reported (major) complications. If the complications for different subgroups were considered, the number of (major) complications was calculated per subgroup. Study-specific risk factors for overall complications and for major complications that were examined are summarized in Table 1.

Inclusion Criteria

Published papers from above-mentioned databases that assessed the complications of CT-guided transthoracic lung biopsy were included. Papers that had all of the following criteria were included: (a) Patients and intervention: cases who underwent CT-guided transthoracic lung biopsy. Investigations that contained data on $\geq$ 10 consecutive cases were included. (b) Study design: observational investigations (retrospective or prospective) were included. (c) Outcomes: papers that included complication rates were included. If an investigation met all of the inclusion criteria but the outcome data were inappropriate, we tried to contact the researchers to receive the necessary data.

Exclusion Criteria

The exclusion criteria included the following: (1) case reports and series with sample size < 10 cases; (2) meta-analysis, narrative and systematic reviews, editorials, letters, comments and conference reports; (3) papers lacking data regarding complications; and (4) investigations with overlapping data on complications. Two reviewers (M.Kh. and S.M.) independently investigated all papers using a designed extraction form. If the two reviewers could not reach a consensus, the study was assessed by a third reviewer (B.Y.).

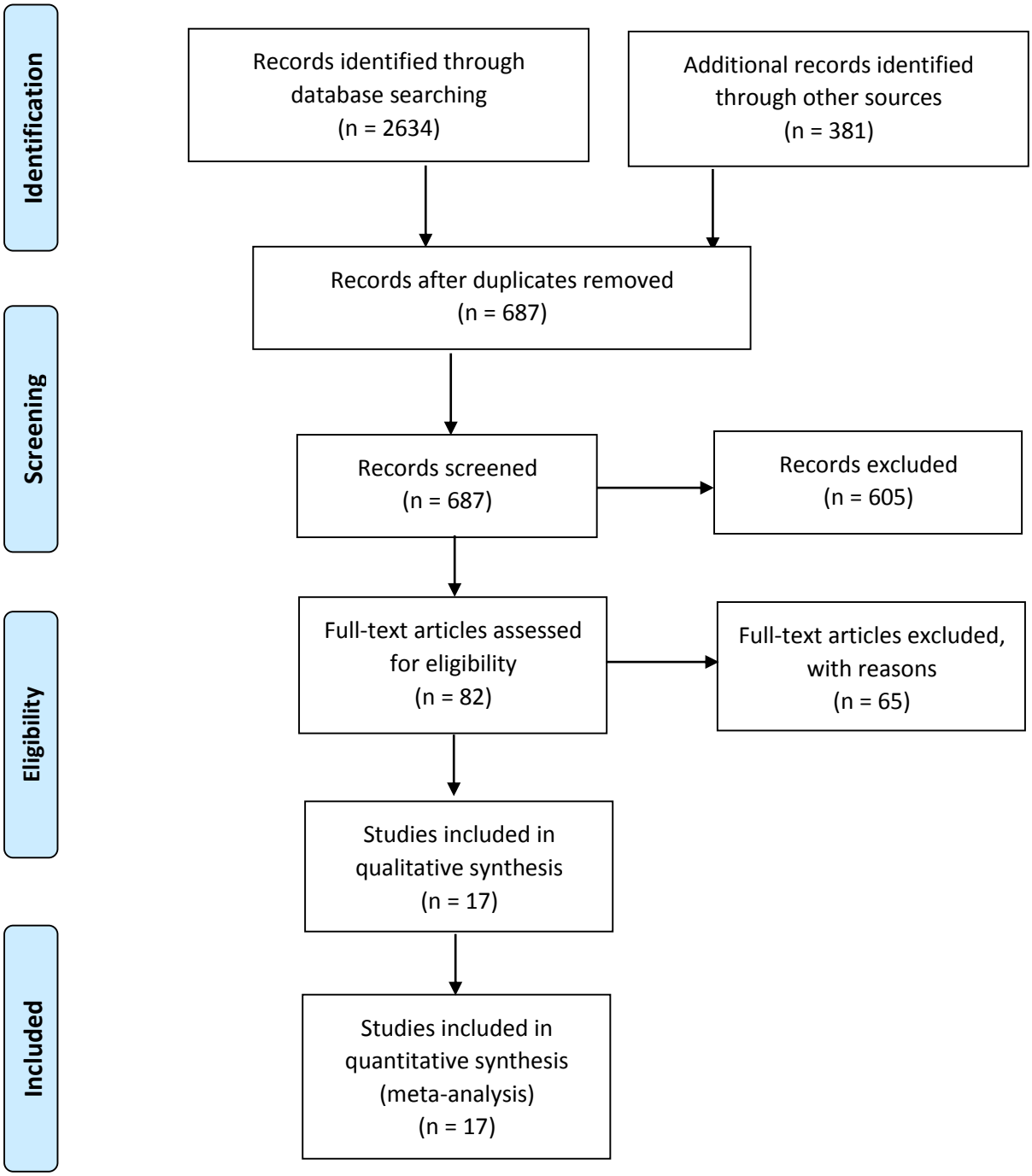

Figure 1. PRISMA flowchart of the literature search and selection of studies that reported complication following CT-guided transthoracic lung biopsy.

Data Extraction

Data extraction of the following variables from the included studies was conducted using standardized extraction forms: (1) study features: authors, date of publication, location of the study, duration of patient recruitment, study design and sample size; (2) demographic and clinical characteristics of the included patients: mean age, lesion diameter; (3) interventions: FNA; and (4) major and minor complications as introduced by the Society of Interventional Radiology. A major complication was considered as an event related to substantial morbidity and/or disability that increased the level of treatment required for the patient, resulted in hospital admission or substantially increased the duration of hospital stay. All other complications

were considered minor. One reviewer (B.Y.) extracted data from the included studies and the second reviewer (M.Kh.) approved the accuracy of the extracted data.

Table 1. Characteristics of the included studies in the meta-analysis.

Author	Years	Cytology	No. of procedures	NOS score	Major complications
Lang et al. (a)	2000	No	50	NR	1
Lang et al. (b)	2000	No	50	NR	8
Laurent et al.	2000	Yes	125	9	3
Shantaveerappa et al.	2002	Yes	128	9	11
Mesurolle et al.	2003	No	85	7	6
Covey et al.	2004	Yes	88	7	4
D'Alessandro et al.	2007	No	594	7	29
Kocijancic et al.	2007	Yes	44	7	2
Laspas et al.	2008	Yes	409	7	1
Lee et al.	2008	No	92	7	0
Ng et al.	2008	Yes	58	6	5
Noh et al.	2009	No	934	9	21
Guimaraes et al.	2010	No	362	7	11
Priola et al.	2010	Yes	321	9	18
Tuna et al.	2013	No	22	8	2
Yazar et al.	2013	Yes	316	9	9
Zhuang et al.	2013	No	102	9	0
Kuban et al.	2015	No	810	6	127

Data Synthesis

Publication bias was evaluated graphically using a funnel plot and with Egger test**.** The pooled proportions of overall and major complications were considered as the principal indices in our meta-analysis. Heterogeneity among studies was assessed by calculating the $\chi 2$ statistic for the pooled estimates ($p<0.05$ indicated significant heterogeneity) and the inconsistency index I^2. An I^2 value of 50 % or greater and/or a Q-statistic value of $P < 0.05$ propose the presence of heterogeneity. Pooled proportions with 95 % confidence intervals (CIs) were calculated with the random or fixed effects modeling based on the findings of heterogeneity evaluation. Publication bias was visually evaluated using funnel plot, and statistical significance was assessed by Egger's test. All the statistical analysis was carried out using Comprehensive Meta-Analysis software (CMA, ver. 3).

Results

Figure 1 is the PRISMA flow diagram of the study. Seventeen included investigations assessed complications of FNA. Tables 1 summarizes the study features, complication rates, NOS scores, and forest plots for major complications of the studies for FNA. The funnel plots and Egger's test showed significant publication bias in terms of prevalence of complications following CT-guided transthoracic lung biopsy (P=0.006) (Fig. 2). The heterogeneity between studies was high (I^2= 89.6%, Q-value 163.74, df (Q) =17, and $p<0.01$). Prevalence of major complication following CT-guided transthoracic lung biopsy was 4.4 % (95 % CI: 2.7–7.0 %) (Figure 3).

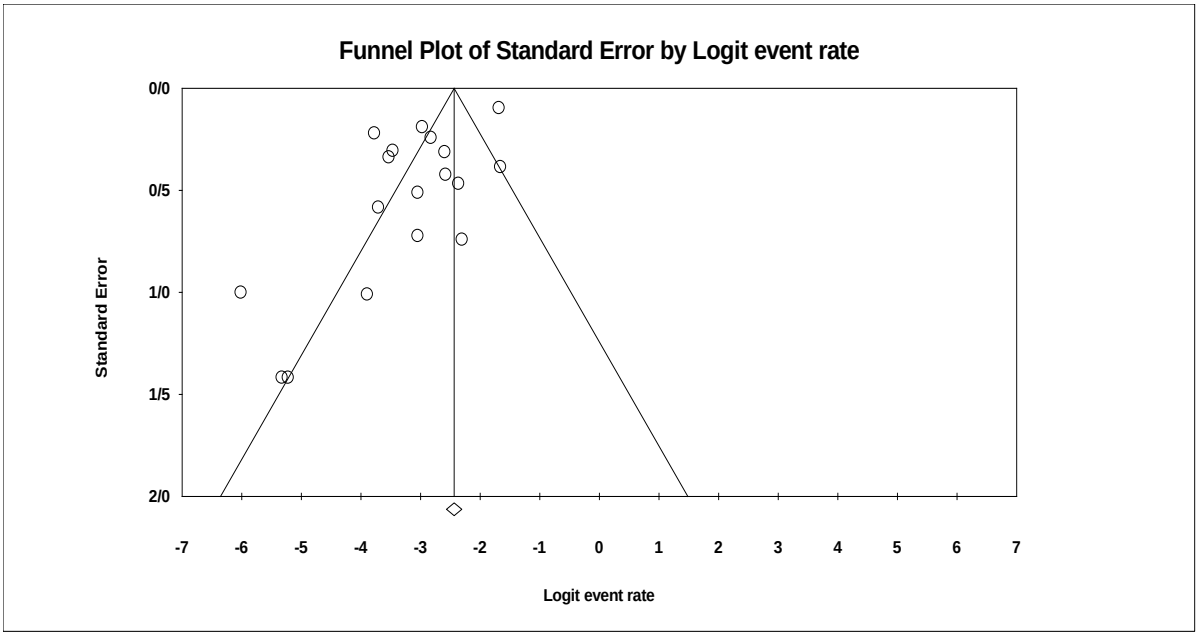

Figure 2. Funnel plot of results of prevalence of complications following CT-guided transthoracic lung biopsy.

Prevalence of pneumothorax and pneumothorax requiring intervention following CT-guided transthoracic lung biopsy were 19.7 % (95 % CI: 15.4–25 %) and 5% (95 % CI: 3.1–8 %), respectively. Furthermore, the pooled prevalence of pulmonary hemorrhage and hemoptysis were 8.5% (95 % CI: 4.5–15.4 %) and 2.2% (95 % CI: 0.8–6.3 %), respectively. Forest plots for all types of complications separately can be found in Figure 4. The median NOS scores of FNA studies was seven. Figure 5 shows a scatter plot of the lesion diameter in FNA studies against the major complication rate. Increased mean lesion diameter decreased the risk of major complications ($P < 0.01$).

Discussion

This meta-analysis investigated the complication rate of CT-guided FNA intervention and found risk factors for complications. For CT-guided FNA the pooled rate of pneumothorax was 19.7 %, of pneumothorax requiring intervention 5 %, of pulmonary haemorrhage 8.5 %, and of hemoptysis 2.2 %. Smaller lesion size was risk factors for major complications.

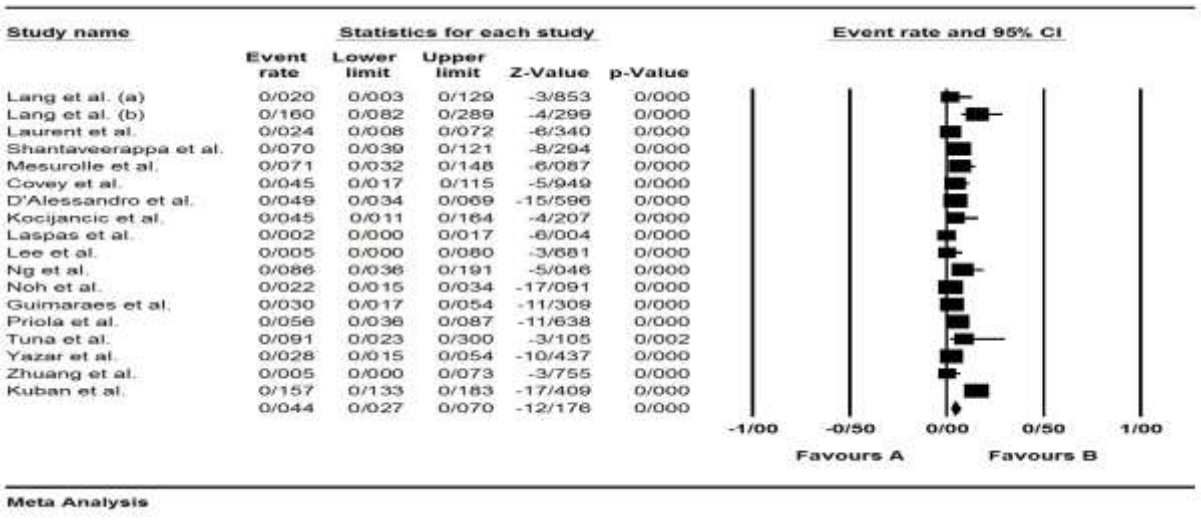

Figure 3. Prevalence of major complication following CT-guided transthoracic lung biopsy.

Two large investigations based on multi-center interventions have been published. Wiener et al. (8) estimated the complications rate of CT-guided lung biopsy by pooling two North American databases containing 15,865 interventions and showed that pneumothorax occurred in 15.0 %, pneumothorax

requiring chest tube in 6.6 %, and pulmonary hemorrhage in 1.0 %.

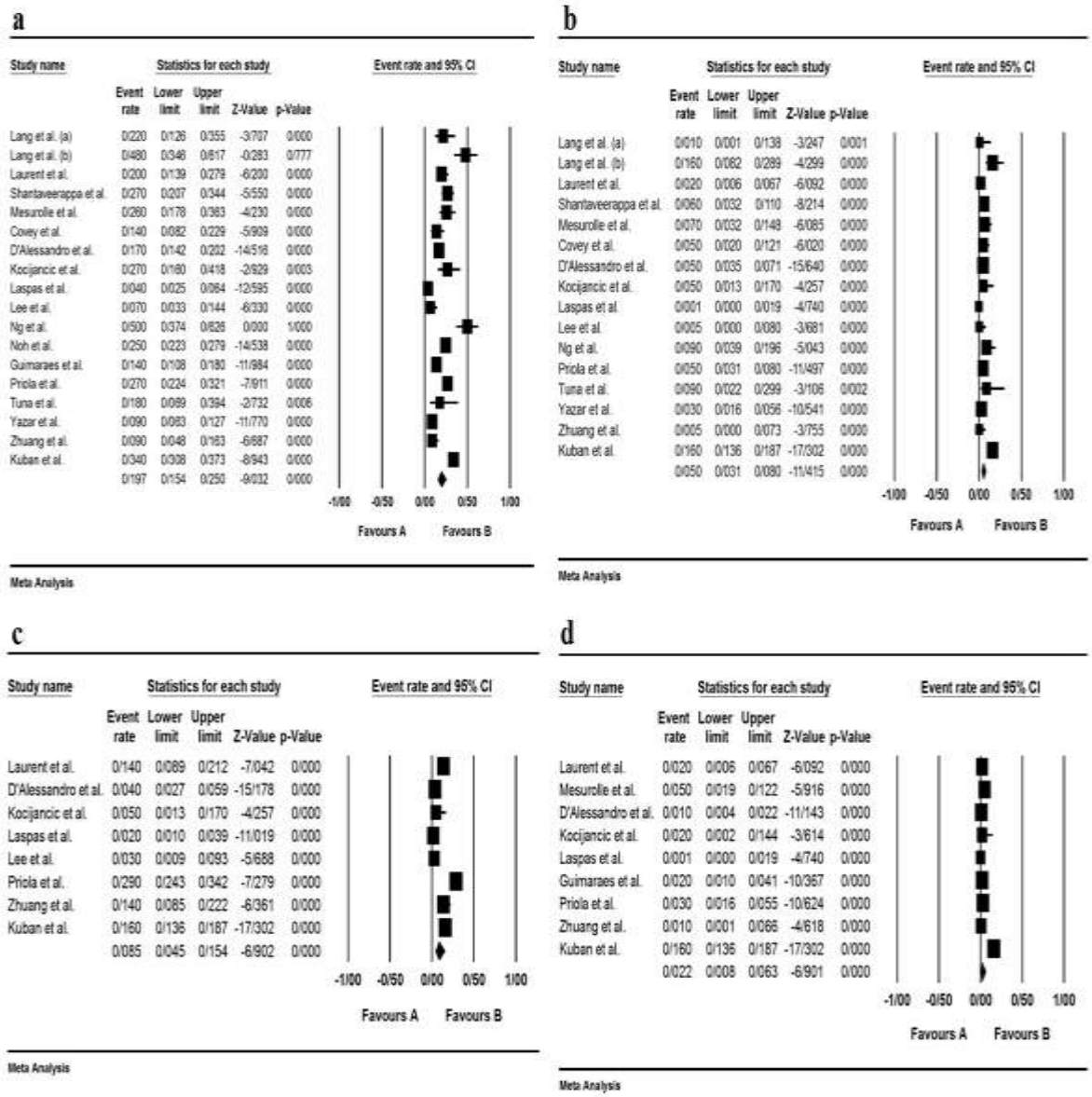

Figure 4. Forest plots for all types of complications following CT-guided transthoracic lung biopsy. **a.** Pooled prevalence of pneumothorax. **b.** Pooled prevalence of pneumothorax requiring intervention. **c.** Pooled prevalence of pulmonary hemorrhage. **d.** Pooled prevalence of hemoptysis.

Tomiyama et al. (9) published a study of severe complications based on 9,783 CT-guided lung biopsies in Japan and identified pneumothorax in 35 %. These findings are quite discrepant. Neither of these investigations was included in this meta-analysis, because they did not meet the inclusion criteria. In Quality Improvement Guidelines for Percutaneous Needle Biopsy, the SIR and ACR reported an estimated pneumothorax rate of 12–45 % and a chest tube placement rate of 2–15 % (10). Similarly, this is a wide range, without differentiation between core biopsy and FNA. However, our predictions of complication rate are approximately in the center of their estimated range. Hemothorax rate could not be estimated exactly, because it was stated in only six investigations. Other rare major complications such as needle tract seeding, air embolism and death were not assessed by any of the included studies. Non-included studies reported a range of 0.02–0.4 % for air embolism(10), 0.012–0.061%for needle tract seeding, and 0.16 % for death (11).

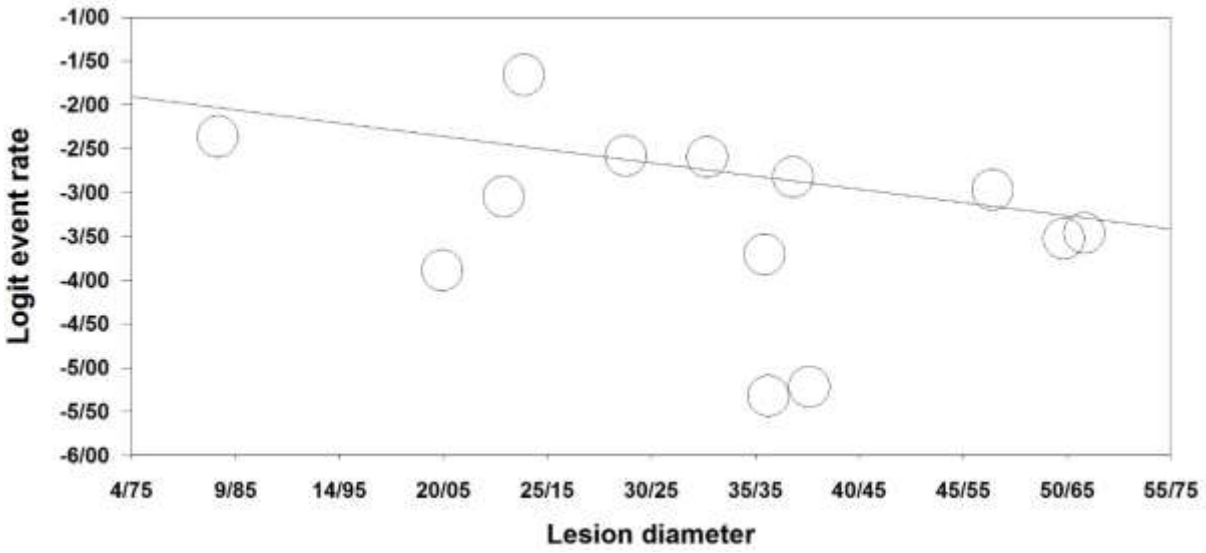

Figure 5. Scatter plot of the lesion diameter in FNA studies against the major complication rate.

In our selected researches (12,753 interventions in total) these complications could have been expected to occur, but such findings are probably not as likely to be published. Therefore, an underrepresentation of these very rare and major complications is likely to be included in this study. Comparing core biopsy with FNA is not clear. Core biopsy and FNA have their own advantages and disadvantages when applied to diagnose lung lesions. For major complications this association was not significant, although a similar trend was visible in favour of FNA. Included investigations that compared FNA with core biopsy did not show significant differences in complication rate, and in a systematic review comparing FNA with core biopsy in lung cancer diagnosis, Yao et al. showed inconsistent findings concerning complication rates (6, 7). In this meta-analysis, a smaller lesion size and an increased distance traversed through lung parenchyma were identified as risk factors for major complications in case of FNA. Patient and nodule features most commonly reported as risk factors are older age, presence of emphysema, smaller lesion size, increased lesion depth, non-pleural contact, and smaller pleural-needle angle (12). However, in most included investigations these features are only reported as a mean, and complications are not stratified based on these findings. Therefore, this study is not ideal to identify patient and nodule specific risk factors. In contrast, a meta-analysis can identify risk factors in study specific features such as needle size, use of coaxial needle, number of biopsies, use of CT-fluoroscopy, on-site cytology, number of surgeons, operator expectation, and institute frequency factors that would be hard to find in a single cohort/ institute, retrospective study.

There was no significant association between the sample size, number of biopsies, number of surgeons, operator expectation, use of coaxial needle, CT-fluoroscopy, on-site cytology, or biopsy site down method and (major) complication rate. Only studies using CT guidance (conventional and/or CT fluoroscopy) were included in this meta-analysis. Conventional CT guidance suggests the advantage of a simulated 3D view making it easy to look along the needle border. Furthermore, there is no ionizing radiation exposure for the operator. CT-fluoroscopy suggests the advantages of a near real-time imaging feedback as the needle is being inserted. It is, however, correlated with an increased patient and operator dose (13). These procedures can be used interchangeably, e.g. initiating with conventional CT guidance and switching to CT-fluoroscopy when the lung lesion is difficult to reach because of risk of respiration. CT-fluoroscopy is commonly reported to have a lower complication rate due to shorter intervention time and fewer needle passes (14). However, if CT-fluoroscopy is indeed used more commonly in cases of hard-to-reach lesions, it could possibly bias the findings, as it often takes longer to sample these. Lastly, it should be considered that none of the included investigations used CT fluoroscopy for FNA. Intuitively, operator experience is seemed to affect complication rate. In a large single-cohort study, Yeow et al. (15) showed operator experience as the third major risk factor for pneumothorax. In our study only a few studies assessed the operator

experience (FNA: n =3). Because of the low number of papers reporting operator experience, and because only overall mean operator experience was reported (so not per operator), it was not possible to more evaluate this potential risk factor in our study. The use of coaxial needles has the advantage of decreasing the number of pleural passes. However, it leads to a prolonged connection with the pleura which might result in increased parenchymal damage due to respiratory motion. Furthermore, it increases the outer needle diameter. None of the included papers specifically evaluated the effect of coaxial needles on complication rate. Two other papers performed (16), but showed no significant association. The biopsy site down method has been cause for some debate; although some studies show no difference in complication rate when repositioning the patient after the intervention, others have reported a significant reduction in pneumothorax and/or chest tube placement rate in case of patient repositioning. A recent study proposed that the main factor for success is to immediately roll the patient over after biopsy, known as rapid needle-out patient-rollover (16). None of the studies included in this study, using the biopsy site down method, reported to roll the patients over immediately, which is why this association could not be assessed. However, Kinoshita et al. (17) have been positioning subjects (n = 147) with the biopsy site downwards during the intervention, using a special table, after which they stayed in biopsy site down position for approximately 15 minutes. They showed a significant drop in pneumothorax rate in comparison with the standard intervention, which also indicates that patient (re) positioning in the initial minutes after, or even during, biopsy is necessary. The use of larger needles was shown to be a risk factor. According to the recommendations of the SIR (10) only interventions conducted with 22 or higher gauge needles should be assumed as fine needle aspiration. Investigations were only included in this study if they had appropriate monitoring of complications. Although that leaded to the exclusion of 75 papers, it made sure that no investigations were included that underreported their complication rate. Because chest radiography has shown to miss a significant number of pneumothorax patients after CT-guided lung biopsy in comparison with CT, an initial control CT scan was a necessary condition for inclusion. Moreover, at least additional chest radiography 2 to 4 h after the intervention was required, because investigations have demonstrated that initially covert pneumothorax identified by delayed chest radiograph sometimes does require chest tube insertion (18). Another inclusion criterion of our meta-analysis was the reporting of complications of at least 50 interventions, leading to the exclusion of 32 papers. Excluding smaller investigations may bias findings, as less experienced centers can be expected to have a higher prevalence of complication. The funnel plots of included papers reveal no clear asymmetry, and regression analysis revealed no association between sample size and complication rate, so we do not expect the exclusion of small investigations to have biased the findings. However, since small investigations were not included in the analyses, this cannot be excluded with certainty. We assessed potential sources of heterogeneity, but much of the variance between investigations could not be clarified. Therefore, a random-effects model was performed to pool complication rates. This makes the estimates more usable as it favours larger investigations relatively less, compared to a fixed effects model. Furthermore, outliers do not get weighted as heavily as they otherwise would. Taken together, we expect that the calculated pooled complication rates are accurate estimates of actual complication rates. This meta-analysis has some limitations. It was not performed to compare specifically the complication rates of core biopsy with FNA. Most included papers only investigated complications of one procedure, so commonly no controls in the same population are available. Furthermore, although the quality of the papers included in both groups is often high according to the NOS score, there are potential sources of bias within the papers. Previously, FNA would be preferred over core biopsy for small nodules, since core samples of high quality were considered hard to achieve. It has been recently reported that smaller lesions are more likely to lead to complications, which may cause the pooled complication rates of core biopsy and FNA to be biased (19). Another possible cause of within study bias could be in the selection of sampling methods in case additional histological subtyping is needed for targeted treatment. Sometimes both techniques (i.e. FNA and core biopsy) are used in the same setting in an effort to increase the diagnostic efficacy, which can inadvertently result in a higher rate of complications (20). This meta-analysis cannot draw conclusions as to whether or not combined usage of sampling methods indeed

increases the complication rate. Finally, this meta-analysis could not indicate the rate of complications that occur infrequently or require a long term follow-up of the cases, such as death, air embolism and needle tract seeding. In the specific context of diagnostic work-up of lung nodules identified in CT-screening FNA should be favoured over core biopsy. This is especially the case for 22-gauge needles, with which the risk of complications decreases significantly. Furthermore, investigations have reported that diagnostic yield does not decrease when using smaller FNA needles, and improvements in FNA cytology have enabled subtyping of lung cancer in cytological material (21). It should be noted that a smaller lesion size is associated with major complications, and that nodules identified by lung cancer CT-screening, needing work-up, are commonly smaller in size (22). However, variables such as younger age and less comorbidity that can be expected in screening cases will have a beneficial effect on the expected complication rate. Taken together, the pooled complication rate indicated in this study cannot be considered to be similar in screen identified nodules. To find the differences between the complications of core biopsy and FNA properly, only randomized controlled trials or even only prospective investigations comparing both methods should be included in the study. However, randomized controlled trials comparing these methods have not been performed, and only two prospective investigations compared complication rates. Therefore, well-designed randomized controlled trials would be suggested to exactly compare the efficacy of CT-guided lung core biopsy and FNA.

Conclusion

Prevalence of major complication following CT-guided transthoracic lung biopsy was 4.4 %. Furthermore, our study showed that smaller nodule diameter, larger needle diameter and increased traversed lung parenchyma are risk factors for complications.

Declarations

Acknowledgement

The authors thank all those who contributed to this study.

Author Contribution

Maria Khurshid: Study design, data collection, writing draft of study.

Bardia Yarmohammadi: Study design, data collection, writing draft of study.

Sassan Mohammadi: Study design, data collection, writing draft of study.

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Conflict of interest

There is no conflict of interest.

Data Availability

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

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