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Original Article

Validation of the Bethesda System for Reporting Thyroid Cytopathology in a Danish tertiary centre

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ABSTRACT

INTRODUCTION. The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) is used to categorise thyroid fine-needle aspiration (FNA). The aim of this study was to validate the BSRTC in a consecutive cohort and to evaluate the derived management in terms of performing repeat FNA or thyroid surgery.

METHODS. Results of thyroid FNAs assessed at the Department of Pathology, Aarhus University Hospital, in the period 2016-2019 were retrieved from The Danish Pathology Registry. FNA category according to the BSRTC along with the histological diagnosis (if available) were linked to the individual patient.

RESULTS. In total, 3,669 biopsies were included from 2,873 thyroid nodules in 2,547 patients. Repeat FNA was performed in 23.6% of nodules. The majority of primary FNAs were Benign (BSRTC II; 52.4%). Non-diagnostic (ND) (BSRTC I) was found in 26.3% and BSRTC III-VI were found in 3.6-7.5%. Compared with the first with the last FNA, the frequency of Benign (BSRTC II) increased (61.3%), whereas the frequency of ND (BSRTC I) decreased (14.8%). Surgery was performed in 38.2% (n = 1,097) of nodules. The malignancy rate of 11.5% correlated positively with the BSRTC category, being 2.8% in Benign (BSRTC II) and 95.7% in Malignant (BSRTC VI).

CONCLUSIONS. The malignancy rates in the BSRTC categories were in accordance with reports from other countries. Since the BSRTC ensures a standardised and concise communication of cytopathology assessments, application of the BSRTC for thyroid nodule management in a Danish setting is recommended.

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The preoperative diagnostic work-up of thyroid nodules relies on multifactorial assessment including thyroid hormone levels, thyroid scintigraphy, ultrasonography (US) and fine-needle aspiration (FNA) [1, 2]. US is used to identify focal lesions and select nodules for FNA, based on suspicious US features [2, 3]. FNA is used to identify nodules with a high risk of cancer and to stratify patients for surgery or follow-up [2, 4].

The Bethesda System for Reporting Thyroid Cytopathology (BSRTC) was introduced to improve and standardise communication between pathologists and clinicians [5]. The BSRTC classifies FNAs into six categories (I-VI), each with an increasing risk of malignancy and a proposed clinical management [4-6]. The BSRTC is considered a cost-effective communication tool with high negative (NPV) and positive predictive values (PPV) for both the

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Benign (BSRTC II; NPV: 93-97%) and the Malignant categories (BSRTC VI; PPV: 90-96%) categories [4, 7]. The categories Atypia of Undetermined Significance (Atypia), Follicular Neoplasm (FN) and Suspect for Malignancy (Suspect) (BSRTC III, IV, V) are collectively referred to as indeterminate, and they convey an increased risk of malignancy [1, 4, 6].

The BSRTC was implemented in the routine setting at the Department of Pathology, Aarhus University Hospital (AUH) in April 2014. The results from the first two years (2014-2016), showing a high diagnostic accuracy, were previously reported in a surgical cohort [7]. The aim of the present study was to further validate the BSRTC of thyroid FNAs in a larger cohort.

METHODS

Patient cohort

Patients undergoing thyroid nodule FNA in the Central Denmark Region (1.3 million citizens) were included in the study. FNAs were performed from January 2016 to December 2019 at private ear-nose-throat (ENT) specialists, radiology departments and ENT or endocrinology departments in secondary or tertiary hospital units. The indication for thyroid nodule FNA complied with national guidelines [2]. Management after the initial diagnostic set-up included clinical and US follow-up, repeat FNA, thyroid surgery or no follow-up. This decision was based on an individual evaluation by the treating physician, the patient's preferences and the results of US and FNA [2, 6].

Pathological examinations

Pathological evaluation of all thyroid FNA was assessed at the Department of Pathology, AUH, and prospectively categorised according to the BSRTC [4] by two specialised thyroid pathologists (**Figure 1**). For this study, data were retrieved from the Danish Pathology Registry, a nation-wide database including all pathology data in Denmark. The search criteria were: 1) thyroid cytology assessed at the Department of Pathology, AUH and 2) topography (T), morphology (M) and sample type (P) according to the following criteria (translated from Danish); T: "Thyroid gland", "Right thyroid lobe", "Left thyroid lobe" or "Thyroid isthmus". M: "Insufficient cellular content" (BSRTC I), "No cells suspect for malignancy" (BSRTC II), "Atypia" (BSRTC III), "Follicular neoplasia, unknown if benign or malignant" (BSRTC IV), "Suspect for malignancy" (BSRTC V) or "Malignant tumour cells" (BSRTC VI). P: "Fine-needle aspiration". Histological data were retrieved for the entire cohort in November 2023 to account for any false negative results of a Benign (BSRTC II) FNA.

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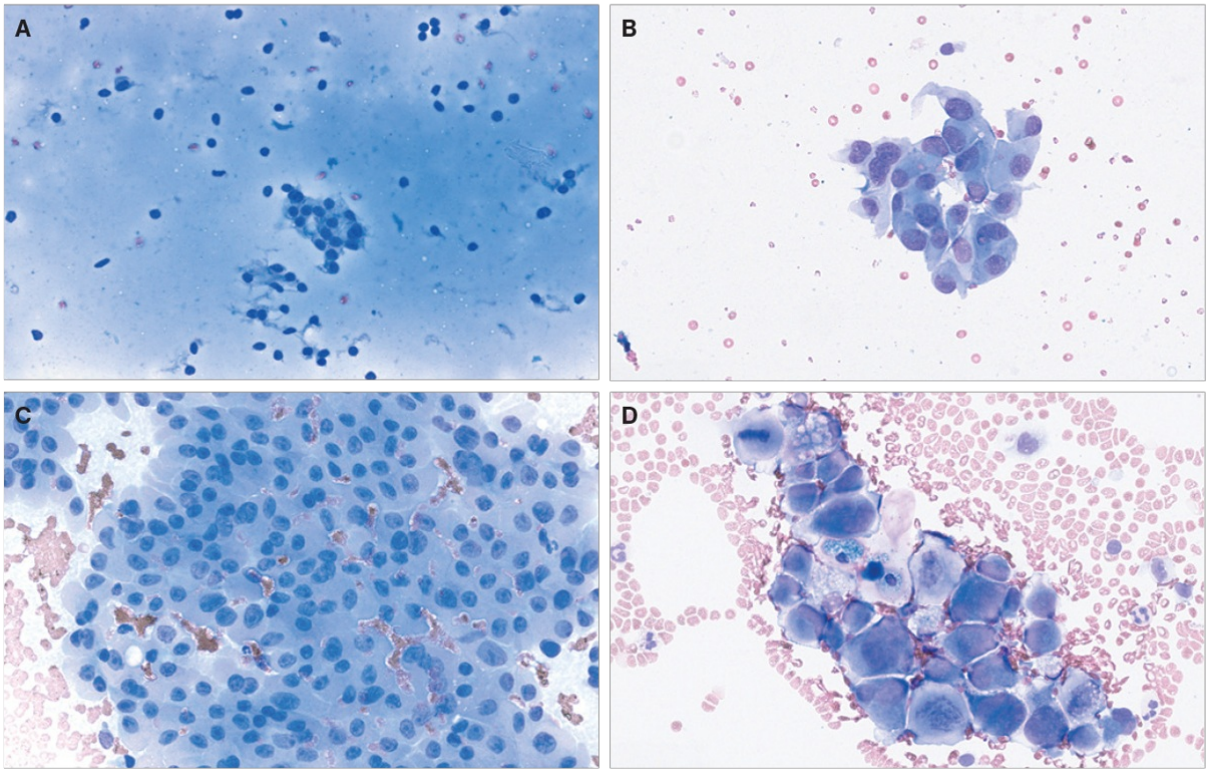
FIGURE 1 Cytological slides of fine-needle aspirations from thyroid nodules. Giemsa staining, magnification 1:40. **A**. Benign (Bethesda System for Reporting Thyroid Cytopathology (BSRTC) II). **B**. Atypia (BSRTC III). **C**. Follicular neoplasm (BSRTC IV), oncocytic variant. **D**. Malignant (BSRTC VI).



FNA results were reported as "primary FNA", "repeat FNA" and "final FNA". Primary FNA was defined as the first FNA available during the study period; repeat FNA as any subsequent FNAs in the same patient and thyroid lobe. Finally, final FNA was defined as the last FNA available during the study period. The data were checked for laterality to ensure consistency between the primary FNA, repeat FNA (if performed) and the histological diagnosis. In a subset of Malignant (BSRTC VI) nodules, the diagnosis was not histologically confirmed. In these cases, the cytology descriptions were reviewed and categorised into primary thyroid carcinoma or metastasis from non-thyroid malignancy. The histological diagnosis followed the World Health Organization (WHO) classification (3rd edition 2016-2017; 4th edition 2017-2019) [8, 9].

Ethical considerations

The local ethics committee of The Central Denmark Region waived approval of this study under Danish legislation (Registration no: 1-10-72-1-22) as data retrieval and analyses were considered part of a quality assessment programme.

Statistical analysis

Continuous variables are presented as mean and range. Categorical variables are presented as numbers and percentages. The statistical analysis was performed using Stata 13 (Metrika Consulting AB, Stockholm, Sweden).

Trial registration: not relevant.

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RESULTS

In total, 2,873 thyroid nodules in 2,547 patients were assessed by FNA. Patients were mainly females (n = 1,918; 75.3%) with a mean age of 59 years (range: 2-95 years). This included nine children (age 2-17 years). A total of 3,669 FNAs were assessed during the study period; one FNA was performed in 2,194 (76.4%) nodules, two FNAs were performed in 576 (20.0%) nodules and 3-5 FNAs were performed in 103 (3.6%) nodules.

Management according to The Bethesda System for Reporting Thyroid Cytopathology

The distribution of the primary FNAs in each BSRTC category along with the clinical management are listed in **Table 1**. In nodules with a primary Benign (BSRTC II) FNA diagnosis, no follow-up was performed in 74.1% of the cases. Malignancy was diagnosed in 42 nodules after surgical resection, resulting in a false negative rate of 13.3% in this category. For the entire cohort, the false negative rate was 2.8%. If FNA was repeated and confirmed Benign (BSRTC II), the false negative rates were only 0.2% in the entire cohort and 0.9% in the surgical subgroup. Most nodules with an Indeterminate or Malignant (BSRTC III-VI) FNA were surgically resected (Table 1). The false positive rate of the Malignant (BSRTC VI) category was 4.3% in the entire cohort and 4.7% in the surgical subgroup (Table 1). Nineteen patients harbouring a nodule classified as Malignant (BSRTC VI) provided no histological diagnosis. According to the cytology description, these represented seven papillary (PTC) and one medullary thyroid carcinoma (MTC), whereas 11 were non-thyroid metastases.

TABLE 1 Management according to the primary Bethesda System for Reporting Thyroid Cytopathology result.

		Management, n (%)			Malignancy rate, %	
BSRTC	Primary FNA, n (%)	repeat FNA only[a]	surgery[b]	no follow-up[c]	all	hist
I: Non-diagnostic	755 (26.3)	306 (40.5)	274 (36.3)	175 (23.2)	6.6	18.2
II: Benign	1,504 (52.4)	75 (5.0)	315 (20.9)	1,114 (74.1)	2.8	13.3
III: Atypia	165 (5.7)	26 (15.8)	108 (65.4)	31 (18.8)	20.6	31.5
IV: Follicular neoplasm	215 (7.5)	3 (1.4)	193 (89.8)	19 (8.8)	22.3	24.9
V: Suspect	130 (4.2)	2 (1.5)	122 (93.8)	6 (4.6)	51.5	54.9
VI: Malignant	104 (3.6)	0	85 (81.7)	19 (18.3)	95.7[d]	95.3
Total	2,873 (100)	412 (14.3)	1,097 (38.2)	1,364 (47.5)	11.5[d]	29.4

BSRTC = Bethesda System for Reporting Thyroid Cytopathology; DPR = Danish Pathology Registry; FNA = fine-needle aspiration; hist = histologically verified nodules.
a) Nodules in which repeat FNA was the last test result in the DPR.
b) Nodules with histological confirmation after surgery in the DPR, including nodules with repeat FNA + histology or histology only.
c) Nodules in which no repeat FNA or histology after surgery was available in the DPR.
d) The calculation of malignancy rate was based on histologically verified thyroid cancers and nodules in which FNA was categorised as malignant (BSRTC VI) and suspect of primary thyroid carcinoma but without histological confirmation (n = 8). Nodules in which FNA was classified as malignant (BSRTC VI) and suspect of non-thyroid metastasis to the thyroid were excluded from the analysis of malignancy rate (n = 11).

Repeat fine-needle aspiration

The repeat FNA (n = 679) was Benign (BSRTC II) in 51.7%, Non-diagnostic (ND, BSRTC I) in 30.0%, Indeterminate (BSRTC III-V) in 16.5% and Malignant (BSRTC VI) in 1.8%. If the primary FNA showed Atypia (BSRTC III) (n = 44), the repeat FNA was categorised as ND (BSRTC I; n = 15), Benign (BSRTC II; n = 14), Atypia (BSRTC III; n = 7), FN (BSRTC IV; n = 6), Suspect (BSRTC V; n = 1) or Malignant (BSRTC VI; n = 1). Comparing the final FNA with the primary FNA, the prevalence of ND (BSRTC I) decreased, whereas the prevalence of Benign (BSRTC II) increased (**Figure 2**). Repeat FNA had only minor effect on the prevalence of the Indeterminate and Malignant (BSRTC III-VI) categories.

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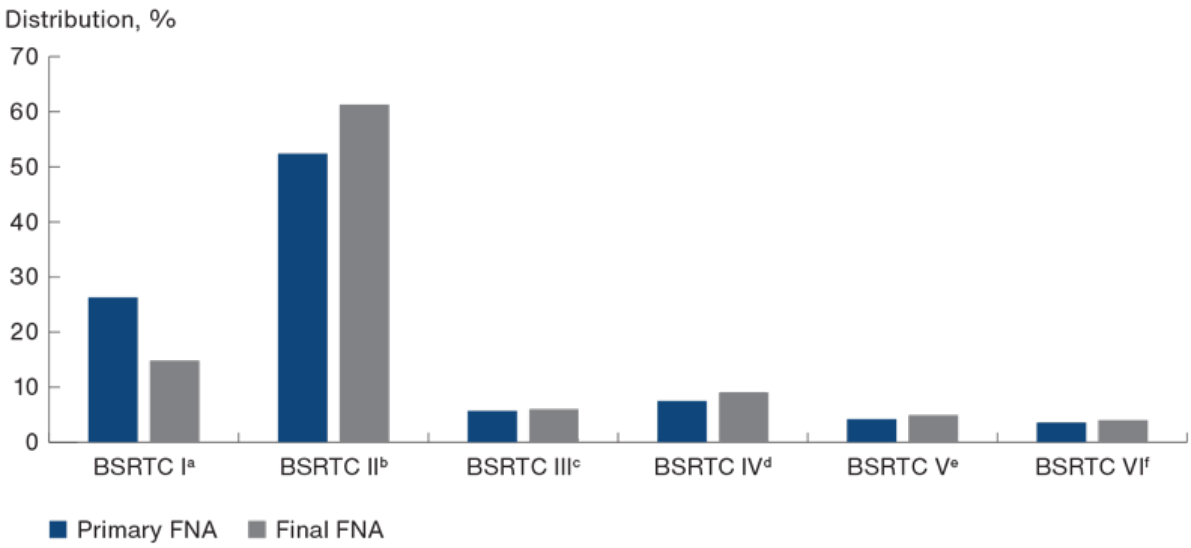
FIGURE 2 Distribution of the primary and the final fine-needle aspiration results.



BSRTC = Bethesda System for Reporting Thyroid Cytopathology; FNA = fine-needle aspiration.
a) Non-diagnostic
b) Benign
c) Atypia of undetermined significance
d) Follicular neoplasm
e) Suspect
f) Malignant

Histopathology

Thyroid surgery was performed in 1,097 (38.2%) nodules. The prevalence of malignancy was 11.5% in the entire cohort and 29.4% in the surgical subgroup (**Table 2**). PTC was diagnosed in 245 nodules (76.1%), of which 69 (28.2%) were micro-PTC (diameter < 10 mm). The remaining malignant lesions comprised 53 FTC (16.5%), 5 MTC (1.5%), five poorly differentiated thyroid carcinomas (PD-TC; 1.5%), seven anaplastic thyroid carcinomas (ATC; 2.2%) and seven other malignancies (2.2%) (Table 2). The prevalence of confirmed malignancy correlated progressively with BSRTC categories II-VI. By excluding micro-PTC from the analyses, the malignancy rate was 9.3% in the entire cohort and 24.6% in the surgical subgroup, whereas the false negative rates of a Benign (BSRTC II) FNA were 1.6% and 8.3%, respectively.

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TABLE 2 Management and diagnosis according to the final Bethesda System for Reporting Thyroid Cytopathology result.

		Management, n (%)		Malignancy rate, %		Histology	
BSRTC	Final FNA, n (%)	surgery[a]	no follow-up[b]	all	hist	type	n
I: Non-diagnostic	426 (14.8)	154 (36.2)	177 (42.5)	4.5	12.3	Benign	135
						MicroPTC	7
						PTC	6
						FTC	2
						MTC	2
						Others[d]	2
II: Benign	1,760 (61.3)	346 (19.7)	1,112 (63.2)	2.6	13.3	Benign	299
						MicroPTC	19
						PTC	20
						FTC	6
						PD-TC	1
						NIFTP	1
III: Atypia	171 (6.0)	133 (77.8)	31 (18.1)	19.3	24.8	Benign	99
						MicroPTC	11
						PTC	17
						FTC	2
						MTC	1
						NIFTP	1
						Others[d]	2
IV: Follicular neoplasm	261 (9.1)	235 (90.0)	19 (7.3)	23.8	26.4	Benign	171
						MicroPTC	14
						PTC	21
						FTC	27
						FT/WD-UMP	2
V: Suspect	141 (4.9)	134 (95.0)	6 (4.3)	52.5	55.2	Benign	56
						MicroPTC	10
						PTC	43
						FTC	15
						MTC	1
						PD-TC	2
						ATC	1
						NIFTP	1
						FT/WD-UMP	3
						Others[d]	2
VI: Malignant	114 (4.0)	95 (83.3)	19 (16.7)	93.2[c]	92.6	Benign	6
						MicroPTC	8
						PTC	69
						FTC	1
						MTC	1
						PD-TC	2
						ATC	6
						FT/WD-UMP	1
						Others[d]	1
Total	2,873 (100)	1,097 (38.2)	1,364 (47.5)	11.5[c]	29.4	-	

ATC = anaplastic/undifferentiated thyroid carcinoma; BSRTC = Bethesda System for Reporting Thyroid Cytopathology; FNA = fine-needle aspiration; FT/WD-UMP = follicular thyroid tumour/well-differentiated neoplasm of uncertain malignant potential; FTC = follicular thyroid carcinoma; hist = histologically verified nodules; MTC = medullary thyroid carcinoma; NIFTP = non-invasive follicular thyroid neoplasm with papillary-like nuclear features; PD-TC = poorly differentiated thyroid carcinoma; PTC = papillary thyroid carcinoma.

a) Nodules with histological confirmation after surgery succeeding the final FNA.

b) Nodules in which no repeat FNA or histology was available in the Danish Pathology Registry after the final FNA.

c) The calculation of malignancy rate was based on histologically verified thyroid cancers and nodules in which FNA was categorised as malignant (BSRTC VI) and suspect of primary thyroid carcinoma but without histological confirmation (n = 8). Nodules in which FNA was classified as malignant (BSRTC VI) and suspect of non-thyroid metastasis to the thyroid were excluded from the analysis of malignancy rate (n = 11).

d) Primary neuroendocrine carcinoma (n = 1), squamous cell carcinoma metastasis (n = 1), lymphoma (n = 3), renal cell carcinoma metastasis (n = 2) (N = 7).

Of the 69 micro-PTCs, 26 were diagnosed incidentally after a Benign or ND (BSRTC I-II) FNA. In the remaining 43 nodules, malignancy was suspected preoperatively by an Indeterminate or Malignant (BSRTC III-VI) FNA result. One patient with micro-PTC presented with lymph node metastases preoperatively. Another four patients had lymph node metastases identified in the surgical specimen.

During follow-up (2019-2023), 71 patients underwent thyroid surgery. Seven were diagnosed with PTC (n = 3) or micro-PTC (n = 4). The preoperative FNA in these patients showed either ND (BSRTC I, n = 1), Benign (BSRTC II, n = 5) or FN (BSRTC IV, n = 1) in the final study FNA.

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DISCUSSION

For the first time in a Danish setting, this study evaluated the validity of the BSRTC on a consecutive cohort undergoing diagnostic work-up of thyroid nodules. The cohort was included from a large region representing approximately 22% of the Danish population. We find our study highly relevant in view of the fact that BSRTC was developed and validated in populations residing in iodine-sufficient areas [4-6], whereas mild iodine deficiency still exists in Denmark despite iodine fortification [10].

The distribution of the BSRTC categories and the corresponding malignancy rates were in accordance with those reported in previous studies [4, 6, 7, 11-14]. The overall malignancy rate was 11.5% but increased to 29.4% when only surgically resected nodules were considered. This discrepancy in malignancy rate between thyroid patients in general and those undergoing surgery is well recognised [4, 6]. The malignancy rate is relatively high in resected nodules because the indication for surgery depends not only on the FNA result but also on clinical and US features indicative of malignancy [15]. On the other hand, the malignancy rate is inevitably underestimated in patients without histological confirmation due to false negative FNA results.

The diagnosis of small carcinomas is challenging because most are asymptomatic and found incidentally by histological examination after thyroid surgery on a benign indication [16]. Fortunately, solitary micro-PTC has an excellent prognosis and may therefore be differentiated from symptomatic and larger carcinomas [17]. In Denmark, small nodules (< 10 mm) do not undergo diagnostic work-up unless suspicious ultrasound features or lymph node metastases are found [2]. On this background, exclusion of micro-PTC from the analyses of diagnostic validity of FNA may be justified. Indeed, by this approach, we found reduced rates of malignancy and fewer false negative FNAs. It should be noted, however, that micro-PTC no longer exists as a unique entity in the recent 2022 WHO classification [18].

According to the BSRTC, repeat FNA is recommended for ND (BSRTC I) nodules, while surgery is recommended in case of persisting ND (BSRTC I) by repeat FNA [4]. If FNA is Benign (BSRTC II), the recommended management is follow-up including thyroid US, unless symptoms are in favour of surgery. In our study, repeat FNA resulted in approximately 10% of the ND (BSRTC I) samples being classified as Benign (BSRTC II), supporting that repeat FNA is worthwhile in these cases. In contrast, the malignancy rate remained unchanged for the Benign (BSRTC II) category, when comparing the primary and the final FNA.

The indeterminate categories (BSRTC III-V) represent the classic dilemmas of thyroid cytology [4] as these categories signify an increased risk of malignancy, without being definitely malignant or benign [4, 6]. Molecular testing addresses this challenge and is recommended in the 2017 and 2023 editions of the BSRTC [4, 6]. Specific molecular markers and combined panels are widely used in the USA as an add-on to an indeterminate FNA [6]. However, molecular testing is currently not recommended for routine use in European and Danish guidelines [2, 19, 20]. Thus, surgical resection is still required to obtain a final diagnosis in nodules presenting with FN (BSRTC IV) or Suspect (BSRTC V) by FNA.

In case of Atypia (BSRTC III), management options include surgery or repeat FNA, based on clinical and US risk assessment [4, 6]. Atypia (BSRTC III) is a heterogeneous category. It may represent malignancy but may also be the consequence of poor preparation of the specimen [4, 6]. A Benign (BSRTC II) repeat FNA succeeding Atypia (BSRTC III) is regarded as a reliable benign result [4, 6]. Our study was too small to support this. Nevertheless, a more conclusive diagnosis was achieved in approximately 50% of repeat FNAs after an initial result showing Atypia (BSRTC III).

Some limitations of this study exist. First, clinical or imaging data are not included in the Danish Pathology Registry. Accordingly, follow-up with US without repeat FNA was not registered and cannot be separated from patients truly lost to follow-up. We do not have specific information about local guidelines at the clinical units

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comprised by our study. However, Danish centres and clinicians largely comply with national guidelines on the use of US risk stratification, thyroid scintigraphy and FNA [2]. Second, environmental (e.g. iodine), epidemiological and logistic conditions specific to Danmark may differ from those of other countries, and this may influence the external validity of our study. Third, an unexpectedly high number of patients with Malignant (BSRTC VI) FNA did not undergo surgery. This is likely due to a subset of patients with non-thyroid metastases to the thyroid and thyroid cancer patients with severe co-morbidities that contraindicated thyroid surgery. Finally, the WHO classification was revised in 2017 [8], introducing new histological categories. This might explain the infrequent occurrence of the diagnoses non-invasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) and follicular thyroid tumour or well-differentiated neoplasm of uncertain malignant potential (FT/WD-UMP) in our study.

CONCLUSIONS

BSRTC proved reliable in a Danish cohort. The distribution of BSRTC categories and corresponding malignancy rates were in accordance with previous reports from other countries [6, 11]. Repeat FNA increased the definitive diagnosis in case of ND (BSRTC I) or Atypia (BSRTC III) in the primary FNA. The BSRTC was an effective and precise communication tool for use in a routine clinical setting. We recommend that BSRTC be included in the Danish National guidelines to standardise thyroid cytology reporting, both nationally and internationally.

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