

# Use and Accuracy of Fine-Needle Aspiration Cytology in Histologically Proven Thyroid Carcinoma

## *An Audit Using a National Pathology Database*

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**BACKGROUND.** Fine-needle aspiration cytology is recommended as the first and most decisive diagnostic step in the workup of patients with nodular thyroid disease.

**METHODS.** A retrospective analysis of all thyroid carcinomas diagnosed was conducted using the Netherlands Pathology Database PALGA, which covers all cytologic and histologic examinations in the Netherlands, with the aim of investigating nationwide whether fine-needle aspiration cytology of the thyroid (FNAC-t) actually had been used prior to surgery for thyroid carcinoma and if so, with what result.

**RESULTS.** FNAC-t was used in 591 of the 890 patients (66%) analyzed, with a total of 769 aspirations (a single FNAC-t in 459 patients, multiple FNAC-ts in 132 patients). The overall sensitivity rate was 57%; when restricting the FNAC-ts to the most recent one for each patient, the sensitivity rate rose to 70%. Sensitivity was lowest for follicular carcinoma (67%) and was highest for anaplastic and medullary carcinomas (89%). Limiting these calculations to aspirations from patients with tumors > 10 mm was found to have very little influence on these rates (FNAC rate: 71%; overall sensitivity rate: 58%).

**CONCLUSIONS.** If the application rate (66%) and sensitivity for the most recent aspiration (70%) were considered regardless of the tumor size, only 47% of the malignancies were detected by FNAC-t. When patients with tumors > 10 mm and all FNAC-ts in this group are considered, only 41% of thyroid carcinoma cases were detected cytologically. Contrary to common belief based on current guidelines for the workup of patients with nodular thyroid disease, the majority of thyroid carcinoma cases are not detected by FNAC-t. [See editorial on pages 325–329 and original article on pages 357–363, this issue]. *Cancer (Cancer Cytopathol)* 2000;90:330–334. © 2000 American Cancer Society.

**KEYWORDS:** thyroid carcinoma, fine-needle aspiration cytology, test evaluation, database research.

In patients with nodular disease, fine-needle aspiration cytology of the thyroid gland (FNAC-t) is widely recommended as an initial and crucial test to select those patients who require excision of the lesion for subsequent histologic diagnosis. If FNAC-t proves to be either suspicious or malignant, surgery is indicated.<sup>1–6</sup> The optimal diagnostic strategy is aiming to avoid surgery in patients with benign thyroid disease, which is very common in the adult population, while at the same time performing prompt surgical treatment of patients with thyroid carcinoma. To achieve this, FNAC-t must score high on test characteristics.

In the Netherlands, a unique national pathology archival system

See editorial on pages 325–329 and original article on pages 357–363, this issue.

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Received May 6, 1999; revision received July 12, 1999; accepted August 6, 1999.

exists, the Pathologisch Anatomisch Landelijk Geautomatiseerd Archief (PALGA) database. The results from virtually all cytologic and histologic examinations from every Dutch pathology laboratory are registered in a central database, covering the total Dutch population of 15.5 million people. This complete national coverage, which has been in existence since 1989, offers unique opportunities for different types of clinical research.

For the current study, we used the PALGA database to retrieve all primary thyroid carcinoma cases that were newly diagnosed histologically during a 3-year period. Again using the PALGA database, we examined this cohort of histologically proven malignancies to answer the following questions: how often was FNAC-t performed prior to the surgery for thyroid carcinoma and what is its sensitivity? With these findings we could appraise the actual and the desired role of FNAC-t in the diagnosis of nodular thyroid disease and its place in the decision-making process regarding whether to perform or withhold surgery.

## MATERIALS AND METHODS

### Study Group

All primary thyroid carcinoma cases that were newly diagnosed histologically during the period between January 1, 1995 and December 31, 1997 were retrieved from the PALGA database. For all these patients it was established whether cytologic examination(s) had been performed up to 10 years prior to surgery for thyroid carcinoma. In accordance with Dutch privacy legislation, an anonymized file regarding each case then was provided by PALGA with the following data: age of the patient (at the time of the histologic examination), patient gender, date of the histologic examination, histologic type of thyroid tumor (four categories: papillary, follicular, medullary, and anaplastic carcinoma; other types were excluded), maximum greatest dimension of the tumor (mm), total number of prior FNAC-ts performed per patient, result from each FNAC-t (using the following ordinal scale: nondiagnostic, normal, atypia, follicular lesion [either adenoma or carcinoma], suspect for a defined type of malignancy, and definitely malignant), and the cytologic type of malignancy (if specified, same categories as used histologic type), and the time elapsed (in months) between FNAC-t and thyroid surgery. The database did not provide detailed information regarding the type of specimens (e.g., air-dried), the staining method(s) used, and who obtained the aspiration (clinician vs. pathologist). Data were reported in frequency distributions and cross-tabulations. The sensitivity of FNAC for detecting thyroid carcinoma was defined as the percentage of abnormal FNAC-t results

(including the outcome categories: definitely malignant, suspect for a defined type of malignancy, follicular lesion, and atypia) among all FNAC-t results (nondiagnostic included). For proportions, the 95% confidence intervals were calculated.

## RESULTS

A histologic diagnosis of primary thyroid carcinoma was established in 890 patients (258 males and 632 females) with a mean age of 49 years. When compared with approximately 300 new cases annually reported by the Dutch Comprehensive Cancer Registry, this suggests almost complete coverage. In 299 patients (34%) thyroid surgery with subsequent histologic examination was performed without any prior FNAC-t. In the remaining 591 patients (66%) thyroid malignancy was confirmed by histology and preceded by  $\geq 1$  cytologic examinations, allowing further analysis. In 459 patients (78%) only 1 cytologic examination was performed and in 132 (22%) patients  $\geq 2$  FNAC-ts were performed. For the most recent FNAC-t, the median time lapse between cytology and thyroid surgery was 6 weeks; for 5% of patients it was  $< 1$  week and for 5% it was  $> 60$  weeks.

Of the 890 carcinomas, 516 were papillary (58%), 215 were follicular (24%), 101 were medullary (11%), and 58 were anaplastic (7%). More detailed figures regarding the types of thyroid carcinomas and patient characteristics are summarized in Table 1. The use of FNAC-t was lowest in the group of patients with medullary carcinoma (39%) and highest in the group of patients with anaplastic carcinoma (78%). Of the 890 tumors detected, 77 (8.7%) were small ( $< 5$  mm), 48 (5.4%) were from tumors measuring 6–10 mm, and 765 (86.0%) had a greatest dimension  $> 10$  mm. Of the 125 tumors measuring  $\leq 10$  mm, 90 (72%) were papillary and 31 (25%) were medullary.

A total of 769 aspirations had been used in 591 of the 890 patients prior to thyroid surgery. Of these aspirations 111 (14%) were reported as nondiagnostic, 217 (28%) as normal, 32 (4%) as atypia, 175 (23%) as follicular neoplasia, 108 (14%) as suspicious, and 126 (16%) as definitely malignant (Fig. 1). A total of 428 aspirations were from patients with histologically proven papillary carcinoma. Of these, 16% were reported as "follicular neoplasia" whereas papillary carcinoma was suggested or confirmed in 36% of the aspirations. The percentage of normal cytologic outcomes was high (30%) in papillary and follicular carcinomas and lower (approximately 15%) in medullary and anaplastic carcinomas. The percentage of nondiagnostic aspirations was approximately 15% in all histologic types. The percentages of normal and nondiagnostic aspirations decreased when data were

**TABLE 1**  
**Characteristics from All 890 Patients with Primary Thyroid Carcinoma That Was Newly Diagnosed Histologically between January 1, 1995 and December 31, 1997 in the Netherlands**

	Papillary	Follicular	Medullary	Anaplastic	Total
<b>All patients</b>					
No. (patients)	516	215	101	58	890
Age (yrs) (mean, range)	46 (3-95)	53 (7-89)	40 (1-85)	68 (40-87)	49 (1-95)
Gender (M/F) (%)	27/73	28/72	43/57	29/71	29/71
Tumor dimension > 10 mm (%)	83	99	69	98	86
<b>With FNAC-t</b>					
No. (patients)	345	162	39	45	591
Age (yrs) (mean, range)	46 (10-93)	51 (7-89)	51 (25-85)	68 (40-87)	49 (7-93)
Gender (M/F) (%)	25/76	31/69	31/69	27/73	27/73
Tumor dimension > 10 mm (%)	87	99	95	100	92
<b>No FNAC-t</b>					
No. (patients)	171	53	62	13	299
Age (yrs) (mean, range)	48 (3-95)	62 (21-86)	33 (1-75)	69 (51-87)	48 (1-95)
Gender (M/F) (%)	30/70	19/81	50/50	38/62	32/68
Tumor dimension > 10 mm (%)	74	96	53	92	75
FNAC-rate (%)	67	75	39	78	66
FNAC-rate (%) for tumors with a greatest dimension > 10 mm	70	76	53	79	71

M: male; F: female; FNAC-t: fine-needle aspiration cytology of the thyroid.

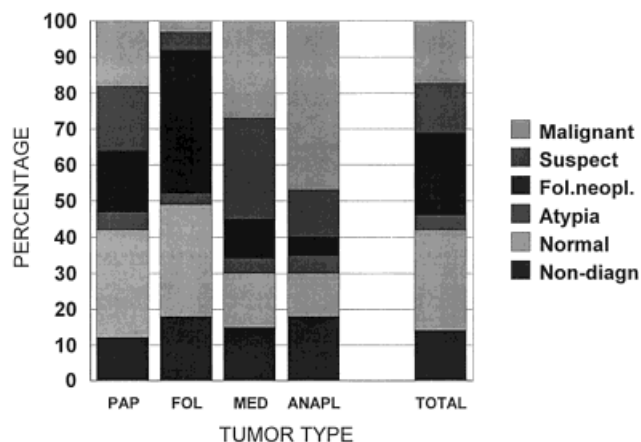
restricted to the 591 most recent aspirations (22% normal and 8% nondiagnostic).

The sensitivities are reported in Table 2. Using all available FNAC-ts, the overall sensitivity was 57%. This percentage rose to 70% when only the most recent FNAC-t performed before histologic examination was taken into account for each patient. Using the most recent FNAC-t the sensitivity was highest for the anaplastic tumors (89%), followed by the medullary carcinomas (74%) and finally the papillary carcinomas (69%) and the follicular carcinomas (67%). Restricting the calculations to aspirations in which the tumor greatest dimension was found to be > 10 mm appeared to have little influence on these figures (overall sensitivity, 58%).

Among all 769 aspirations, there were 328 false-negative aspirations (43%). When only using the 591 most recent aspirations, the number of false-negative results fell to 177 (30%). These 177 false-negative cases had a median interval between cytology and histology of 10 weeks; 160 (90%) were from tumors measuring > 10 mm.

**DISCUSSION**

In a recent review article the authors stated their belief that fine-needle aspiration cytology is superior for distinguishing between benign and malignant thyroid nodules, regardless of presentation.<sup>7</sup> Because of its accuracy, simplicity, and low cost, FNAC-t is recommended as the primary diagnostic procedure to select



**FIGURE 1.** Distribution of cytologic outcomes within each histologic type of thyroid carcinoma (all aspirations; N = 769). PAP: papillary carcinoma; FOL: follicular carcinoma; MED: medullary carcinoma; ANAPL: anaplastic carcinoma; Fol. neopl.: follicular neoplasia; non-diagn: nondiagnostic.

**Dataset (Percentage)**

	Non-diagn	Normal	Atypia	Fol. neopl	Suspect	Malignant
PAP	12	30	5	17	18	18
FOL	18	31	3	40	5	3
MED	15	15	4	11	28	27
ANAPL	18	12	5	5	13	47
Total	14	28	4	23	14	17

**TABLE 2**  
Sensitivities Calculated for Different Groups within the Study Group

	Histologic outcome				Total
	Papillary	Follicular	Medullary	Anaplastic	
All aspirations					
FNAC-t neg	180	116	14	18	328
FNAC-t pos	248	118	32	43	441
Total	428	234	46	61	769
Sensitivity	58%	50%	70%	71%	57%
95% CL	53–63%	44–57%	54–82%	57–81%	54–61%
All aspirations, tumor > 10 mm					
FNAC-t neg	151	116	13	18	298
FNAC-t pos	216	117	31	43	407
Total	367	233	44	61	705
Sensitivity	59%	50%	70%	71%	58%
95% CL	54–64%	44–57%	55–83%	57–81%	54–61%
Most recent aspiration					
FNAC-t neg	108	54	10	5	177
FNAC-t pos	237	108	29	40	414
Total	345	162	39	45	591
Sensitivity	69%	67%	74%	89%	70%
95% CL	64–74%	59–74%	58–87%	76–96%	66–74%

FNAC-t: fine-needle aspiration cytology of the thyroid; neg: negative; pos: positive; 95% CL: 95% confidence limits.

those patients who will benefit therapeutically from thyroid surgery.<sup>2–6</sup> Contrary to these recommendations our aggregated results of all patients who underwent thyroid surgery in the Netherlands in 1995, 1996, and 1997 for thyroid carcinoma showed that FNAC-t had not been used in 29% of those patients with tumors showing a greatest dimension of > 10 mm. The low FNAC rate in patients with medullary carcinoma can be attributed to many cases of elective surgery in patients from type 2 multiple endocrine neoplasia families, in whom the result of FNAC-t has little influence on the decision to perform surgery and in whom the majority of medullary carcinomas tend to be very small.

Reported performance characteristics of FNAC-t show a rather wide range both for sensitivity (range, 65–98%) and specificity (range, 72–100%).<sup>3</sup> Because the majority of such articles will come from centers with a special interest and skill concerning this subject, these ranges might be even wider in most general hospitals. In the current study, we could only appraise sensitivity figures because we only studied patients with histologically proven thyroid carcinoma. Using all outcomes from FNAC-t, the overall sensitivity was unexpectedly low but when only the most recent aspiration was considered, the sensitivity rose to 70%, indicating that repetition of the aspiration increased the detection of malignant tumors. Even this figure contrasts with claims of a sensitivity as high as 98%.

Remarkably, our low sensitivity especially pertains to the papillary and follicular tumors, which are by far the most prevalent (in the majority of series, approximately 80–85%). For the anaplastic tumors, the sensitivity of the most recent aspiration was the highest.

In this study of the collective Dutch experience, we could not analyze which factors were especially responsible for the great number of false-negative or unsatisfactory aspirations. In the Netherlands, aspirations are performed either by the attending clinicians or by the cytopathologists and the use of air-dried specimens with Romanovsky stains is very popular. The case load of primary thyroid carcinoma is low: there are 70 pathology laboratories and 106 hospitals in the Netherlands with 300 new cases of thyroid carcinoma diagnosed each year, resulting on average in 4.3 cases per year per laboratory and 3 cases per year per hospital. Given these low numbers, the desired buildup of experience both in the performance and the interpretation of FNAC-t is arduous.

In all patients who underwent surgery for thyroid carcinoma, combining the actual performance of FNAC-t with a positive outcome for the most recent aspiration, FNAC-t did not contribute to the decision to perform surgery in 53% of cases. When this same calculation is performed for carcinomas > 10 mm and all aspirations, as little as 41% of thyroid malignancies are detected with FNAC-t. Other, most likely clinical factors, were more meaningful when deciding

whether to perform surgery. The majority of minute thyroid carcinomas were detected accidentally when FNAC-t was not abnormal or in thyroids removed for suspicious cytology. Less than 5% of patients with nodular thyroid disease will have malignancy and the principal contribution of FNAC-t is not ruling in but ruling out thyroid malignancy because all thyroid tumors finally will be confirmed histologically. However, a false-negative rate of 30% is very high for this objective. Given the very low prior probability of thyroid carcinoma and the vast number of FNAC-ts, the post-test probability of a diagnosis of thyroid carcinoma given a normal result from FNAC-t will be very low. The majority of patients will be rightly reassured, but in cancer patients the false-negative result may delay surgical treatment substantially. In the current series, 15% of all false-negative cases had an interval between FNAC-t and histology of > 1 year.

Given the results from our national audit, the following issues come forth. First, our data should prompt the practitioners in the Netherlands to improve the quality of their specimen procurement and cytomorphologic interpretation. Second, we found a much lower sensitivity for this test than that claimed in medical literature using a different approach for evaluation with a complete national coverage. If the contribution of technical and interpretational factors

should prove to be only of lesser importance, then the issue is raised reconsidering the best diagnostic approach in patients with nodular thyroid disease. This certainly will not mean discarding FNAC-t but rather adding relevant data from other tests to diminish the chance of a false-negative outcome with subsequent delay in treatment.

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