

Appendix 1. Study protocol

1. **Title:** Comprehensive assessment of harms of fine-needle aspiration biopsy in thyroid nodules: a systematic review
2. **Objectives:** This study is conducted to evaluate the harms of fine-needle aspiration for patients with thyroid nodules in various perspectives.
3. **Protocol and registration:** Methods of database search, study selection, data extraction, assessment of study quality and risk of bias are predefined in the protocol at the beginning of the study.
4. **Reporting:** This systematic review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

5. Eligible criteria

1) Study characteristics

- (1) Population: adult patients with thyroid nodules
- (2) Intervention: ultrasonography-guided fine-needle aspiration biopsy
- (3) Comparison: none
- (4) Outcomes of interests: procedure-related complications (pain, discomfort, bleeding events, tracheal puncture, neurological symptoms, vasovagal reaction, needle tract implantation of thyroid cancer) effects on diagnosis (overdiagnosis, beneficial outcomes related with diagnosis)
- (5) Study design: primary studies including prospective, retrospective cohort/case-control studies, and randomized clinical trials

2) Report characteristics

- (1) Years considered: 2012 to 2022
- (2) Language: English
- (3) Publication status: full-text articles without limitation of publication status
- (4) Reports included in the previous systematic reviews were also reviewed

3) Inclusion and exclusion criteria

- (1) We included studies which include patients:
who are over 18 years old with thyroid nodules on ultrasonography; who had ultrasound-guided fine-needle aspiration biopsy for evaluation of thyroid nodule; whose complications were reported in the report
- (2) We excluded studies which include patients
who are under 18 years old; who did not have ultrasound-guided fine-needle aspiration biopsy for evaluation of thyroid nodules; whose complication rates were not reported in the report; case reports, editorial, secondary studies (review articles, systematic review, meta-analysis)

6. **Information sources:** We searched electronic databases of MEDLINE, Embase, Cochrane, and KoreaMed.

7. **Search strategy:** Studies related with the harm of fine-needle aspiration biopsy for patients with thyroid nodules were searched using following search strategies.

1) MEDLINE

- (1) exp Thyroid Neoplasms/
- (2) (thyroid adj6 (cancer or carcinom\$ or tumo?r\$ or neoplasm\$)).tw,kw
- (3) or/1-2

- (4) exp ultrasonography/
- (5) (ultrasonogra* or sonogra* or ultrasonic or ultrasound).tw,kw
- (6) 4 OR 5
- (7) Biopsy, Fine-Needle/ or (fine?needle or needle Biopsy or Needle aspiration or FNA or cytology).tw,kw
- (8) 3 AND 6 AND 7
- (9) exp Vocal Cord Paralysis/ or (complication* or side effect or harm* or (laryngeal adj2 palsy) or Laryngeal Paralysis or Laryngeal Pareses or vocal cord palsy or (nerve adj2 injury) or hematoma or infection or pain or hospitalization or admission or needle tract seed* or implantation).tw
- (10) 8 AND 9
- (11) limit 10 to yr="2012 -Current"

2) Embase

- (1) 'Thyroid tumor'/exp
- (2) (Thyroid NEAR/6 (cancer or carcinom* or tumor?r* or neoplasm*)):ab,ti,kw
- (3) #1 OR #2
- (4) 'echography'/exp
- (5) (ultrasonogra* or sonogra* or ultrasonic or ultrasound):ab,ti,kw
- (6) #4 OR #5
- (7) 'fine needle aspiration biopsy'/exp or (fine?needle or 'needle Biopsy' or 'Needle aspiration' or FNA or cytology):ab,ti,kw
- (8) #3 AND #6 AND #7
- (9) 'vocal cord paralysis'/exp or (complication* or side effect or harm* or (laryngeal NEAR/2 palsy) or 'Laryngeal Paralysis' or 'Laryngeal Pareses' or 'vocal cord palsy' or (nerve NEAR/2 injury) or hematoma or infection or pain or hospitalization or admission or 'needle tract seed*' or implantation):ab,ti,kw
- (10) #8 AND #9
- (11) #10 AND ('article'/it OR 'article in press'/it OR 'review'/it OR 'short survey'/it)
- (12) limit #11 AND [2012-2022]/py

3) Cochrane library

- (1) [mh "Thyroid Neoplasms"]
- (2) (Thyroid NEAR/6 (cancer or carcinom* or tumor?r* or neoplasm*)):ab,ti,kw
- (3) #1 OR #2
- (4) [mh "Ultrasonography"]
- (5) (ultrasonogra* or sonogra* or ultrasonic or ultrasound):ab,ti,kw
- (6) #4 OR #5
- (7) (fine?needle or 'needle Biopsy' or 'Needle aspiration' or FNA or cytology):ab,ti,kw
- (8) #3 AND #6 AND #7
- (9) [mh "Vocal Cord Paralysis"] or (complication* or side effect or harm* or (laryngeal NEAR/2 palsy) or 'Laryngeal Paralysis' or 'Laryngeal Pareses' or 'vocal cord palsy' or (nerve NEAR/2 injury) or hematoma or infection or pain or hospitalization or admission or 'needle tract seed*' or implantation):ab,ti,kw
- (10) #8 AND #9
- (11) #10 with Publication Year from 2012 to 2022, in Trials

4) KoreaMed

- (1) ("Thyroid Neoplasms"[MH]) AND ("echography"[ALL] OR "early cancer diagnosis"[ALL] OR "FNA"[ALL]) AND ("metastasis"[ALL])

- 8. Study selection:** All identified records were evaluated for eligibility by two reviewers independently. We reviewed titles, abstracts, and full texts of the studies. Any disagreements were resolved by a third reviewer.
- 9. Data extraction:** Standardized data extraction was performed by two reviewers independently as follows. Any disagreements were resolved by a third reviewer.
- 1) First author
 - 2) Publication year
 - 3) Country
 - 4) Number of study participants
 - 5) Characteristics of study participants: mean or median age,
 - 6) HR
- 10. Assessment of study quality and risk of bias:** Quality assessment was done using the Cochrane Risk of Bias tool 2.0 (ROB 2.0) for randomized controlled studies and the Newcastle-Ottawa Quality Assessment Scale for non-randomized studies. Two reviewers independently evaluated each study based on the following aspects of trials:
- 1) Selection: representativeness of the cohort, selection of the non-exposed cohort,
 - 2) Comparability: comparability of cohorts based on the design or analysis
 - 3) Outcome: assessment of outcome, adequacy of follow-up of cohorts
- 11. Data synthesis:** Due to the data insufficient for meta-analysis, we showed narrative summary of studies included with this review.