Expression of Galectin-3 and Galectin-7 in thyroid malignancy as potential diagnostic indicators

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ABSTRACT

Introduction: It has been suggested that Galectin-3 (Gal-3) and Galectin-7 (Gal-7) are potential tumour markers for differentiating thyroid carcinoma from its benign counter part. Galectins are beta-galactoside-binding proteins with Gal-3 being a redundant pre-mRNA splicing factor. They are supposed to be p53-related regulators in cell growth and apoptosis, being either anti-apoptotic or pro-apoptotic. Although the value of Gal-3 has been studied extensively, there is little knowledge regarding the expression of Gal-7 in thyroid malignancy.

Methods: We initiated an immunohistochemical (IHC) study on the expression of Gal-3 and Gal-7 on various thyroid lesions. Formalin-fixed paraffin embedded thyroid tissues were stained for IHC expression of Gal-3 and Gal-7 using monoclonal anti-human Gal-3 antibody and anti-human Gal-7 antibody (R&D Systems Inc, MN, USA). Gal-3 and Gal-7 expressions were measured semi-quantitatively on their distribution and staining intensity.

Results: A total of 95 cases were collected, including 32 benign and 63 malignant thyroid lesions. These contained 37 cases of papillary thyroid carcinoma, nine cases of papillary thyroid carcinoma follicular variant, 16 cases of follicular carcinoma, one case of anaplastic carcinoma, 14 cases of follicular adenomas and 18 cases of nodular goitre. Gal-3 expression was significantly strong in cancer cases compared to non-cancer cases (p-value is 0.000), while no significant difference was noted with Gal-7 expression (p-value is 0.870).

Conclusion: Our findings suggested that the IHC localisation of Gal-3 is a useful marker in conjunction with routine haematoylin and eosin staining in differentiating benign from malignant thyroid lesions, while there is no significant adjunct diagnostic value in Gal-7 for thyroid malignancy.

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INTRODUCTION

Thyroid cancer is a common endocrine malignancy with an apparent increasing incidence. It has a wide spectrum of clinical behaviour and therapeutic responsiveness. In the United States, approximately 20,000 new cases are diagnosed yearly, and more than 200,000 patients are monitored for cancer recurrence or progression, according to the latest statistics from the American Cancer Society. Among thyroid malignancies, papillary thyroid carcinoma (PTC) is the most common malignant tumour of the thyroid gland, accounting for 80% of all thyroid cancers in the United States.[1] For reasons that are uncertain, the incidence of thyroid cancer appears to be rising, although the outcome remains excellent with long-term, disease-free survival rates. Appropriate clinical management and prognosis largely depends on the diagnostic reliability of histopathological examination on the surgically-removed thyroid tissue.[1,2] Histological differentiation of various thyroid swellings and their characteristic features of identifying malignancy are usually done by applying standard World Health Organisation (WHO) histological classification for thyroid cancers.[3] However, even with application of the diagnostic criteria, such as characteristic nuclear appearances in PTC, problems on observer variations still lead to low diagnostic reproducibility, especially in the diagnosis of follicular carcinoma (FCA).[4,5]

Galectins are a structurally-related family of proteins, defined by having at least one characteristic carbohydrate recognition domain with an affinity for β-galactosides.[6,7] To date, 14 different galectins have been characterised.[8] They are cytosolic proteins and may also be translocated into the nucleus, into vesicles, or accumulate at sub-cytosolic sites.[9] Due to the potential of galectins to participate in cell-cell and cell-matrix adhesion,[9,10] growth regulation and internal processes such as pre-mRNA splicing,[10] it is deduced that this lectin family should be involved in pathological expression.[11] Galectin expression in normal human thyroid tissue and thyroid tumours has been

reported by several investigators.[12-18] Xu et al examined the expression of Galectin-1 (Gal-1) and Galectin-3 (Gal-3) in various neoplastic and non-neoplastic tissues, and observed increased expression of both galectins in all types of thyroid neoplasms of epithelial origin.[14] High levels of Gal-1 and 3 were found in PTCs, but not in FCAs, follicular adenomas (FA), or normal tissue.[14-18] It was suggested that these different expressions of Gal-3 among thyroid neoplasms are related to the different biological behaviours, though the mechanisms of Gal-3 regulation are not well understood.[19] Among various galectins, Gal-1, Gal-3 and Galectin-7 (Gal-7) are of interest in thyroid malignancy.[19,20] Although extensive studies have been done on the diagnostic value of Gal-3 expression in thyroid malignancy, to our knowledge so far, there was only one investigation done on Gal-7 expression together with Cytokeratin-19. It was mentioned that a combination of these two markers have some important diagnostic value in distinguishing the encapsulated follicular variant of PTC from microfollicular adenomas.[20] We assume that Gal-7 could also have a value as an adjunct diagnostic indicator. Thus, this study was carried out to evaluate the diagnostic value of Gal-7 based on the knowledge of Gal-3 as a well-studied diagnostic marker in thyroid malignancy.

METHODS

A total of 95 surgically-removed thyroid swellings, including 32 benign and 63 malignant lesions, from the archived collection of cases from the Histopathology Laboratory of Sarawak General Hospital were collected. All patients had undergone surgical removal of thyroid lesions between the years 2000 and 2004. Ethical approval was obtained from the Medical Research and Ethic Committee, Ministry of Health Malaysia. Blocks suitable for immunohistochemical study (IHC) were selected by two pathologists (TTH & GKS). Tissue blocks with sufficient thyroid tissue, including capsular components, were selected. Cases included PTC (n = 37), PTC follicular variant (PTCFV) (n = 9), FCA (n = 16), anaplastic carcinoma (ACA) (n = 1), FA (n = 14) and nodular goitre (NG) (n = 18). IHC staining for Gal-3 and Gal-7 were done simultaneously. It was performed only after getting the report on routine haematoxylin and eosin (H&E) staining method, considered to be the gold standard for the diagnosis.

Formalin-fixed paraffin-embedded thyroid tissues were cut and mounted onto self-prepared aminopropyltriethoxysilane-coated slides. The sections were dewaxed, rehydrated and boiled in Tris buffer (pH 7.4) for one minute in order to allow antigen retrieval. Endogenous peroxidase activity was blocked by treating with 0.5% hydrogen peroxide in methanol for 15 minutes. Following a wash in Tris-buffered saline (TBS; 0.005M Tris, pH7.4), slides were covered in mouse serum blocking reagent for 15 minutes followed by Avidin and Biotin blocking reagent for 15 minutes each (all from R&D Systems, MN, USA). Relevant optimum dilutions for the respective antibodies were calculated prior to a proper experiment. Slides were incubated for 30 minutes at room temperature with anti-Gal-3 monoclonal antibody (R&D Systems, MN,USA) diluted 1:50 and anti-Gal-7 in 1:15 followed by incubation with appropriate secondary antibody in 0.01M PBS containing 0.1% NaN_3 for 30 minutes. After several washings, slides were incubated with HSS-AP conjugate for 30 minutes. Peroxidase activity was revealed with 3,3'-DAB solution (R&D Systems, MN, USA). Slides were subsequently counterstained with H&E, and DPX mounted for microscopic evaluation. Procedures were performed only when the control tissues showed a true positive and negative reaction. Colon tissue was used as a positive and negative control for Gal-3 and normal skin tissue was applied for Gal-7.

Slides were screened and observed by three pathologists (TTH, GKS, JW), who had no prior access to the H&E report of the specimens by using code numbers for each block, to avoid bias. Morphology and cytological appearances were recorded. Scoring was done based on the intensity of staining characteristics on a scale of 1 to 3; a score of 1 indicates focal/weak staining, a score of 2 indicates moderate staining, and a score of 3 for strongly positive staining reaction. A mean scoring among the three pathologists was calculated. Data analysis was performed with the Statistical Package for Social Sciences version 12.0.1 (SPSS Inc, Chicago, IL, USA). Descriptive analysis of the variables and statistical significance of the tests were expressed in receiver operating characteristic (ROC) curve plot and p-value.

RESULTS

In identification of Gal-3 positive staining in thyroid tissue and tumours, a positive staining reaction was noted as intracytoplasmic brown staining within thyroid epithelial cells. It varied from diffuse extensive deposition to fine granularity and occasional membranous deposition towards the luminal aspect of the epithelial cells. Nuclear staining was rarely observed and only in pale intensity. Macrophages and red blood cells within vascular spaces that also showed cytoplasmic granular staining were taken, in caution, as interferences in the scoring. Adjacent normal thyroid tissue and multinodular goitre showed scattered insignificant foci of positive staining reaction. A strongly-positive staining reaction was noted preferably in PTC, moderate staining reaction in PTCFV, weak and

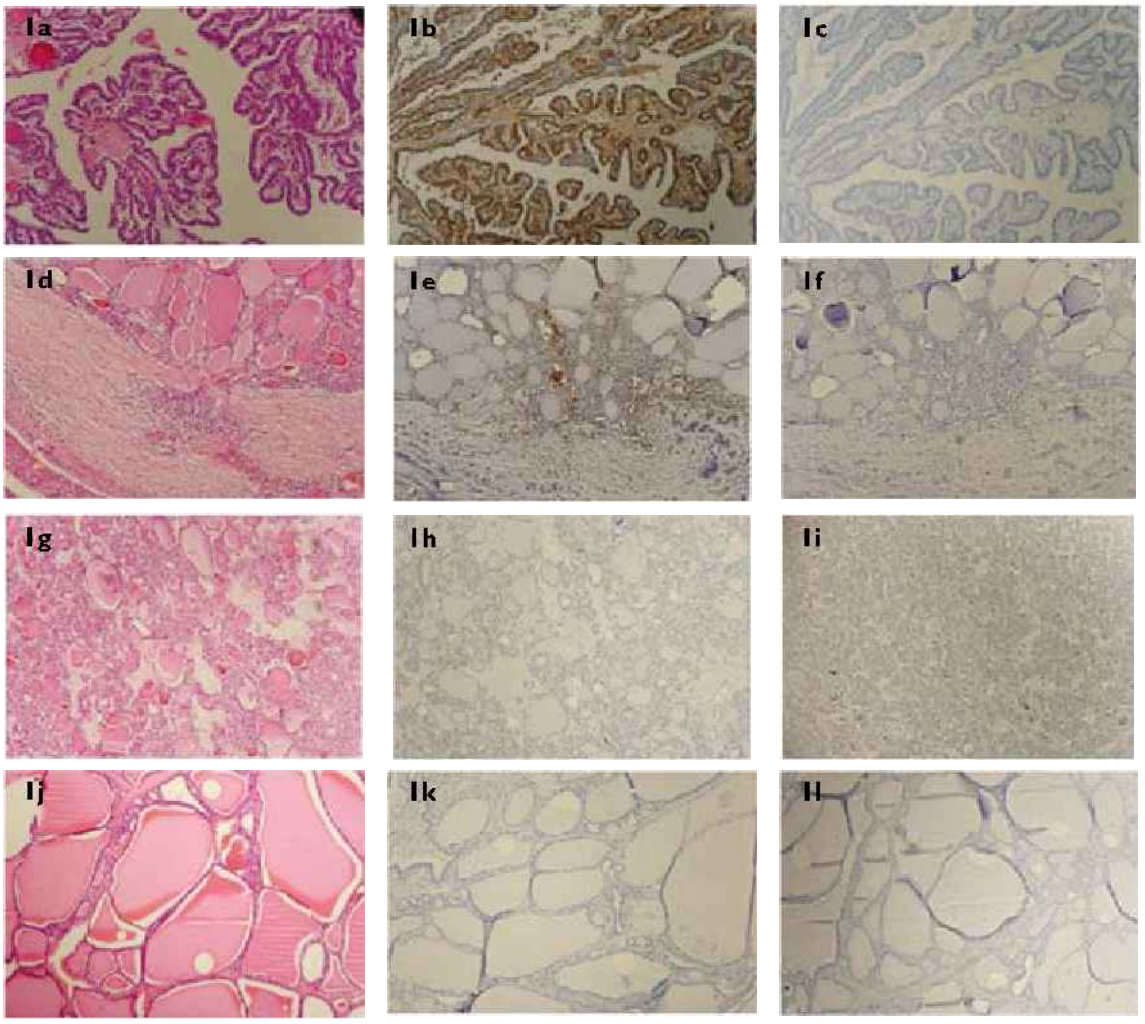

Fig. 1 Immunohistochemical expression of Gal-3 and Gal-7 in different thyroid lesions. (a) Photomicrograph of papillary thyroid carcinoma shows (b) strong cytoplasmic immunostaining for Gal-3 and (c) negative staining reaction to Gal-7. (d) Photomicrograph of follicular carcinoma with capsular invasion shows (e) moderate positivity for Gal-3 and (f) negative reaction to Gal-7. (g) Photomicrograph of follicular adenoma shows (h) negative staining reaction to Gal-3 as well as (i) Gal-7. (j) Photomicrograph of a nodular goitre shows (k) negative staining reaction to galectin-3 as well as (l) Gal-7. (all: Haematoxylin & eosin, × 100).

focal staining in FCA and no staining reaction in FA. No positive staining reaction was detected with Gal-7 monoclonal antibody (Figs. 1a–l), except for a very weak focal staining reaction in two cases; one with PTC (case no 4426/02) and the other with FCA (case no 2290/03).

ROC curve plot analysis for Gal-3 IHC expression shows Gal-3 expression as significantly strong in cancer cases compared to non-cancer cases ($p = 0.000$) (Fig. 2a). However, no significant value of Gal-7 in differentiating benign from malignant thyroid lesions is observed ($p = 0.870$) (Fig. 2b). Table I shows the specificity, sensitivity, positive predictive value, negative predictive value, test accuracy and significance value of Gal-3 IHC in various thyroid lesions. Gal-3 expression was significantly strong in cancer cases compared to non-cancer cases ($p = 0.000$) as well as in PTC compared to PTCFV ($p = 0.000$), PTC and PTCFV to FCA ($p = 0.000$), PTC to FCA ($p = 0.000$). Gal-3 expression was sensitive but not to a significant enough level to differentiate PTCFV from FCA ($p = 0.080$), and PTCFV from FA ($p = 0.420$).

DISCUSSION

Many studies have been done on the IHC expression of Gal-3 on thyroid lesions, with the aim of studying its reliability as a diagnostic indicator, particularly in differentiating problematic cases that are inconclusive with routine H&E staining technique. These include PTCFV and minimally-invasive FCA. By doing so, it is supposed to facilitate surgical management and treatment. In a series of recent reports, Gal-3 has been found over-expressed in most malignant thyroid neoplasm. However, it was not detectable in normal and non-malignant tissue.[14-17,21,22] Based on our results, we agreed that Gal-3 is a useful marker to differentiate benign from malignant

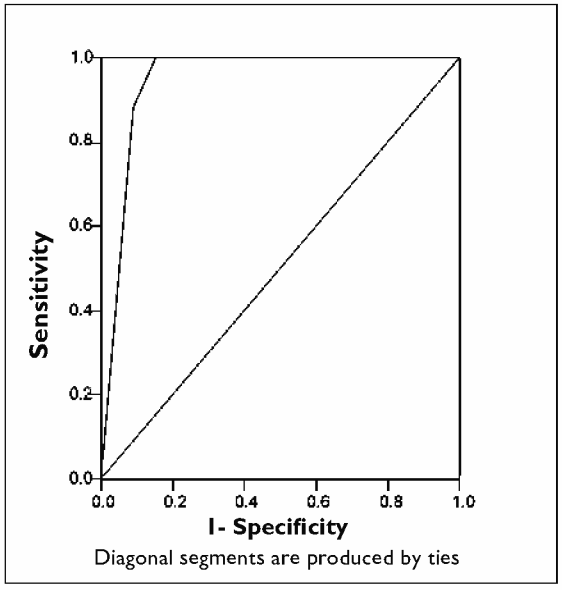

Fig. 2a ROC curve plot expression of Gal-3 IHC in benign vs malignant thyroid lesions using classical H&E report as a gold standard. Area under the curve 0.946; asymptotic significance 0.000; standard error 0.033 with asymptotic 95% confidence interval 0.882–1.010. Gal-3 is significantly sensitive in differentiating benign from malignant thyroid lesions.

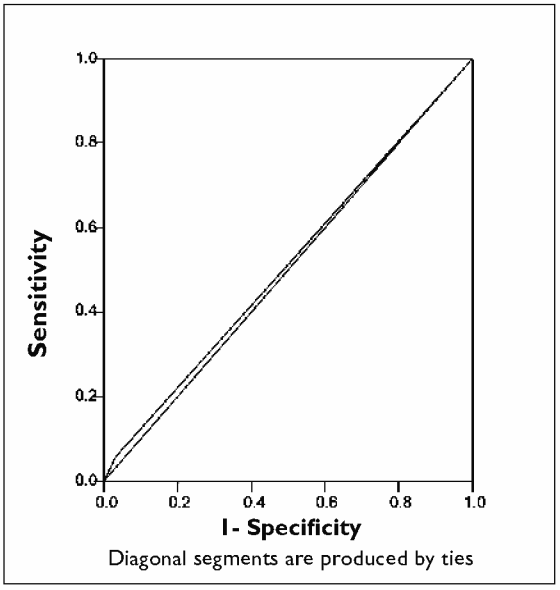

Fig. 2b ROC curve plot expression of Gal-7 IHC in benign vs malignant thyroid lesions using classical H&E as a gold standard. Area under the curve 0.514; asymptotic significance 0.870; standard error 0.088 with aymptotic 95% confidence interval 0.342–0.686. Gal- 7 has no significant value in differentiating benign and malignant thyroid lesions.

thyroid neoplasm.

Recent work done by Coli et al in 2002 again confirmed Gal-3 as a reliable marker of differentiated thyroid carcinoma.[23] It also appeared expressed in nodules with cytological atypia, and could thus provide a valuable clue in the detection of undetermined malignant potential, like in nodules with an overall benign appearance but with focal areas suspicious for malignancy. From our study, we also observed that Gal-3 is valuable in differentiating a non-malignant hyperplastic papilla from that of a papilla formed in PTC, suggestive to be useful in the early detection of occult PTC in a toxic or hyperplastic goitre (unpublished data). With a strong expression of Gal-3 in PTC, we believe that Gal-3 is a good indicator in early detection of malignant transformation towards occult PTC, like in cases of Hashimoto's thyroiditis. A further experimental confirmation would be necessary. As observed by Coli et al,[23] we also found a high uptake of Gal-3 expression in fibroblasts, endothelial cells, macrophages, histiocytes, red blood cells and inflammatory infiltrates, Although the interpretation of this observation should be made with caution, it is applicable as an internal positive control.

A characteristic positive staining reaction, particularly in the capsular invading cells in FCA, as shown in Fig. 1e by Gal-3 staining, would be of significant value in supporting the recent study done by Kawachi et al that this marker has a possible role in metastasis formation.[24] Very recently, it is also expressed by Cvejic et al that although Gal-3 expression is an excellent marker for classical PTC, its role in local metastatic spread and extrathyroid invasion should be interpreted with caution.[25] Further investigation will be necessary to assess and evaluate the value of Gal-3 in detecting local and distant metastatic foci and its value in fine-needle aspiration cytology.

Saggiorato et al revealed that Gal-3 is a reliable presurgical immunocytodiagnostic marker in minimally-invasive FCA, with improved accuracy of conventional fine-needle aspiration biopsy (FNAB). This corroborated with our findings that Gal-3 is a valuable adjunct diagnostic indicator, preferably in PTC, and could be of great value in preoperative diagnostic FNAB.[26]

Very recent controversial work done by Jakubiak-Wielganowicz et al and Mehrotra et al showed that Gal-3 is not a reliable IHC marker to distinguish benign from malignant thyroid lesions, and that it is not a highly specific marker in differentiating between follicular benign and malignant tumours, although it may be used as an additional tool.[27,28] Furthermore, Davies et al had concluded that Gal-3 does not discriminate between FAs and carcinomas; it is neither specific nor sensitive enough to be used satisfactorily and cost-effectively in clinical practice as a marker of thyroid malignancy.[29]

Nevertheless, we agree with comments by Martins et al that IHC detection of Gal-3 could be helpful for the pre-surgical diagnosis of cancer if its expression was really restricted to the malignant process.[30] This view was also supported by Hermann et al and Oestreicher-Kedem Y et al that Gal-3 is a useful adjunct diagnostic marker [31,32] Although a study done by Rorive et al

Table I. The specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), test accuracy (TA) and significance value of Gal-3 IHC in thyroid lesions.

Thyroid lesions	Sensitivity (%)	Specificity (%)	df	PPV (%)	NPV (%)	TA (%)	p-value
Non-malignant vs. malignant	87.3	56.25	27	79.7	69.2	76.8	0.000*
PTC vs. PTCFV	100	5.9	3	82.2	100	32.6	0.000*
PTC + PTCFV vs. FCA	97.6	37.5	6	80.4	85.7	75.8	0.000*
PTC vs. FCA	100	37.5	3	78.7	100	81.1	0.000*
PTCFV vs. FCA	88.9	37.5	3	44.4	85.7	56.0	0.080
PTCFV vs. FA	88.9	21.4	3	42.1	75.0	47.8	0.420

Non-malignant lesions include follicular adenoma (FA) and nodular goitre (NG); malignant lesions include papillary thyroid carcinoma (PTC), papillary thyroid carcinoma follicular variant (PTCFV), follicular carcinoma (FCA) and anaplastic carcinoma (ANA).
* p-value is statistically significant

found that a combination of Gal-7 and Cytokeratin-19 is efficient in differentiating microfollicular adenomas from the encapsulated PTCFV,[20] we did not observe any diagnostic value of Gal-7 in thyroid malignancy, even for a simple differentiation between obvious benign and malignant thyroid lesions. Magnaldo et al,[33,34] Timmons et al,[35] Ostergaard et al[36] and Bernerd et al[37] stated that Gal-7 is more expressive in stratified squanous epithelium. From our results, we also believe that Gal-7 might not have any role in thyroid epithelium, which is cuboidal to columnar in nature, until and unless there is a squamous epithelial metaplasia. However, we opine that this will be an interesting focus in future research, by looking at squamous epithelial metaplasia, including oncocytic changes in Hurthle cell adenoma and carcinoma.

In conclusion, our findings support that the IHC localisation of Gal-3 is a useful marker in conjunction with routine H&E staining, in differentiating benign from malignant thyroid lesions, while there is no significant adjunct diagnostic value in Gal-7 for thyroid malignancy. It would be interesting in a future study, to compare Gal-3 staining with other potential markers to see if Gal-3 is superior.

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