Risk of Thyroid Cancer in 1,504 Patients Referred for Thyroid Surgery with Assumed Benign Histology

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Keywords

Fine-needle aspiration · Thyroid cancer · Thyroid cytology · Benign lesion · Thyroid surgery

Abstract

Objectives: The aims of this study were to report the risk of thyroid malignancy in cases of either benign fine-needle aspiration (FNA) or without FNA performed, and to investigate possible predictive factors for thyroid malignancy in a population with recent moderately low iodine intake. **Methods:** All patients referred for thyroid surgery in a tertiary cancer centre between 2000 and 2016 were included ($n = 3,703$). After excluding cases indicating malignant histology, we included group 1: patients with benign FNA ($n = 764$), and group 2: patients without FNA ($n = 740$), leaving 1,504 eligible for further investigation. Information on age, gender, tracheal compression or dislocation, thyroid specimen weight, scintigraphy, ultrasound, medically treated thyrotoxicosis, serum stimulating thyroid hormone, indication for surgery, TNM classification, stage, and outcome were retrieved. **Results:** The malignancy risk was 7.6% (58/764) in group 1 and 6.8% (50/740) in group 2. Patients with T2–4 tumours constituted 2.2% (33/1,504). In the combined groups, ultrasound

verified that solitary solid tumour was predictive for malignancy ($p = 0.01$ by χ^2 , and $OR = 1.69$, $p = 0.02$ in multiple logistic regression). For group 1 patients, thyrotoxicosis (which in this case was medically treated) was a significant predictive factor for malignancy ($p = 0.04$). **Conclusions:** The risk of malignancy of 7.6% and 6.8% was high, considering that patients with malignant FNA, suspicious FNA, or clinical findings indicating malignancy were excluded, and 2.2% of these malignancies were stages T2–4. In cases with solitary solid tumour on ultrasound, the risk of malignancy should not be ignored, even with benign FNA.

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Introduction

Thyroid carcinoma is the most common endocrine malignancy. Two Danish studies report an incidence of 1.57 cases per 100,000 men, 4.11 cases per 100,000 women [1], and 4.5 cases per 100,000 men and women [2]. With a rapidly growing incidence – caused almost exclusively by low-mortality papillary tumours – accurate diagnostic methods become increasingly important in order to deal

Fig. 1. Study population. FNA, fine-needle aspiration; THYKIR, the Danish Thyroid Surgery Database.

with the growing number of patients [3, 4]. Preoperative assessment of thyroid nodules, however, remains a diagnostic challenge. In Denmark, scintigraphy and ultrasound are performed as part of the investigation in which cold nodules on scintigraphy and suspicious nodules on ultrasound are further investigated with fine-needle aspiration (FNA) [5]. Accurate FNA cytology diagnosis is dependent upon a number of factors including the skills of the operator, FNA techniques, specimen preparation, and cytology interpretation, altogether affecting the false-negative rate of benign cytology diagnosis [6–8]. Another diagnostic problem concerns patients with thyrotoxicosis or multinodular goitre without a cold nodule by scintigraphy, in which case FNA is not performed due to low risk of malignancy or because the patient will be referred to surgery for hyperthyroidism regardless.

Two autopsy studies concluded that the prevalence of occult papillary carcinoma in the thyroid was between 11 and 36% [9, 10], and 2 recent studies suggested observation rather than surgery in papillary microcarcinomas (PMC) [11, 12]. Taking this into account, it should be considered when a preoperative diagnosis is relevant. Non-lethal PMC might not affect the management or treatment of the patient. Nevertheless, a preoperative diagnosis of thyroid cancer is important in order to avoid delay in surgery. Regarding patients with clinical thyroid carcinomas, avoiding reoperation, recurrence, metastasis, and death is important.

This study advances present knowledge by investigating the fate of patients with missed preoperative cancer diagnosis. Our aims were (1) to report the risk of malignancy in cases referred for surgery either with benign FNA or without FNA and identify possible predictive risk factors of malignancy in a population with recent moderately low iodine intake, and (2) to investigate the TNM classification and assess the outcome in patients with stages T2–4.

Materials and Methods

Investigation

All patients who had thyroid surgery performed at the Department of Otorhinolaryngology, Head and Neck Surgery and Audiology, Rigshospitalet University of Copenhagen, between 2000 and 2016 were investigated according to guidelines from the Danish Endocrine Society (DES). Eighty percent of the patients were referred from endocrinology departments.

If patients had a fast-growing nodule or paresis of the recurrent laryngeal nerve, they were admitted to a fast-track program; otherwise a further investigation of thyroid stimulating hormone (TSH) was performed. Normal TSH resulted in subsequent investigation with ultrasound and scintigraphy. FNA, which is always guided by ultrasound in Denmark, was performed in cases with a suspicious nodule on ultrasound, or if scintigraphy revealed a cold solitary nodule or a multinodular goitre with a dominant cold nodule. Hot nodule, multinodular goitre without a dominant cold area, or toxic thyroid nodules are usually not investigated with FNA [5]. Consultant pathologists performed the pathological investigation in this study.

Included Patients

All patients who had thyroid surgery performed were identified from the prospectively registered database, the Danish Thyroid Surgery Database (THYKIR), and were evaluated concerning histological diagnosis.

Only patients referred for thyroid surgery and with benign clinical findings and benign FNA, corresponding to The Bethesda group II, or patients with no FNA performed were included in this study. All patients in the group with benign FNA had a nodule, but the patients without FNA performed did not necessarily have any.

All patients who underwent surgery would generally have a preceding FNA performed. However, in our current study, 740 patients with no preceding FNA underwent surgery. This was a consequence of either thyrotoxicosis or pressure symptoms combined with a multinodular goitre without a cold nodule on scintigraphy.

TNM Classification, Stage, and Outcome

In this study, data on TNM classification and stage of the thyroid malignancies and outcome for patients with T2–4 were retrieved from DATHYRCA and The Danish Pathology Registry. The DATHYRCA database is contained within the Danish Head and Neck Cancer study group (DAHANCA), which prospectively registers clinical, surgical, histopathological, and follow-up data from Danish thyroid cancer patients nationwide. The Danish Pathology Registry is a national database that includes all histological and cytological reports in Denmark, and in the current study six or seven pathologists were involved.

Statistics

The correlation between age, gender, tracheal compression or dislocation, scintigraphy, ultrasound, TSH, distribution of malignant histology, and patients with thyrotoxicosis (which in this case was medically treated), were tested with χ^2 or Fisher's exact test. The Mann-Whitney U test was used to determine the total weight of the surgically removed thyroid specimen. Ultrasound and scintigraphy were dichotomized and a p value <0.05 was considered significant. Ultrasound, scintigraphy, and gender were further included in multiple logistic regressions. All statistical analyses were performed in IBM SPSS Statistics 22.

Results

Inclusion, Exclusion, and Patient Characteristics

Rigshospitalet manages the treatment of thyroid cancers in Eastern Denmark, which has a population of 2.6 million people. Rigshospitalet attends to 1.2 million of this population with specific regard to benign thyroid surgery. In total, 3,703 patients, referred for thyroid surgery, were included in this study, and 1,504 were eligible for further analysis after excluding patients with malignant FNA, suspicious FNA, and clinical findings indicating malignancy. Figure 1 depicts a consort diagram of patient inclusion and exclusion. Table 1 shows patient characteristics. The patients were divided into

group 1: with benign FNA ($n = 764$), and group 2: where FNA was not performed ($n = 740$). Tables 2 and 3 show the patient characteristics of these two groups. We retrieved and evaluated clinical information concerning histological diagnosis, age, gender, tracheal compression or dislocation, total weight of surgically removed thyroid specimen, scintigraphy, ultrasound, serum TSH, indication for surgery, TNM classification, stage, outcome and thyrotoxicosis (in this case medically treated or not). Patients with malignant histological diagnosis constituted 7.6% (58/764) of group 1 and 6.8% of group 2 (50/740).

Histological Diagnoses

Table 4 depicts the distribution of malignant histological diagnoses in the whole study population ($n = 3,703$) and specifically within the two groups concerned. There was no statistical difference in the distribution of malignancy types between the two groups compared to the whole study population. In group 1, 79.3% of the malignant tumours ($n = 58$) were diagnosed as papillary carcinoma, 12.1% as follicular carcinoma, 3.5% as medullary carcinoma, 1.7% as undifferentiated carcinoma, and 3.4% as other types of malignancy. Correspondingly, 62.0% of the malignant tumours ($n = 50$) in group 2 were diagnosed as papillary carcinoma, 14.0% as follicular carcinoma, 4.0% as medullary carcinoma, 6% as undifferentiated carcinoma, and 14% as other malignancies.

Predictive Factors for Malignancy

A number of variables were analysed to identify possible predictive factors for malignancy, the results of which are presented in Tables 1–3 and Table 5. The presence of a solitary solid tumour assessed by ultrasound was a significant predictor for malignancy ($p = 0.01$) in the 1,504 patients with benign FNA or no FNA performed. For group 1 patients, thyrotoxicosis (which in this case was medically treated) was a significant predictive factor for malignancy ($p = 0.04$). Multiple logistic regression analyses determined solitary solid tumour on ultrasound to be a significant predictor for malignancy (OR = 1.69, $p = 0.02$).

Surgery Indication

The indication for surgery was evaluated and the results are presented in Table 6. Generally, the typical patient with FNA performed had pressure symptoms or a nodule, and the patients without FNA performed had thyrotoxicosis or pressure symptoms and a multinodular goitre without dominant cold areas. Pressure symptoms,

Table 1. Factors possibly predictive of malignancy among patients with both a benign FNA and without FNA performed

	Malignant histology		Benign histology		<i>p</i> value
	<i>n</i>	% ^a	<i>n</i>	% ^b	
Total	108	100	1,396	100	
Age					
<20 years	4	4	28	2	
>70 years	12	11	159	11	
Sex					0.69
Female	89	82	1,128	81	
Male	19	18	268	19	
Serum TSH					0.62
Hypothyroid	5	5	36	3	
Hyperthyroid	16	15	233	17	
Euthyroid	82	76	1,078	77	
Missing	5	5	49	4	
Ultrasound finding					0.01*
Solitary solid tumour	37	34	333	24	
Other	43	40	751	54	
Missing	28	26	312	22	
Scintigraphic finding					0.07
Cold nodule	47	44	574	41	
Other	35	32	626	45	
Missing	26	24	196	14	
Compression of trachea					0.49
No	72	67	849	61	
Yes	16	15	254	18	
Missing	20	19	293	21	
Dislocation of trachea					0.33
No	70	65	812	58	
Yes	19	18	313	22	
Missing	19	18	271	19	
Medically treated thyrotoxicosis					0.45
No	77	71	894	64	
Yes	20	19	282	20	
Missing	11	10	220	16	
Weight ^c					0.90
Median	39		44		
Minimum	4		0.4		
Maximum	360		1,655		

FNA, fine-needle aspiration; TSH, thyroid stimulating hormone. ^a Percent of predictive factor out of total number of patients with malignant histology (*n* = 108). ^b Percent of predictive factor out of total number of patients with benign histology (*n* = 1,396). ^c Total weight of surgically removed thyroid specimen. * *p* < 0.05, statistically significant.

thyrotoxicosis, or respiratory influence were not related to malignant or benign histology.

TNM, Stage, and Outcome

Table 7 depicts the TNM classification and Table 8 the stage of the thyroid malignancies. In Table 9 the

outcome of patients with T2–4 malignancies is presented. In group 1, most thyroid malignancies were T1 (56.9%, *n* = 33) and stage I (75.9%, *n* = 44) and the remaining malignancies were classified as T2 (15.5%, *n* = 9), T3 (15.5%, *n* = 9), and T4 (3.4%, *n* = 2), and stage II (6.9%, *n* = 4), III (3.4%, *n* = 2), and IV (5.2%, *n* = 3).

Table 2. Factors possibly predictive of malignancy among patients with a benign FNA

	Malignant histology		Benign histology		<i>p</i> value
	<i>n</i>	% ^a	<i>n</i>	% ^b	
Total	58	100	706	100	
Age					
<20 years	3	5	10	1	
>70 years	4	7	53	8	
Sex					0.55
Female	46	79	582	82	
Male	12	21	124	18	
Serum TSH					0.34
Hypothyroid	1	2	14	2	
Hyperthyroid	4	7	19	3	
Euthyroid	52	90	664	94	
Missing	1	2	9	1	
Ultrasound finding					0.06
Solitary solid tumour	30	52	410	58	
Other	28	48	265	38	
Missing	0		31	4	
Scintigraphic finding					0.19
Cold nodule	44	76	472	67	
Other	11	19	186	26	
Missing	3	5	48	7	
Compression of trachea					0.22
No	44	76	468	66	
Yes	4	7	90	13	
Missing	10	17	148	21	
Dislocation of trachea					0.07
No	42	72	423	60	
Yes	7	12	146	21	
Missing	9	16	137	19	
Medically treated thyrotoxicosis					0.04*
No	48	83	561	79	
Yes	5	9	19	3	
Missing	5	9	126	18	
Weight ^c					0.23
Median	38		33		
Minimum	4		2		
Maximum	360		1,655		

FNA, fine-needle aspiration, TSH, thyroid stimulating hormone. ^a Percent of predictive factor out of total number of patients with malignant histology and benign FNA (*n* = 58). ^b Percent of predictive factor out of total number of patients with benign histology and benign FNA (*n* = 706). ^c Total weight of surgically removed thyroid specimen. * *p* < 0.05, statistically significant.

Similarly, in group 2, most malignancies were T1 (56%, *n* = 28) and stage I (54%, *n* = 27) and the rest were classified as T2 (10%, *n* = 5), T3 (6%, *n* = 3), and T4 (10%, *n* = 5), and stages II (8%, *n* = 4), III (6%, *n* = 3), and IV (14%, *n* = 7). Patients with T2–4 accounted for 2.2% in total (33/1504), and the outcome of these patients

showed that 23 patients (76.7 %) were alive, 5 patients (16.7%) had reoperation, 1 patient (3.3%) had recurrence, and 4 patients (12.1%) were dead (3 from undifferentiated thyroid carcinoma and 1 from an aortic aneurism).

Table 3. Factors possibly predictive of malignancy among patients without FNA performed

	Malignant histology		Benign histology		<i>p</i> value
	<i>n</i>	% ^a	<i>n</i>	% ^b	
Total	50	100	690	100	
Age					
<20 years	1	2	18	3	
>70 years	8	16	106	15	
Sex					0.24
Female	43	86	546	79	
Male	7	14	144	21	
Serum TSH					0.27
Hypothyroid	4	8	22	3	
Hyperthyroid	12	24	214	31	
Euthyroid	30	60	414	60	
Missing	4	8	40	6	
Ultrasound finding					0.07
Solitary solid tumour	7	14	68	10	
Other	15	30	341	49	
Missing	28	56	281	41	
Scintigraphic finding					0.23
Cold nodule	3	6	102	15	
Other	24	48	440	64	
Missing	23	46	148	21	
Compression of trachea					0.99
No	28	56	381	55	
Yes	12	24	164	24	
Missing	10	20	145	21	
Dislocation of trachea					0.87
No	28	56	389	56	
Yes	12	24	167	24	
Missing	10	20	134	19	
Medically treated thyrotoxicosis					0.20
No	29	58	333	48	
Yes	15	30	263	38	
Missing	6	12	94	14	
Weight ^c					0.13
median	66		63		
minimum	6		0.4		
maximum	286		907		

FNA, fine-needle aspiration; TSH, thyroid stimulating hormone. ^a Percent of predictive factor out of total number of patients with malignant histology and no FNA performed (*n* = 50). ^b Percent of predictive factor out of total number of patients with benign histology and no FNA performed (*n* = 690). ^c Total weight of surgically removed thyroid specimen. * *p* < 0.05, statistically significant.

Discussion

As FNA is currently one of the triaging procedures in diagnosing thyroid malignancy, it is of great importance to investigate data on malignancy and possible predictive factors in cases of benign or no FNA. We

found the risk of malignancy to be 7.6% in the group with benign FNA and 6.8% in the group without FNA. Whether the risk of malignancy is actually problematic can be discussed, since incidentalomas upon further inspection merely turn out to be predominantly non-lethal PMC [4], which might not affect the management

Table 4. Distribution of malignant histological diagnoses among the total study population with malignant histology compared with malignant histological diagnoses in group 1 (benign FNA) and group 2 (without FNA)

	All patients		Benign FNA		<i>p</i> value*	FNA not performed		<i>p</i> value**
	<i>n</i>	%	<i>n</i>	%		<i>n</i>	%	
Total	793	100	58	100		50	100	
Papillary carcinoma	523	65.9	46	79.3	0.37	31	62.0	0.79
Follicular carcinoma	145	18.3	7	12.1	0.31	7	14.0	0.52
Medullary carcinoma	39	4.9	2	3.5	0.63	2	4.0	0.78
Undifferentiated carcinoma	31	3.9	1	1.7	0.41	3	6.0	0.49
Other malignancy	55	7	2	3.4	0.53	7	14.0	0.79

FNA, fine needle aspiration. * The total study population with malignant histology vs. patients with benign FNA and malignant histology. ** The total study population with malignant histology vs. patients without FNA and malignant histology.

and treatment of these patients. However, in the current study 2.2% (*n* = 33) of the patients had malignancies of stages T2, T3, and T4, and 9 of these experienced reoperation, recurrence, or death by thyroid cancer. Due to the unfavourable prognosis of these stages, it is essential to identify, diagnose, and adequately treat these patients. A correct preoperative diagnosis would improve outcome due to earlier and more comprehensive treatment.

This study is characterized by a high degree of referral and selection bias as the patients are from a cohort already referred for surgery, thus obscuring them from any other medical context.

In comparison to previously published studies on benign FNA, our results indicate a higher risk of malignancy: a review of 12 studies showed that of 4,055 patients with benign cytology who underwent surgery, 3.2% (range 1.0–18.1%) had a malignancy [13]. Furthermore, large retrospective series on the utility of repeated FNA in nodules with prior benign cytology results found a malignancy rate of only 1–2% [14–16]. The high malignancy incidence in this study could have been due to differences in the indication for surgery or differences in the investigation of the patients, e.g., scintigraphy is standard procedure in Denmark as opposed to many other countries with a longer period of iodine sufficiency. The main reason for performing scintigraphy is the high prevalence of warm/hot nodules, particularly in multinodular goitres due to a moderately low iodine intake for more than half a century until the year 2000. If examined carefully, surgical specimens of these multinodular goitres might harbour low-mortality papillary tumours, thus contributing to a higher risk of malignancy.

Table 5. Multiple regression testing factors possibly predictive for malignancy among patients with both benign FNA and without FNA performed (*n* = 1,504)

Variable	Odds ratio	<i>p</i> value	95% CI
Sex	0.89	0.66	0.52–1.53
Ultrasound finding	1.69	0.02	1.09–2.61
Scintigraphic finding	1.15	0.54	0.74–1.79

FNA, fine-needle aspiration.

Attempts have also been made to correlate higher malignancy with nodules greater than 3–4 cm [17, 18]. Recent studies found that 10.4% of cytologically benign nodules ≥4 cm were malignant and 3.6% of cytologically benign nodules >3 cm were malignant on postoperative histopathology [19, 20]. This might be the cause of the high percentage of false-negative FNA in our study since it is Danish clinical procedure not to perform surgery in patients with a tumour <4 cm.

We found that 2.9% of the patients with a cold nodule on scintigraphy had no FNA performed. It might be otherwise expected that all cold nodules would result in FNA being performed. Probable explanations include intra-thoracic nodule and nodule inaccessible with FNA.

Surprisingly, 5.3% of the patients with no FNA had both thyrotoxicosis and malignant histological diagnosis, possibly due to that fact that many patients with Graves disease and thyrotoxicosis have a higher risk of small papillary foci by histology. Hyper-functioning thyroid carcinomas are generally rare, and to our knowledge only case

Table 6. Surgery indication in patients grouped by histology, subgrouped by FNA (benign/without)

	Malignant histology				Benign histology			
	benign FNA		without FNA performed		benign FNA		without FNA performed	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Total	58	100	50	100.0	706	100.0	690	100.0
Nodules	8	14	5	10.0	131	18.6	32	4.6
Paresis of the recurrent nerve	0	0	0	0.0	7	1.0	2	0.3
Cosmetics	1	2	1	2.0	7	1.0	3	0.4
Pressure symptoms	39	67	10	20.0	520	73.7	277	40.1
Respiratory influence	2	3	7	14.0	19	2.7	66	9.6
Thyrotoxicosis	7	12	15	30.0	6	0.8	239	34.6
Thyroiditis	0	0	1	2.0	1	0.1	1	0.1
Parathyroid disease	0	0	7	14.0	11	1.6	49	7.1
Other	0	0	2	4.0	3	0.4	10	1.4
Missing	1	2	2	4.0	1	0.1	11	1.6

FNA, Fine-needle aspiration.

Table 7. TNM in patients with malignant histology, subgrouped by FNA (benign/without)

	T1		T2		T3 ^a		T4 ^a		N0		N1		M0		M1		Not classified	
	B	W/O	B	W/O	B	W/O	B	W/O	B	W/O	B	W/O	B	W/O	B	W/O	B	W/O
Papillary carcinoma	31	25	7	4	6	1	0	0	42	25	2	5	44	29	0	1	2	1
Follicular carcinoma	1	1	1	1	3	2	2	2	7	6	0	0	7	6	0	0	0	1
Medullary carcinoma	1	2	1	0	0	0	0	0	2	2	0	0	2	2	0	0	0	0
Undifferentiated carcinoma	0	0	0	0	0	0	0	3	0	2	0	1	0	1	0	2	1	0
Other malignant histology	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	7
Total with given TNM stage in FNA group	33	28	9	5	9	3	2	5	51	35	2	6	53	38	0	3	5	9
Total as % of FNA group	56.9	56.0	15.5	10.0	15.5	6.0	3.4	10.0	87.9	70.0	3.4	12.0	91.4	76.0	0.0	6.0	8.6	18.0

B, benign FNA (*n* = 58); W/O, without FNA performed (*n* = 50). ^a The size of T3 and T4 tumours are >4 cm.

reports, small studies, and a few reviews have been reported in the past [21–23].

Although no statistical difference could be determined when comparing the group of benign FNA (*n* = 764) with the total thyroid cancer population (*n* = 3703), it was remarkable that more papillary carcinomas (79.3%) were found in the group with benign FNA. This was likely due to PMC, which inaccurate FNA may have trouble detecting [24, 25]. The improvement in the overall mortality of thyroid carcinoma can be attributed to an increased number of detected low-mortality PMC. As seen with prostate cancer, it is also possible that an increasing share of thy-

roid cancer patients will die with, rather than from, the disease [1]. The group without FNA performed were distributed similarly to the total thyroid cancer population, but the high number of undifferentiated carcinomas (6.0%) was noteworthy due to the severe prognosis in these cases.

It is advisable to suspect malignancy in thyroid nodules in cases of stridor, fast-growing nodules, rigid and immobile nodules, and paresis of the recurrent laryngeal nerve [26]. Additionally, associations between Hashimoto's thyroiditis and papillary thyroid carcinoma have been found [27]. Indicators of thyroid malignancy are

Table 8. Stage in patients with malignant histology ($n = 108$), subgrouped by FNA

	I		II		III		IV		Not classified	
	B	W/O	B	W/O	B	W/O	B	W/O	B	W/O
Papillary carcinoma	38	22	3	4	1	2	2	2	2	1
Follicular carcinoma	5	3	0	0	1	1	1	2	0	1
Medullary carcinoma	1	2	1	0	0	0	0	0	0	0
Undifferentiated carcinoma	0	0	0	0	0	0	0	3	1	0
Other malignant histology	–	–	–	–	–	–	–	–	2	7
Sum	44	27	4	4	2	3	3	7	5	9
FNA group with respective stage, %	75.9	54.0	6.9	8.0	3.4	6.0	5.2	14.0	8.6	18.0

B, benign FNA ($n = 58$); W/O, without FNA ($n = 50$).

valuable as they help prevent delayed diagnosis and the worsened outcome as a result hereof. We evaluated a broad selection of possible predictive factors and discovered solitary solid tumour on ultrasound to be a predictive factor tested with both multiple logistic regression and χ^2 test. Thyrotoxicosis (in this case medically treated) was also a significant predictive factor for malignancy. Compared to the guidelines for ultrasound malignancy risk stratification in the EU-TIRADS [28], we compared solid tumour on ultrasound with a composite group of other findings, thus not taking microcalcifications, “taller-than-wide” shapes, and irregular margins into account – all candidate limitations to the study. Additionally, data from this study were probably not comparable to studies from countries with a longer history of iodine sufficiency, as Denmark has a high occurrence of multinodular goitres, thus more benign nodules and consequently a lower risk of malignant nodule histology. When endocrinologists attend to the patients first, those referred for thyroid surgery constitute a selected cohort, whereas data from an unselected cohort would have shown very different characteristics. Correlations detected in this study were extremely dependant on descriptions of ultrasound and cytological definitions. As an example, from 2000 to 2005 Rigshospitalet employed thyroperoxidase immunostaining of the solitary solid thyroid nodule when distinguishing between benign and malignant tumour cells in coarse-needle biopsy and it is currently used in FNA [29, 30].

In conclusion, in a Danish population of moderately low iodine insufficiency until the year 2000 and thus a low a priori likelihood for cancer in thyroid nodules, our finding of a risk of malignancy of 7.6 and 6.8% (in patients with benign FNA and without FNA, respectively) indi-

Table 9. Outcome in patients with malignant histology $\geq T2$ ($n = 33$)

	T2	T3	T4	Total	%
Alive with no disease	12	9	2	23	76.7
Reoperation	2	2	1	5	16.7
Recurrence	0	1	0	1	3.3
Dead	0	0	4	4	12.1

cates that in cases with a solitary solid tumour on ultrasound, risk of malignancy should be considered, even with benign FNA. Patients with thyroid malignancy classified as T2–4 (2.2%, $n = 33$) within both groups were found, and 9 of these experienced reoperation, recurrence, or death by thyroid cancer, making it essential to identify and adequately treat these cases.

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Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors have no conflicts of interest to declare.

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