



A Comprehensive Assessment of the Harms of Fine-Needle Aspiration Biopsy for Thyroid Nodules: A Systematic Review

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Background: There have concerns related with the potential harms of fine-needle aspiration biopsy (FNAB). We aimed to summarize the clinical complications and evaluate the safety of FNAB.

Methods: Studies related with the harms of FNAB were searched on MEDLINE, Embase, Cochrane library, and KoreaMed from 2012 to 2022. Also, studies reviewed in the previous systematic reviews were evaluated. Included clinical complications were post-procedural pain, bleeding events, neurological symptoms, tracheal puncture, infections, post-FNAB thyrotoxicosis, and needle tract implantation of thyroid cancers.

Results: Twenty-three cohort studies were included in this review. Nine studies which were related with FNAB-related pain showed that most of the subjects had no or mild discomfort. The 0% to 6.4% of the patients had hematoma or hemorrhage after FNAB, according to 15 studies. Vasovagal reaction, vocal cord palsy, and tracheal puncture have rarely described in the included studies. Needle tract implantation of thyroid malignancies was described in three studies reporting 0.02% to 0.19% of the incidence rate.

Conclusion: FNAB is considered to be a safe diagnostic procedure with rare complications, which are mainly minor events. Thorough assessment of the patients' medical condition when deciding to perform FNABs would be advisable to lower potential complications.

Keywords: Biopsy, fine-needle; Thyroid neoplasms; Thyroid nodule; Complications

INTRODUCTION

Fine-needle aspiration biopsy (FNAB) is the most widely accepted preoperative diagnostic technique for thyroid malignancies because of its high accuracy, safety, simplicity, and cost-effectiveness [1,2]. The cytological findings obtained from FNAB are used to classify thyroid nodules into various categories in

thyroid imaging reporting and data systems, and to decide whether to perform surgery or conduct surveillance [3-5]. FNAB can be performed with guidance by palpation or ultrasound, the latter of which has become more popular in recent years, and the specimen can be obtained by a needle attached to a syringe or by using capillary action [6]. Although FNAB is considered to be very safe, it is important to be aware of the

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clinical complications that can occur after FNAB, as the increasing number of performed FNAB procedures can lead to an increased frequency of clinical complications. Herein, we present a thorough review of FNAB-related adverse events to evaluate the safety of FNAB and help clinicians to have a comprehensive perspective on the procedure to prevent complications.

METHODS

Search strategy

We performed a literature search on MEDLINE, Embase, Cochrane Library, and KoreaMed from 2012 to 2022. We also reviewed references from previous systematic reviews, reviews and consensus statements related to the complications of FNAB [7-9]. The search strategy was conducted using medical terms (“thyroid neoplasm,” “ultrasonography,” “fine needle aspiration biopsy,” “complication”). The study protocol with detailed search strategies is included in Appendix 1. We reported the results in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Supplemental Table S1). Only articles written in English were included.

Study selection

First, two reviewers (J.Y.P. and H.K.K.) independently reviewed the titles and abstracts, and excluded irrelevant articles. Any discrepancies between the two reviewers were settled by consultation with a third investigator (H.C.K.). A full-text review was performed following the inclusion criteria as follows: (1) studies designed as cohort studies; (2) adult patients who underwent ultrasound-guided FNAB for thyroid nodules; (3) studies reporting clinical complication rates related to FNAB; and (4) studies that were written in English. The following studies were excluded: (1) studies including patients under 18 years of age; (2) studies with patients who did not undergo FNAB; and (3) studies that did not mention the adverse events of FNAB.

Data extraction and quality assessment

Two independent reviewers (J.Y.P. and H.K.K.) extracted the data as follows: first author’s name, country where the study was done, publication year, number of cases and patients who underwent FNAB, study design, age, sex, gauge size of the needles used for FNAB, and outcomes related to clinical harms after FNAB.

Quality assessment was done using the Cochrane Risk of Bias tool 2.0 for randomized controlled studies and the Newcastle-

Ottawa Quality Assessment Scale for non-randomized studies (Supplemental Table S2, Supplemental Fig. S1). After a thorough assessment using items of the Newcastle-Ottawa Quality Assessment Scale (selection of studies, comparability, and outcomes), we rated the scores of the studies. Any disagreements were resolved by a third reviewer (H.C.K.).

Ethical approval

Ethical approval can be waived as this study was not performed on human participants.

Registration information

The study protocol is registered in International Prospective Register of Systematic Reviews (PROSPERO) with the title of: “Comprehensive assessment of harms caused by fine-needle aspiration for screening and diagnosing thyroid neoplasms: a systematic review (ID: CRD42022364961).”

RESULTS

Characteristics of the studies

The flow diagram of the present study is described in Fig. 1. A total of 199 studies were initially identified, and 59 remained after the first screening. The excluded studies included reviews, case reports or case series, studies with different topics of interest, meta-analyses, and conference abstracts. After reviewing 59 studies based on the full-text, 16 studies were finally included for review. Moreover, seven studies were added through an additional literature search, resulting in 23 studies in total. The characteristics of the studies relevant to the clinical harms of ultrasound-guided FNAB are summarized in Table 1. Three randomized studies and 20 non-randomized studies were analyzed.

Pain related to FNAB

According to the nine studies that reported pain at the puncture site during FNAB, most of the patients showed mild or no pain, although the pain rating scales were inconsistent [10-18]. Researchers tried to find any significant factors that would alleviate pain during the procedure. A comparative study conducted by Lee et al. [12] showed similar results of pain scales according to whether patients underwent FNAB with 23-gauge needles or 25-gauge needles. Jung et al. [13] also reported consistent results that the mean pain scale values in the 21-gauge needle group and the 23-gauge needle group were 1.8 ± 1.3 (range, 0 to 6) and 1.4 ± 1.1 (range, 0 to 5), respectively, showing no statistically significant difference depending on the gauge size. The as-

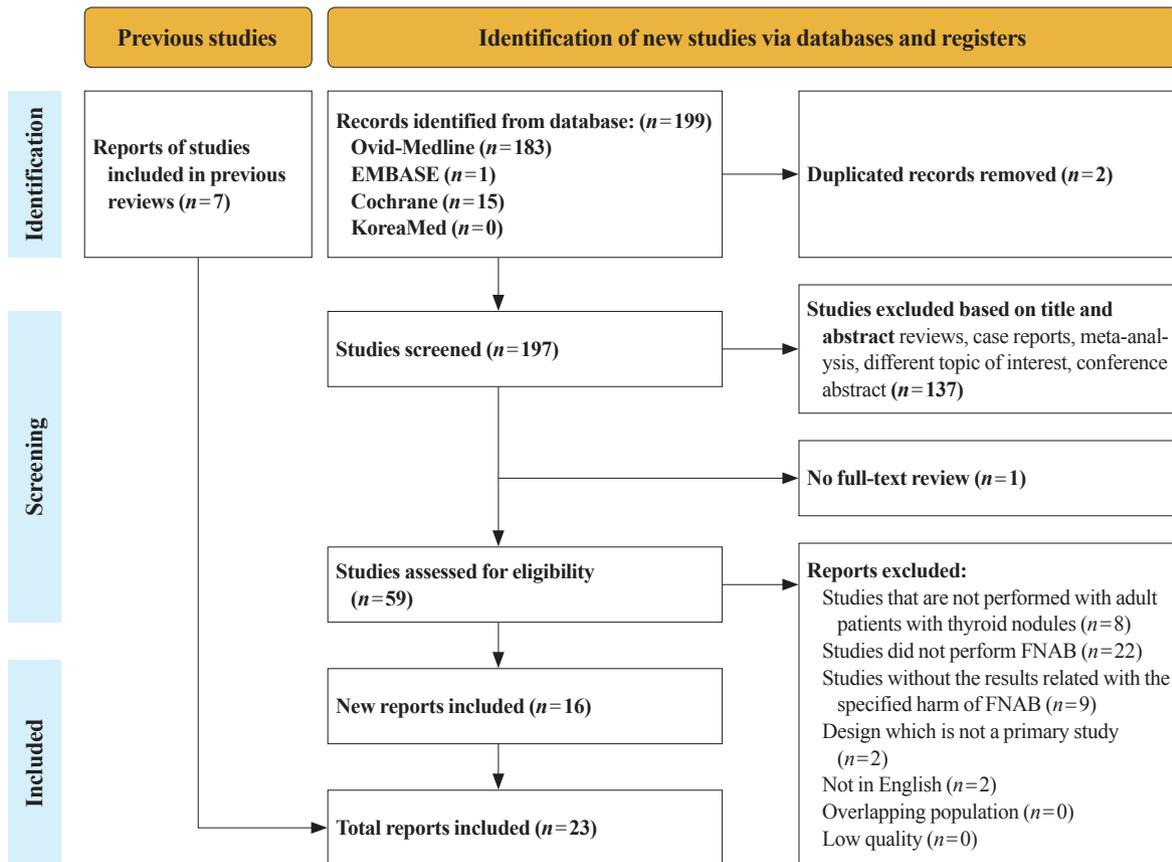


Fig. 1. Flow diagram of study screening and selection for the present review. FNAB, fine-needle aspiration biopsy.

sociation between the characteristics of thyroid nodules and the severity of pain was also evaluated. Cordes et al. [14] noted that neither the volume nor the type of thyroid nodules showed any significant differences in terms of adverse event rates, mainly pain at the puncture site. Toman et al. [15] emphasized that the depth of thyroid nodules was correlated with the pain score, and recommended using anesthesia to alleviate FNAB-induced pain for patients who had thyroid nodules in the deep portion of their necks. As some patients are very sensitive to pain, the efficacy of anesthesia when performing FNAB has been an issue. Gursoy et al. [17,18] reported in their randomized double-blind trial that local anesthesia prominently alleviated pain after FNAB. The relationship between the expertise of the clinicians and pain after FNAB was also evaluated. A comparative study by Lee et al. [16] analyzed the pain scores of two groups divided according to the career of the operator ($\geq 1,200$ ultrasound-guided FNAB procedures per year for 10 years vs. 500 ultrasound-guided FNAB procedures for 1 year) and did not show any statistically significant difference.

Bleeding or hematoma

Fifteen studies describing episodes of bleeding events or hematoma are listed in Table 1 [11,13,14,16,19-29]. Some studies showed superior or non-inferior safety outcomes of FNAB compared to those of core needle biopsy (CNB). Ahn et al. [22] reported that no complications took place in the FNAB group, while perithyroidal or intrathyroidal hemorrhage occurred in 0.7% (5/705) of patients in the CNB group, without a significant difference ($P=0.069$). Kim et al. [23] stated that the incidence of subcapsular hematoma was similar in the FNAB group (3/87) and the CNB group (2/80). Chae et al. [24] reported that 0.8% (43/5,121) of the patients in FNAB group and 4.9% (9/183) of the patients in CNB group had hematoma, and emphasized that CNB was the only significant factor associated with an increased risk of post-biopsy bleeding events, showing an adjusted odds ratio of 6.458 (95% confidence interval, 2.348 to 17.766; $P<0.001$). Khoo et al. [25] stated that three patients in the FNAB-only group ($n=311$) and eight patients in the FNAB and CNB group ($n=320$) had bleeding events. Chen et al. [26] reported one episode of minor hematoma in both the

Table 1. Summary of Studies Related to the Harms of Ultrasonography-Guided Fine-Needle Aspiration Biopsy for Thyroid Neoplasms

Study	Country recruitment period	Study design	No. of cases/ patients	Age, yr	Female, %	Needle gauge	Outcomes
Pain after FNA							
Lee et al. (2019) [12]	South Korea 2018	Randomized, double-blind	99/99 (23G n=49, 25G n=50)	51.5	79.8	23, 25	Rated with NRS ^a 23G: none 3 (6.1%), mild 39 (79.6%), moderate 6 (12.2%), severe 1 (2.0%) 25G: none 10 (20%), mild 36 (72.0%), moderate 4 (8.0%), severe 0 (0.0%)
Jung et al. (2018) [13]	South Korea 2017	Retrospective	88/88 (21G n=38, 23G n=50)	54.6	84.1	21, 23	Rated with NRS ^a 21G: none 1 (2.6%), mild 33 (86.8%), moderate 4 (10.5%), severe 0 (0.0%) 23G: none 6 (12.0%), mild 42 (84.0%), moderate 2 (4.0%) severe 0 (0.0%)
Cordes et al. (2018) [14]	Germany 2017–2018	Prospective	205/205	55	71.2	22, 24	Pain at the puncture site 5 (2.4%)
Birgi et al. (2016) [11]	Turkey 2014	Prospective	138/138	49.4	88.4	21	No pain 33.3% Pain 66.6% (low 48.3% medium 15.7%, high 2.7%)
Toman et al. (2016) [15]	Turkey 2012	Retrospective	98/98	49.8	82.7	23	100-mm VAS ≥30 (70.5%) A higher pain score correlated with the nodule depth ($r=0.43, P<0.001$)
Lee et al. (2013) [16]	South Korea 2012	Retrospective	157/157 (experienced radiologist n=75, less experienced radiologist n=82)	51.4	89.2	23	Rated with NRS ^a Experienced radiologist: none 14 (18.7%), mild 48 (64.0%), moderate 11 (14.7%), severe 3 (4.0%) Less experienced radiologist: none 12 (14.6%), mild 48 (58.5%), moderate 20 (24.4%), severe 5 (6.1%)
Kim et al. (2012) [10]	South Korea 2007–2009	Retrospective	1,456/977	49.0	85.8	23	Mild pain 87 (8.9%) No other major complications
Gursoy et al. (2007) [18]	Turkey Apr.–Sep. 2006	Randomized, double-blind	99/99 (placebo n=49, EMLA n=50)	46.8	19.5	25	Rated with VRS Placebo group: none 4, mild 16 (32.7%), moderate 14 (28.6%), severe 15 (30.6%) EMLA group: none 9 (18%), mild 26 (52%), moderate 11 (22%), severe 4 (8%)
Gursoy et al. (2007) [17]	Turkey Aug.–Dec. 2006	Randomized, double-blind	107/107 (placebo n=52, lidocaine n=55)	46.5	15.6	25	Rated with VRS Placebo group: none 6 (11.5%), mild 17 (32.7%), moderate 14 (26.9%), severe 15 (28.8%) Lidocaine group: none 23 (41.8%), mild 27 (49.1%), moderate 5 (9.1%), severe 0 (0%)
Hematoma or any bleeding events after the procedure							
Ahn et al. (2021) [22]	South Korea 2010–2014	Retrospective	627/583	49.6	67.5	23	Comparison with the CNB group FNAB group 0 (0.0%)
Kim et al. (2019) [23]	South Korea 2015	Retrospective	87/87	52.5	87.4	26	Subcapsular hematoma 3 (3.4%)
Khadra et al. (2018) [28]	USA 2008–2016	Retrospective	1,568/802	63.0 (AT/AC) 50.1 (control)	80.2	25	Total 9/1,568 (0.6%) AT/AC 3/336 (0.9%) No agent 6/1,232 (0.5%)
Jung et al. (2018) [13]	South Korea 2017	Retrospective	88/88	54.6	84.1	21, 23	Intrathyroidal 1 (2.6%)
Cordes et al. (2018) [14]	Germany 2017–2018	Prospective	205/205	55	71.2	22, 24	Minor hematomas 2 (0.9%)

(Continued to the next page)

Table 1. Continued

Study	Country recruitment period	Study design	No. of cases/patients	Age, yr	Female, %	Needle gauge	Outcomes
Kavanagh et al. (2017) [19]	Ireland 2006–2013	Retrospective	724/724	40	82.5	20, 23	Post-procedural 6 (0.8%)
Chae et al. (2017) [24]	South Korea 2013–2015	Retrospective	5,121/5,121	50.9	78.8	23	Comparison with the CNB group FNAB group 43 (0.8%)
Cappelli et al. (2017) [21]	Italy 2007–2016	Retrospective	7,449/6,323	54.3	81.0	25	Intrathyroidal 4 (0.06%) Carotid intramural 1 (0.02%)
Birgi et al. (2016) [11]	Turkey 2014	Prospective	138/138	49.4	88.4	21	Minor hematoma 1 (0.7%)
Uchida et al. (2016) [27]	Japan 2011–2013	Retrospective	742/653	59.0	74.1	22	Acute thyroid swelling or anechoic lesions 8 (1.2%)
Chen et al. (2015) [26]	USA 2007–2011	Retrospective	96/96	56.0	83.0	25, 27	Local hematoma 1 (1.0%)
Lee et al. (2013) [16]	South Korea 2012	Retrospective	157/157	51.4	89.2	23	Small intraglandular hematoma 1 (0.6%)
Abu-Yousef et al. (2011) [29]	USA 2006–2007	Retrospective	788/593	NR	NR	22, 25	Including AT/AC patients AT/AC 2 (1.4%) Control 4 (0.9%)
Khoo et al. (2008) [25]	USA 1999–2001	Retrospective	311/311	54.6	74.3	NR	Compared with FNAB+CNB group FNAB-only group 3 (1%)
Newkirk et al. (2000) [20]	USA 1996–1998	Retrospective	234/215	51.9 (female) 57.8 (male)	82.9	22, 23, 25	Perithyroidal or superficial 15 (6.4%)
Neurological symptoms							
Cordes et al. (2018) [14]	Germany 2017–2018	Prospective	205/205	55	71.2	22, 24	Total complications 9 (4.4%) Paresthesia 8 (3.9%) Dysphonia 1 (0.5%)
Kavanagh et al. (2017) [19]	Ireland 2006–2013	Retrospective	724/724	40	82.5	20, 23	Vasovagal reaction 2 (0.3%)
Cappelli et al. (2017) [21]	Italy 2007–2016	Retrospective	7,449/6,323	54.3	81.0	25	Vasovagal reaction 1 (0.02%)
Tomoda et al. (2006) [30]	Japan 2004–2005	Retrospective	10,974/10,974	NR	NR	23	Transient vocal cord paralysis 4 (0.04%)
Newkirk et al. (2000) [20]	USA 1996–1998	Retrospective	234/215	51.9 (female) 57.8 (male)	82.9	22, 23, 25	Hoarseness (transient) 2 (0.9%) Vasovagal reaction 3 (1.3%)
Tracheal puncture during the procedure							
Cappelli et al. (2017) [21]	Italy 2007–2016	Retrospective	7,449/6,323	54.3	81.0	25	Tracheal puncture 2 (0.04%)
Needle tract implantation of thyroid cancer							
Hayashi et al. (2020) [33]	Japan 2006–2017	Retrospective	11,745/11,745	70.6	NR	NR	NTI in thyroid 22 (0.19%)
Cappelli et al. (2017) [21]	Italy 2007–2016	Retrospective	7,449/6,323	54.3	81.0	25	Cancer seeding along the track of the needle 1 (0.02%)
Ito et al. (2005) [31]	Japan 1990–2002	Retrospective	4,912/4,912	NR	NR	22	Needle tract implantation of papillary thyroid carcinoma 7 (0.14%)

FNA, fine-needle aspiration; NRS, numeric rating scale; VAS, visual analogue scale; EMLA, eutectic mixture of local anesthetics; VRS, verbal rating scale; CNB, core needle biopsy; FNAB, fine-needle aspiration biopsy; AT/AC, antithrombotic/anticoagulant agent; NR, not reported; NTI, needle tract implantation.

*Patients who were scored with an NRS (numeric rating scale) were regrouped as mild (1–3), moderate (4–6), and severe (7–10).

Table 2. Key Points for Reducing FNAB-Related Complications

Pain	Smaller needle gauge Local anesthesia (for patients sensitive to pain, anxious about the procedure, or with thyroid nodules in the deep portion)
Hematoma	Investigate the bleeding tendency, discontinue AC/AT depending on individual circumstances Doppler ultrasonography (to find thyroid nodules with high vascularity) Careful procedure for elderly patients (due to increased venous fragility and possible arteriovenous shunts)
NTI	Cautious procedure when withdrawing the needle following FNAB Thorough follow-up ultrasonography to detect NTI
Vocal cord injury	Avoid puncturing the dorsal part of the nodule Evaluate the vascularity of the thyroid nodule before FNAB
Infection	Sterile procedure, especially for immunocompromised patients (diabetes, cancer, atopic dermatitis, etc.) Early suspicion with empirical antibiotic treatment and drainage to prevent life-threatening conditions
Post-aspiration thyrotoxicosis	Early suspicion if patients have symptoms of thyrotoxicosis, and perform thyroid function tests

FNAB, fine-needle aspiration biopsy; AC/AT, anticoagulants and antithrombotic agent; NTI, needle tract implantation.

FNAB ($n=96$) and CNB ($n=365$) groups, respectively.

The discontinuation of anticoagulants or antithrombotic agents has also been an issue for clinicians when performing ultrasound-guided fine-needle aspiration. Khadra et al. [28] stated that the incidence of hematoma was similar between the antithrombotic/anticoagulant (AT/AC) group and the control group. Abu-Yousef et al. [29] also emphasized that the risk of bleeding events was not significantly different between patients taking AT/AC medications and patients not using AT/AC medications. Cordes et al. [14] reported two cases of minor hematomas, but the odds ratio for patients taking anticoagulant medications versus patients not taking anticoagulants did not show any statistical significance.

Neurological symptoms

Five studies included in this study reported neurological symptoms after FNAB [14,19-21,30]. Cordes et al. [14] stated that 3.9% of patients experienced paresthesia and 0.5% of patients had dysphonia episodes after FNAB. Kavanagh et al. [19] and Cappelli et al. [21] reported incidence rates of 0.3% and 0.02% of vasovagal reaction after performing FNAB, respectively. Tomoda et al. [30] reported that four patients had transient vocal cord paralysis after reviewing 10,974 patients retrospectively. Newkirk et al. [20] found in their retrospective study that transient hoarseness occurred in 0.9% and vasovagal reaction in 1.3% of patients who underwent FNAB.

Tracheal puncture

Of the included studies, one study described episodes of tracheal puncture. Cappelli et al. [21] reported that tracheal puncture

occurred in 0.04% of enrolled patients (2/6,323) during FNAB.

Needle tract implantation of thyroid cancer

Several studies reported the risk of needle tract implantation (NTI) of thyroid cancer after FNAB. Ito et al. [31] reported that NTI occurred in 0.14% (7/4,912) of papillary thyroid cancer patients and that the age of the patients and aggressive characteristics of the tumor were risk factors for NTI. They also reported a case of subcutaneous seeding of follicular neoplasm after FNAB [32]. However, based on their results, Ito et al. [31,32] noted that the incidence of NTI was very rare and that NTI had high cure rates after surgery; therefore, they concluded that FNAB should not be discouraged for the preoperative diagnosis of thyroid malignancies. Cappelli et al. [21] also reported a very low incidence of cancer implantation along the needle tract (0.02%, 1/6,323). A large study conducted by Hayashi et al. [33] stated that 0.19% of the patients (22/11,745) experienced NTI of thyroid cancer.

Infection and post-FNAB thyrotoxicosis

Unfortunately, we could not find any data related to the incidence of infection or post-FNAB thyrotoxicosis in the included studies. Instead, we described the case reports of FNAB-related infection and thyrotoxicosis in the Discussion section.

DISCUSSION

FNAB is a safe, simple, cost-effective, and highly accurate diagnostic modality for thyroid malignancies and has long been the gold standard. FNAB-related complications are rare, but it is

crucial to be aware of various types of adverse events so that we can predict and prepare for potential complications.

Associations between pain after FNAB, which is the most common complication, and several clinical factors have been evaluated. Various sizes of needles ranging from 21 to 27 gauge have been used in clinical practice, and it is believed that larger needles might cause more pain without a difference in cytologic adequacy [13,21,34]. Although it was not statistically significant, multiple studies have shown lower pain scale scores in groups using smaller needles, which has prompted operators to favor smaller needles [12,13]. The depth of nodules, but not their volume, has been found to be related to the severity of pain during FNAB [14,15]. FNAB is generally performed without local anesthesia and the patients usually do not need any previous preparation, but some patients who are very sensitive to pain or are anxious about needles may require anesthesia before doing the procedure [6]. It is noteworthy that the efficacy of local anesthesia for FNAB was proven by Gursoy et al. [17,18]. It seems reasonable to use local anesthesia to relieve pain when clinicians perform FNAB for thyroid nodules located in the deep portion of the patient's neck, as well as in patients who are intolerant to pain or anxious [15,17,18]. It is well known that the examiner's expertise is important to obtain excellent diagnostic performance [6]. An interesting study conducted by Lee et al. [16] showed similar outcomes in terms of cytological adequacy and complications, including pain scale ratings between two operators with different expertise; the researchers concluded that a clinician with experience of over 500 ultrasound-guided FNAB procedures can be expected to have comparable performance to a more experienced clinician.

Hematoma is also a rare, but non-negligible complication after FNAB. According to recent comparative studies, FNAB consistently showed comparable or better outcomes related to bleeding events than FNAB [22-26]. Stopping anticoagulants or antithrombotic agents before performing FNAB has been debated. Based on recent studies showing no statistical significance between patient groups with or without anticoagulants or antithrombotic agents, researchers concluded that clinicians should decide whether to discontinue anticoagulants or antithrombotic agents based on patients' individual circumstances due to the low risk of bleeding events after FNAB of thyroid nodules [9,14,28,29]. Unfortunately, rare but sometimes fatal thyroid hemorrhages after FNAB requiring intubation or surgery have been reported in case reports. Bonsignore et al. [35] reported a case of a 78-year-old woman who died due to a massive hematoma leading to tracheal compression and conducted a literature

review of 12 cases of fatal thyroid hemorrhages, which were mostly managed with surgery or conservative measures [35-43]. Based on the fact that both cases of death identified in the literature review were in older women, the authors stated that increased venous fragility with age and arteriovenous shunts might have contributed to a higher risk of fatal vascular complications [35,44,45]. It would be advisable to thoroughly investigate the bleeding risk of patients before FNAB, although routine screening for anticoagulants or antithrombotic agents is not mandatory, and Doppler ultrasonography of the thyroid nodule should be performed before the examination, especially for hypervascular nodules and older patients [9].

Needle tract seeding with FNAB can occur by disseminated cancer cells when withdrawing the needle during FNAB. Reports stated that the incidence of NTI was very low, which could be explained by the indolent characteristics of papillary thyroid cancers [21,31-33]. Hayashi et al. [33] reported that NTI had a higher incidence from lymph nodes than from thyroid nodules and more commonly occurred from follicular thyroid cancers and anaplastic thyroid cancers than from papillary thyroid cancers, showing the importance of tumor aggressiveness for the occurrence and potential histopathological transformation of NTI. Most NTI cases could be controlled with surgical resection, but we should still be cautious when performing FNAB because NTI could possibly affect the patient's disease course [31,33].

Episodes of voice change were reported in a few studies [14,20,30]. Possible mechanisms of recurrent laryngeal nerve palsy after FNAB include rapid stretching of the nerve caused by thyroid swelling or direct needle injury to the nerve, which can be prevented by not stabbing the dorsal part of the nodule and evaluating the vascularity of the thyroid nodule before performing FNAB [30]. Exceedingly rare complications that were reported in limited studies include vasovagal reactions after FNAB and tracheal puncture [19-21].

Because of its various protective mechanisms against pathogens, the incidence of infection within the thyroid gland after FNAB is very rare. Park and Jeon [46] reported a case of a 33-year-old immunocompetent woman who suffered from acute suppurative thyroiditis after FNAB and was successfully treated with antibiotics. Moreover, based on their literature review of five cases of FNAB-related thyroid infections, in which most patients had impaired immunity, they emphasized that clinicians should be aware of potential infections after FNAB, particularly in immunocompromised patients [46-51].

Post-aspiration thyrotoxicosis has been described in a limited number of reports [49,52,53]. The researchers stated that most

of the patients had large nodules, and suggested that destructive thyroiditis caused by the traumatic leakage of thyroid hormones might cause thyrotoxicosis after FNAB [52,53]. We summarized the key points for preventing FNAB-related complications in Table 2.

The present study has several limitations. First, most of the included studies had small sample sizes and retrospective designs, which might weaken the conclusions of the present study. Second, the measures of the outcomes of interest were not unified (e.g., different pain scales or inconsistent outcomes of interest among the studies), which made it difficult to analyze the summarized data in greater detail. Moreover, as pain rating scales have subjective characteristics, some degree of bias would be inevitable. Third, the gauge of the needles was not unified, although needle size can affect some of the outcomes of interest.

In conclusion, FNAB of thyroid nodules is a safe diagnostic technique with a very low complication rate. We believe that the results related to adverse events from recent studies are insufficient to discourage performing FNAB for preoperative diagnoses of thyroid malignancies. Performing FNAB with special caution based on individual circumstances is recommended to prevent possible complications.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: J.Y.P., W.C., A.R.H., J.H.Y., H.K.K., H.C.K. Acquisition, analysis, or interpretation of data: J.Y.P., W.C., A.R.H., J.H.Y., H.K.K., H.C.K. Drafting the work or revising: J.Y.P., H.K.K. Final approval of the manuscript: J.Y.P., H.K.K.

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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.