Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 May 25; 10(A):1565-1573.
https://doi.org/10.3889/oamjms.2022.8090
eISSN: 1857-9655
Category: *A - Basic Sciences*
Section: *Pathology*

Expression of β-Catenin in Thyroid Neoplasms (Histopathological and Immunohistochemical Study)

Mohamed Sherif Ismail[1], Amr Mousa Abdel Gawad Mousa[2], Mohammed Faisal Darwish[3], M. Mostafa Salem[1], Randa Said[4]*

[1]Department of Pathology, Cairo University of Medicine, Cairo, Egypt; [2]Department of Pathology, Faculty of Medicine, October 6 University, 6th of October City, Egypt; [3]Department of Pathology, King Salman International University, El-Tor, Egypt; [4]Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt

Edited by: Sinisa Stojanoski
Citation: Ismail MS, Mousa AMAG, Darwish MF, Salem MM, Said R. Expression of β-Catenin in Thyroid Neoplasms (Histopathological and Immunohistochemical Study). Open Access Maced J Med Sci. 2022 May 25; 10(A):1565-1573.https://doi.org/10.3889/oamjms.2022.8090
Keywords: β-catenin; Immunohistochemistry; Malignant thyroid neoplasms; Benign thyroid neoplasms
***Correspondence:** Randa Said, Department of Pathology, Faculty of Medicine, Cairo University, Cairo, Egypt. E-mail: randa.taha@kasraalainy.edu.eg
Received: 26-Nov-2021
Revised: 29-Sep-2021
Accepted: 08-Jan-2022

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Thyroid cancer is the most common malignant tumor of the endocrine system accounting for more than 90% of all endocrine cancer and 63% of all endocrine cancer deaths. β-catenin is a multifunctional protein that plays a key role in Wnt (wingless type) pathway and influences the expression of different genes and their proliferation, thus making it a potential therapeutic target.

AIM: This work aimed to examine immunohistochemical expression of β-catenin in different cases of thyroid neoplasms and to correlate between β-catenin expression and clinicopathological features of these thyroid neoplasms.

METHODS: This retrospective study was conducted on 60 cases of archived, formalin fixed, and paraffin embedded tissue blocks that included different histologic types of thyroid neoplasms. Immunohistochemistry using β-catenin monoclonal antibody was performed using a standard avidin-biotin-peroxidase system. β-catenin expression was quantified both at membranous and cytoplasmic level. Immunostaining scores were based on the staining intensity (I) and the percentage of positive cells (P). β-catenin final score (H score) resulted by summation of I and P (ranging from 0 to 7). Cases with H score between 1 and 3 were considered with low score and cases with H score between 4 and 7 were considered with high score.

RESULTS: Of the malignant thyroid neoplasms in the studied cases, 81% showed positive β-catenin expression with the majority (86%) of the benign thyroid cases showing positive expression. Both membranous and cytoplasmic staining were both assessed in which the majority of the negative and high positive membranous cases also showed the same interpretation for cytoplasmic β-catenin expression. Positive correlations were proved between β-catenin expression of diagnosed malignant cases, ($p = 0.042$) where all hurthle cell, follicular and medullary carcinoma cases, 87.5% of studied papillary carcinoma cases and 50% of poorly differentiated carcinoma cases showed β-catenin positivity while all anaplastic carcinoma cases were negative. Furthermore, statistically significant findings were seen in cases with absence of extrathyroid extension ($p = 0.045$) especially those displaying β-Catenin cytoplasmic expression with extrathyroid extension of studied malignant cases showing $p = 0.011$. No significant correlation was found between β-catenin expression and patients' pathological diagnosis, gender, extent of primary tumor, lymph node metastasis, multifocality, and coexisting pathology among studied malignant cases.

CONCLUSION: The present study suggests the prognostic role of β-catenin and its possible usage to identify patients who may benefit from adjuvant β-catenin targeted mono- or combined therapy for tumors expressing this protein, especially for thyroid cases that cannot be removed surgically or that do not respond to traditional treatment options.

Introduction

Thyroid cancer is the most common endocrine malignancy accounting for more than 90% of all endocrine cancer and 63% of all the death due to endocrine cancer death [1], [2]. In Egypt, according to the National Cancer Registry Program, thyroid cancer is the fifth most frequent cancer in females accounting for 3.6% of all malignancy in women [3].

Most thyroid neoplasms are well-differentiated thyroid cancers derived from epithelial follicular cells, comprising the papillary thyroid carcinoma and the follicular thyroid carcinoma histotypes, which may progress toward the poorly differentiated thyroid carcinoma and the anaplastic thyroid carcinoma (Figures 1-3) [4].

Although originating from the same cell type, thyroid cancers display different morphological features, functional behavior, and grade of differentiation as a result of heterogeneous genetic alterations [5].

Although histology is considered as the standard diagnostic method for thyroid cancer, it shows some limitation where the morphological features are ambiguous. The diagnosis of papillary cancer by histological study is mainly based on architectural changes along with presence of nuclear clearing, overlapping, grooving, and pseudo inclusions [6]. In the absence of papillary architecture, follicular variant of papillary carcinoma is difficult to distinguish from nodular thyroid adenoma as well as failure to detect capsular and vascular invasion in thyroid tissue, limiting its usefulness in cancer diagnosis [7].

Several studies have suggested immunohistochemical expression of β-catenin as diagnostic tool for thyroid carcinoma, in which its expression is seen both cytoplasmic and nuclear, while membranous staining may be weak and seen more evident in the normal thyroid and follicular adenoma cases (Figures 4-6) [2], [8].

The present study is focused on β-catenin immunohistochemical marker and its prognostic importance in thyroid cancer where loss of membranous β-catenin immunostaining and its accumulation in cytoplasm may lead to an aggressive clinicopathologic behavior portrayed in invasion, extrathyroid extension, lymph node involvement, distant metastasis, and more recurrences. Thus, β-catenin can be used as a prognostic marker in thyroid carcinoma as mentioned in studies done by Ziari *et al*., 2018, Urbanczuk *et al*., 2018, Rossi *et al*., 2013, Sethi *et al*., 2011, Rezk *et al*., 2004 [1], [2], [8], [9], [10].

The efficacy of radioiodine therapy toward aggressive thyroid cancer cells was affected by β-catenin activity where Lan *et al*., 2017 [11] found that only after inhibiting β-catenin expression, can the radioiodine treatment promote apoptosis other than repress proliferation and survival in xeno graft tumor cells so β-catenin targeted therapy shows promising results to improve the clinical outcomes in thyroid cancer cases.

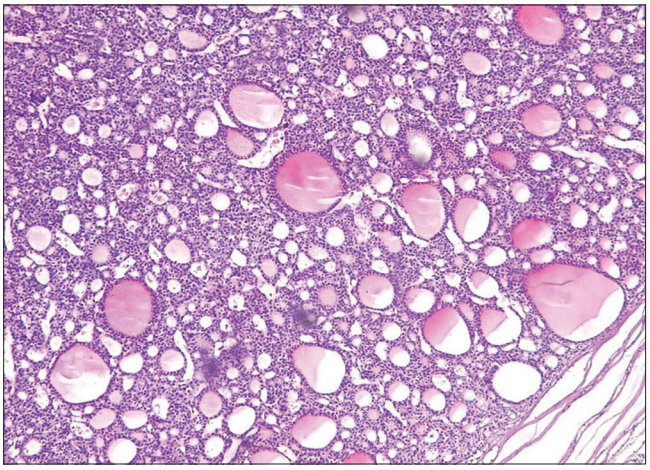

Figure 1: A case of follicular adenoma showing mainly microfollicular pattern (H&E original magnification x100)

Methods

This study was conducted on sixty cases of both benign and malignant thyroid neoplasms. The period of case collection was from March 2019 up to June 2020. The clinical data of these patients such as age and gender were taken from their pathology requisition sheets enclosed with the specimens.

Processing

Sections of 4-µm thickness were cut by microtome from the formalin fixed, paraffin embedded tumor blocks. Two sections were prepared from each tumor tissue paraffin block:

One slide for Hematoxylin and Eosin (H&E) staining for histopathological reassessment.

One positively charged slide for immunohistochemical staining by β-catenin antibody.

All slides were examined under light microscope.

Inclusion Criteria

Benign Neoplasms: Follicular adenoma, Hurthle cell adenoma.

Malignant neoplasms: papillary carcinoma, Hurthle cell carcinoma, follicular carcinoma, medullary carcinoma, poorly differentiated carcinoma and anaplastic carcinoma.

Exclusion Criteria

Other benign lesions and Patients received Neoadjuvant radiotherapy and/or chemotherapy.

Demographic Data

Age at time of diagnosis and gender of the patients.

Equipment and material

A. Autostainer

Dako Autostainer a product of Dako Colorado, Inc. An Agilent Technologies Company.

B. Primary antibody

β-catenin antibody: Mouse monoclonal to β-catenin, clone number 5H10, catalog number ab231305 (Prediluted antibody which was ready-to-use for immunohistochemical staining) from (Abcam company, UK).

β-catenin antibody was used as primary antibody for the detection of β- catenin protein.

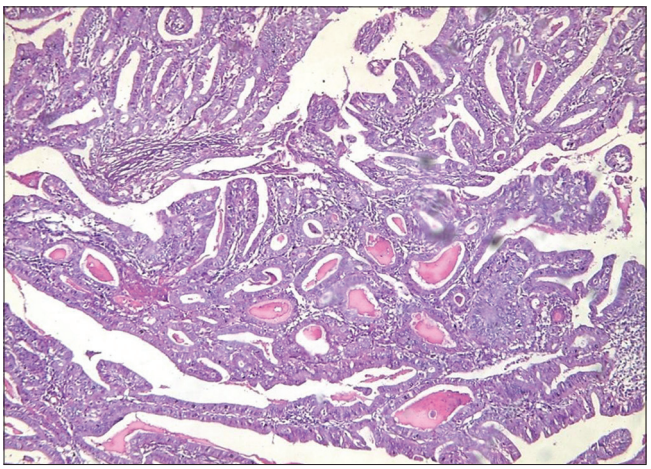

Figure 2: A case of papillary thyroid carcinoma (H&E original magnification x200)

Histopathological Evaluation

Site and size of the tumor were retrieved from pathology reports.

H&E sections were evaluated for revision of histological type of the tumor [according to WHO histological classification of tumors of the thyroid (2017) (Lloyd *et al*., 2017)], laterality, multicentricity, extra- thyroid extension, lymph node metastasis and co-existing pathology.

Tumor extent of invasion and nodal involvement were staged according to the TNM staging system of thyroid cancer, AJCC 8th edition (Amin *et al*., 2017).

Table 1: Correlation between β-Catenin immunohistochemical expression and pathological diagnosis among all studied cases

β-Catenin expression	Pathological diagnosis								Total
	Follicular adenoma	Hurthle cell adenoma	Papillary carcinoma	Hurthle cell carcinoma	Follicular carcinoma	Medullary carcinoma	Poorly differentiated carcinoma	Anaplastic carcinoma	
Positive									
Count	19	6	21	1	1	1	1	0	50
%	31.7	10.0	35.0	1.7	1.7	1.7	1.7	0	83.3
Negative									
Count	3	1	3	0	0	0	1	2	10
%	5.0	1.7	5.0	0	0	0	1.7	3.3	16.7
Total									
Count	22	7	24	1	1	1	2	2	60
%	36.7	11.7	40.0	1.7	1.7	1.7	3.3	3.3	100.0

Evaluation of β-catenin immunostaining

All sections were screened to disclose the areas with well-preserved tissue architecture and cell morphology for scoring of immunoreactivity. Areas with deterioration of tissue morphology due to processing were discarded in the analysis.

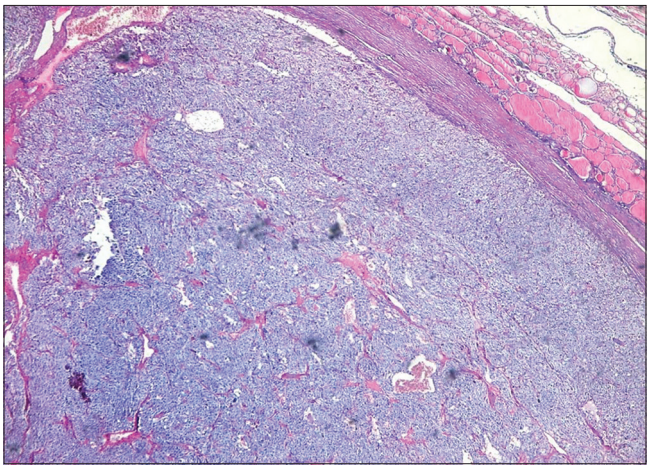

Figure 3: A case of medullary thyroid carcinoma (H&E original magnification x100)

The β-catenin expression was quantified both at membranous and cytoplasmic level where brown membrane staining is defined as membranous β- catenin positivity and brown cytoplasmic staining is defined as cytoplasmic β-catenin positivity.

The semi-quantitative assessment was done by using adapted scores based on the literature report (Andriescu et al., 2018) that took into account the staining intensity (I) and the percentage of positive cells (P).

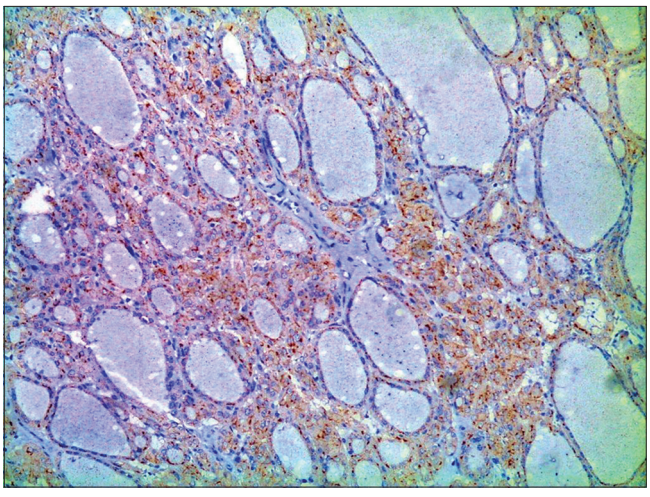

Figure 4: A case of follicular adenoma showing strong cytoplasmic and weak membranous staining by β-catenin (original magnification x100)

The intensity of the immunoreaction for the β-catenin was scored as: 0 – absent, 1 – weak, 2 – moderate, and 3 – strong. The percentage of β-catenin immuno-positive cells was scored as: 0 – <10%, 1 – 10–30%, 2 – 31–50%, 3 – 51–70%, 4 – >70%. The β-catenin final score (H score) resulted by summation of I and P (ranging from 0 to 7). Cases with H score between 1–3 were considered with low score and cases with H score between 4–7 were considered with high score. (Andriescu *et al*., 2018).

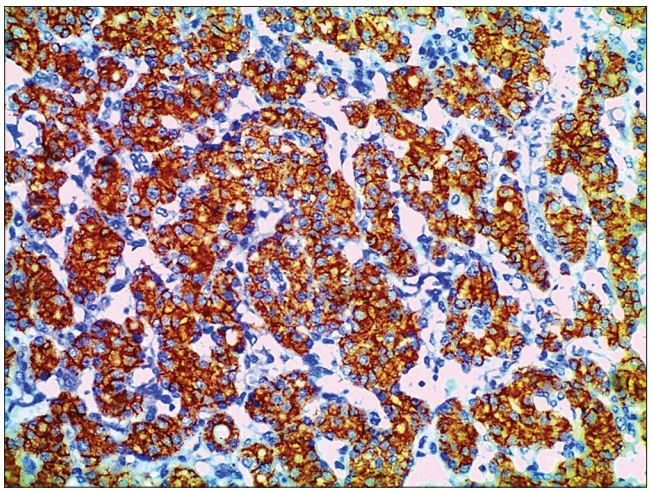

Figure 5: A case of follicular adenoma showing strong cytoplasmic and membranous staining by β-catenin (original magnification x200)

Positive control

Parallel positive sections of positive β-catenin colon adenocarcinoma cases were served as positive control for each set of slides.

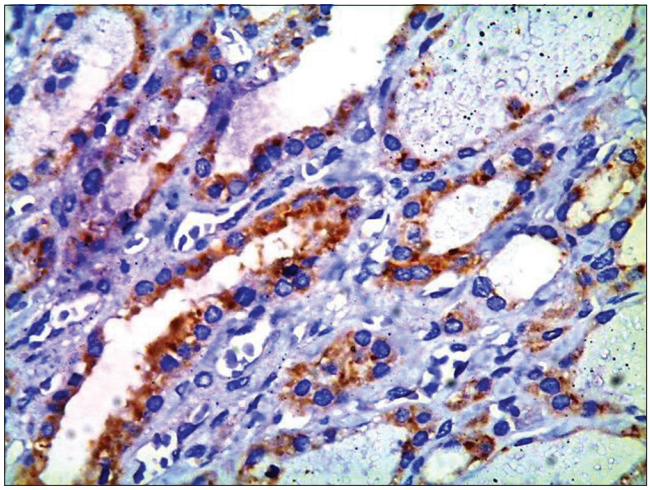

Figure 6: A case of follicular adenoma showing strong cytoplasmic and weak membranous staining by β-catenin (original magnification x400)

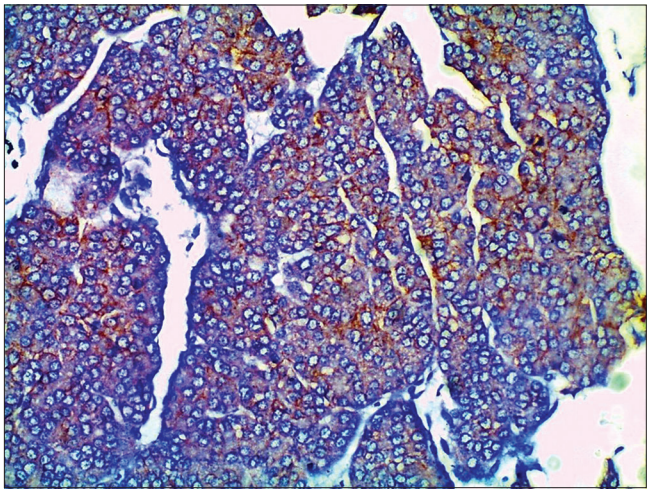

Figure 7: A case of Hurthle cell carcinoma showing strong cytoplasmic and membranous staining by β-catenin (original magnification x200)

Negative control

Sections untreated with primary antibody (β-catenin) were considered as negative controls for each set of slides.

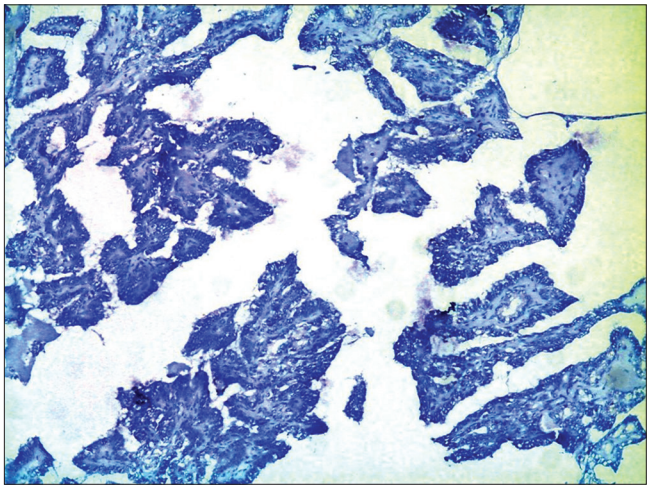

Figure 8: A case of papillary carcinoma showing negative cytoplasmic and membranous staining by β-catenin (original magnification x100)

Photography

The digital images of the selected tissue preparations were photographed using Leica EC3 digital color camera attached to Leica DM 2500 Microscope.

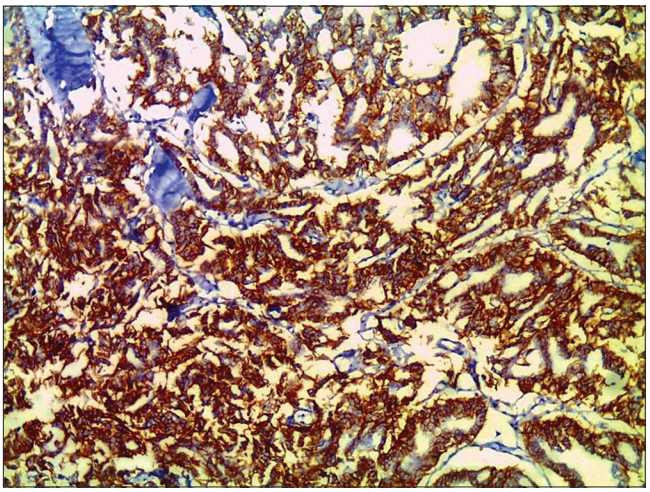

Figure 9: A case of follicular variant of papillary carcinoma showing strong cytoplasmic & membranous staining by β-catenin (original magnification x100)

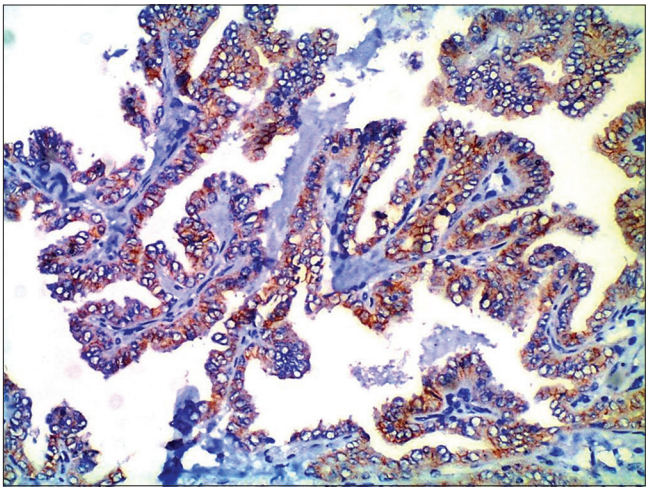

Figure 10: A case of papillary carcinoma showing weak cytoplasmic and membranous staining by βcatenin (original magnification x200)

Statistical analysis

All analyses were done using SPSS (Statistical Package for Social Sciences) software, version 26 Chicago, IL, USA. Categorical variables were expressed as frequencies and percentages. Chi-square, independent T test and Anova tests were used for testing proportion independence to rule out any significant correlation between β-catenin expression and other clinicopathological variables included in the study. P value was set significant if ≤ 0.05 level. The graphs were done using Microsoft Excel 2019.

Results

The present study was conducted on 60 cases of both benign and malignant thyroid neoplasms. The patients' age in this study ranged from 14 to 63 years with a mean age of 39.3 years where 25 cases (42%) of all studied cases were in (>30–40 years) age group. Regarding malignant cases, the patients' age ranged from 14 to 63 years with a mean age of 40.16 ± 12.5 years where the majority of malignant cases (18.3%) and benign cases (23.3%) were in (>30–40 years) age group.

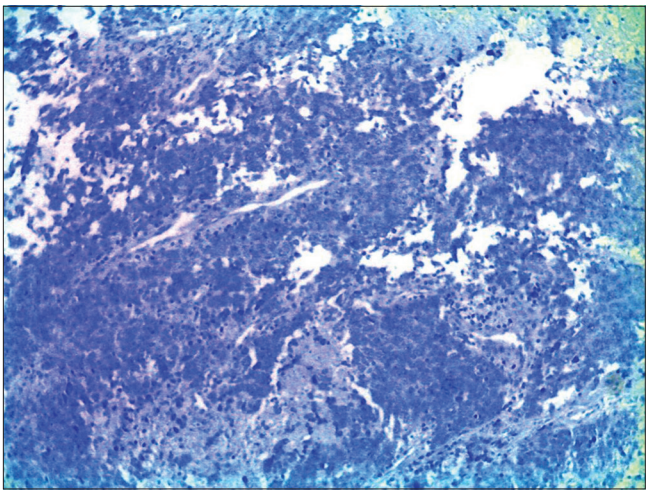

Figure 11: A case of anaplastic carcinoma showing negative cytoplasmic and membranous staining by β-catenin (original magnification x100)

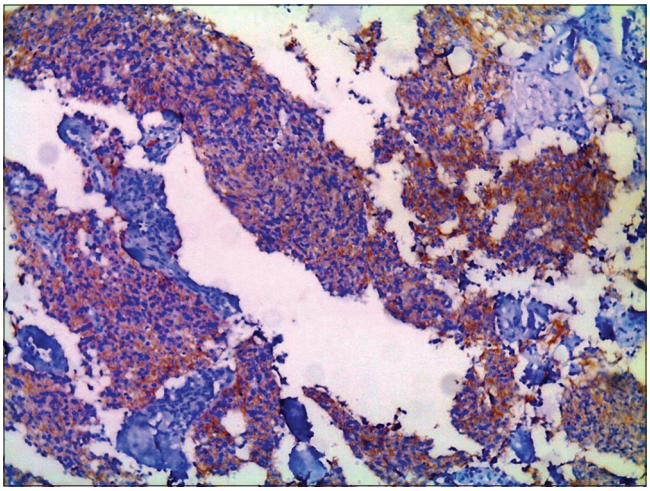

Figure 12: A case of medullary carcinoma showing strong cytoplasmic and membranous staining by β-catenin (original magnification x100)

The studied cases were predominantly females (85%), with female to male ratio 5.6:1. Among malignant cases; females were 26 cases (84%) while males were 5 cases (16%) with female to male ratio was 5.2:1. Among benign cases; females were 25 (86%) while males were 4 (14%) with female to male ratio was 6.25:1.

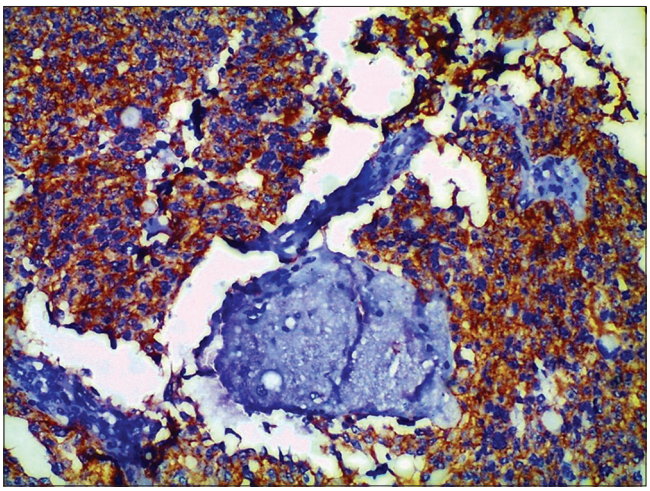

Figure 13: A case of medullary carcinoma showing strong cytoplasmic and membranous staining by β-catenin (original magnification x200)

According to pathologic diagnosis, cases were as follows: 29 cases (48.3%) were benign tumors [22 (36.7%) follicular adenoma and 7 (11.7%) Hurthle cell adenoma] and 31 cases (51.7%) were malignant tumors [24 (40%) papillary carcinomas, 1 (1.7%) Hurthle cell carcinoma, 1 (1.7%) follicular carcinoma, 1 (1.7%) medullary carcinoma, 2 (3.3%) poorly differentiated carcinoma, and 2 (3.3%) anaplastic carcinomas.

Regarding the tumor size of the cases in this study was as follows: Tumors of (pT1) ≤ 2 cm in maximal diameter were found in 10 (32%) patients, tumors of (pT2) >2–4 cm in maximal diameter were present in 9 (29%) patients, tumors (pT3) >4 cm were present in 12 (39%) patients and no reported pT4 cases, this was in line with studies reported by An *et al*., 2018 [12] where 54/116 cases (46.6%) at T1, 3/116 (2.6%) at T2, 59/116 cases (50.9%) at T3 and T4: 0 (0%) and Kapran *et al*., 2002 [13] who reported 11 (27%) cases at pT1-2 and 30 (73%) cases at pT3-4.

Regarding LN metastasis, 3 cases (10%) showed positive LN metastasis (two cases were papillary and one was medullary) while 28 cases (90%) did not. These findings were compatible with those posted by Ivanova *et al*., 2017, Balta *et al*., 2012, Rossi *et al*., 2013, Kapran *et al*., 2002 [10], [13], [14], [15], where lymph node metastasis was only noted in 16%, 34%, 8%, and 34% of their cases, respectively.

As regards multifocality, 13 cases (42%) showed multifocality (nine papillary, two poorly differentiated, one medullary, and one anaplastic carcinoma cases) while 18 cases (58%) did not.

Concerning extra thyroid extension in the current analysis: 10 cases showed extra thyroid extension (32%) while 21 cases (68%) did not. This was in agreement with studies done by Ito *et al*., 2007, Choi *et al*., 2009 [16], [17] where 39.1%, 39.9% of cases showed extra thyroid extension, respectively. Regarding extra thyroid extension, 10 cases (32%) showed extra thyroid extension (seven papillary, seven anaplastic, and one poorly differentiated carcinoma cases) while 21 cases (68%) did not. As regards coexisting pathology, the majority of cases (68%) showed no coexisting pathology ($p = 0.001$)

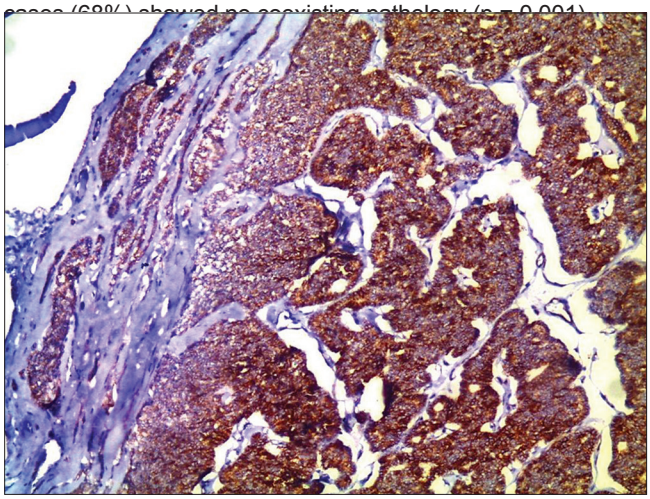

Figure 14: A case of poorly differentiated carcinoma showing strong cytoplasmic and weak membranous staining by β-catenin (original magnification x100)

As regards β-catenin immunohistochemical expression in the present study; 50 cases (83%) were positive while 10 cases (17%) were negative. Among malignant cases, 25 cases (81%)

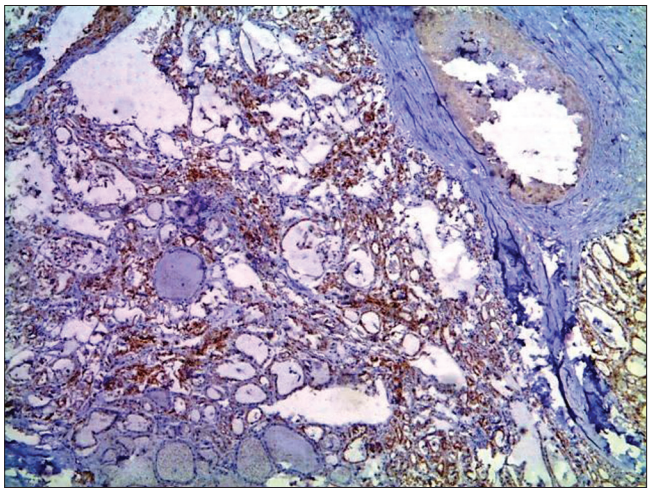

Figure 15: A case of follicular carcinoma showing strong cytoplasmic and membranous staining by β-catenin (original magnification x100)

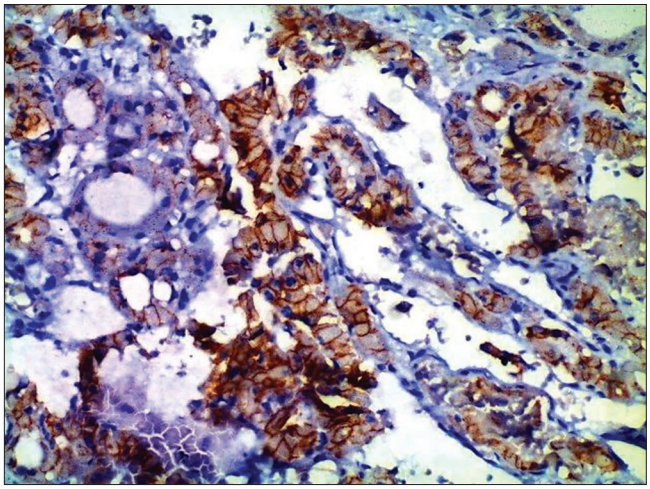

Figure 16: A case of follicular carcinoma showing strong cytoplasmic and membranous staining by β-catenin (original magnification x200)

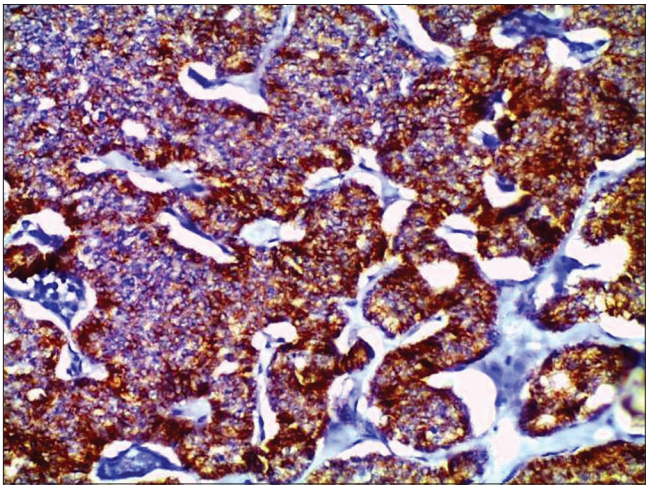

Figure 17: A case of poorly differentiated carcinoma showing strong cytoplasmic and weak membranous staining by β-catenin (original magnification x200)

were positive while 6 cases (9%) were negative. Among benign cases, 25 cases (86%) were positive while 4 cases (4%) were negative.

From the results of this thesis, statistically significant correlations were found between β-catenin immunohistochemical expression and the following: Patients' age among age groups in all studied cases (p = 0.038) where the majority of positive cases (40%) were among (>30–40 years) age group, pathological diagnosis among studied malignant cases (p = 0.042) where all hurthle cell, follicular, and medullary carcinoma cases, 87.5% of studied papillary carcinoma cases and 50% of poorly differentiated carcinoma cases showed β-catenin positivity while all anaplastic carcinoma cases were negative (Table 1), patients' age among studied malignant cases (p = 0.023) where the majority of positive cases (36%) were among (>30–40 years) age group, extra thyroid extension (p = 0.045) where the majority of cases without extra thyroid extension (61.3%) were positive to β-catenin.

Regarding patterns of β-catenin immunohistochemical expression in the present study, statistically significant correlation was detected between β-catenin membranous expression and cytoplasmic expression among all studied cases (p = 0.001), where the majority of negative cases (17%) for β-catenin membranous expression were also negative for the cytoplasmic expression and the majority of high positive cases (27%) for β-catenin membranous expression were also high positive for the cytoplasmic expression (Table 2). Moreover, statistically significant correlation was detected between β-Catenin cytoplasmic expression and extra thyroid extension among studied malignant cases (p = 0.011), where the majority of cases without extra thyroid extension (35.5%) showed high positivity for β-Catenin cytoplasmic expression.

Table 2: Correlation between β-Catenin immunohistochemical expression and tumor behavior

Tumor Behavior	β- Catenin expression		Total
	Positive	Negative	
Benign			
Count	25	4	29
% of Total	41.7	6.7	48.3
Malignant			
Count	25	6	31
% of Total	41.7	10.0	51.7
Total			
Count	50	10	60
% of Total	83.3	16.7	100.0

On the other hand, there were no significant correlations detected between patterns of β-Catenin immunohistochemical expression and patients' age, gender, pathological diagnosis, extent of primary tumor (pT), positive lymph node metastasis, multifocality, and coexisting pathology among studied malignant cases.

These findings may have clinical implications for management of β-catenin-positive thyroid carcinoma patients and β-catenin status would be helpful in formulating a treatment strategy for thyroid carcinoma patients.

Discussion

β-catenin is a multifunctional protein used in embryogenesis, organogenesis, and maintenance of cellular homeostasis [18]. Changes that occur in the cell as a result of this process lead to inhibition of the β-catenin protein degradation and, consequently, to the stabilization of its molecule and its accumulation, initially in the cytoplasm, and then in the cell nucleus, where it forms a complex with the TCF/LEF transcription factor (T cell factor/lymphoid enhancer factor). The resulting complex activates the transcription of many different genes involved in the regulation of important cellular processes, such as proliferation, differentiation, and maturation [19], while it also stimulates a number of oncogenes, such as C-myc or cyclin-D1 [20]. Furthermore, it increased accumulation of β-catenin in the cell nucleus, which, in turn, impacts the increased tumor invasion by facilitating the growth and infiltration of the tumor through activation of the genes responsible for encoding metalloproteinases [21].

Among our studied malignant cases, statistically significant correlation was detected between β-Catenin immunohistochemical expression and pathological diagnosis (p = 0.042), where β-Catenin positivity was found among all hurthle cell, follicular, and medullary carcinoma cases, 87.5% in papillary carcinoma cases and 50% in poorly differentiated carcinoma cases while all anaplastic carcinoma cases were negative for β-Catenin (Figure 7).

Regarding papillary carcinoma cases, our results were in concordance to studies done by Sethi *et al*., 2011, Kapran *et al*., 2002 [1], [13] where 97% of papillary carcinoma

cases were positive to β-Catenin respectively (Figures 8-10). As regards anaplastic carcinoma cases, all were negative to β-Catenin expression and this was in agreement with studies done by Ivanova *et al*., 2017, Rossi *et al*., 2013 (Figure 11) [10], [14]. Concerning medullary thyroid carcinoma, this study showed that all cases were positive to β-Catenin where there were no published paper supports this finding or refuses it up to date (Figures 12-14).

As regards follicular carcinoma, all cases showed positive β-Catenin expression and this was in line with study done by Sethi *et al*., 2011 [1] who reported that 87.5% of follicular carcinoma cases were positive to β-Catenin (Figures 15-16).

Concerning poorly differentiated carcinoma cases, our results were in concordance to study done by Rossi *et al*., 2013 [10] who reported that 80% of poorly differentiated carcinoma showed β-Catenin positivity (Figures 14, 17).

The mean age in present study is lower than that reported by Chowdhury *et al*., 2016, An *et al*., 2018, Rangaswamy *et al*., 2013, Der *et al*., 2018 [12], [22], [23], [24] where mean age was 47 years, 49.5 years, 40.57 years, and 40.7 years, respectively. Among the studied malignant cases in this study, the mean age was 40.16 years which is consistent with prior relevant study performed in Egypt by Aboelnaga and Ahmed, 2015 [25] who reported the mean age 40 years but lower than that reported by Ivanova *et al*., 2017, Rossi *et al*., 2013 [10], [14], where mean age was 57.9 years and 50 years, respectively, and higher than that reported by Kapran *et al*., 2002 [13] who found mean age was 37.3 years. This differences probably due to small volume and random sample included in the present study.

Regarding the gender, the present study showed female predilection where females were 85% with female to male ratio 5.6:1 this ratio was inconcordance to studies done by Ziari *et al*., 2018 [9] where females were 87% with female to male ratio 6.8:1 and Kapran *et al*., 2002 [13] where 83% where females with female to male ratio 4.8:1. Our ratio was higher than these obtained by: Ivanova *et al*., 2017, Andreotti *et al*., 2018, Gupta *et al*., 2015, Tuccilli *et al*., 2018, Rossi *et al*., 2013 [10], [14], [26], [27], [28], where females were 80%, 73%, 77%, 78%, and 54%, respectively, with female to male ratio 4.1:1, 2.7:1, 3.3:1, 3.5:1, and 1.2:1, respectively. That might be explained by different modes of selection of cases (in our study, it was according to availability of data and paraffin blocks) or by difference in sex preponderance to develop thyroid lesions in different geographic locations and among different races.

In the present study, 50 cases (83%) showed positive β-catenin expression while 10 cases (17%) showed negative β-catenin expression where 86% of studied benign cases showed positive β-catenin expression and 81% of studied malignant cases showed positive β-catenin expression. This was in line with study done by Sethi *et al*., 2011 [1] where 100% of benign cases showed positive β-catenin expression and 96% of malignant cases showed positive β-catenin expression.

In the current analysis, correlation between extra thyroid extension and β-Catenin expression in studied malignant cases was statistically significant (p = 0.045), where the majority of cases without extra thyroid extension (61.3%) showed positive β-Catenin immunohistochemical expression.

In the present work, patterns of β-catenin expression were seen and statistically significant correlation was detected between β-Catenin membranous expression and cytoplasmic expression among all studied cases as well as among studied malignant cases (p = 0.001). The majority of negative cases (17%) and (19%) for β-Catenin Membranous Expression were also negative for β-Catenin Cytoplasmic Expression and the majority of high positive cases (27%), (29%) for β-Catenin Membranous Expression were also high positive for β-Catenin Cytoplasmic Expression, respectively. However, no published papers have supported or refused this finding so far.

In this present research, most of studied malignant cases showed high β-Catenin cytoplasmic expression (42%) and low β-Catenin membranous expression (39%). Similar results were reported by Ziari *et al*., 2018 [9]. Furthermore, our results matched with that obtained in the previous studies performed by Urbanczuk *et al*., 2018 [2] who reported that expression of β-catenin in thyroid malignant tumor cells showed strong expression of β-catenin within the cytoplasm and weak expression within the cell membrane.

Among the studied malignant cases in this present work, no significant correlations were detected between either β-Catenin membranous expression and the pathological diagnosis nor β-Catenin cytoplasmic expression and the pathological diagnosis (p = 0.240), (p = 0.283), respectively. This was in agreement with study done by Ziari *et al*., 2018 [9].

In this study, insignificant correlations were detected between β-Catenin membranous expression and patients' age groups in all studied cases as well as in studied malignant cases (p = 0.579), (p = 0.308), respectively. Furthermore, no significant correlations were detected between β-Catenin cytoplasmic expression and patients' age groups in all studied cases as well as in studied malignant cases (p = 0.122), (p = 0.079), respectively. This was in concordance to studies done by Ivanova *et al*., 2017, Kapran *et al*., 2002 [13], [14].

Among the studied malignant cases in this present research, both correlations between β-Catenin membranous expression and the lymph node metastasis as well as β-Catenin cytoplasmic expression and the lymph node metastasis were statistically insignificant (p = 0.283), (p = 0.443), respectively. Similar results were reported by Ivanova *et al*., 2017, Kapran *et al*., 2002 [13], [14]. On the contrary, Ziari *et al*., 2018 [9] reported significant correlations between loss of β-Catenin membranous expression and the lymph node metastasis as well as between intensity of β-catenin cytoplasmic expression and the lymph node metastasis (p < 0.001), (p = 0.003), respectively. This difference may be due to the low number of cases included lymph node specimens in the present study.

In the present work, no significant correlations were detected between either β-Catenin membranous expression and multifocality of the studied malignant cases nor β-Catenin cytoplasmic expression and multifocality of the studied malignant cases (p = 0.306), (p = 0.640), respectively. Among the studied malignant cases in this present analysis, both correlations between β-Catenin membranous expression and the coexisting pathology as well as β-Catenin cytoplasmic expression and the coexisting pathology were statistically insignificant (p = 0.202), (p = 0.443), respectively. Similar results were reported by Ziari *et al*., 2018 [9].

In this present research, no correlation was found between β-catenin expression and the following clinicopathological parameters: Gender, pathological tumor stage (pT), lymph node metastases (pN), multifocality, and coexisting pathology. There have been no published papers to support or refuse these findings so far. The different sample size, different variants, and different methodology adopted in the studies might explain the contradictory results

regarding correlation between β-Catenin expression in thyroid neoplasms and other clinicopathological parameters.

In this present analysis, none of the cases showed true nuclear staining for β-catenin, this was in agreement with studies done by Ziari *et al*., 2018, Ivanova *et al*., 2017, Rezk *et al*., 2004, Bohm *et al*., 2000 [8], [9], [14], [29].

Finally, the present study suggests the prognostic role of β-catenin but does not suggest its diagnostic utility where this was in agreement with Ziari *et al*., 2018 [9].

As 83% of cases in this study showed β-Catenin expression, these cases may potentially benefit from molecular targeted therapy targeting β-Catenin in thyroid neoplasms as Lan *et al*., 2017 [11] found that only after inhibiting β-catenin expression can the radioiodine treatment promote apoptosis other than repress proliferation and survival in tumor cells as well as stated by Sethi *et al*., 2011 [1].

Conclusion

The present research pointed that 50 (83%) of studied 60 cases showed positive β-catenin expression. This finding suggests that molecular-targeted therapy against β-catenin could be an effective therapy. Most of studied malignant cases showed high β-catenin cytoplasmic expression (42%) and lower β-catenin membranous expression confirming the shifting of β-catenin from the membrane to the cytoplasm in thyroid cancer. The present analysis demonstrates that expression of β-catenin with its direct relationship with the pathological T stage.

This study suggests that the assessment of β-catenin status can be used to identify patients who may benefit from adjuvant β-catenin targeted mono- or combined therapy after thyroidectomy. Immunotherapy may potentially provide effective treatment for tumors expressing this protein, especially for those that cannot be removed surgically or that do not respond to traditional treatment options.

Further studies should be done on β-catenin variants to differentiate between the different subtypes and their effect on local invasion as well as tumor metastasis to demonstrate the role of different subtypes and their therapeutic implications.

References

1. Sethi K, Sarkar S, Das S, Rajput S, Mazumder A, Roy B, *et al*. Expressions of CK-19, NF-kappaB, E-Cadherin, beta-Catenin and EGFR as diagnostic and prognostic markers by immunohistochemical analysis in thyroid carcinoma. J Exp Ther Oncol. 2011;9(3):187-99.
   PMid:22070050
2. Urbanczyk S, Stein M, Schuh W, Jäck HM, Mougiakakos D, Mielenz D. Regulation of energy metabolism during early B lymphocyte development. Int J Mol Sci. 2018;19(8):2192. https://doi.org/10.3390/ijms19082192
   PMid:30060475
3. Ibrahim AS, Khaled HM, Mikhail NN, Baraka H, Kamel H. Cancer incidence in Egypt: Results of the national population-based cancer registry program. J Cancer Epidemiol. 2014;2014:437971. https://doi.org/10.1155/2014/437971
   PMid:25328522
4. Nikiforov YE, Nikiforova MN. Molecular genetics and diagnosis of thyroid cancer. Nature Reviews Endocrinology 7.10 (2011): 569-580.
5. Molinaro E, Romei C, Biagini A, Sabini E, Agate L, Mazzeo S, *et al*. Anaplastic thyroid carcinoma: From clinicopathology to genetics and advanced therapies. Nat Rev Endocrinol. 2017;13(11):644-60. https://doi.org/10.1038/nrendo.2017.76
   PMid:28707679
6. Nasr MR, Mukhopadhyay S, Zhang S, Katzenstein AL. Immunohistochemical markers in diagnosis of papillary thyroid carcinoma: Utility of HBME1 combined with CK19 immunostaining. Mod Pathol. 2006;19(12):1631-7. https://doi.org/10.1038/modpathol.3800705
   PMid:16998461
7. De Micco C, Savchenko V, Giorgi R, Sebag F, Henry JF. Utility of malignancy markers in fie-needle aspiration cytology of thyroid nodules: Comparison of Hector Battifora mesothelial antigen-1, thyroid peroxidase and dipeptidyl aminopeptidase IV. Br J Cancer. 2008;98(4):818-23. https://doi.org/10.1038/sj.bjc.6604194
   PMid:18212751
8. Rezk S, Brynes RK, Nelson V, Thein M, Patwardhan N, Fisher A, *et al*. Beta-Catenin expression in thyroid follicular lesions: Potential role in nuclear envelope changes in papillary carcinomas. Endocr Pathol. 2004;15(4):329-37. https://doi.org/10.1385/ep:15:4:329
   PMid:15681857
9. Ziari K, Mojgan S, Moeinadin S. Immunohistochemical evaluation of β-Catenin marker in papillary thyroid cancer: Clinicopathologic significance. Iran J Pathol. 2018;13(2):151-6.
   PMid:30697284
10. Rossi ED, Patrizia S, Marianna P, Egidio S, Luca R, Lombardi CP, *et al*. Diagnostic and prognostic role of hbme-1, galectin-3 and β-catenin in poorly differentiated and anaplastic thyroid carcinomas. Appl Immunohistochem Mol Morphol. 2013;21(3):237-41. https://doi.org/10.1097/PAI.0b013e3182688d0f
    PMid:23235344
11. Lan L, Basourakos S, Cui D, Zuo X, Deng W, Huo L, *et al*. Inhibiting β-catenin expression promotes efficiency of radioiodine treatment in aggressive follicular thyroid cancer cells probably through mediating NIS localization. Oncol Rep. 2017;37(1):426-34. https://doi.org/10.3892/or.2016.5228
    PMid:27840971
12. An HJ, Ko GH, Lee JH, Lee JS, Kim DC, Yang JW, *et al*. Programmed death-ligand 1expression and its correlation with lymph node metastasis in papillary thyroid carcinoma. J Pathol Transl Med. 2018;52(1):9-13. https://doi.org/10.4132/jptm.2017.07.26
    PMid:28994272
13. Kapran Y, Ozbey N, Molvalilar S, Sencer E, Dizdargolu F, Ozarmagan S. Immunohistochemical detection of E-cadherin, alpha-and beta-catenins in papillary thyroid carcinoma. J Endocrinol Invest. 2002;25(7):578-85. https://doi.org/10.1007/BF03345079
    PMid:12150330
14. Ivanova K, Julian A, Elina A, Maria MI, Maya G. Expression of E-cadherin/beta-catenin in epithelial carcinomas of the thyroid gland. Open Access Maced J Med Sci. 2017;5(2):155-9. https://doi.org/10.3889/oamjms.2017.043
    PMid:28507620
15. Balta AZ, Filiz AI, Kurt Y, Sucullu I, Yucel E, Akin ML. Prognostic value of oncoprotein expressions in thyroid papillary carcinoma. Med Oncol. 2012;29(2):734-41. https://doi.org/10.1007/s12032-011-9969-x
    PMid:21547408
16. Ito Y, Hirokawa M, Higashiyama T, Takamura Y, Miya A, Kobayashi K, *et al*. Prognosis and prognostic factors of follicular

carcinoma in Japan: Importance of postoperative pathological examination. World J Surg. 2007;31(7):1417-24. https://doi.org/10.1007/s00268-007-9095-2

PMid:17534542

17. Choi JS, Kim J, Kwak JY, Kim MJ, Chang HS, Kim EK. Preoperative staging of papillary thyroid carcinoma: Comparison of ultrasound imaging and CT. AJR Am J Roentgenol. 2009;193(3):871-8. https://doi.org/10.2214/AJR.09.2386

PMid:19696304

18. Farahani E, Patra HK, Jangamreddy JR, Rashedi I, Kawalec M, Pariti RK, *et al*. Cell adhesion molecules and their relation to (cancer) cell stemness. Carcinogenesis. 2014;35(4):747-59. https://doi.org/10.1093/carcin/bgu045

PMid:24531939

19. Durie BG, Kyle RA, Belch A, Bensinger W, Blade J, Boccadoro M, *et al*. Myeloma management guidelines: A consensus report from the scientific advisors of the international myeloma foundation. Hematol J. 2003;4(6):379-98.

PMid:14671610

20. Tetsu O, McCormick F. Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. Nature. 1999;398(6726):422-6. https://doi.org/10.1038/18884

PMid:10201372

21. Gilissen C, Hehir-Kwa JY, Thung DT, Van de Vorst M, Van Bon BW, Willemsen MH, *et al*. Genome sequencing identifies major causes of severe intellectual disability. Nature. 2014;511(7509):344-7. https://doi.org/10.1038/nature13394

PMid:24896178

22. Chowdhury S, Veyhl J, Jessa F, Polyakova O, Alenzi A, MacMillan C, *et al*. Programmed death-ligand 1 overexpression is a prognostic marker for aggressive papillary thyroid cancer and its variants. Oncotarget. 2016;7(22):32318-28. https://doi.org/10.18632/oncotarget.8698

PMid:27086918

23. Rangaswamy M, Narendra KL, Patel S, Guruprasad C, Manjunath GV. Insight to neoplastic thyroid lesions by fine needle aspiration cytology. J Cytol. 2013;30(1):23-6. https://doi.org/10.4103/0970-9371.107508

PMid:23661936

24. Der EM, Quayson SE, Clegg-Lamptey JN, Wiredu EK, Ephraim RKD, Gyasi RK. Thyroid disorders in Accra Ghana: A retrospective histopathological study at the Korle-Bu Teaching Hospital. J Med Biomed 2013;2:1-7.

25. Aboelnaga EM, Rehab AA. Difference between papillary and follicular thyroid carcinoma outcomes: An experience from Egyptian institution. Cancer Biol Med. 2015;12(1):53-9. https://doi.org/10.7497/j.issn.2095-3941.2015.0005

PMid:25859412

26. Andreotti G, Koutros S, Hofmann JN, Sandler DP, Lubin JH, Lynch CF, *et al*. Glyphosate use and cancer incidence in the agricultural health study. J Natl Cancer Inst. 2018;110(5):509-16. https://doi.org/10.1093/jnci/djx233

PMid:29136183

27. Gupta S, Sodhani P, Jain S, Kumar N. Morphologic spectrum of papillary carcinoma of the thyroid: Role of cytology in identifying the variants. Acta Cytol. 2004;48(6):795-800. https://doi.org/10.1159/000326448

PMid:15581164

28. Tuccilli, C, Baldini E, Arlot-Bonnemains Y, Chesnel F, Sorrenti S, De Vito C, et al. Expression and prognostic value of the cell polarity PAR complex members in thyroid cancer. Int J Oncol 2017;50:1413–1422.

29. Machens A, Gimm O, Hinze R, Höppner W, Boehm BO, Dralle H. Genotype-phenotype correlations in hereditary medullary thyroid carcinoma: oncological features and biochemical properties. J Clin Endocrinol Metabol 2001; 863:1104-1109.