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Diagnostic Value and Cost Considerations of Routine Fine-Needle Aspirations in the Follow-Up of Thyroid Nodules with Benign Readings

Jeroen van Roosmalen,¹ Bettien van Hemel,² Albert Suurmeijer,² Henk Groen,³
Teus Ruitenbeek,² Thera P. Links,⁴ and John T.M. Plukker¹

Background: Fine-needle aspiration (FNA) is the most accurate tool to identify malignancy in solitary thyroid nodules. Although some recommend routinely repeating FNA for nodules that are initially read as benign, there is no consensus. We evaluated clinical relevancy and considered costs of routine follow-up FNA in nodules initially read as benign.

Methods: We reviewed the records of all 739 patients who underwent FNA of solitary thyroid nodules at our institution from 1988 to 2004. A total of 815 aspirations were required to obtain satisfactory specimens. According to their physicians practice, some patients had a "follow-up biopsy" after an initially benign FNA reading as a matter of routine (Group I approach) or if their clinical status changed (Group II approach). The outcome information for at least 4 years after the initial FNA in these two groups was compared. In addition, hypothetical costs relating to both methods for deciding whether to do a follow-up FNA were considered.

Results: The initial FNA was benign in 576 (78%), suspicious for follicular neoplasms in 106 (14.4%), and malignant in 57 patients (7.7%). Follow-up FNA was performed in 292 patients with initially benign lesions, 235 in Group I approach and 57 in Group II approach. The FNA diagnosis according to Group I approach remained benign on follow-up biopsy in 96.2% (226/235), was altered to follicular neoplasm in 3% (7/235), and was suspicious for malignancy in 0.8% (2/235). When following Group II approach, the follow-up FNA was benign in 93% (53/57), undetermined in 1.7% (1/57), and showed follicular neoplasm in 5.3% (3/57). Combining Groups I and II methods, 5 of 292 patients had a malignant nodule on histological examination, a false-negative rate of 1.7% for the initial FNA, but without a difference in prevalence of thyroid malignancy between the groups. Cost-consequence analysis showed no benefit in routine follow-up FNA after initially benign FNA readings.

Conclusions: Routine follow-up FNA in patients whose initial FNA is benign has a low diagnostic upgrading value and is relatively costly. In patients whose initial FNA is benign, we recommend the FNA be repeated only if clinically suspicious signs or complaints develop.

Introduction

LESS THAN 10% OF SOLITARY THYROID nodules are malignant. Usually, surgery is only performed in nodules with a high probability of malignancy, avoiding unnecessary operations for benign disease (1–4). Currently, fine-needle aspiration (FNA) biopsy of solitary thyroid nodules is the most reliable test to identify malignant or suspected malignant lesions and is widely recommended for deciding whether to perform thyroid surgery (2–5). Based on the NCI terminology,

patients with thyroid lesions suspicious for follicular and Hurthle cell neoplasm or malignant lesion on FNA are usually treated surgically, either for diagnostic purposes or as a part of the curative process. This clear and uniform reporting system in thyroid cytopathology leads to better communication facilitating reliable exchange of information in the decision making and in studies across institutions (6–9).

Despite the utilization of experienced cytologists, false-negative cytological results may occur, ranging from 1.3% to 11.5%, leading to a delay in adequate treatment. Better

Departments of ¹Surgical Oncology, ²Pathology, ³Epidemiology, and ⁴Endocrinology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

sampling techniques, including ultrasound (US)-guided FNA and repeat FNA during follow-up, can reduce the false-negative rate (2,7,10,11). There is no consensus, however, on the role of re-aspiration or follow-up biopsy after initially benign FNA findings (3,12–19). Some authors advise a follow-up FNA in all patients (4,13,14); others suggest repeat FNA only for patients who develop clinically suspicious findings (3,12,15,19). To determine the value of follow-up FNA in the management of solitary or prominent thyroid nodules initially classified as benign by FNA, we reviewed our patient records as well as the literature on this subject. We also performed a cost-consequence analysis of this strategy and compared it with that in which follow-up biopsy was performed only in cases where there was development of clinically suspicious findings.

Patients and Methods

From 1988 onward, two endocrine surgeons at the University Medical Center Groningen performed routinely "follow-up biopsies" within 6 months after an initial benign FNA reading (Group I approach), whereas other members of the surgical team did not repeat an FNA biopsy that was benign unless there were clinical indications (Group II approach). According to the recommendations of the local ethics committee, we retrospectively analyzed the results of all 739 patients who underwent FNA of a solitary or dominant thyroid nodule during the period 1988–2004. The biopsy was repeated in some patients in whom satisfactory cytology was not obtained on the initial FNA biopsy. For adequate initial FNA reading, a total of 815 aspirations (i.e., 1.1/patient) were necessary. Based on the initial results, 163 patients (163/739, 22%) underwent a surgical procedure. All patients with a benign

FNA reading were followed for at least 4 years after the final diagnosis. Medical records were reviewed for clinically suspicious signs and symptoms of growth of the nodule. We also examined the initial and follow-up cytology and the histological examination of the resected specimen in patients, who subsequently underwent surgery. Of the 576 patients with an initially benign FNA reading, 341 patients (including 8 who were lost to follow-up) were discharged with appropriate instructions for follow-up (Fig. 1). Of the 292 patients who had a "follow-up FNA," 235 patients were diagnosed routinely according to the Group I approach. Fifty seven (16.7%) of the 341 discharged patients with an initial benign FNA reading had a follow-up biopsy according to the Group II approach on clinical indications such as a growing thyroid nodule, increased swallowing difficulties, or suspicious signs including hoarseness, previous irradiation, and presence of lymph nodes.

Two experienced pathologists independently reviewed the cytological specimens. Aspiration was performed by using a Cameco syringe pistol (Cameco, Täby, Sweden). In difficult cases, FNA was performed under US guidance. Smears were air-dried and stained by the Giemsa method and the residual aspirate was suspended in alcohol-carbowax. Cytological diagnoses of adequate samples were classified as follows: benign, follicular neoplasm, suspicious or undetermined, and malignant. The specimen was determined as adequate when at least five to six groups of 10 or more well-preserved follicular cells could be visualized. When cytological examination showed an inadequate aspiration, re-aspiration was performed.

To perform a cost-consequence analysis, a hypothetical identification model with repeat FNA on indication (Fig. 2) was designed based on our empirical data (Figs. 1 and 3). The flow of patients through the hypothetical model and its per-

FIG. 1. Satisfactory initial and follow-up FNA, including costs of repeated cytology and surgery. *Histology showed three follicular adenomas, one multinodular goiter, two follicular carcinomas, and one follicular variant of papillary carcinoma. **Histology showed one multinodular goiter and one papillary carcinoma. ***This patient underwent a second Fu FNA revealing a benign lesion. ****Histology showed two multinodular goiters and one Hurthle cell adenoma. #€100 = \$135. Fu, follow-up; FNA, fine-needle aspiration.

FIG. 2. Hypothetical identification model based on complaints: costs of FNA and surgery. #€100 = \$135.

formance with respect to detecting or missing a malignant lesion were estimated. We compared the costs of both policies based on the Dutch Health Care Tariffs (COTG). The costs of cytological examination with and without US guidance are €232.43 (\$313.78) and €171.90 (\$232.06), respectively. The

cost of a hemithyroidectomy and a total thyroidectomy is €2,797.03 (\$3,775.99) and €2,834.24 (\$3,826.22), respectively, based on 2008 costs. As the follow-up of patients in The Netherlands is entirely on an outpatient basis but inside the hospital, the hospital costs, and not costs outside the hospital, were considered. To enhance the analysis, we also compared our results with those in the literature.

Results

Outcomes

Adequate initial FNA of the thyroid nodules in the 739 patients revealed a malignant lesion in 57 (7.7%), a follicular neoplasm in 106 (14.4%), and a benign FNA reading in 576 (77.9%) patients (Fig. 1). A routinely planned repeat FNA (Group I approach) was performed in 235 patients. In 57 patients the repeat FNA was based on clinical indications (Group II approach). In 276 of the 341 patients discharged with recommendation for follow-up without routinely repeating FNA after an initially benign reading, the thyroid nodule was stable or in regression, whereas 8 patients were lost to follow-up. There were no significant differences between Groups I and II approaches with respect to age, sex, or tumor-related characteristics (solitary vs. dominant, size, cystic vs. solid).

Outcome in Group I approach. To obtain satisfactory specimens on the initial FNA in the 235 patients, 257 aspirations

FIG. 3. Patients after a first follow-up FNA in the follow-up period with FNA, including costs of FNA and surgery. *Histology showed a follicular adenoma. **Histology showed a papillary carcinoma. ***This patient underwent surgery because of severe mechanical problems and histology showed a multinodular goiter. #€100 = \$135. adeq., adequate.

had to be performed. In eight patients, US-guided aspiration was necessary. In 91.9% of the cases, one aspiration sample was sufficient to achieve adequate specimens. For adequate cytological assessment of the first follow-up FNA, 252 aspirations were obtained. Twelve aspirations were performed under US guidance. In 93.2% of the cases, one aspiration sample was sufficient for adequate analysis.

In nine patients, a diagnostic hemithyroidectomy was performed as the cytological diagnosis changed into a follicular neoplasm in seven (3.0%) patients and was suspicious in two (0.8%) patients. The histology of seven cytologically diagnosed follicular neoplasms showed malignant form in three patients, two follicular carcinomas and one follicular variant of papillary carcinoma. The histological examination of the two patients with a suspicious follow-up FNA revealed a papillary carcinoma in one and a multinodular goiter in the other. After follow-up FNA, the cytological diagnosis remained benign in 226 (226/235, 96.2%) patients (Fig. 1). Ten of these patients with a benign follow-up FNA underwent a hemithyroidectomy or total thyroidectomy because of mechanical problems ($n = 4$) or clinical symptoms ($n = 5$), and one had a difficult-to-interpret lesion. Histological examination confirmed the benign cytological diagnosis in all patients; eight had a multinodular goiter, one a follicular adenoma, and the other a thyroid cyst.

During the follow-up period of the 216 remaining patients in Group I approach with a benign cytology on the first adequate follow-up FNA, 35 patients had a second (mean interval: 94 weeks) and even a third ($n = 9$) or fourth ($n = 1$) follow-up FNA based on clinical symptoms (Fig. 3). To obtain satisfactory specimens in these patients, 42 had a second (10 US-guided), 10 a third, and one a fourth FNA. After an adequate second follow-up FNA, the cytological diagnoses remained benign in 34 patients (97.1%) and changed to a follicular neoplasm in 1 (2.9%). Thyroid surgery of the last patient revealed a follicular adenoma at histological examination. Three patients with a benign second follow-up FNA underwent surgery, because of severe mechanical problems ($n = 1$) and growth of the nodule ($n = 2$). On the third follow-up FNA, the previous benign cytological results did not change in eight (88.9%) patients, and a follicular neoplasm was found in one patient (11.1%), which proved to be malignant on diagnostic hemithyroidectomy. Two of the eight patients with a benign cytology at the third follow-up FNA opted for surgery. Histology confirmed the cytological outcome in both patients. In one patient a fourth follow-up FNA was performed. Although benign, he underwent surgery because of relatively rapid growth. Fortunately, pathological examination revealed a multinodular goiter.

Outcome in Group II approach. To obtain satisfactory specimens on the initial FNA in the 57 patients in this group, 69 aspirations (three under US guidance) were performed. In 86% of the patients, one aspiration sample was sufficient, whereas up to four aspirations were necessary to obtain adequate samples in the others. The first follow-up FNA in this group was performed at a mean interval of 59 weeks after the initial FNA. For adequate cytological specimens, 73 aspirations (2 US-guided) had to be performed. In 82.5% of the patients, one aspiration sample was sufficient to obtain satisfactory cytology. In 53 (93.0%) patients the initial benign diagnosis did not change, in 3 (5.3%) a follicular neoplasm was found, and in 1 (1.7%) an undetermined lesion was

ascertained (Fig. 1). In the three patients with a changed cytological diagnosis to a follicular neoplasm, the nodule was histologically confirmed to be benign after diagnostic hemithyroidectomy. Two patients had a multinodular goiter and one a Hurthle cell adenoma. The patient with an undetermined lesion had a second follow-up FNA, revealing a benign lesion. Of the 53 patients with a second benign cytological outcome, 4 patients underwent surgery. Two of them had surgery for severe mechanical problems, one for suspicious clinical symptoms, and one patient opted for surgery for reassurance. Three patients had a multinodular goiter and one a follicular adenoma at histological examination.

During follow-up, 10 patients had a second follow-up FNA, and even a third ($n = 2$) or a fourth follow-up FNA in one patient (Fig. 3). To obtain adequate specimens, a total of 13 second (three US-guided), 2 third, and 2 fourth aspirations had to be performed. All adequate specimens were benign. One patient with inadequate FNA underwent surgery because of severe mechanical problems and histological examination revealed a multinodular goiter. No malignancy developed during follow-up of 4 or more years in patients of the Group II approach.

Summary of outcomes in combined Group I and II approaches. Five patients with a benign reading on their first follow-up FNA, all of them females, were eventually diagnosed malignant. In three of these patients the first follow-up FNA was read as follicular neoplasm and in one as suspicious lesion. In the remaining patient a follicular neoplasm was read after three subsequent benign FNAs. The false-negative rate for both methods was 1.7% (5/292) based on negative results for FNA but malignancy on histological examination.

Cost-consequence analysis

Costs in the Group I approach. As previously noted, 235 of the 576 patients (40.8%) with initially benign FNA readings had a routinely planned follow-up FNA (Fig. 1). The total cost in the Group I approach was €80,406.55/\$108,548.84, which consists the costs of FNA (€44,045.16/\$59,460.97, including 240 FNAs + 12 US-guided = €41,256 + €2,789.16) plus costs of subsequent surgical resections (€36,361.39/\$49,087.88, including nine hemithyroidectomies followed by four total thyroidectomies, because of thyroid cancer). Cost for a balanced surgical procedure was €8,934.06/\$12,060.98.

Costs in the Group II approach. In 57 (16.7%) of the 341 initially "discharged" patients with benign FNA readings and appropriate instructions, a follow-up FNA biopsy was performed on clinical indications. The total cost following this Group II method was €21,060.85/\$28,432.15, which consists of FNA costs (€12,669.76; 71 FNAs + 2 US-guided FNA = €12,204.90 + €464.86) plus subsequent costs of three hemithyroidectomies (€8,391.09). Cost per well-considered surgical procedure was €7,020.28/\$9,477.38.

Summary of costs in combined Group I and II approaches. The total cost of first follow-up FNA was €101,467.40/\$136,980.99 (Group I: €80,406.55/\$108,548.84 and Group II: €21,060.85/\$28,432.15). The aggregate cost, including costs of initial adequate FNA and surgery in these patients (nine hemithyroidectomies and four total thyroidectomies),

was €243,250.74 (\$328,388.49) (Fig. 1). The cost after a second adequate follow-up cytological readings in patients revisiting the out-patients clinic was €21,208.69/\$28,631.73 (€15,307.77 and €5,900.92 in Group I and II methods, respectively), given a total cost of € 264,459.43 (\$357,020.23) in patients diagnosed according to the empirical approach (Fig. 3).

Hypothetical identification model

Based on our empirical data it was estimated that 96 of the 576 well-instructed patients (16.7%; Fig. 2) who hypothetically underwent repeat follow-up FNAs (≤ 4) would return to the clinic with signs or complaints. In this scenario according to the Group II approach, 116 aspirations would have to be performed, 5 under US guidance. In this model, the nodules of 92 patients (96.2%) remain benign, whereas 3 (3%) changed to a follicular neoplasm and 1 as suspicious (0.8%). Therefore, four patients would need surgery, leading to an initial cost of €175,939.54 (\$237,518.37) including cost of first FNA. Based on the aforementioned data (Figs. 1 and 3), it was estimated that 15 of the 92 patients (16.7%), 4 of the 15 patients (26%), and 1 of these 4 patients would undergo a second, third, and fourth follow-up FNA, respectively. For adequate cytological readings we would need a total number of 19 second FNAs, 4 third FNAs, and 1 fourth FNA, respectively, at a cost of €4,246.66, leading to a total cost of €180,186.20 (\$243,251.37) in this hypothetical identification model. The cost per patient would be €243.82/\$329.16 compared with €357.86/\$483.11 in the empirical approach (Figs. 1 and 3).

Discussion

In the evaluation of patients with palpable thyroid nodules of ≥ 1.0 cm, FNA examination remains the most important test (2,3,5,11–22). The accuracy of FNA determines the strength of cytological tests to select patients who will benefit from a

diagnostic surgical procedure. With 1.7% the false-negative rate of the first FNA in the present study is in line with the reported false-negative rate of 5.2% (range: 1.3%–11.5%) and comparable with a reported rate of $<2\%$ in the guidelines of the Papanicolaou Society of Cytopathology for the examination of FNA specimens from thyroid nodules (20). However, there is no consensus in the literature regarding the optimal management of patients with solitary thyroid nodules whose first FNA reading was benign. In the present study, we describe the results and costs of two management strategies. In one of these strategies, follow-up FNA was systematically repeated (Group I approach), and in the other, the follow-up FNA was repeated only when clinical symptoms had been developed (Group II approach).

In 13 of the 292 patients (4.5%) with a follow-up FNA after an initially benign cytological reading (9/235, 3.8% and 4/57, 7% in Group I and II approaches, respectively), there was a change in the diagnostic strategy of solitary thyroid nodules. Surgery was required in these 13 patients as cytological examination of these nodules was suggestive for malignancy. In five patients, histological examination revealed a malignant thyroid disease, justifying the change in strategy.

FNA upgrading in this retrospective study is comparable with the reported reduction of false-negative rates (Table 1) (2,3,12–18,23,24). Of the patients with an adequate first FNA, 16.7% (57/341) will return to the clinician for further diagnosis (i.e., Group II approach; Fig. 1). In the cost-consequence analysis, a planned follow-up FNA (i.e., Group I approach) showed to be expensive and of limited value, as the detected rate of malignant thyroid disease was equal in both the empirical model (5/292, 1.7%) and hypothetical model (1/96, 1.0%). In the hypothetical model, we estimated that we would miss four patients with malignant thyroid diseases. Assuming that these four patients would return with local signs or complaints after the initial FNA, we considered there will be no delay in diagnosis of a malignant thyroid disease. Based on

TABLE 1. REVIEW OF REPORTED STUDIES ON FOLLOW-UP BIOPSY AFTER INITIALLY BENIGN FINE-NEEDLE ASPIRATION

Publication	Year	Initial FNA ^a (benign)	Follow-up FNA (benign)	Follow-up FNA (suspicious)	Follow-up FNA (malignant)	Histology (malignant)	False-negative rate (%)
Dwarakanathan <i>et al.</i> (13)	1993	196	183	9	4	5	2.5
Hamburger (14)	1987	157	147	5	5	4 ^b	2.5
Erdogan <i>et al.</i> (15)	1998	216	197	16	3	3	1.4
Chehade <i>et al.</i> (12)	2001	235	204	11	1	3	1.3
Lucas <i>et al.</i> (16)	1995	116	116	0	0	0	0
Aguilar <i>et al.</i> (17)	1998	184	183	1	0	1	0.5
Mittendorf and McHenry (24)	1999	45	39	3	1	1	2.2
Merchant <i>et al.</i> (18)	2000	44	44	0	0	0	0
Orlandi <i>et al.</i> (2)	2005	306	299	3	4	3 ^c	1.0
Flanagan <i>et al.</i> (3)	2006	57	29	26 ^d	2	13	22.8
Oertel <i>et al.</i> (23)	2007	1410	1277	18 + 91 ^e + 13 ^f	11	67	4.7
Present study	2010	292	279	12	1	5	1.7

^aValues refer to number of patients.

^bOne patient did not agree to surgery, but the biopsy findings clearly indicate papillary carcinoma.

^cOne patient (female, 86 years old) with a cytologically proven papillary carcinoma refused surgery because of her age.

^dThyroid lesions were all cytologically diagnosed as indeterminate.

^eThe 91 FNAs were inconclusive.

^fThese 13 FNAs were unsatisfactory.

FNA, fine-needle aspiration.

these findings, we recommend repeating FNA only when clinical changes are present.

Generally, the results of FNA of thyroid nodules rely on the quality of the diagnostic team, including the endocrine surgeon and radiologist. Especially, FNAs guided by ultrasonography are operator dependent. On the other hand, the clinical problem of nondiagnostic thyroid nodules, which occurred in 4%–20%, is best solved by direct needle localization with US-guided FNA and direct cytological assessment of adequacy whenever possible. Although this article gives important information about results and costs of management of two concurrent (Groups I and II) approaches, we have to underline that these figures related only to the experience of one particular center, whose generalizability to others centers or others countries is unknown. Further, in our study, most patients were seen at the outpatient department by two surgeons with large endocrinological experiences. Another important point in the discussion is the comparability of the empirical and hypothetical groups (Figs. 1–3). We have to realize that the method used to constitute these two groups is based on the investigators who perform the FNA biopsies and therefore may induce a bias between the groups. Some difference can exist in the recruitment of patients between different investigators. For an optimal comparison of the results, a randomized study should be performed as the final results may be biased. However, based on reviewing the literature, our results including the false-negatives are in line with those in the literature, supporting our approach and the cost minimization analysis determining the least costly alternative.

There are no clear guidelines about repeating follow-up FNA in benign lesions found on the first FNA examination. Table 1 summarizes the studies reporting on the value of repeat FNA in thyroid nodules (2,3,12–18,23,24). In a study of 196 patients with initially benign cytological examination, the benign diagnosis was confirmed in 93.4%, but changed into possible malignant in 4.6% and malignant in 2% by follow-up FNA (13). Five malignancies were missed by the first FNA readings, resulting in a false-negative rate of 2.5%. Hamburger (14) studied 157 patients with a benign cytological result on the first adequate FNA examination. On follow-up FNA, the thyroid nodules were benign in 93.6%, possible malignant in 3.2%, and probably malignant in 3.2%. The false-negative rate was 2.5%. Flanagan *et al.* (3) studied a total of 394 aspirations. Follow-up FNA was performed in 57 patients, with a change into a suspicious cytology in 28 patients, which was confirmed as malignant in 13 patients, given a false-negative rate of 22.8%. These three studies underlined the usefulness of repeating FNA in the follow-up of a benign thyroid nodule in improving the diagnostic accuracy. Others, however, found that follow-up FNA was only useful in a selected group of patients with clinically suspicious symptoms, reducing the false-negative rates (2,12,15,23). Erdogan *et al.* (15) studied 216 patients; in 91.2% the cytology remained benign after repeat FNA. The cytology changed from benign into suspicious in 17.4% and the false-negativity was 1.4% as confirmed by histological examination. Chehade *et al.* (12) reviewed 235 patients with a benign cytology. The follow-up FNA diagnosis was equal in 86.8%, but the initial cytology changed into suspicious in 4.7% and into malignant in 0.4%, with a false-negative rate of 1.3%. In the study by Oertel *et al.* (23), with over 10,000 FNAs, follow-up FNA after a first benign result was performed in 1470 patients. Initial benign result did not

change in 86.9% of the patients. In the study by Orlandi *et al.* (2), with 306 initial cytological benign aspirations, 97.7% remained benign after a repeat FNA. These authors recommended follow-up FNA only if a new suspicious clinical finding appears, or in high-risk cases. Lucas *et al.* (16) did not find any malignancy after follow-up FNA in 116 patients. In a follow-up of 184 patients with a benign cytological diagnosis with repeat FNA, Aguilar *et al.* (17) found no change in the initial diagnosis in 99.5% of the patients and only one (0.5%) in malignant disease. The initial benign cytological diagnosis in the study by Mittendorf and McHenry (24) ($n = 45$) remained benign in 86.7% and changed into a follicular lesions and malignant thyroid disease in 6.7% and 2.2%, respectively. Merchant *et al.* (18) found a benign lesion in 88.6% of the 44 patients at initial cytological diagnosis, which was not changed after repeated FNA. Most studies showed that follow-up FNA in the management of initial benign thyroid nodules is of limited value. Based on these and our results, we conclude that follow-up FNA is of limited value and relatively expensive. Therefore, follow-up FNA should only be recommended on indication in patients with increased clinical signs and suggestive complaints during follow-up, preferably under US guidance.

Disclosure Statement

The authors declare that no competing financial interests exist.

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Address correspondence to:
John Th.M. Plukker, M.D., Ph.D.
Department of Surgical Oncology
University Medical Center Groningen
Hanzeplein 1
9700 RB Groningen
The Netherlands

E-mail: j.th.plukker@chir.umcg.nl