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Long-Term Follow-Up of Patients with Initially Benign Thyroid Fine-Needle Aspirations

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Fine-needle aspiration (FNA) is currently the most reliable diagnostic means in the clinical work-up of thyroid nodules. However, most of the available data on the diagnostic reliability of thyroid FNA derives from biopsies done just before surgery or from short-term observations, whereas data on the long-term reliability of benign FNA results, is extremely limited. Over the 17-year period between 1979 and 1996, thyroid FNA performed on 849 patients in our endocrine clinic. An initially benign result was reported in 578 patients for a total of 631 nodules. Mean follow-up period was 8.1 ± 4.4 years (±standard deviation [SD]; median, 6.9 years). In order to ensure the completeness of our follow-up data, we supplemented our own patients' data with data from the Israel Cancer Registry for documentation of thyroid malignancy. Sixty-six of the patients with an initially benign FNA diagnosis were rebiopsied during follow-up. Five patients (0.85%) of all those with an initial benign FNA diagnosis, were subsequently found to have thyroid malignancy diagnosed 6 months or more after the initial evaluation. Three of the newly diagnosed malignancies were follicular and two were papillary carcinomas. Three of the patients had elements of being at high-risk: previous head irradiation, previous thyroid surgery with an occult cancer, and a growing goiter, respectively. Only 1 of 35 patients who had more than one benign FNA results was subsequently diagnosed with thyroid malignancy (follicular carcinoma). These results indicate that the rate of subsequent thyroid malignancies in patients with an initial benign FNA diagnosis is low, and thus benign thyroid FNA results provide a high level of long-term assurance. Still, repeating FNA is warranted in patients with longstanding thyroid nodules, particularly if at increased risk for cancer, or if a goiter is found to have changed its morphological characteristics over time.

Introduction

Fine-needle aspiration (FNA) is currently the best available tool for the evaluation of thyroid nodules (1). Performed at the initial step in the evaluation of thyroid nodules in patients with hypofunctional or isofunctional (cold and warm, respectively) nodules, FNA is favorably cost effective compared to other diagnostic strategies for the evaluation of thyroid nodules (2). FNA greatly improves patients' selection for surgery, resulting in doubling of the detection rate of thyroid cancer, while considerably reducing the number of related surgical procedures (2,3).

The apparent high diagnostic precision of thyroid FNA (4) should ensure the patient and the attending physician a favorable outcome when FNA results are reported as benign. However, most of the data on patients undergoing thyroid FNA is based on short-term observations, and long-term follow-up data on the reliability of benign results is extremely limited.

Theoretically, the long-term clinical reliability of benign thyroid FNA results could be adversely affected due to several reasons. Occult foci of thyroid malignancies have been observed in 6%–36% of autopsy specimens (5) and while it is commonly held that occult thyroid malignancies have small, if any, clinical significance, there is little solid data to support this idea. Dominant thyroid nodules are often part of multinodular goiters (MNG); small malignant foci could be associated with larger benign nodules, in which case it is often impractical to sample and rule out malignancy in every single nodule. Finally, FNA is not infallible, and based on short-term follow-up studies, false-negative FNA results occur in between 1.5%–11% (4). Any of these could contribute to subsequent emergence of a thyroid malignancy in patients with thyroid nodule initially diagnosed by FNA as having a benign nodule.

The present study was set to evaluate the long-term risk for thyroid cancer in patients with thyroid nodules with initially benign thyroid FNA results.

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Table 1. Patient Population

Initial FNA diagnosis	*No. of patients (%)*
Benign	578 (68)
Follicular	86 (10)
Suspected	54 (6)
Malignant	36 (4)
Inadequate	95 (11)
Total	849 (100)

FNA, fine-needle aspiration.

Patients and Methods

Over the 17-year period between 1979 and 1996, we performed FNA on 849 patients in our endocrine clinic; the follow-up data regarding these patients were summarized to the end of 1998. The data on the patients and FNA results were routinely stored in a computerized database. The initial FNA results in our patient population is presented in Table 1.

The Soroka University Medical Center is the only secondary and tertiary referral center in its area, and is by far the largest provider of specialized diagnostic services. Population flow out of the area is relatively small, which allows considerable control over patients' medical data. In addition, in order to ensure the completeness of the follow-up data, we compared our own patients' data with data from the Israeli Cancer Registry (ICR) concerning thyroid malignancy. The follow-up period for each individual patient was the time elapsed between the performance of the initial FNA and 31 December 1998 or to an earlier death date according to the National Population Registry.

FNA was guided by palpation alone. According to our practice routine, all patients with FNA results suggesting malignancy and most patients with suspicious results are immediately referred for surgery. Patients with follicular tumors often undergo a repeat aspiration and if the second result is still follicular they are referred for a thyroid scan, after which most of those with warm or cold lesions are referred for surgery and the rest are followed periodically. There are no formal guidelines for repeating FNA; the decision for which is guided, in each particular case, by the attending physician's clinical judgment.

Results

An initial benign result was reported in 578 patients for a total of 631 nodules. The mean follow-up period was 8.1 ± 4.4 years (±standard deviation [SD]; median, 6.9 years; range, 1.3 to 19 years). Sixty-six of the patients with initially benign nodules were rebiopsied (some of them more than once) during follow-up.

By means of physical examination, 344 of the patients with initially benign FNA had solitary nodules and 200 had MNG. Fifty-three of the patients with MNG underwent concurrent sampling of more than one dominant nodule. Twenty-one of the patients had diffusely enlarged nodular goiters with no apparent dominant mass. Data on goiter characteristics were missing in 13 cases.

Overall, eight patients (1.4%) were diagnosed with thyroid malignancy after benign FNA results; three of these underwent surgery shortly after the biopsy and were categorized as false-negatives or incidentally discovered occult carcinoma (data regarding the precise relationship between the malignant focus and the dominant nodule were not available in every case). Only five patients (0.85%) of all those with an initial benign FNA diagnosis were subsequently found to have a thyroid malignancy 6 or more months after the initial evaluation. The mean period of time from the initial FNA to the diagnosis of thyroid malignancy was 4.8 years (range, 2–10.3 years). Two of the patients presented with clinically solitary nodules and three had MNG. Two had papillary carcinoma and three had follicular carcinoma. In four of the five instances the malignancy was suggested by a subsequent FNA and confirmed at surgery. Table 2 summarizes the data on the five patients with delayed diagnosis of thyroid malignancy.

Malignancy was diagnosed in only 1 out of 35 of our patients who had more than one benign FNA result.

Discussion

Our results indicate that patients diagnosed by FNA as having benign thyroid lesions are unlikely to present later on with a malignant lesions of clinical significance. Only 5 of our 578 (0.85%) patients initially diagnosed as having benign thyroid nodules by FNA were subsequently found to have thyroid malignancies. There was an apparent increase in the representation of follicular carcinomas among the patients with delayed diagnosis of thyroid malignancy. Benign

Table 2. Characteristics of Patients with Delayed Diagnosis of Thyroid Carcinoma after an Initial Benign FNA

Patient age (years)	*Goiter*	*FNA 1*	*FNA 2*	*Delay (years)*	*Histological Dx*	*Comments*
1. 37f	Solitary	Benign	Benign	2	Follicular Ca	Patient insisted on surgery
2. 41m	MNG	Benign	Malignant	4	Papillary Ca	History of head irradiation
		Benign	Suspected	4	Follicular adenoma	
3. 22f	Solitary	Benign	Suspected	2.8	Papillary Ca	Previous thyroid surgery with occult cancer
4. 54f	MNG	Benign	Follicular	10.3	Follicular Ca	
5. 5f	MNG	Benign	Follicular	4.7	Follicular Ca	Growing goiter; previous thyroid surgery with benign histology

FNA, fine-needle aspiration; MNG, multinodular goiter; MNG, multinodular goiter; Ca, cancer.

Table 3. Summary on Literature on Long-Term Follow-Up Studies of Patients with Initially Benign Thyroid FNA Results

Reference	*No. of patients*	*Years follow-up (range)*	*Malignancies detected (%)*	*Comments*
Grant et al. (7)	439	6.1 (0.25–8.8)	3 (0.7)	
Julian et al. (8)	54	4.75 (1.3–7.7)	0	
Yokozawa et al. (10)	678	0.2–2	99 (14.6)	Japanese cohort, ultrasonographic follow-up
Mazzawi et al. (9)	93	5–11	1 (1.1)	
Present study	578	8.1 (1.3–19)	5 (0.85)	

FNA, fine-needle aspiration.

FNA diagnosis on more than one occasion confers a high degree of assurance regarding the benign nature of the lesion.

These results of long-term follow-up of patients with initially benign FNA results are reassuring regarding the high reliability attributed to FNA as the main tool in selecting patients with thyroid nodules for surgery; however, it should be acknowledged that FNA does not provide absolute assurance against future development of thyroid malignancy. Malignancies discovered during the follow-up period could represent true false-negatives, new malignant foci arising associated with preexisting benign lesion (6) or progression of previously occult malignant foci. Although in each of the patients, the malignancy was ipsilateral to the lobe that was previously biopsied, we were unable to ascertain whether malignancy occurred in the very same nodule that was previously biopsied.

Previous observations on long-term follow-up on patients with initially benign FNA results are summarized in Table 3. Grant et al. (7) reported that 3 of 439 (0.7%) initially benign nodules proved to be malignant during a mean 6.1 years follow-up. A smaller series, of 54 patients with initially benign FNAs followed for a mean period of 4.7 years revealed no new thyroid malignancies (8). Mazzawi et al. (9) have recently published 5- to 11-year follow-up results on 93 patients with initially benign FNA results and observed only one case of late thyroid malignancy. Yokozawa et al. (10) reported on 678 patients with initially benign conventional FNA results, rebiopsied 2–24 months later under ultrasound guidance, revealed 107 lesions suspected of malignancy, 99 (14.6%) of which proved malignant at surgery. Because many of these cancers were small, the clinical relevance of this finding is uncertain. The reason for the higher rate of subsequent malignancies in this Japanese series is unclear, but may be related to genetic attributes (6), environmental factors (e.g., previous irradiation exposure) or the use of a particularly sensitive diagnostic technique (ultrasound guidance) (10).

Certain factors may predispose for subsequent diagnosis of thyroid malignancies in patients with initially benign FNA. Among our five patients with late thyroid cancer diagnosis, one had a history of head irradiation, one had a history of an occult thyroid cancer, and one had an enlarging MNG.

Our study is somewhat limited by its retrospective design, by loss of patients to direct follow-up, and by lack of full account of the surgical procedures performed on the patients. However, these shortcomings are offset by the availability of data from the national population and cancer registries, providing true information on the long-term outcome of the patients with respect to clinically significant thyroid cancers. Moreover, because the majority of thyroid cancers are only minimally aggressive, it is possible that additional patients could bear malignant foci that have not become clinically relevant.

Despite attempts at improving differentiation between benign and malignant follicular lesions, cytomorphological criteria have not changed much over the 17 years of the study; however, criteria for establishing specimen adequacy were defined (11). The results presented in this report are based on the original cytological reports, relying on the prevailing criteria at the time of biopsy. If the changes in criteria that took place during the study period are indeed of practical importance with regard to our results is not clear. We assume that a certain proportion of benign specimens that might have been considered inadequate by current criteria would have translated into in a disproportionately higher rate of malignancies. Thus, if neoplastic cells already existed in the nodule at the time of biopsy, it is plausible to assume, that under the current more stringent criteria, the rate of malignancies among patients with initially "benign" FNA results would be even lower than the low rate observed in the present study.

Irrespective of the reason for the delay in diagnosing thyroid malignancy in our patients, the impact of the delay in diagnosis on our patients was small, because none of them had local or remote spread of the tumor or required surgery more extensive than a routine near-total thyroidectomy.

We conclude that the likelihood of subsequent clinically significant thyroid malignancies in patients with a benign thyroid FNA diagnosis is low, and that benign thyroid FNA results provide a high level of long-term assurance. Nevertheless, it would be prudent to repeat FNA in patients with predisposing risk factors for thyroid malignancy or those in whom changes are noticed in the morphological characteristics of the thyroid gland over time.

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