

# Risk of malignancy in fine-needle aspiration biopsy in patients with thyroid nodules

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## ABSTRACT

**INTRODUCTION:** Fine-needle aspiration biopsy (FNAB) is the cornerstone of thyroid nodule evaluation. In most cases, FNAB can discriminate between benign and malignant disease. In other cases, it is only indicative of malignancy and the results are considered “suspicious”. In Denmark, thyroid FNAB results are categorised into six groups; “inadequate”, “cystic”, “inconclusive”, “benign”, “suspicious” and “malignant”. The risk of malignancy in the Danish “suspicious” group is of interest for patients as well as doctors participating in the diagnosis and treatment. The Danish Thyroid Surgery Database (THYKIR) registers preoperative thyroid FNAB and final histology. The aim of this study was to assess the malignancy risk among patients with a suspicious thyroid FNAB according to the Danish criteria and to identify possible predictors of malignant histology.

**METHODS:** A prospective cohort counting 483 patients with a “suspicious” thyroid FNAB who had been treated surgically in The Region of Southern Denmark in the 2001-2013 period was retrieved from the THYKIR database.

**RESULTS:** The risk of malignancy in the Danish thyroid FNAB “suspicious” group is 22%. Serum thyroid-stimulating hormone outside the normal range and vocal cord palsy may be patient-related predictors of malignancy.

**CONCLUSION:** Awaiting the introduction of reliable tools for preoperative evaluation, the current practice with histological clarification of the “suspicious” thyroid FNAB seems justified.

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Palpable thyroid nodules are frequent with a prevalence of 3-7% in the Western population [1]. Most nodules are benign, while approximately 5% are malignant [2]. Thyroid carcinoma is the most common endocrine malignancy in Europe [3]. The Danish Thyroid Cancer Database (DATHYRCA) had 327 patients registered with thyroid carcinoma in 2014 [4]. The population in Denmark is 5.6 million. A recent Danish study showed that 67% of thyroid carcinomas are of the papillary type, 18% of the follicular type, 7% of the medullary type and 8% of the undifferentiated (anaplastic) type. The same study reported a significant rise in the incidence of papillary thyroid carcinoma in Denmark from 1996 to 2008 [5].

Great efforts are aimed at providing a cost-effective diagnostic strategy for thyroid nodules in order to reduce unnecessary surgery. However, preoperative assessment of thyroid nodules remains a diagnostic challenge [2]. Fine-needle aspiration biopsy (FNAB), often ultrasound (US)-guided, is a cornerstone in the evaluation of the nodular thyroid lesion [6-8] due to its cost-effectiveness and because it is an easily applicable method. A Danish study from 2012 investigated the diagnostic accuracy of US-guided FNAB in thyroid nodules and found a sensitivity for malignancy of 73.9% and a specificity of 99.2% [2]. The positive and negative predictive values of thyroid FNAB for malignancy were 89.5% and 97.7%, respectively [2]. In most cases, thyroid FNAB provides a definitive diagnosis of a malignant or benign nodule. However, it was reported that in 10-42% of all nodules, a conclusive diagnosis cannot be obtained by FNAB alone [7-9].

Increasingly more centres use The Bethesda Classification System for Reporting Thyroid Cytopathology [10]. In Denmark, thyroid cytology is categorised according to the definition in the National Thyroid Surgery Database (THYKIR), in which Bethesda group III (atypia of undetermined significance or follicular lesion of undetermined significance), group IV (follicular neoplasm or suspicious of follicular neoplasia) and group V (suspicious of malignancy) are merged in only one group named “suspicious” FNAB finding. In the literature, these Bethesda groups are variably included in the term “indeterminate” FNAB, with a reported risk of malignancy ranging from 19% to 49% [11-14]. Data from the suspicious group from the THYKIR Database have never been published. Several studies have focused on identifying factors that may predict malignancy in thyroid nodules that have a “suspicious” cytology, but with varying results [2, 9, 11, 13, 15-17].

By 1 January 2009, a “cancer package solution” for patients with suspicion of head and neck cancer (HNC) was implemented in Denmark. This fast-track programme includes pre-booked slots for diagnostic procedures, and it significantly reduces the waiting time for patients with suspicion of HNC [6]. Patients with a suspicious thyroid FNAB are included in the programme, and lobectomy including exploration or dissection of ipsilat-

## ORIGINAL ARTICLE

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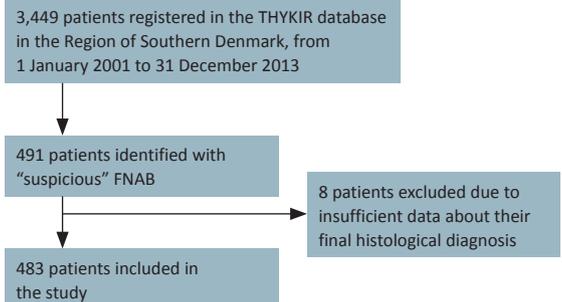
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Fine-needle aspiration in clinical setup.

FIGURE 1

Study population.



FNAB = fine-needle aspiration biopsy; THYKIR = The Danish Thyroid Surgery Database.

eral level 6 is the procedure for most of these patients. If suspicious lymph nodes are detected during surgery, frozen-section histological analysis may be performed intraoperatively and the treatment is adjusted accordingly [18].

The aim of this study was to calculate the frequency of malignancy in patients with a “suspicious” thyroid FNAB according to the Danish criteria, and to identify possible preoperative patient-related predictors of malignancy.

## METHODS

This study is descriptive and based on a prospectively registered cohort. Patients with a “suspicious” thyroid FNAB who had thyroid surgery performed at the departments of otorhinolaryngology Head & Neck Surgery in the Region of Southern Denmark (Odense University Hospital, Vejle Hospital, Esbjerg Hospital and Sønderborg Hospital) from 1 January 2001 to 31 December 2013 were identified through the THYKIR database. Basic clinical parameters, cytology findings, surgical procedures and histology were analysed. In the THYKIR database, thyroid cytology is categorised as; “FNAB not performed”, “inadequate”, “cystic”, “inconclusive”, “benign”, “suspicious”, “malignant” or “information missing”. Among 3,449 patients from the Region of Southern Denmark, 491 patients were identified with a suspicious thyroid FNAB. Eight patients were excluded due to insufficient data concerning their histological diagnosis. The final study population consisted of 483 patients (Figure 1) of whom 374 (77%) were women. The median age was 53 years at the time of surgery. Data were stored and processed in EXCEL, and STATA (14/IC) was used for statistical analysis. Non-parametric statistic methods, primarily the chi2-test, were used. To identify potential predictive factors for malignant histology, selected pre-

operative variables were dichotomized and analysed (Table 1). The level of significance was set to  $p < 0.05$ . The study was approved by the Danish Data Protection Agency/Region of Southern Denmark (r.no.:15/36370 and 15/28871). All information was identified from an already approved database and no other patient records were used.

*Trial registration:* not relevant.

## RESULTS

### Frequency of malignancy

Malignant histology was found in 108 (22.4%) of the 483 patients with a suspicious cytology. Thyroid-derived cancer was diagnosed in 98 (90.7%) patients, of which 91.1% was papillary or follicular carcinoma. The remaining ten patients (9.3%) were diagnosed with lymphoma, metastasis or other malignant histology (Table 2).

A total of 350 patients out of the 483 (72%) patients included had a diagnostic thyroid scintigraphy performed. Of these, 279 (80%) had a focal hypo-functioning area (a “cold nodule”). The rest of the scintigraphy results were distributed as follows: normal thyroid uptake 12; diffuse uptake six; “hot” area five; alternating uptake 42; reduced or no uptake six. The pathologist was not routinely informed about this information before evaluation of the cytologies, but could access the information from the patient records at will. Dichotomized data are shown in Table 1.

### Possible patient-related predictors of malignant histology

To identify possible factors capable of predicting malignancy among patients with a suspicious thyroid FNAB, patient-related variables were analysed. The results are presented in Table 1.

## DISCUSSION

This study presents the frequency of malignancy among patients with suspicious thyroid FNAB according to the Danish criteria. The information is important for medical counselling of the thyroid nodule patient and therefore important for doctors in several specialties. We found a 22.4% risk for malignancy when thyroid FNAB was “suspicious” according to the Danish criteria. Additionally, we found that malignancy was associated with serum thyroid-stimulating hormone (S-TSH) values outside the normal range and with dysfunctional vocal cords.

Previously, a Danish single-centre study reported a frequency of 20.5% [2]. Using the Bethesda classification system, the risk of malignancy of a thyroid nodule within group III, IV and V ranges from 5% to 75%, depending on the diagnostic subgroup [10]. The “indeterminate” category of thyroid nodules includes atypia of undetermined significance, follicular lesion of undetermined significance, suspicious of follicular neoplasm, follicular neoplasm, and suspicious of malignancy [19]. This group is almost similar to the Danish “suspicious” group and previous studies have shown malignancy frequencies in the 19-49% range, which is comparable to our findings [11-14].

When comparing Danish and US thyroid FNAB results, differences in the occurrence of hyper-functioning thyroid nodules have to be taken into consideration. Denmark is a relatively iodine-deficient country, while the US has a high level of dietary iodine which explains this difference. Almost all hyper-functioning “hot” thyroid nodules are benign and should not routinely be investigated with thyroid FNAB. Therefore, information about scintigraphy is important in the diagnostic work-up.

Gene expression classifiers (panels of genetic mutations and rearrangements) have recently been developed to discriminate between benign and malignant thyroid nodule FNABs. Studies indicate the potential for reduction of the number of patients having surgery due to an indeterminate FNAB [19]. The results seem promising, but the technique is expensive and currently commercial genetic analysis has been implemented in routine diagnostic workup only at a limited number of centres.

Longstanding hoarseness is a known red flag for malignancy [6], and - as expected - the risk of this was increased in the group of patients with impaired vocal cord mobility at the time of their diagnosis. However, the finding that S-TSH values outside the normal ranges should be an indicator of increased risk of malignancy among patients with a “suspicious” FNAB was surprising even though a systematic review and meta-analysis by McLeod et al [16] found that a higher serum TSH concentration is associated with higher odds of thyroid can-

**TABLE 1**

Factors possibly predictive of malignancy among patients with a “suspicious” thyroid fine-needle aspiration biopsy.

Dichotomization (N)	Malignant histology		Benign histology		p-value	Odds ratio
	n	%	n	%		
<i>Age<sup>a</sup></i>					NS	NS
≥ 53.0 yrs (241)	62	25.7	179	74.3		
< 53.0 yrs (242)	46	19.0	196	81.0		
<i>Sex</i>					NS	NS
Female (374)	83	22.2	291	77.8		
Male (109)	25	22.9	84	77.1		
<i>Ultrasound finding</i>					NS	NS
Solitary solid tumour (232)	57	24.6	175	75.4		
Other (240)	47	19.6	193	80.4		
<i>Serum stimulating thyroid hormone</i>					< 0.05	3.1
Outside normal ranges (22)	10	45.5	12	54.5		
Inside normal ranges (456)	96	21.0	360	79.0		
<i>Vocal cord mobility</i>					< 0.01	8.9
Impaired or no mobility (7)	5	71.4	2	28.6		
Normal mobility (468)	103	22.0	365	78.0		
<i>Earlier thyroid surgery</i>					NS	NS
Yes (26)	9	34.6	17	65.4		
No (456)	98	21.5	358	78.5		
<i>Earlier radioactive iodine treatment<sup>b</sup></i>					NS	NS
Yes (6)	2	33.3	4	66.7		
No (477)	106	22.2	371	77.8		
<i>Scintigraphic finding</i>					NS	NS
“Cold nodule” (279)	50	14.3	229	65.5		
Other (71)	11	3.1	60	17.1		

NS = non-significant.

a) Dichotomized at the median age of the patients at the time of surgery.

b) Given before surgery on benign indication.

**TABLE 2**

Diagnosis	n (%)	Distribution of malignant histological diagnoses among patients with a “suspicious” thyroid fine-needle aspiration biopsy (N = 108).
Papillary carcinoma	55 (50.9)	
Follicular carcinoma	34 (31.5)	
Medullary carcinoma	4 (3.7)	
Undifferentiated carcinoma	5 (4.6)	
Lymphoma	2 (1.9)	
Metastasis	2 (1.9)	
Other malignant histology	6 (5.6)	

cer, even within the normal TSH ranges. Other studies support this [15, 17]. In contrast hereto, Castro et al [13] found no association between S-TSH and risk of thyroid malignancy and it must be concluded that the literature seems weak and rather contradictory in this field. In our study, it was only registered if the S-TSH was inside or outside the reference level and we cannot contribute further to the discussion. However, our results do suggest that abnormal levels of thyroid hormone may play a role as a predictor of thyroid carcinoma.

This study has limitations concerning data reporting. Data were accepted as reported and failures may occur. Due to the limited number of malignant cases, significant predictors of malignancy may have been overlooked. Further, the direct correlation between “suspicious” thyroid FNAB and histology may be uncertain since the design of this study does not secure that the nodule biopsied is the same as the one containing a malignant diagnosis. The study is only able to evaluate the overall frequency of malignancy in the group of patients with a “suspicious” thyroid FNAB.

The prospective design, the high completeness in the THYKIR database [20] and the coverage of a specific geographical referral area (Region of Southern Denmark) are strengths which reduce any risk of bias and increase the generalisability of results.

## CONCLUSION

The risk of malignancy in the Danish thyroid FNAB “suspicious” group is 22% and S-TSH outside the normal range and vocal cord palsy may be patient-related predictors of malignancy. Awaiting the introduction of reliable tools for preoperative evaluation, current practice with histological clarification of the “suspicious” thyroid FNAB seems justified.

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