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Diagnostic Value of Galectin-3 in Benign Thyroid Neoplasm *vs*. Differentiated Thyroid Carcinoma

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ABSTRACT

Discrimination between malignant nodules and their precursors – and interim forms remain a diagnostic dilemma; specially to avoid over therapy. Even though Galectin-3 (Gal-3) expression is a marker investigated quite often, this marker is the focus of this manuscript to compare risk constellations in subgroups. In total 283 specimens were investigated regarding their Galectin-3 expression by applying immunohistochemistry. Subgroups were performed (cPTC n=28, FVPTC n= 44, FTC n=51, FA n= 85 and PH n=14) and compared in the risk constella-tions. Sensitivity and specificity of Galectin-3 expression were checked against each other. Like-lihood ratio (LR+) has been determined as prediction parameter. A significant difference in Ga-lectin-3 expression could be shown comparing cPTC and PH with an acceptable LR+= 3.5. FVPTC compared with FA showed also a significant different Galection-3 expression. LR+ with barely 2 is considered borderline. Galectin-3 as single marker is not suitable to differentiate between cPTC and FVPTC as well as FTC and FA (LR+ = 1.14 resp 1.49). At the best of our knowledge this is the first methodical investigation regarding the value of Galectin-3 as single marker compar-ing immunohistochemical differentiation of cPTC and PH, FVPTC and FA, cPTC and FVPTC as well as FTC and FA. A limited additional value exists for cPTC vs. PH and FVPTC vs. FA. No value exists for comparing cPTC vs. FVPTC and FTC vs. FA. In general Gal-3 alone has a limited value in FFPE staining.

Keywords: Galectin-3; Differentiated Thyroid Cancer; Immunohistochemistry

Abbreviations: FN: Follicular Neoplasm; FA: Follicular Adenomas; FTC: Follicular Carcinomas; PTC: Papillary Thyroid Carcinoma; RCT: Randomized Clinical Trials; FVPTC: Follicular Variant of PTC

Introduction

The incidence of thyroid nodules in the adult Western World reaches up to 30% of the whole population [1,2]. Since the fine needle diagnostic has been established in the 1950ies a highly accurate discrimination between benign and malignant lesions is possible [3]. The first persistent diagnostic quandary is the differentiation in so-called follicular neoplasm (FN) (which includes follicular adenomas [FA]) and follicular carcinomas (FTC) [4]. Sec-ond difficulty in diagnostics are the subtypes of papillary thyroid carcinoma (PTC). The preoperative diagnosis of so called noninvasive follicular thyroid neoplasm with papil-lary-like nuclear features (NIFTP) or invasive follicular variant of the PTC (FVPTC) remains a difficult situation. Whereas consequences for the patients are drastic, unnecessary operations could be avoided [5]. In the above cases fine needle aspiration is overstrained since malignancy of the nodule is defined via invasion through the capsule or into the blood vessels [6,7]. However, for most of the patients´ surgery gets recommended having in mind that only 20% of these thyroid lesions will be malignant [5]. Several markers have been investigated to solve the dilemma described above. One of them with special interest is Galectin-3 (Gal-3). It is a 31kDa member of the β-galactoside – binding proteins. Besides its physiological func-

tion, Gal-3 is involved in different patholog-ical processes especially in tumor progression and metastasis [8]. Former studies showed a high sensitivity and specificity for Gal-3 regarding the detection in differentiated thyroid carcinomas [9].

Randomized Clinical Trials (RCT) to discriminate between the subtypes of thyroid cancer described above are currently not available. Having identified the need for further investigation of the above-described situation we used in a first step frozen sec-tions of thyroid tissue to determine Gal-3 specificity and sensitivity for comparing various thyroid neoplasms. At the best of our knowledge there exists not any methodical evalua-tion regarding the comparison of the subgroups defined above. We have formulated four hypotheses: Gal-3 expression helps to distinguish.

i) Between classic papillary thyroid carcinoma (cPTC) and FVPTC

ii) Between FTC and follicu-lar adenoma (FA)

iii) Between cPTC and PH and iv) between FVPTC and FA.

Patients and Methods

Patients

Cumulatively 283 thyroid specimens obtained from subjects under surgery were im-munohistochemically investigated regarding Gal-3 expression. Among them were 84 follicular adenomas (FA) and 54 follicular thyroid carcinomas (FTC), and 102 papillary thyroid carcinomas (PTC) were found. Among those 102 PTCs 28 were classified as classic PTC (cPTC) and 44 as follicular variant of PTC (FVPTC).

Materials and Methods

The obtained specimens were fixed in formalin and embedded in paraffin. From these blocks' slices with a thickness of six micrometer (6 µm) were produced with a micro-tome. After de-paraffining with Xylol irrigation with alcohol (100% to 70%) was done. As next step heat induced preconditioning with Target Retrieval Solution (DAKO, Germany) was performed at 97.5°C for 40 min. Incubation with primary antibody (monoclonal mouse antibody against Gal-3, clone 9C4, Novocastra, UK) at 4°C for 24h followed after blocking of the endogen peroxidases with hydrogen peroxide. Subsequent incubation with the detection system Monoclonal PowerVision (Immunovision Technology, Co/NL) last-ing an hour at room temperature preceded the core staining with Mayer's Haemalaun (Merck, Germany) and coloring with warm water. After embedding with Immu-Mount (Shandon, Germany) was completed an evaluation of the slices with a light microscope (Olympus BX50, Germany) with a 400-fold magnification was conducted. Four fields of vision were evaluated at every slice. Two blinded independent people evaluated the re-sults.

Statistics

Given the retrospective assessment of the data and relatively small sample sizes all statistical computations were carry out in an exploratory intention. The program SPSS Sta-tistics for Windows, Version 19 (IBM Corp, Armonk, NY, USA) and open-source R (R Core Team, A language and environment for statistical computing (2018), R Foundation for Sta-tistical Computing, Vienna, Austria, URL https://www.R-projekt.org) was used for evalua-tion. Differentiation between selected diagnostic subgroups was based on the analysis of fourfold tables. Mosaic plots were used for graphical presentations [10,11]. Sensitivity and specificity were computed including 95% confidence intervals (CI). To assess the diagnostic win of Gal-3 for compared diagnostic subgroups Likelihood ratios (LR+) were calculat-ed. A Likelihood ratio >3 is "acceptable"; a Likelihood ratio >10 is "good" [12-14]. Associations were evaluated by 2-test (p-values). A power calculation was not per-formed due to the limited sample size [15].

Ethics

The study was approved by the Ethic Board of the University of Luebeck. The in-formed consent signed at hospitalization also informs the patients at their tissue may be used anonymized for scientific purposes. The patients may decline this request.

Results

Of 283 specimens harvested from 283 patients 101 were benign tumors and 182 malignancies have been determined. Overall, Gal-3 positivity was detected in 152 (53.7%) and 131 (46.3%) were Gal-3 negative. Demographic data of the different subgroups are shown in (Table 1).

Table 1: Demographic data in selected diagnostic subgroups.

Subgroup	N	Gender Female / male	age [years] mean ± SD
cPTC	28	17 / 11	46.2 ± 16.5
FA	85	64 / 21	51.1 ± 14.8
PH	14	12 / 2	44.4 ± 16.5
FVPTC	44	38 / 6	46.3 ± 14.4
FTC	51	34 / 17	49.0 ± 15.2

Classic Papillary Thyroid Carcinoma (cPTC) Versus Papillary Hyperplasia (PH)

Twenty-eight specimens were defined as cPTC. Of those 28 cPTC samples 21 were Gal-3 positive (75.0%). Fourteen samples were defined as PH. Three of 14 (21.4%) were Gal-3 positive. Statistical data are shown in (Table 2). LR+ is 3.50. With this a Gal-3 positive result is 3.5-fold more likely for a cPTC than a PH.

Table 2: Diagnostic differentiation of cPTC versus PH (p=0.003).

Gal-3 positive Gal-3 negitive	cPTC(n=28) 21 7	PH(n=14) 3 11
Prevalence	28/42=0.67	
Sensitivity (95%-CI)	0.75(0.55-0.89)	LR+=3.50
Specificity (95%-CI)	0.79(0.49-0.95)	

Classic Papillary Thyroid Carcinoma (cPTC) Versus Follicular Variant of the Papillary Thyroid Carcinoma (FVPTC)

Comparing Gal-3 expression between cPTC (n=28, 21 positives for Gal-3) and FVPTC (n=44, 29 positive for Gal-3) does not show any significant difference (p=0.580). Calculated statistical data are shown in (Table 3). The positive likelihood has been determined at LR+ as 1.14. With this a Gal-3 positive finding is not more likely in a cPTC than in a FVPTC.

Table 3: Diagnostic differentiation of cPTC versus FVPTC (p=0.580).

	cPTC (n=28)	FVPTC (n=44)
Gal-3 positive	21	29
Gal-3 negative	7	15
prevalence	28 / 72 = 0.39	
sensitivity (95%-CI)	0.75 (0.55 – 0.89)	LR+=1.14
specificity (95%-CI)	0.34 (0.20 – 0.50)	

Follicular Variant of the Papillary Thyroid Carcinoma (FVPTC) Versus Follicular Adenoma (FA)

Forty-four specimens were classified as FVPTC. Among this subgroup 29 (65.9%) samples showed positivity for Gal-3, whereas only 29 of 85 FA (34.1%) showed positivity for Gal-3 (p=0.001). The LR+ is 1.93; with this a Gal-3 positive result is to be expected with two-fold mor likely for a FVPTC than for FA (Table 4).

Table 4: Diagnostic differentiation of FVPTC versus FA (p=0.001).

	FVPTC (n=44)	FA (n=85)
Gal-3 positive	29	29
Gal-3 negative	15	56
prevalence	44 / 129 = 0.34	
sensitivity (95%-CI)	0.66 (0.50 – 0.80)	LR+=1.93
specificity (95%-CI)	0.66 (0.55 – 0.76)	

Follicular Thyroid Carcinoma (FTC) Versus Follicular Adenoma (FA)

Fifty-one of the differentiated thyroid cancers were classified as FTC. Twenty-six showed positivity for Gal-3 (51.0%). Eighty-five specimens were defined as FA, among which 29 Gal-3 positive (34.1%) specimen were seen. The difference shows a trend but does not reach significant level (p=0.08). LR+ is calculated with 1.49 (Table 5). A complete overview of Gal-3 expression is seen in (Figure 1).

Table 5: Diagnostic differentiation of FTC versus FA (p=0.08).

	FTC (n=51)	FA (n=85)
Gal-3 positive	26	29
Gal-3 negative	25	56
prevalence	51 / 136 = 0.38	
sensitivity (95%-CI)	0.51 (0.37 – 0.65)	LR+=1.49
specificity (95%-CI)	0.65 (0.55 – 0.76)	

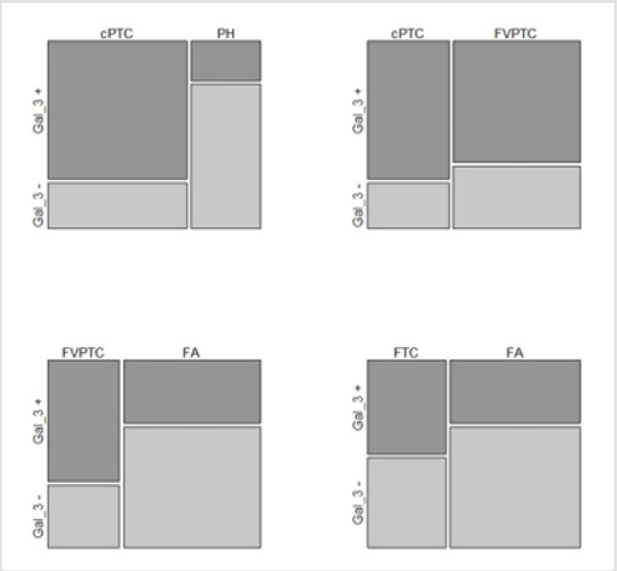

Figure 1: Expression of Gal-3 in comparison of different subgroups.

Discussion

Papillary thyroid carcinoma and follicular thyroid carcinoma have been diagnosti-cally distinct for many years. This distinction was predicted on the predominant (i.e.>50%) tumor growth pattern [16]. However, the histologic diagnosis of follicular vari-ant of papillary thyroid carcinoma raised several issues [17]. Characterization of FVPTC was expected to reflect a biological behavior that would be more like cPTC, with a propensity for regional lymph node spread as opposed to the hematogenous spread and distant metastases seen in the FTC [16]. Following the clinical picture, it is differentiated between the encapsulated FVPTC (clinically closer to the follicular neoplasm – nowadays called more often NIFTP [18,19]) and the invasive type (I-FVPTC) akin to FTC. This clinical proximity can also be shown on a molecular level [20]. Since the differentiation FN vs NIFTP vs cPTC has a relevance for the therapy concept of a patient an early diagnostic de-cision would be appreciated. Currently FNA criteria for a differentiation are investigated; for the time being it a postoperative decision based on resected specimen [21,22]. Perspec-tive is found in the application of IHC- markers like Gal-3. In our analysis with Gal-3 we did not perform a distinction between encapsulated (the so called NIFTP) and the invasive form of FVPTC (I-FVPTC). However, even under this rough scaling it was not possible to differentiate this entity to cPTC through Gal-3 IHC. With a sensitivity of 0.75 and a speci-ficity of 0.34 we are fare below the requirements of clinical daily routine.

LR+ with barely above 1 is not suitable for a safe distinction. For Gal-3 alone this correlates with the results of other studies [23]. An improvement approach may be to employ Gal-3 in a panel together with other markers [24]. But combination with other markers was not the aim of this study. In our study Gal-3 expression is significantly lower for cPTC and FVPTC compared to other investigations [25]. A similar problem in differentiation exists between FVPTC and FN where among others the FA also belongs to. Especially with FNAC diagnostics have shown to be exceedingly difficult [26,27]. Just the IHC of the resected specimen seem to enable a safe decision [27]. Considering that especially the encapsulated FVPTC show a very good course regarding metastasis and are more similar to the FH a trend towards over-therapy is seen due to the diagnostic incertitude [28]. We could show that FVPTC samples were significantly more often Gal-3 positive than FA; this calculates to a sensitivity of 0.66 with a similar high specificity (0.66). Thus, Gal-3 may be employed as a marker for the differentiation between FVPTC and FA, since the difference reached statistical significance (p=0.001); but the LR+ is only nearly two. It can be considered remarkable that the positivity for Gal-3 in FA is in our study higher than in other investigations [29]. Our FA samples are not in general Gal-3 negative. The reasons for this remain unclear. In the end, the final meaning of Gal-3 as ad-juvant marker for differentiation between these thyroid tumor subtypes remains subject of further investigations [30,31].

Typical PTC is characterized by papillary structures with characteristic nuclear mor-phology; but it is difficult to distinguish from thyroid benign lesions with papillary growth [32]. PH is a benign follicular nodule which sometimes can be extensive, and this entity has been considered by some authors to represent the "papillary variant of follicular adenoma" [33]. Benign PH in a thyroid nodule is an underrecognized diagnostic pitfall mimicking cPTC [33]. PH is often a diagnostic challenge even in resection specimen [34]. This would be interesting for patients suffering from Hashimoto´s thyroiditis, since these have a higher risk of PTC [35]. Earlier studies show conflicting results regarding PH and Gal-3 expression [36]. It is certain that PH specimen can be positive for Gal-3 in IHC [37]. This correlates with our results where 21% of the samples showed a positivity for Gal-3. LR+ shows a 3.5-fold higher likelihood that a Gal-3 positive finding is a cPTC. Discrimination between FA and FTC is an additional histological quandary. In our study Gal-3 does not provide additional certainty to solve this problem. In FA 34% of specimen were positive for Gal-3 compared to 47% FTC. Sensitivity (0.48) and specificity (0.65) are limited. However, our results are comparable with previously conducted studies [38] Although our results are more stringent than previously performed studies, there is no significant difference to these studies determined [39].

Given many reports have been published on this issue during the last decades some authors experienced conflicting results with the use of Gal-3 for improving diagnosis of follicular thyroid proliferations [40]. This emphasizes that the discussion regarding the value of Gal-3 in diagnostics remains on debate. The study presented here evaluates sub-groups, which have not been assessed with our focus on detail in the existing literature. Our study presents some limitations, first there is the positivity for Gal-3 in cPTC (75%) which is lower than in other studies published before at an earlier date [41]. Something similar applies for the negativity of benign variances, here we are with our samples far away from the nearly 100% negativity of FA that is described in other studies [42]. Given that all available recommendations to avoid false-positive results were observed we exclude human errors in the application of the detection system [43]. In the con-text of this still wide grey area regarding the Gal-3 expression between benign and malig-nant thyroid nodules one should question the conceptual approach of Gal-3 labeling for in vitro assessments in a critical fashion [44]. Independent of these deficits, there are only very few studies investigating only Gal-3 expression in the subtypes of differentiated thyroid carcinoma [39]. To the best of our knowledge, we present a real-world data subgroup analysis for the value of Gal-3 in the differentiation between benign, semi-malignant and malignant variances of thyroid nodules.

Conclusion

Referring to our hypothesis we can conclude:

i) cPTC versus FVPTC shows no significant differences in Gal-3 expression. The positive likelihood ratio shows no relevance for discrimination of a positive Gal-3 probe to be a cPTC.

ii) Discrimination between FTC and FA with Gal-3 as single marker is not possible.

iii) Gal-3 allows discrimination between cPTC and PH. LR+ is with 3.5 acceptable.

iv) Gal-3 expression between FVPTC and FA is significantly different but LR+ of less than two shows the limited prognostic value. Considering the low diagnostic value of Gal-3 in FFPE the additional insights for FNC may even be lower.

Authors Contribution

E.B. histological investigation, manuscript writing A.P. manuscript writing, statistical evaluation, language editing, M.K. concept of the manuscript, manuscript writing, final editing.

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Institutional Review Board Statement

This study was approved by the Ethic Committee of the University of Luebeck.

Informed Consent Statement

All patients declare with the Hospital Admittance Contract their agreement with the histological investigations, scientific evaluation, and publication of their specimen. Since only anonymized data have been used for the manuscript, no further consent is required according to German regulations.

Data Availability Statement

All relevant data are transparent in the manuscript. The histological slides are available by e.berger@klinikum-guetersloh.de.

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None.

Conflict of Interest

The authors have no competing interests to declare.

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