Diagnostic Value of CK19 and HMWCK 34BE12 in Differentiation between Selected Thyroid Neoplasms

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Abstract

Thyroid cancer is an uncommon oncological entity, representing about 1% of all malignant neoplasms. In Egypt, malignant thyroid tumors account for 1.48% of total malignant cases. Histological findings may not be sufficient to establish a precise diagnosis for some thyroid lesions and consequently can’t predict their clinical course; common dilemma is encountered with encapsulated tumors exhibiting follicular growth pattern with presence or absence of capsular and/or vascular invasion, aiming to distinguish benign from malignant follicular tumors, another challenging situation is encountered when diagnostic nuclear features of papillary carcinoma are not rising to threshold of classic papillary thyroid carcinoma (PTC). CK19 and High molecular weight CK (HMWCK-34BE12) have been used as markers for prognosis in many cancers, but their role in segregating benign thyroid adenomas from atypical nodules and to complete malignant criteria supplied in histopathologically-examined tumors is still unclear.

Aim of the Work: The Purpose of current study is to investigate role of CK19 and HMWCK in separating benign and atypical thyroid nodules from malignant tumors in cases with histopathological criteria not enough to reach accurate diagnosis.

Patients and Methods: This retrospective study was carried upon 70 selected patients with different thyroid lesions including: 12 cases of adenomas (Ad), 9 cases of Atypical nodules (AN), and 49 malignant cases (22 cases of papillary thyroid carcinoma (PTC), 17 cases of follicular carcinoma (FTC), 5 cases of anaplastic carcinoma (AC) and 5 cases of Medullary carcinoma (MC). Ten cases of non-neoplastic thyroid lesions were taken as control. Materials included formalin-fixed, paraffin-embedded blocks of thyroid lesions received during period from 2005-2011, where sections were stained with Hematoxylin & Eosin and immunostained with polyclonal antibodies against CK19 and HMWCK.

Results: Benign and atypical cases didn’t show diffuse positivity for CK19 in relation to 47% diffuse positivity in malignant cases which was statistically highly significant, p<0.01, statistically significant higher CK19 diffuse positivity was found in follicular carcinoma cases compared to PTC, while CK19 was not expressed in Medullary carcinomas or anaplastic carcinoma variants, p<0.05. cases of PTC expressed HMWCK while cases of FTC, anaplastic carcinomas and Medullary carcinomas did not express HMWCK which was statistically highly significant, p-value<0.05.

Conclusions: HMWCK and CK19 can be considered as good diagnostic markers for evaluating benign versus malignant thyroid lesions. HMWCK may play an important role to separate benign adenomas from atypical nodules, CK19 can successfully separate atypical encapsulated nodules (completely negative for CK19) from early follicular thyroid carcinomas especially minimally invasive cases (diffusely positive for CK19), and can separate atypical nodules exhibiting incomplete nuclear features supplied for PTC (completely negative for CK19) from cases with ordinary PTC, HMWCK can confirm diagnosis of follicular variant of PTC and successfully segregating them from follicular thyroid carcinomas, CK19 and HMWCK can separate dedifferentiated thyroid carcinoma with minimal follicular pattern from cases with Medullary and anaplastic carcinomas exhibiting follicular arrangement. Further researches may be mandatory to elicit role of HMWCK and CK19 in prognostic purposes regarding out come in patients with malignant thyroid tumors.

Key Words: CK19 – HMWCK – 34BE12 – Thyroid – Neoplasms.

Introduction

THYROID cancer is an uncommon oncological entity, representing about 1% of all malignant neoplasms [1]. In Egypt, malignant thyroid tumors accounts for 1.48% of total malignant cases and 65.3% of total endocrine malignant tumors. Papillary carcinoma is the most common malignant neoplasm of thyroid gland accounting for 67.6% [2].

Histological findings may not be sufficient to establish a precise diagnosis and, consequently, to predict clinical courses of these cases. Objective criteria and identification of markers that permit better characterization of thyroid tumors are therefore required [3].
A common dilemma is encountered with encapsulated tumors showing follicular growth pattern, presence or absence of capsular and/or vascular invasion distinguishes benign from malignant follicular tumors, but identification of this finding can be challenging due to incomplete capsular penetration, equivocal vascular invasion or technical difficulties due to processing or sectioning artifacts, another challenging situation is encountered when some but not all of diagnostic nuclear features of papillary carcinoma are present [3].

Many investigators have focused during last several years on finding immunohistochemical markers to help in distinction between benign and malignant thyroid lesions and subtypes of thyroid cancer [3].

Cytokeratins (CKs) constitute largest intermediate filament protein; Human epidermal keratins can be separated into proteins of different molecular weight. CK19 is one of three main keratins besides CK8 and CK18 expressed in simple or stratified epithelium and in various carcinomas, CK19 has been used extensively as marker of micrometastasis and for detection of circulating tumor cells in many cancers as adenocarcinomas breast, pancreas, and bile ducts as well as in transitional cell carcinomas [4]. Similarly, High molecular weight CK (34BE12), also known as CK903 is cytoplasmic marker corresponding to cytokeratins 1, 5, 10, and 14, which expressed in epithelial and myoepithelial cells [5]. However, their role in evaluating benign thyroid lesion, separating atypical nodules from malignant tumors as well as offering histopathological variant in malignant cases is still unclear and under trial researches. Therefore, it is important to identify a biological marker, independent of the different clinicopathologic factors that can guide the pathologists in accurate diagnosis and subsequently predicating patient’s outcome.

Aim of this work:

This study aimed at evaluating role of CK19 and HMWCK (34BE12) in diagnosis and differentiation between some benign, atypical and malignant thyroid lesions.

Material and Methods

This retrospective study was carried upon selected 70 patients with different thyroid lesions including: 12 cases of adenomas (Ad), 9 cases of Atypical nodules (AN), and malignant lesions consisted of 49 cases that further sub classified into: 22 cases of papillary thyroid carcinoma (PTC), 17 cases of follicular carcinoma (FTC), 5 cases of anaplastic carcinoma (AC) and 5 cases of Medullary carcinoma (MC). Ten cases of non-neoplastic thyroid lesions were taken as control, materials included formalin-fixed, paraffin-embedded blocks of thyroid lesions received during period from 2005-2011, blocks were selected from Early Cancer detection unit, Benha University, Pathology Department of Benha Faculty of Medicine and National Cancer Institute, Cairo University. Three sections of 4 micron thickness were obtained for each case, one section was H & E stained for diagnosis and histopathological reviewing, 2 sections were immunohistochemically stained using monoclonal antibodies against CK19 and HMWCK.

Immunostaining:

Formalin-fixed Paraffin-embedded tissue sections mounted on positive charged slides were heated at 60 degree centigrade for 30 minutes then deparaffinized and rehydrated through a series of xylene and alcohol before staining, antigen retrieval was done using microwave treatment in 10mM citrate buffer (Neo-markers, cat”AP-9003), Ph 6, Endogenous peroxidase was blocked with 3% hydrogen peroxide for 20 minutes. Sections were washed three times with cold 0.01 phosphate buffered saline (PBS), after blocking with 10% normal rabbit serum, sections were incubated with rabbit anticow polyclonal antibody against CK19 (Santa cruz biochemicals, santacruz CA dilution 1:50) and with mouse anti swine monoclonal antibody against HMWCK (Decton Dickenson, san jose Dako) dilution 1:200. Immunohistochemical stain was performed using the avidin-peroxidase complex technique (ABC kit-vector laboratories, Burlingue, CA). Primary antibody was incubated overnight for CK19 and HMWCK proteins. ABC reaction was developed in presence of freshly prepared Diamino Benzidine supplement with hydrogen peroxide (DAB). Lastly, sections were counterstained with Mayer’s Hematoxylin, dehydrated, cleared and covered by cover slips.

Interpretation of HMWCK (34BE12) and CK19-stained thyroid lesions:

HMWCK and CK19 were expressed in cell cytoplasm with or without membranous accentuation according to Park et al., [6].

Cut off point of positive cells was 10% so:
- Score 1+: staining in 11%-25% of cells.
- Score 2+: staining in 26%-50% of cells.
- Score 3+: staining in 51% to 75% of cells.
- Score 4+: staining in >75%.
Staining of 1+ or 2+ was defined as focal positive, and staining of 3+ or +4 was defined as diffuse positive [7,8].

**Results**

All control cases showed negative CK19 and HMWCK.

Benign adenomas showed negative CK19 expression in 11 out of 12 cases (91.6%), focal positivity in one out of 12 cases (8.4%) and diffuse CK19 positivity in no cases (0%). Atypical nodules showed focal CK19 positivity in 3 out of 9 cases (33.3%) and diffuse positivity in no cases.

Malignant cases showed diffuse CK19 positivity in 23 out of 49 (47%) cases.

All examined adenomas showed negative HMWCK (100%), atypical nodules showed diffuse HMWCK positivity in 2 out of 9 (22.2%) cases examined while malignant cases showed diffuse HMWCK positivity in 20 out of 49 (40.8%) cases, Table (1).

### Table (1): Immunostaining for CK19 and HMWCK in benign, atypical and malignant cases.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Immunostaining</th>
<th>Benign adenomas</th>
<th>Atypical nodules</th>
<th>Malignant cases</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK19</td>
<td>Negative</td>
<td>11 (91.6%)</td>
<td>6 (66.7%)</td>
<td>15 (30.6%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Focal positive</td>
<td>1 (8.4%)</td>
<td>3 (33.3%)</td>
<td>11 (22.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse positive</td>
<td>0</td>
<td>0</td>
<td>23 (47%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>12</td>
<td>9</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>HMWCK</td>
<td>Negative</td>
<td>12 (100%)</td>
<td>4 (44.4%)</td>
<td>27 (55.1%)</td>
<td>&lt;0.01 **</td>
</tr>
<tr>
<td></td>
<td>Focal positive</td>
<td>0</td>
<td>3 (33.4%)</td>
<td>2 (4.1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse positive</td>
<td>0</td>
<td>2 (22.2%)</td>
<td>20 (40.8%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>12</td>
<td>9</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

NB: * = Significant. ** = Highly significant.

- CK19 and HMWCK showed statistically significant higher diffuse positivity in malignant group in relation to atypical nodules & adenomas cases, p-value <0.05.

Benign and atypical cases didn’t show diffuse positivity for CK19 in relation to 47% diffuse positivity in malignant cases which was Statistically significant, p-value <0.05.

**Immunostaining of CK19 and HMWCK in malignant thyroid carcinomas variants were shown in Table (2):**

PTC cases showed negative CK19 expression in 6 out of 22 cases (27.3%), focal positivity in 7 out of 22 cases (31.6%) and diffuse CK19 positivity in 9 out of 22 cases examined (41 %), FTC cases showed diffuse CK19 positivity in 14 out of 17 cases (82.4%), and focal positivity in 3 out of 17 cases (17.6%), AC cases showed focal positivity in 1 out of 5 cases (20%), MC cases showed negative CK expression in all examined 5 cases (100%).

PTC cases showed focal HMWCK positivity in 2 out of 22 cases (9%) and diffuse HMWCK positivity in 20 out of 22 cases examined (91%), FTC, AC and MC cases showed negative reactivity for HMWCK, Table (2).

A statistically significant higher CK19 diffuse positivity was found in follicular carcinoma cases compared to PTC while CK19 was not expressed in Medullary carcinomas or anaplastic carcinoma variants, p-value <0.05.

Conversely, only cases of PTC expressed HMWCK while cases of FTC, anaplastic carcinomas and Medullary carcinomas not expressed HMWCK.
which was statistically highly significant, \( p \) value <0.01, Table (2).

Table (3) elicit CK19 and HMWCK diffuse positivity in PTCand FTC in relation to atypical nodules aiming to separate them from malignant cases: Diffuse CK19 positivity was seen in 14 out of 17 (82.4%) FTC cases, not seen in cases of atypical nodules and seen in 9 out of 22 (41%) cases of PTC which revealed statistically significant correlation, \( p < 0.05 \), HMWCK showed diffuse positivity in 20 out of 22 (90%) of PTC cases, not seen in FTC and was present in 2 out of 9 (22%) of atypical nodules with statistically significant correlation, \( p < 0.05 \), Table (3).

CK19 diffuse positivity not present in atypical nodules (0%), HMWCK diffuse positivity not seen in FTC cases, CK19 diffuse positivity can separate atypical nodules from PTC and FTC cases and could be considered more sensitive than HMWCK which showed diffuse positivity in PTC and atypical nodules. Similarly, HMWCK diffuse positivity can separate PTC from FTC cases (completely negative for HMWCK).

### Table (2): Correlation between CK-19 and HMWCK expression in examined malignant thyroid carcinoma variants.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Immunostaining</th>
<th>PTC</th>
<th>FTC</th>
<th>AC</th>
<th>MC</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK19</td>
<td>Negative</td>
<td>6 (27.3%)</td>
<td>0</td>
<td>4 (80%)</td>
<td>5 (100%)</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Focal positive</td>
<td>7 (31.6%)</td>
<td>3 (17.6%)</td>
<td>1 (20%)</td>
<td>0</td>
<td>&lt;0.05*</td>
</tr>
<tr>
<td></td>
<td>Diffuse positive</td>
<td>9 (41%)</td>
<td>14 (82.4%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22</td>
<td>17</td>
<td>5</td>
<td>5</td>
<td>70</td>
</tr>
<tr>
<td>HMWCK</td>
<td>Negative</td>
<td>0</td>
<td>17 (100%)</td>
<td>5 (100%)</td>
<td>5 (100%)</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td></td>
<td>Focal positive</td>
<td>2 (9%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&lt;0.01**</td>
</tr>
<tr>
<td></td>
<td>Diffuse positive</td>
<td>20 (91%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22</td>
<td>17</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

**NB:**
- PTC = Papillary thyroid carcinoma.
- FTC = Follicular thyroid carcinoma.
- AC = Anaplastic carcinoma.
- MC = Medullary carcinoma.

### Table (3): Immunoreactivity of CK-19 and HMWCK (34BE12) in PTC, FTC in relation atypical nodules.

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Immunostaining</th>
<th>PTC</th>
<th>Atypical nodule</th>
<th>FTC</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK19</td>
<td>Negative</td>
<td>6 (27.7%)</td>
<td>6 (66.7%)</td>
<td>0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Focal positive</td>
<td>7 (31.6%)</td>
<td>3 (33.3%)</td>
<td>3 (17.6%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Diffuse positive</td>
<td>9 (41%)</td>
<td>0</td>
<td>14 (82.4%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22</td>
<td>9</td>
<td>17</td>
<td>31</td>
</tr>
<tr>
<td>HMWCK</td>
<td>Negative</td>
<td>0</td>
<td>4 (44%)</td>
<td>17 (100%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Focal positive</td>
<td>2 (9%)</td>
<td>3 (33.4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diffuse positive</td>
<td>20 (91%)</td>
<td>2 (22%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>22</td>
<td>9</td>
<td>17</td>
<td>31</td>
</tr>
</tbody>
</table>

**NB:**
- PTC = Papillary thyroid carcinoma.
- FTC = Follicular thyroid carcinoma.
- AN = Atypical nodules.
Fig. (1): A case of atypical nodule with questionable papillary thyroid carcinoma showing incomplete nuclear features (H & E, x200).

Fig. (2): Atypical thyroid nodule with incomplete nuclear features (clearing) showing diffuse Cytoplasmic immunostaining for HMWCK (arrow) (ABC, x200).

Fig. (3): PTC showing diffuse positive cytoplasmic staining for HMWCK (ABC, x100).

Fig. (4): Follicular thyroid carcinoma showing diffuse positive cytoplasmic (arrow) staining for CK19 (ABC, x400).

Fig. (5): Papillary thyroid carcinoma/follicular variant showing diffuse positive Cytoplasmic staining with membranous accentuation of tumor cells with HMWCK (ABC, x100).

Fig. (6): Follicular thyroid carcinoma showed diffuse positive Cytoplasmic (arrow) staining of CK-19 (ABC, x400).
Discussion

Human thyroid carcinoma is the most common cancer of endocrine system in United States Siegel et al., [9]. In western countries, thyroid cancer is more common in women than in men and is ranked seventh of all cancers affecting women [10,11].

According to Egyptian National Cancer Institute, malignant thyroid tumors constitute 65.31% of endocrine malignant tumors with highest incidence of PTC forming 67.59% [2].

Accurate diagnosis is critical for post-operative management of patients with thyroid nodules. Nowadays, most controversial issue in thyroid pathology is differential diagnosis of an encapsulated thyroid nodule with follicular architecture such as follicular adenoma, atypical nodule, follicular carcinoma, and follicular variant of papillary thyroid carcinoma [12].

Several immunohistochemical markers using different antibodies, alone or in panels have been proposed to overcome this challenge, including CK19, HMWCK (34 BE 12) and others, in the present work, adenomas showed negative CK19 expression in 11 out of 12 cases (91.6%), focal positivity in one out of 12 cases (8.4%) and diffuse CK19 positivity in no cases (0%). Similarly, atypical nodules showed diffuse CK19 positivity in no case (0%), and focal positivity in 3 out of 9 cases (33.3%). Conversely, malignant cases showed diffuse CK19 positivity in 23 out of 49 (47%) cases and focal positivity in 11 out of 49 (22.4%), these results coincided with results done by Choi et al., [13], Shelis [14] and Saleh et al., [12] who stated that diffuse positive CK-19 immunostaining is not seen in follicular adenomas or in atypical encapsulated nodules but were evident in 86% of follicular carcinoma cases. Regarding variants of malignant cases, PTC cases showed negative CK19 expression in 6 out of 22 cases (27.3%), focal positivity in 7 out of 22 cases (31.6%) and diffuse CK19 positivity in 9 out of 22 cases examined (41%), while FTC cases showed diffuse CK19 positivity in 14 out of 17 cases (82.4%), and focal positivity in 3 out of 17 cases (17.6%), conversely, AC and MC cases did not show diffuse CK19 positivity in all examined 5 cases (100%) which was statistically highly significant (p<0.01), these results were supported by that done by many authors as Arora et al., [15], Kosem et al., [16] and Liu et al., [17] regarding CK19 immunoreactivity, in which malignant thyroid neoplasms originating from follicular epithelium can be separated from other malignant thyroid tumors as MC and AC, similarly, follicular thyroid carcinomas had higher diffuse CK19 positivity than PTC cases, this finding may provide evidence supporting CK19 as sensitive up to diagnostic marker for malignant thyroid tumors originating from follicular epithelium and successfully can separate them from follicular adenomas and atypical nodules (borderline) in which CK19 diffuse positivity is completely absent.

All examined adenomas showed negative HMWCK (100%), atypical nodules showed diffuse HMWCK positivity in 2 out of 9 (22%) cases examined and malignant cases showed diffuse HMWCK positivity in 20 out of 49 (40.8%) cases examined. So, HMWCK diffuse positivity is not seen in benign cases while was present in atypical and malignant cases, these results were coincide with that done by Scognamiglio et al., [18] and Nasr et al., [19] and Liu et al., [17] who stated that HMWCK is a marker of malignancy detection in thyroid tumors and can separate benign cases from atypical nodules and malignant thyroid tumors but can’t separate atypical nodules from malignant cases. As regard HMWCK expression in malignant thyroid tumors variants, PTC cases showed negative HMWCK expression in no cases (0%), focal positivity in 2 out of 22 cases (9%) and diffuse HMWCK positivity in 20 out of 22 cases examined (91%), FTC, AC and MC cases showed diffuse HMWCK positivity in no cases (0%), these results were in agreement with that done by Nakamura et al., [20] and Liu et al., [17] concerning outcome of papillary thyroid carcinoma cases, in which diffuse HMWCK (34BE12) expression was statistically correlated with diagnosis of PTC regardless its variants (p-value<0.01), 100% of papillary thyroid carcinoma cases were positive HMWCK (34BE12). Similarly, Yang et al., [21] and Salajegheh et al., [22] recorded that HMWCK (34BE12) immunostaining was useful in papillary thyroid carcinoma diagnosis and can separate PTC/ follicular variant cases from FTC cases, these results were in accordance with the present work in which FTC cases showed diffuse positive staining in 14 out of 17 (82.4%) cases while showed diffuse HMWCK staining in no cases examined with statistically significant correlations, p<0.05. Accordingly, we can consider CK19 is a good diagnostic marker seperating FTC from Follicular variant of PTC. In the current work, HMWCK showed diffuse positivity in 2 out of 9 (22%) cases of atypical nodules, conversely, atypical nodules didn’t show diffuse positivity for CK19 in examined cases (0%), this statistically significant difference (p-value <0.05) can put CK19 superior to HMWCK in separating
atypical nodules from malignant thyroid lesions successfully. Regarding HMWCK diffuse positivity in atypical cases, it may be able to separate adenomas from atypical nodules with incomplete nuclear features not rising to threshold of classic papillary thyroid carcinoma, these results were coincide with that done by Kosem et al., [16], Prasad et al., [23], Scognamiglio et al., [18] and Arora et al., [15] who stated that lesions representing a biologic spectrum of papillary thyroid carcinoma still at early stage of malignant transformation with incomplete nuclear features that referred to them as atypical nodules can show immunoreactivity for HMWCK in this early stage. Moreover, HMWCK may be integrated in carcinogenic cascade for papillary thyroid carcinoma cases.

According to the present work, cases with atypical nodules showing incomplete nuclear features not rising to threshold of PTC can be separated from follicular variants of PTC using CK19 that showed completely negative expression pattern in adenomas as well as in atypical nodules in relation to diffuse positivity in 9 out of 22 (41%) of PTC cases examined. Results published by many authors as Kosem et al., [16], Prasad et al., [23], Scognamiglio et al., [18], Nasr et al., [19], Nakamura et al., [20] and Liu et al., [17] showed that HMWCK and CK19 immunoreactivity were very useful in discriminating follicular variant PTC from follicular adenomas and atypical nodules, at the same time all cases of follicular variant PTC showed positive HMWCK immunostaining, while it was absent in all cases of benign group.

In conclusion, HMWCK and CK19 can be considered as good diagnostic markers for evaluating benign versus malignant thyroid lesions, HMWCK may play an important role to separate adenomas from atypical nodules, CK19 can successfully separate atypical encapsulated nodules from early follicular thyroid carcinomas especially minimally invasive cases, and can separate atypical nodules exhibiting incomplete nuclear features supplied for PTC from cases with ordinary PTC. HMWCK can confirm diagnosis of follicular variant of PTC and successfully segregating them from follicular thyroid carcinomas, CK19 and HMWCK can separate dedifferentiated thyroid carcinoma with minimal follicular pattern from cases with Medullary and anaplastic carcinomas exhibiting follicular arrangement. Further researches may be mandatory to elicit role of HMWCK and CK19 in prognostic purposes regarding out come in patients with malignant thyroid tumors.

References

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