Chapter 6

Thyroid Nodules in Diagnostic Pathology: From Classic Concepts to Innovations

Ilze Fridrihsone, Ilze Strumfa, Boriss Strumfs, Andrejs Vanags, Dainis Balodis, Arvids Jakovlevs, Arnis Abolins and Janis Gardovskis

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/intechopen.77117

Abstract

Thyroid nodules are frequent in general population, found in 3.7–7% of people by palpation and 42–67% by ultrasonography (US). The differential diagnosis ranges from papillary (PC), follicular (FC) and medullary (MC) carcinomas to follicular adenoma (FA) and colloid goitre. Cancer risk in thyroid nodules varies: 5% in masses found by palpation, 1.6–15% by US, 3.9–11.3% by computed tomography (CT), 5–6% by magnetic resonance imaging (MRI) and 30–50% by positron emission tomography (PET). The final diagnosis depends on fine needle aspiration (FNA) findings and histopathology. The recent WHO classification (2017) is based on classic morphology, including assessment of invasion and nuclei. New entities are defined to designate tumours with doubtful invasion or controversial nuclear features. By immunohistochemistry, PC expresses HBME-1, TROP-2, CITED1 and CK19. Notably, PC can stain for CD20. MC is recognised by neuroendocrine differentiation. To distinguish FA *vs*. FC, evaluation of HBME-1, p27 and galectin has been suggested. Regarding miRNAs, miR-146b, miR-222, miR-221 and miR-181b are upregulated, while miR-145, miR-451, miR-613 and miR-137 are downregulated in PC. FC features downregulated miR-199a-5p and upregulated miR-197 and miR-346. In MC, miR-21 and miR-129-5p are downregulated. In addition, increased systemic inflammatory reaction can be poor prognostic factor in thyroid cancer. The aim of this chapter is to review classic and innovative histopathology of thyroid nodules for diagnostic pathology practice and research in multidisciplinary thyroid teams.

Keywords: thyroid nodule, thyroid carcinoma, papillary carcinoma, follicular carcinoma, medullary carcinoma, histopathology, immunohistochemistry, miRNA, follicular adenoma

1. Introduction

Thyroid nodules represent an extremely frequent finding in the general population [1] and therefore enter the spectrum of the most common diagnostic dilemmas in endocrine surgery, cytology and surgical pathology. By palpation, such nodules can be found in 3.7–7% of general population, more frequently in females: 6.4% contrasting with 1.5% in males [2]. Three quarters of palpable nodules are solitary [3], raising increased suspicion of neoplasm. By ultrasonography (US), thyroid nodules can be disclosed even more frequently: in 42–67% of patients, and other radiological investigations also yield incidental nodules in a significant proportion of cases [2, 4–6] as shown in **Table 1**.

Malignant tumours do occur in thyroid albeit infrequently and can present as an incidentally found thyroid nodule (**Table 1**); therefore, reliable investigation is mandatory. The differential diagnostic approach should not be formal as evidence from a tertiary referral centre indicates that incidentally found thyroid carcinomas are even more frequently associated with lymphatic invasion and lymph node metastases [7]. However, the discrimination between malignant and benign thyroid masses can be difficult at all levels—radiology, fine needle aspiration (FNA) cytology and histopathology.

On the other hand, overdiagnosis of malignancy would lead to an unnecessary operation, carrying risks of complications. For instance, in a large group of 27,912 patients, included in the Surveillance, Epidemiology and End Results (SEER)-Medicare database, thyroid surgery-specific complications developed in 12.3% cases, while general postoperative complications were seen in 6.5% of patients [9]. Among the specific complications, hypoparathyroidism and vocal cord paralysis are the most frequent. The frequency of hypoparathyroidism in different studies ranges from 0.5 to 65% [10]. Transient hypoparathyroidism has been observed in 28.4–44.2% of patients, and 0.3–1.1% developed permanent hypoparathyroidism [11, 12]. After total thyroidectomy for well-differentiated thyroid carcinoma in 5670 SEER-Medicare patients (1991–2009), the frequency of unilateral *vs.* bilateral vocal cord paralysis was 8.2 *vs.* 1.3% [13]. Postoperative hematoma develops in 0.1–1% of patients and can lead to airway compression [14]. In addition, lifelong thyroid replacement treatment [15] is unavoidable after thyroidectomy. Psychological concerns and additional financial burden must be considered as well.

Evaluation method of the thyroid gland	Frequency of thyroid nodule, %	Cancer risk in the identified nodule, %	References
Palpation	3.7–7	5	[2]
Ultrasonography	42–67	1.6–15	[2, 8]
Computed tomography	16	3.9–11.3	[2]
Magnetic resonance imaging	4.5–5.1	5–6	[4–6]
Positron emission tomography	1.6 (for solitary pattern)	30–50 34.8 in meta-analysis	[2]

Table 1. Frequency of thyroid nodule and risk of malignancy by the method of investigation.

http://dx.doi.org/10.5772/intechopen.77117

The rate of surgical complications is decreasing [13] due to novel approaches including continuous intraoperative neuromonitoring [10, 16, 17], novel haemostatic equipment, e.g., advanced bipolar electrocautery, ultrasound or hybrid devices and haemostatic agents for use close to vulnerable structures [14]; evaluation of surgeons' experience [18] and implementation of carbon nanoparticles to identify parathyroid glands [12, 19]. However, unnecessary surgery must be avoided. This, in turn, places greater demands on preoperative diagnostics, including immunohistochemical and/or molecular evaluation within the frames of multidisciplinary approach. Thus, the aim of this literature review is to summarise the present evidence in diagnostic pathology of thyroid nodules for the needs of practising pathologists as well as other colleagues working in multidisciplinary thyroid teams.

2. Epidemiology of thyroid carcinoma

The global incidence of thyroid cancer in 2012 was estimated as 6.1 per 100,000 women and 1.9 per 100,000 men. The gender-specific mortality rates were assessed as 0.6 and 0.3 per 100,000 respectively [20]. Generally, the epidemiology of thyroid carcinoma is characterised by growing incidence, decreasing global mortality and predominance of papillary carcinoma (PC). PC constitutes 65–93% of thyroid carcinomas [21, 22], while follicular carcinoma (FC) is responsible for 6–10% of thyroid carcinoma cases [21, 23]. Medullary carcinoma (MC) accounts for 2–5% of thyroid carcinomas [21, 24].

The incidence of thyroid cancer is growing in most countries and in both genders [20, 25], e.g., increasing from 4.9 to 14.3 per 100,000 individuals in USA over time period between 1975 and 2009 [26]. In the time period between 2000 and 2010, thyroid cancer-induced mortality in males has decreased in most European countries. However, it has increased significantly in Moldova (for 49.9%), Latvia (26.2%) and Portugal (15.7%). Regarding Americas, significant increase in mortality was seen in Costa Rica (66.9%), Uruguay (47.9%) and Ecuador (36.3%), while moderate – in USA (8.1%). New Zealand has also experienced increase in thyroid cancer-induced male mortality (14.5%). Regarding females, mortality from thyroid cancer has increased in Greece (13.3%), Colombia and Ecuador (both 17.8%), USA (6.8%) and Australia (14.0%). The 2008–2012 mortality levels were highest in Latvia, Estonia, Hungary, Moldova and Israel for males and in Ecuador, Colombia, Israel, Mexico and Latvia for females [20].

The growing incidence of thyroid carcinoma parallels increasing frequency of PC [26] and especially papillary microcarcinoma. Therefore, part of the scientific world considers the increase in incidence as the result of better diagnostics, yielding more incident nodules and enabling evaluation by US and biopsy even in as small lesions as measuring 2 mm in diameter. However, SEER-based data have clearly disclosed increased incidence of large PC as well. This corroborates the opinion that incidence growth purely reflects better diagnostics and incidental findings [2] and suggests true growth of incidence. In addition, incidental thyroid nodules are less frequently reported in clinical practice than in research. In a large retrospective analysis of 97,908 radiological reports, carried out in Chicago, USA, such nodules were noted in 0.4%, including 0.14% of computed tomography (CT), 0.64% of magnetic resonance imaging (MRI), 0.36% positron emission tomography (PET) scans and 6.59% US examinations. In contrast, on dedicated review, nodules were found in 10% of CT scans [27].

The reporting pattern is highly variable, depending both on nodule size and radiologist's specialisation [28]. Thus, the real input of incidental nodules in the growing incidence may be moderate.

The true increase of the incidence of thyroid carcinoma can be attributed to several risk factors, including changes in iodine supplement [25], adiposity [29, 30], oestrogens [31, 32], parity [33, 34], pregnancy-related increases in TSH levels [25], ionising radiation [35], and chemicals, e.g., polybrominated diphenyl ethers that are or have been used as flame retardants [25].

Many authors accentuate the gap between stable death rates and increasing numbers of new thyroid carcinoma cases suggesting "overestimation" of thyroid cancer [15], mainly small indolent PCs [20]. Existence of self-limiting thyroid cancers has been hypothesised based on: (1) lack of mortality reduction by surgery for papillary microcarcinoma; (2) low growth rate of papillary microcarcinoma and (3) high prevalence of papillary microcarcinoma in young people, contrasting with higher mortality in middle-aged patients. The consequences of this point of view include the conclusion that "the early detection of self-limiting cancers results in over-diagnosis" [36]. Possibly, most patients may not need treatment but those with high-risk disease must be promptly distinguished [20].

3. Radiological evaluation of a thyroid nodule

Neck US is the essential method in thyroid evaluation [37]. It can be both the starting point disclosing an incidental nodule and a reliable source of significant information for the final diagnosis. Thyroid nodule can be identified if US is performed for palpable neck mass, lymphadenopathy, suspected parathyroid or vascular pathology. The yield of thyroid nodules in such patients is 42–67%. In patients evaluated by cervical US for parathyroid disease, thyroid nodules are found in 20–56%, and the frequency of cancer in these lesions is 2–6%. By carotid artery duplex US, thyroid nodules have occasionally been more frequent (28%) than significant carotid stenosis (13%); the frequency of cancer in these nodules was 7.4%. The benefits of US include exact size measurements and possibility to disclose the features of malignant growth: hypoechoic nodule with irregular borders, central hypervascularity, presence of microcalcifications and elongated shape being taller than wide. US-guided FNA should be performed if the nodule exceeds the size of 1 cm or has additional worrisome features. Cancer risk in an incidental thyroid nodule, found by US, is 15% (not counting papillary microcarcinoma), being three times higher than in palpable nodule [2].

The innovations in ultrasonography include contrast-enhanced ultrasonography, elastography and superb microvascular imaging [1, 38, 39].

Computed tomography has a limited role in thyroid pathology. It is more informative in the beginning of the diagnostic way and in special situations. CT can provide the first evidence of thyroid nodule. In patients undergoing radiological examination for non-thyroid disease, cervical and thoracic CT yields thyroid nodules in up to 16% of cases. The risk of malignancy in CT-detected nodule ranges between 3.9 and 11.3%. Several pitfalls limit the informativity of CT in thyroid disease. These include the assessment of nodule size, number of lesions and risk of cancer. In studies comparing CT, US and postoperative findings, CT was shown to be

less informative than US although both methods correlated with the findings in resected tissues. The size is the only reliable predictor of malignancy in CT, while presence of microcalcifications and attenuation in Hounsfield units are not specific. Because of these limitations, thyroid CT should be followed by US. CT can be useful in the further assessment of advanced cases to detect retrosternal spread, invasion into trachea and/or large vessels, metastases and recurrence in the site of operation, lymph nodes or distant tissue [2, 40].

Positron emission tomography usually is not included in the primary evaluation of thyroid. However, PET is increasingly performed for surveillance and staging of other malignant tumours. Occasionally, increased uptake in the thyroid has been noted in these patients. PET-positivity in the thyroid can manifest as diffuse uptake throughout the whole gland or as a solitary focus. The diffuse pattern is characteristic for Hashimoto thyroiditis or Graves' disease and carries low risk of malignancy: 4.4% comparable with 5% risk in palpable nodules. In contrast, solitary focus is a rare but worrisome finding: it is seen only in 1.6% of examined patients but the risk of malignant tumour reaches 30–50% (34.8% in a meta-analysis) as described by Wilhelm [2]. Therefore, US and FNA of a PET-positive focus are suggested regardless of size [2].

4. Histology and immunohistochemistry: From classics to innovations

4.1. Follicular adenoma

Follicular adenoma (FA) is defined as a benign, encapsulated, non-invasive thyroid tumour differentiating towards follicular epithelium and lacking the nuclear features of papillary thyroid carcinoma.

By autopsy findings, FAs have been reported in 3–5% of adults. Not surprisingly, this frequency is close to the prevalence of palpable solitary thyroid nodules. The known risk factors of FA include radiation exposure, especially in childhood and adolescence, and lack of iodine. Radiation exposure can cause FA after prolonged latent period (10–50 years), and the relative risk can reach 15. The role of iodine deficiency has been substantiated on more frequent findings of palpable thyroid nodules in areas of low iodine consumption. Although a fraction of such nodules will represent true FA, endemic sporadic goitre is classically triggered by iodine deficiency. Regarding hereditary factors, FAs are more frequent in patients having Cowden syndrome or familial adenomatous polyposis [3].

On US, FA represents a solid, well-demarcated, hypo- or isoechoic homogeneous mass. On radionuclide scan, most FAs are "cold" nodules, although "hot" adenomas are possible and can be associated by clinical hyperthyroidism [3].

FNA specimens from FA are characterised by high cellularity, rich presence of follicular cells, including microfollicles, and scant colloid. Macrofollicular FAs yield more colloid and monolayered sheets of epithelium. Inflammation, PC-type nuclei or psammoma bodies are absent. On FNA, differential diagnosis with follicular carcinoma is impossible as this would request identification of invasive growth. In addition, colloid-rich cytological specimens are similar to hyperplastic nodules [3].

Grossly, FAs are solitary, rounded, grey, whitish, tan or brown masses with smooth outline, contrasting with normal surrounding thyroid tissues. Microscopic structure is variable, but several key features are observed: (1) origin from follicular epithelium, mostly reflected in the follicular architecture; (2) structural difference from surrounding tissues; (3) presence of complete fibrous capsule; (4) lack of invasion; (5) lack of PC nuclear features and (6) lack of neuroendocrine differentiation. The architecture can be follicular (normo-, micro- or macro-), solid or trabecular. The cells are cuboidal or polygonal but can be cylindrical in "hot" adenomas. Cytoplasm is easily seen, eosinophilic or light. Nuclei are round, smooth, uniform, with evenly distributed, moderately dark chromatin. Mitoses are rare. Although stroma is usually scant, it can be more abundant in some tumours, exhibiting oedema, myxoid structure, haemorrhage, fibrosis and hyaline change as well as calcification. In distinction from hyperplastic nodule, solitary occurrence, presence of capsule and difference from surrounding thyroid tissues are helpful. In differential diagnosis with follicular carcinoma, lack of capsular and vascular invasion is the central criterion [3, 41].

FA has multiple histological variants including FA with papillary hyperplasia, lipoadenoma, FA with bizarre nuclei, signet ring cell FA, clear cell FA and spindle cell FA [3, 42].

4.2. Papillary thyroid carcinoma

Papillary carcinoma is a well-differentiated malignant thyroid tumour characterised by (1) origin from/differentiation towards follicular epithelium and (2) diagnostic nuclear features [22].

PC is the leading histological type of thyroid carcinomas, thus the risk factors are in line with the general risk factors of thyroid cancer, comprising ionising radiation, oestrogens, obesity, diabetes mellitus and ingestion of nitrates via food [22]. In contrast with FC, high iodine intake increases the risk of PC. Thus, iodine supplementation decreases the FC incidence and increases the PC occurrence. Despite higher PC frequency, the epidemiological change might be considered beneficial due to the favourable prognosis of papillary carcinoma.

On US examination, PC is hypo- or isoechoic, solid or cystic, irregularly shaped nodule that is taller than wide, contains microcalcifications and features disorganised vascular supply. By scintigraphy, papillary carcinomas mostly are "cold" [22].

By FNA, high cellularity is characteristic. Architecturally, papillae or monolayer sheets can be observed. Psammoma bodies are present. The cells are tall, showing visible cytoplasm. Nuclear changes are the most characteristic and diagnostically most important findings. These include thickened nuclear membranes and chromatin clearing, nuclear grooves and pseudoinclusions. The colloid can be either watery or thick, so-called ropy colloid. It might be more difficult to recognise the follicular variant and columnar variant having scarce nuclear features. Multiple nuclear inclusions can be seen in tall cell variant resulting in "soap bubble" appearance of the nuclei. Squamous metaplasia is possible in diffuse sclerosing variant; however, typical nuclear features are also present [22].

Grossly, PC is seen as a white, hard mass with irregular outline. Cystic change can be present while necrosis (in the absence of FNA history that might induce vascular collapse) is not characteristic and might indicate transformation to more aggressive tumour [22].

http://dx.doi.org/10.5772/intechopen.77117

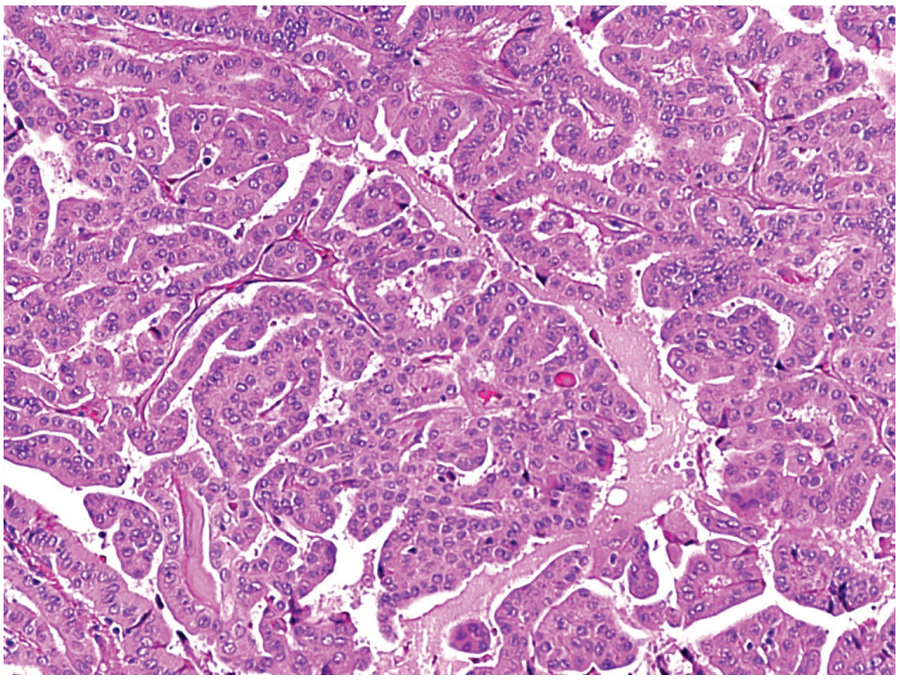

Figure 1. Papillary thyroid carcinoma. Note the characteristic architecture and nuclear features. Haematoxylin-eosin, original magnification 200×.

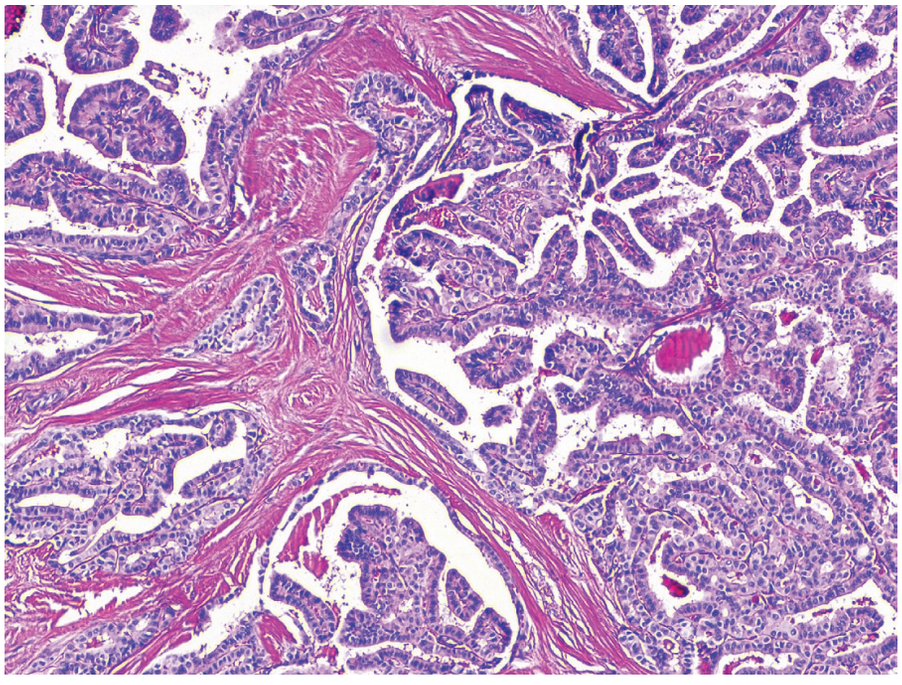

Figure 2. Stromal desmoplasia in papillary carcinoma. Haematoxylin-eosin, original magnification 100×.

Microscopically, PC is characterised by papillary architecture (**Figure 1**) and the diagnostic nuclear features. The papillae show significant variability between tumours, being straight or branched, loosely or tightly packed, long or short. Cystic or follicular foci are frequent. Solid and trabecular architecture can occur as well. Nuclei are enlarged, overlapping, elongated, characterised by membrane irregularity and optically empty "ground

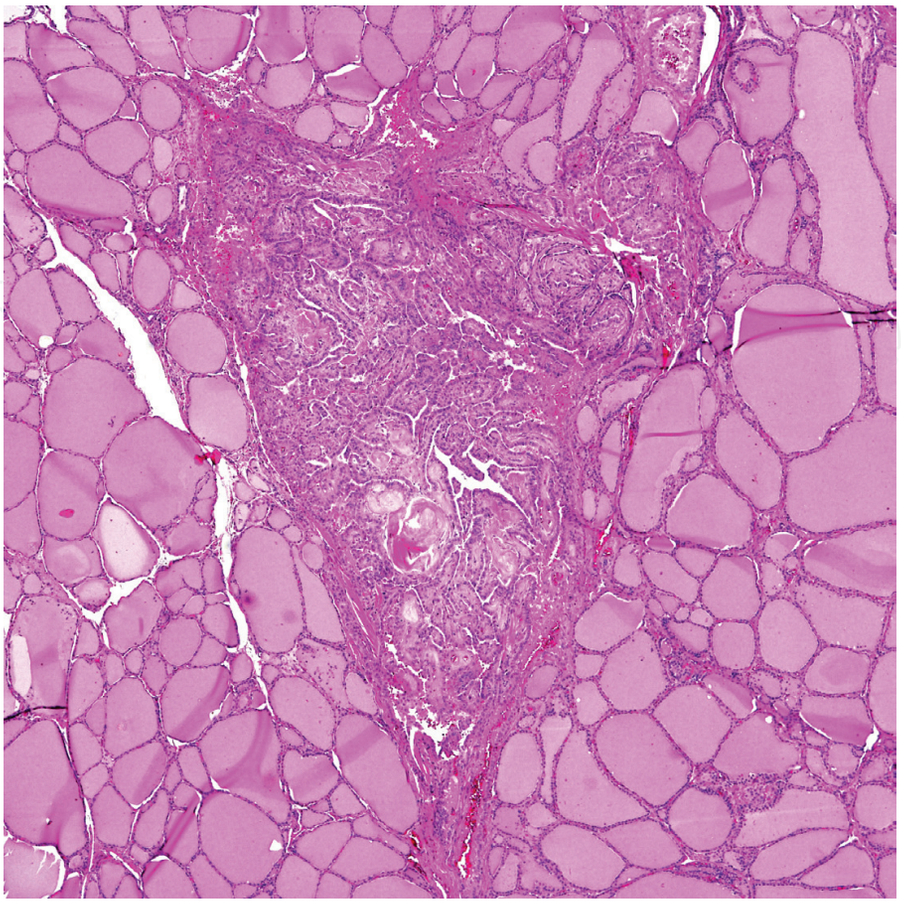

Figure 3. Papillary microcarcinoma in thyroid tissues. Haematoxylin-eosin, original magnification 50×.

glass" appearance. The "ground glass" appearance is very helpful in diagnostic evaluation of formalin-fixed, paraffin-embedded tissues. However, it is not seen in frozen sections compromising intraoperative assessment. The nuclear contour irregularity is seen as nuclear pseudoinclusions (of cytoplasm) and longitudinal grooves. Mitoses are rare. Psammoma bodies, present in 50% of cases, are small, rounded, laminated calcifications in stroma or lymphatic channels but not in colloid. Squamous metaplasia can be present. Stroma (**Figure 2**) is well developed [22, 41].

The histological variants of PC include papillary microcarcinoma (smaller than 1 cm; see **Figure 3**), encapsulated, follicular, diffuse sclerosing, tall cell, columnar cell, cribriform morular, hobnail, solid, oncocytic, spindle cell, clear cell and Warthin-like variants as well as PC with fibromatosis-like stroma [22, 43]. Carcinomas showing true papillary architecture are dominated by *BRAF* (*V600E*) mutations, while tumours holding follicular architecture mostly carry *RAS* mutations [44].

4.3. Follicular carcinoma

Follicular carcinoma is a malignant thyroid epithelial tumour characterised by follicular differentiation, invasive growth morphologically reflected in the invasion through capsule or into blood vessels and absence of the nuclear features of papillary carcinoma [23].

http://dx.doi.org/10.5772/intechopen.77117

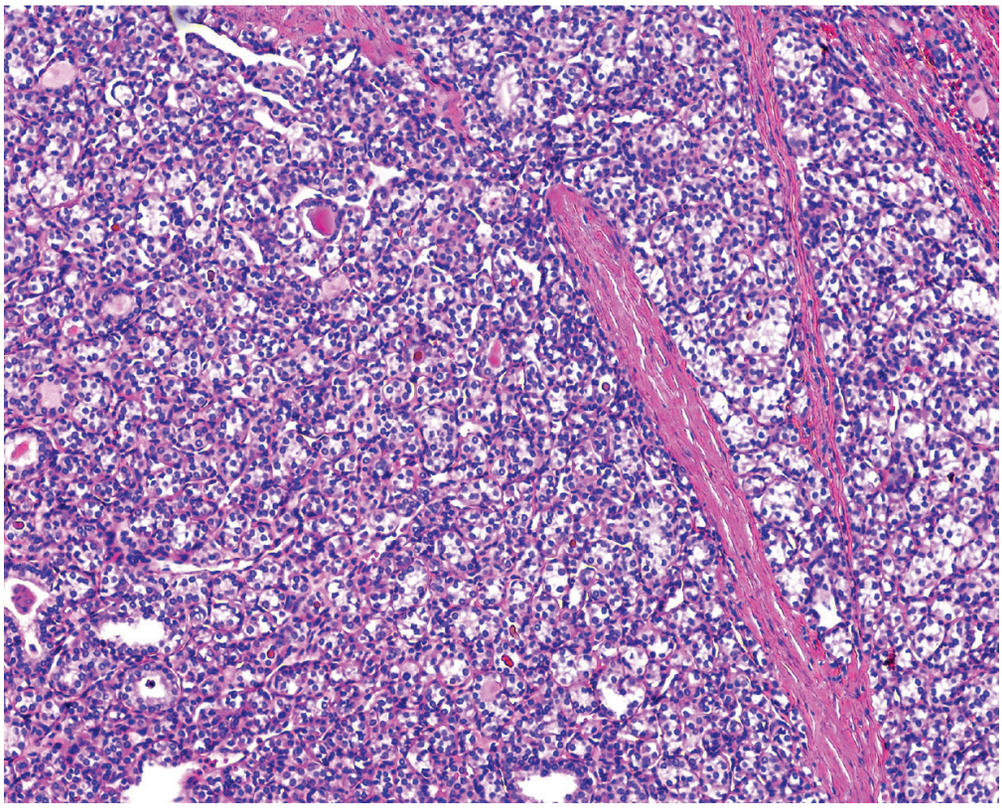

Figure 4. Follicular thyroid carcinoma. Note the invasion through the capsule. Haematoxylin-eosin, original magnification 200×.

The risk factors include low iodine supply and ionising irradiation although the association with radiation is weaker than for PC [23]. By FNA, FC cannot be distinguished from FA. Grossly, FCs are solid masses. Occasionally, the capsules seem thicker than in FA. Rarely, invasion through the capsule or into extrathyroid tissues is grossly evident.

Microscopically, the tumour is characterised by follicular architecture. By definition, there are no nuclear features that would define PC. The distinction from FA requires identification of invasion that can manifest as either minimal or wide capsular invasion (**Figure 4**) or angioinvasion (**Figure 5**). Minimal invasion is defined as focal, but unequivocal invasive growth that penetrates the full thickness of capsule. Irregular outline of the inner surface of the capsule or tumour cell groups within the capsule are insufficient for diagnosis. FC also must be strictly distinguished from artefacts such as surgery- or FNA-induced capsular lesions or curling of the tumour in the edges of tissue block. Vascular invasion must be assessed only in the capsule or extratumourally, not in the middle of the mass. To distinguish angioinvasion from artefactual contamination of blood vessels by tumour cells, e.g., during grossing, any intravascular tumour cell group should be qualified as an evidence of invasion only if the tumour tissues are adherent to blood vessel walls, covered by either endothelium or fibrin, or thrombus [23, 41]. Morphologic variants are rare, including clear cell [23], signet ring cell [45], microcystic and spindle cell variants, FC with fat cells and FC with glomeruloid pattern [23]. Mucinous variant has been reported [46].

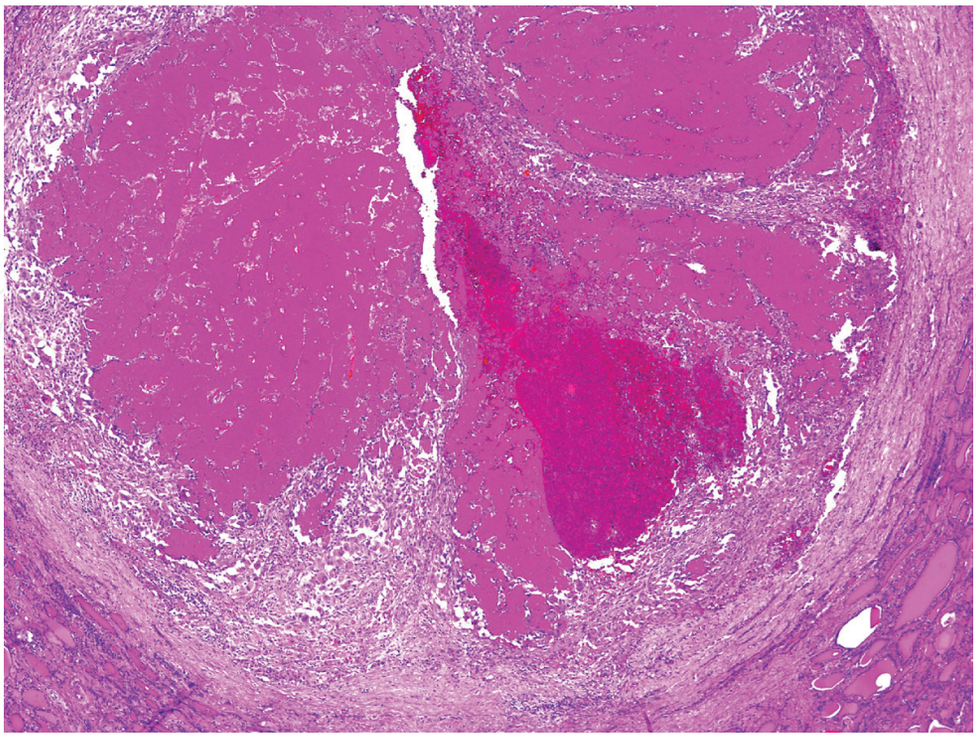

Figure 5. Invasion of a follicular thyroid carcinoma in a large blood vessel. Haematoxylin-eosin, original magnification 50×.

4.4. Follicular tumours with controversial morphology

In the recent WHO classification (2017), certain new entities have been defined to classify thyroid tumours with controversial morphological appearance, doubtful invasion or questionable nuclear features [47].

Follicular-patterned tumours showing unequivocal capsular or vascular invasion are designated as (1) invasive follicular variant of PC, if the nuclei show typical structure of PC; (2) well differentiated thyroid carcinoma, not otherwise specified, if the nuclear features are controversial; and (3) FC, if the nuclei lack any traits of PC.

Tumours that are definitely non-invasive are designated FA, if the nuclear structure is certainly of non-papillary type. Otherwise, the diagnosis of non-invasive follicular thyroid neoplasm with papillary-like nuclear features is issued [48]. Finally, tumours with questionable invasion are designated either follicular tumours of uncertain malignant potential if the nuclei are of non-papillary type or well-differentiated tumour of uncertain malignant potential in all other cases.

These new entities provide pathologists with the long-awaited benefit of accurate diagnosis. However, the biological potential of these groups still remains to be assessed. Generally, the risk of recurrence or metastasis is low, but exceptions still have been reported [47].

4.5. Medullary carcinoma

Medullary carcinoma is a malignant thyroid tumour showing C-cell differentiation [49].

MC is characterised by high fraction of hereditary tumours, reaching up to 30%. In contrast, the risk factors of sporadic MC are almost unknown [49]. Activating *RET* mutations are present in 40% of sporadic MC and over 90% of hereditary cases, mostly with almost complete penetrance [50].

FNA shows round, ovoid or spindle cells. Eccentric position of the nucleus can impart plasmacytoid appearance. Chromatin is granular. Amyloid can be present in the specimen. Despite immunohistochemical investigation, diagnosis is correctly recognised in only 46.1% of cases [49]. In our experience, systematic immunohistochemical approach to all thyroid tumours lacking typical papillary type nuclei is helpful to avoid a diagnostic mistake. Serum calcitonin level would also disclose the diagnosis in most cases.

Grossly, the lesions are grey to yellow, featuring different consistencies. Bilateral and multicentric growth is characteristic for inherited tumours [49]. Microscopic picture can be very confusing due to the variety of histological patterns—MC is the "great mimic." However, the immunophenotype is distinctive in most cases, and the presence of local amyloidosis can significantly guide the diagnostic thinking, enhancing the suspicion for MC.

The architecture of MC is solid, trabecular, lobular or insular. The cells are polygonal, plasmacytoid, spindled or show mixed morphology. Nuclei are round, with coarse chromatin and small nucleoli. The cytoplasm ranges from eosinophilic to amphophilic. Calcitonin-containing amyloid is present in 90% of cases. The presence of nuclear pseudoinclusions and rare psammoma bodies can be misleading. Hereditary tumours are accompanied by C cell hyperplasia. The variants include papillary, follicular, spindle cell, giant cell, clear cell, oncocytic, melanotic, squamous, amphicrine, paraganglioma-like, angiosarcoma-like, encapsulated and small cell MC [41, 49, 51]. MC is characterised by neuroendocrine phenotype, and immunohistochemistry for chromogranin A, calcitonin or related peptides, and carcinoembryonic antigen is highly advised to confirm the diagnosis.

4.6. Metastases to the thyroid gland

Metastases of extrathyroid tumours (MTS) to the thyroid gland are rare. In FNA cytology, MTS constituted 2.2% of cases [52]. However, they are encountered in diagnostic surgical pathology as well as in FNA cytology and can have very misleading morphology. The authors of a recent clinical series have reported on 32 such cases [53]. Among these patients, lung was the most frequent site of primary tumour (14/32), followed by renal and gastrointestinal cancers at equal frequency of 5/32. Interestingly, MTS affecting the thyroid were diagnosed over wide time range, from manifestation simultaneously with the primary cancer to delayed presentation 16 years after the initial diagnosis. Although thyroidectomy was not considered in patients affected by an aggressive cancer at high stage, it still has been performed in 34.5% of patients having secondary thyroid tumour, and the longest survival was 7 years [53].

The spectrum of MTS differs between hospitals, e.g., renal cell carcinoma (48.1%), colorectal (10.4%), pulmonary (8.3%) and breast carcinoma (7.8%) as well as sarcomas (4.0%) were observed in German series [54]. Wide scope of primary tumours was disclosed in cytologically investigated cases, including pulmonary (6/20), gastrointestinal, breast (each 5/20), laryngeal (3/20) and renal cell (1/20) carcinoma [52].

In the largest series of secondary thyroid tumours, comprising 97 patients who underwent FNA in Mayo Clinic, lung and kidney were the most frequent primary sites (22% each), followed by head and neck cancer (12%) as reported by Hegerova et al. [55]. Similarly to the observations by Zhang et al. [53], prolonged survival was seen in some patients, reaching 228 months (median, 20 months). Thyroid resection was not infrequent: it was performed in 41/97 patients reaching survival of 30 months (range, 3–171 months), while the median survival in non-operated patients was 12 months (range, 1–228 months). The difference was statistically insignificant [55].

Metastases of cutaneous or uveal melanomas have been reported and can present a major diagnostic problem considering that melanoma is another "great mimic" in pathology [56].

4.7. Immunohistochemistry of thyroid neoplasms

Although in most cases routine stains are sufficient for correct classification of a thyroid nodule, ancillary methods are occasionally necessary. Immunohistochemistry (IHC) is a well-known, easily applicable technology, nowadays complemented with automatization and digital evaluation. The expenses are moderate, making IHC a widely available approach. It benefits from high accuracy of antigen-antibody reaction and visual evaluation of the positive targets resulting in correct interpretation.

In thyroid pathology, several antigen groups have been explored. Antigens that are specific for thyroid follicular cells (thyroglobulin, TTF-1) are useful to identify the follicular origin of a neoplasm. Expression is observed in PC [22], FA [3] and FC [23] as well as in Hurtle cell tumours. MC is negative for thyroglobulin but can exhibit a weak staining for TTF-1 [49], although controversial opinions have been expressed. A possible pitfall is nuclear expression of TTF-1 in non-squamous lung cancer MTS (adenocarcinoma, small cell carcinoma, large cell carcinoma). Lung cancer lacks thyroglobulin but can express surfactant apoprotein A (adenocarcinoma), napsin A (adenocarcinoma; however, positive reaction in thyroid cancers has been reported) or neuroendocrine markers (small cell carcinoma and large cell neuroendocrine carcinoma).

Neuroendocrine markers (chromogranin A, synaptophysin) along with calcitonin are characteristic of MC [49] and C-cell hyperplasia. PC and FA are negative for chromogranin A, other neuroendocrine markers and calcitonin [3, 22].

Membrane proteins, including HBME-1, TROP-2, beta-galactoside-binding protein family galectins and glypicans (one of the two protein families within heparin sulphate proteoglycan class), are helpful in PC diagnostics. Cytoskeleton composition by certain intermediate filaments (cytokeratin (CK) 19, vimentin) also shows correlation with specific pathological processes. Proliferation activity in carcinomas is generally higher than in benign nodules but the levels in differentiated cancers are too low to set a reliable diagnostic threshold. Nevertheless, proteins that are involved in cell cycle regulation and apoptosis have been evaluated in thyroid pathology.

Hector Battifora mesothelial epitope, widely known by the abbreviation HBME-1, is a membranous antigen, located on microvilli of benign and malignant mesothelial cells [57, 58]. In the thyroid, intense HBME-1 expression is characteristic for PC [22, 59]. Membranous pattern is the most specific [22]. Diffuse and intense membranous expression is strongly supportive for PC diagnosis [60]. A fraction of FC is positive [23], but reactivity in FA is considered rare [3].

The reported expression rate of HBME-1 in PC ranges between 73.8% [61], 75.9% [62], 85.0% [63] and 96.1% [64]. Higher frequency has been found in classic PC, e.g., ranging between 95.9 and 100% in contrast to 45.0–81.1% in follicular variants [61, 65]. However, some authors report close findings in classic or follicular variant. Thus, in a large IHC study of 127 thyroid tumours, including 49 classic PCs, 29 cases of follicular variant of papillary carcinoma (FVPC) and 49 FAs, HBME-1 was expressed in 88% of classic PC and 86% cases of FVPC, contrasting with 4% in FA [60].

The expression of HBME-1 in PC differs from surrounding benign thyroid tissues [66]. In a large study of 177 thyroid glands (including 53 PCs, 11 FVPC cases, 13 FCs and 100 benign thyroids), HBME-1 was expressed in 74% of PC and 89% of FVPC, but was not found (0%) in Graves' disease or nodular colloid goitre [67]. Prasad et al. also confirmed the absence of HBME-1 in Graves' disease and normal thyroid but experienced a single case (1%) of positive nodular goitre [63]. Higher expression rate in benign thyroid tissues (7.0%) has been reported by Nasr et al. [64]. The HMBE-1 reactivity in follicular neoplasms also differs remarkably between studies: 17% [67] *vs.* 26.7% [62] *vs.* 50.0% [63] *vs.* 85.7% [68] of FC and 4% [60] *vs.* 10% [63] *vs.* 11% [67] *vs.* 14.8% [62] *vs.* 64% [68] of FA.

The differences might be attributable to the evaluation (pattern: membranous only *vs.* membranous and cytoplasmic), cut-off threshold, selection of primary antibodies, epitope retrieval, dilution, incubation temperature and incubation time. Thus, although HBME-1 is among the most sensitive and specific antigens in the PC diagnostics [61] and has been included in most diagnostic panels [58] for PC or thyroid cancer (predominated by PC), controversies remain.

Few, but promising reports are available on human trophoblast cell surface antigen TROP-2 in PC, which seems to be a reliable marker in histology and cytology, holding high specificity and sensitivity [61, 69–71]. The TROP-2 protein is absent from MC, follicular tumours and non-neoplastic thyroid tissue [70, 71], while it is present in 82.5% of PC. The limits of the marker include diagnostics of follicular variant which shows less frequent and focal staining. Nevertheless, the presence of 10% positive cells in a tumour indicates PC, and the heterogeneity is sufficiently low to apply TROP-2 IHC on FNA specimens [70]. Again, data on expression frequency are variable. Thus, in a recent study, TROP-2 was found in between 90.0 and 95.3% PC and 70.0% follicular variants [71]. However, other research groups have described significantly less frequent reactivity: 50% [61].

CITED1 (the abbreviation for CREB (cAMP-response element-binding protein)/ p300 interacting transactivator with glutamic acid/ aspartic acid-rich carboxy-terminal domain 1) protein, encoded by *CITED1* gene, acts as transcriptional activator. The expression pattern is nuclear and cytoplasmic [63]. CITED1 enhances SMAD-mediated transcription by strengthening the interaction between DNA, transcription factors and coactivators (SMAD is an acronym coined by the fusion of names for the *Sma* gene in *Caenorhabditis elegans* and the "mothers against decapentaplegic" *Mad* gene in *Drosophila*). In association with SMAD pathway, CITED1 promotes signalling via transforming growth factor beta (TGF-beta) molecular pathway. CITED1 also stabilises interaction between oestrogen receptors and histone acetyltransferase, enhancing oestrogen-dependent gene expression, and associates with chromatin in oestrogen-dependent way.

CITED1 is expressed in PC [22]. Some authors consider it useful in differential diagnostics between PC, including follicular variant, and FA [43, 72] as expression of CITED1 in FA is considered rare [3]. However, CITED1 has been found in both benign and malignant pathologies. Thus, in a large study of 177 thyroid glands (including 53 PCs, 11 FVPC cases, 13 FCs and 100 benign thyroids), CITED1 was expressed not only in 98% of PC, 100% of FVPC, and 86% of FC but also in 89% of Graves' disease cases, 79% of nodular colloid goitre and 80% of FA [67]. More promising data were obtained in another large IHC study of 127 thyroid tumours, including 49 classic PCs, 29 FVPC cases and 49 FAs. CITED1 was expressed in 90% of classic PC and 83% FVPC cases, contrasting with 16% of FA [60]. Similarly, CITED1 was expressed in 93% of PC, 25% of FC, 10% of FA and 8% of nodular goitre, but it was not found in normal thyroid glands and Graves' disease cases [63]. Among 215 formalin-fixed, paraffin-embedded thyroid specimens, CITED1 was expressed in 87% PC and 50% FC while only 10% of FA and 24% of nodular goitre were positive, but cases of Graves' disease and normal thyroid were invariably negative [63].

CITED1 expression is dependent on technological issues. One of the described rabbit antibodies has been associated with increased background to such a degree that interferes with reliable evaluation. However, another rabbit antibody has also been considered as having lower sensitivity and specificity in comparison with HBME-1 and CK19 [60].

Knowing the role of CITED1 in PC and the epidemiological evidence of higher incidence in females, it is not surprising to find expression of oestrogen and progesterone receptors in papillary carcinoma. Expression of oestrogen receptor alpha and progesterone receptor has been reported in 19% and 38.7–57% of PC cases, correspondingly [73, 74].

Galectins represent a family of proteins that are defined by the capacity to bind beta-galactoside carbohydrates. Galectins are located in cell nuclei, cytoplasm or extracellular space. Galectins are classified into dimeric, tandem and chimera classes. Dimeric galectins, e.g., galectin-1, are simple homodimers. Tandem galectins contain one or more carbohydrate recognition domains in a single peptide chain. Chimeric class, represented only by galectin-3, has long non-lectin domain. Such chimeric molecule can exist as a monomer (at low concentration) or form multimers (at high concentration), if up to five monomers are linked by non-lectin domain. The physiologic effects are different: while monomers inhibit adhesion by blocking adhesion proteins, pentamers create intercellular bridges or link cells and extracellular matrix.

Expression of galectin-3 in FA is rare [3]. Galectin-3 is more frequently seen in malignant thyroid tumours [75], and this finding has strong pathogenetic basis. Knockdown or antagonists of galectin-3 suppress the migratory capacity of PC cells. Galectin-3 is upregulated by hypoxia-inducible factor (HIF)-1 [76]. In PC, the expression rate has been estimated as 64.7% [65] *vs.* 69% [61] *vs.* 92% [67] or even 100% [77]. Lower rate has been reported in follicular variant: 33 *vs.* 92% in classic cases [67]. However, some authors describe close findings in classic or follicular variant. Thus, in a large IHC study of 127 thyroid tumours, including 49 classic PCs, 29 FVPC cases and 49 FAs, galectin-3 was expressed in 96% of classic PC and 90% FVPC cases, contrasting with 18% in FA [60]. The expression frequency reached 97% in a small mixed group of carcinomas, comprising 22 PCs (16 classic and six FVPC cases), 3 FCs, 5 MCs and a single Hurtle cell carcinoma [75]. Among 13 FCs, the expression rate was 33% [67]. The staining pattern should be both nuclear and cytoplasmic [22]. Notably, benign reactive epithelial

and inflammatory cells in Hashimoto thyroiditis can express galectin-3 [22, 60]. No expression was found in Graves' disease and nodular colloid goitre by Liu et al. [67]. However, other research groups have noted the presence of galectin-3 in 55% of nodular goitre and 7% of Graves' diseases cases while normal thyroid tissues were invariably negative [63]. FA has been described as negative [67] or occasionally (18%) positive [60]. In general, galectin-3 has been found in 10% [63] *vs.* 30% [75] *vs.* 43% [77] FA, more frequently (80%) in Hurtle cell adenomas [77]. Even the authors reporting less frequent positivity in FA, consider galectin-3 as a second-line marker due to lower specificity and sensitivity [60].

Along with CK19 and galectin-3, galectin-1 is more frequently expressed in PC than in FA. Loss of galectin-1 activity suppresses proliferation, migration and invasion [78]. In cell cultures, galectin-1 has been evaluated as the target for vectorised contrast agent, bearing peptide-conjugated ultrasmall superparamagnetic iron oxide particles for MRI [79].

Glypicans along with syndecans represent the major protein families of heparin sulphate proteoglycans. Glypicans are involved in developmental processes as well as regulation of cell signalling by Wnt and Hedgehog pathways. Glypican-3 is more frequently expressed in malignant thyroid tumours. Among 17 FA, the expression rate was 24%. Higher positivity rate (81%) was observed in a small mixed group of carcinomas, comprising 22 PCs, 3 FCs, 5 MCs and one case of Hurtle cell carcinoma [75]. In a larger group, glypican-3 was found in 100% (20/20) of FC and 70% (48/69) of PC [80].

PCs are characterised by upregulation of CD44 and its ligand osteopontin. Expression of osteopontin in PC is statistically significantly higher than normal thyroid tissue, colloid goitre and FA. In addition, the presence and intensity of osteopontin expression correlates with proliferation activity [81], capacity to invade and occurrence of adverse prognostic factors such as lymph node metastases and large size of the tumour [82]. Expression of osteopontin is found in 83.3% of PC, 70.0% of benign thyroid nodules and 50.0% of normal thyroid tissues [83]. Limited amount of information is available on osteopontin in FC, but upregulation has been shown in dogs [84]. In MC, osteopontin is expressed in 78.4% of cases and shows association with good prognostic features [85]. The levels of bone sialoprotein are increased in PC. Thus, expression of bone sialoprotein is found in 87.9% of PC, 55.0% of benign thyroid nodules and 42.5% of normal thyroid tissues [83]. PC is characterised by statistically significant cytoplasmic and membranous upregulation of vitamin D receptor in comparison to non-neoplastic thyroid tissues. Cancer cells also possess vitamin-D inactivating 24-hydroxylase but not activating enzyme, namely, 1-alpha-hydroxylase. Overexpression of 24-hydroxylase is associated with extrathyroid invasion and lymph node metastases [74].

Regarding CD44 variant 6 protein, the positive cell fraction in PC constitutes 80.3% while only 37.1% of cells in benign thyroid nodules and 22.9% of normal thyroid epithelial cells are positive [86]. Stem cell marker CD44 is involved in epithelial-mesenchymal transition (EMT), characterised by loss of epithelial markers, e.g., E-cadherin, and appearance of mesenchymal proteins, e.g., vimentin. Expression of vimentin was found in 53.8% of PC and 75% of FC [87]. PCs feature loss of E-cadherin in contrast to surrounding benign thyroid tissues. Nevertheless, E-cadherin along with CD56 is upregulated in FA [88]. However, if cancer is assessed separately, not within the context with surrounding tissues, E-cadherin is still retained. Thus, expression of E-cadherin was found in 84.6% of PC and 75% of FC [87].

Claudins are another class of EMT-associated proteins [89]. In FC, transmembrane tight junction protein claudin is dislocated from membrane to nucleus. Switch in subcellular compartmentalisation leads to increased proliferation, invasion and migration [90].

Among cytokeratins, CK19 has attracted attention. Intense expression of CK19 is considered a valuable diagnostic marker in PC [91], although it is the least specific marker of malignancy [22, 59]. In PC, reported expression rates of CK19 range between 45.6% [65], 83.3% [61] and 84.6% [87]. Expression of CK19 was found in 25% of FC [87]. However, in a large study of 177 thyroids (including 53 PCs, 11 FVPC cases, 13 FCs and 100 benign glands), CK19 was found in 78% of PC, 22% of follicular variants, but was absent from FC, FA, Graves' disease cases and nodular colloid goitre [67]. Promising data were obtained in another IHC study of 127 thyroid tumours, including 49 classic PC, 29 FVPC cases and 49 FA. CK19 was expressed in 100% of classic PC and 90% FVPC cases, contrasting with 14% of FA [60]. Nevertheless, in another study, CK19 was found in 100% PC and even 68.4% of benign thyroid tissues [64]. In a significant cohort of 215 thyroids, CK19 was expressed in 72% of PC, 50% of FC, 5% of FA, 31% of nodular goitre, 0% of Graves' disease and 7% of normal thyroids [63].

CK19 is considered to have high sensitivity but lower specificity in the differential diagnosis between PC and FA. However, not mere presence but also the intensity and distribution of expression matters. The expression in PC tends to be strong and diffuse while FA shows focal and weaker staining. The expression in nodular hyperplasia and normal thyroid tissues also tends to be focal and weak [60]. The comparison between nodule and surrounding tissues would be important. In addition, PC is positive for pancytokeratin and CK7, but negative for CK20—a fact that in rare circumstances is helpful to distinguish between PC and thyroid metastases from a colorectal adenocarcinoma known to express CK20 [22].

In contrast with surrounding benign thyroid tissues, PC is characterised by downregulation of CD56 [59, 88]. The frequency of CD56 loss ranges from 93.9% in classic PC to 73.3% in FVPC cases [65]. In contrast, CD56 is upregulated in FA [88].

Regarding regulation of cell proliferation and apoptosis, PC is associated with increased expression of phosphorylated histone H3 and cyclin D1. Metastatic PCs exhibit upregulated caspase-3 and loss of anti-apoptotic Bcl-2 [92]. Cyclins A and B1 are found in PC as well [93]. Autophagy-related protein Beclin-1 is more frequently seen in thyroid carcinomas. The expression rate is 98.9% in PC and 57.1% in FC while only 21.4% of FAs are positive for Beclin-1. The level of Beclin-1 correlates with proliferation activity by Ki-67 [68]. Survivin is more frequently expressed in carcinomas and is associated with the biological potential of the neoplasm [94]. Cytoplasmic location of p27 has been observed in PC [95], and p27 along with galectin has been advised to discriminate between FA and FC [96].

PC is characterised by complete or almost complete loss of c-kit/CD117 protein contrasting with benign thyroid nodules and normal follicular epithelium [97].

Aberrant membranous expression of CD20 has recently been reported in PC [98, 99]. In a small group of PC, expression was found in 5/22 (23%) tumours [99]. The findings were confirmed in a large cohort of 538 PCs [98] disclosing reactivity in 10% of cases. Although CD20 was associated with less aggressive morphological features of PC, expression in anaplastic

Panel	Aim	Cohort	References
HBME-1, galectin-3, CK19	FVPC *vs.* FA	157 thyroid tumours, 5 normal glands	[72]
HBME-1, galectin-3, CITED1	FVPC *vs.* FA	157 thyroid tumours, 5 normal glands	[72]
HBME-1, CK19 Second line: CITED1, galectin-3	PC *vs.* FA	127 thyroid tumours: 49 classic PC, 29 FVPC, 49 FA	[60]
HBME-1, CK19	PC *vs.* benign thyroid tissues	51 PC, 57 benign cases	[64]

HBME, Hector Battifora mesothelial epitope; CK, cytokeratin; CITED1, the abbreviation for CREB (cAMP-response element-binding protein)/ p300 interacting transactivator with glutamic acid/ aspartic acid-rich carboxy-terminal domain 1; FVPC, follicular variant of papillary carcinoma; FA, follicular adenoma and PC, papillary carcinoma.

Table 2. Immunohistochemical panels in the diagnostics of thyroid nodules.

thyroid cancers was observed with similar frequency (6–20%) as in PC. FAs (47) were negative. Positivity of CD20 was not associated with other B lymphocyte lineage markers as CD79alpha or PAX5 [98] but was confirmed by two different clones of primary antibody [99].

Neuroendocrine differentiation is the hallmark of MC that is positive for chromogranin A in 92.9% of cases [100]. Regarding the other regional causes of chromogranin A-positive mass lesions, parathyroid adenoma (that can occur intrathyroidally) and parathyroid hyperplasia are characterised by expression rates of 28/28 and 7/8 [100]. IHC panels should include calcitonin and carcinoembryonic antigen CEA (to identify MC with 100% specificity, as reported by Wuertz et al.) and parathyroid hormone that is expressed in 72.2% parathyroid nodules [100].

In most MCs, calcitonin is present [101]. In the rare cases of non-secretory MC, IHC diagnosis is still possible by panel of calcitonin, CEA and chromogranin A [102]. Among 75 MC, calcitonin receptor was expressed in 82.7% of cases. It showed strong positive correlation with calcitonin ($p = 0.001$) and osteocalcin ($p = 0.009$) as reported by Cappagli et al. [103]. CEA expression is characteristic and is mostly widespread and moderate to strong by intensity [104]. Presence of CD56 has been reported [101].

Clusterin is another lineage-specific IHC marker, expressed in C cells, C cell hyperplasia and primary and metastatic MC. In addition, prognostic value of clusterin score has been reported, with inverse correlation between clusterin score and presence of lymph node metastases [105]. Survivin and X-linked inhibitor of apoptosis (XIAP) are expressed in C cells and MC and are associated with worse survival [106]. Expression of HIF-1alpha is another prognostic marker. Positive expression has been shown to be associated with worse 5-year survival and progression free survival [107]. Stem cell markers CD133 and CD44 are unfavourable prognostic predictors. Both CD133 and CD44 are independent factors associated with worse overall survival, while CD44 is also significantly associated with recurrence-free survival [108]. Expression of somatostatin receptors 2A and 5 correlates with advanced stages [109]. Heat shock proteins HSP70, HSP90 and GRP78 are upregulated in MC in comparison with normal thyroid tissues [110]. Upregulation of cancer/testis antigens is seen, contrasting with negative normal thyroid tissues and goitre as well as with rare expression in PC and FC. However, poorly differentiated and anaplastic carcinomas are also positive [111].

Recognising the diversity of thyroid nodules and variability of IHC data, panel diagnostics is advised (see examples in **Table 2**).

5. miRNAs in thyroid tumours

Biochemical and biological alterations of cancer cells are largely supported by non-coding RNA (ncRNA) dysregulation in the tumour. Non-coding RNAs lack an open-reading frame and do not have protein-coding ability. Based on the size of the functional RNA molecule, regulatory ncRNAs are classified as long ncRNAs and small ncRNAs or microRNAs [112]. MicroRNAs (miRNA) are small, evolutionary conserved, single-stranded, non-coding RNA molecules (approximately 22 nucleotides in length) that bind target mRNA to regulate gene expression [113, 114]. MicroRNAs are involved in various physiological and pathological functions, such as apoptosis, cell proliferation and differentiation, which indicate their functionality in carcinogenesis as tumour suppressor genes or oncogenes [115]. Up or downregulation of miRNA can influence the tumorigenic outcome depending on the role(s) of the target genes on vital signalling processes [116].

The most often upregulated miRNAs in PC are miR-146b, miR-222, miR-221 and miR-181b. Overexpressed miR-146b targets retinoic acid receptor beta (RARβ) and reduces expression of this gene leading to increased tumour aggressiveness and extrathyroidal invasion [117–120]. MiR-221 and miR-222 target tumour suppressor and cell cycle regulator p27. Reduced expression of p27 results in increased proliferation of tumour cells. These processes are related to aggressive behaviour of tumour, extrathyroidal invasion and spread to lymph nodes [117–120]. MiR-181b is also overexpressed in PC compared to normal thyroid tissue. MiR-181b inhibits expression of cylindromatosis *CYLD* gene, which acts as tumour suppressor and normally induces apoptosis [118, 121].

The most often downregulated miRNAs in PC are miR-145, miR-451, miR-613 and miR-137. MiR-145 acts as a tumour suppressor in thyroid cancer, and its downregulation enhances cancer growth via several pathways [118]. MiR-451 functions as a tumour suppressor by targeting the PI3/AKT pathway. Downregulation of miR-451a is associated with aggressive tumour course and the presence of extrathyroidal invasion [118, 120]. In PC, miR-613 is involved in cell proliferation and invasion [117, 118], but downregulated miR-137 leads to increased cellular proliferation, invasion and migration [118].

The miRNAs found in FC are also frequently present in other subtypes of thyroid cancer [120]. MiR-199a-5p is downregulated, but miR-197 and miR-346 are upregulated in FC resulting in increased cancer cell proliferation [118].

Many miRNAs have been found to be dysregulated in thyroid cancer, but only few miRNAs are exclusively associated with anaplastic thyroid cancer [118]. Loss of miR-200 expression in anaplastic carcinoma results in EMT that represses the epithelial features of cancer cells and disrupts the cell-cell adhesion mediated by loss of E-cadherin. This process enables cells to migrate and invade [116, 118, 120].

In MC, miR-21 is recently studied. It is downregulated, especially in the aggressive cases [120]. MiR-129-5p is significantly downregulated in MC compared to normal tissue leading to increased cellular invasion and migration [118].

6. Systemic inflammatory reaction in thyroid carcinoma patients

Systemic inflammatory response (SIR) is induced by different types of cancer [122, 123]. Interaction between the tumour and the host inflammatory response is crucial in cancer development [122, 124]. Many studies confirm the association between increased SIR and poor outcome in cancer patients [124, 125]. To evaluate SIR, different parameters are used: neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), concentration of acute phase proteins, clotting factors and albumins, e.g., Glasgow Prognostic Score (GPS) and others [123, 126]. The role of SIR in thyroid cancer is still poorly understood. Authors of several studies have suggested that increased NLR is associated with larger tumour size and increased recurrence risk of thyroid cancer [127, 128].

7. Conclusions

In conclusion, thyroid nodules represent an important problem in endocrine surgery as a frequent finding inducing complicated differential diagnostics. In general population, such nodules are found in 3.7–7% by palpation and 42–67% by US. Cancer risk in thyroid nodule varies: 5% in masses found by palpation, 1.6–15% by US, 3.9–11.3% by CT, 5–6% by MRI and 30–50% by PET.

The epidemiological picture of thyroid carcinoma is characterised by growing incidence and stable or decreasing mortality, suggesting overtreatment of an indolent disease. However, mortality growth is seen in some countries, e.g., in Costa Rica (for 66.9%), Moldova (49.9%), Uruguay (47.9%), Latvia (26.2%), Ecuador (36.3%), New Zealand (14.5%) and Portugal (15.7%) for males and Colombia, Ecuador (both 17.8%) or Greece (13.3%) for females. In addition, SEER data disclose growing incidence of large carcinomas. Clinically, incidental thyroid nodules are reported less frequently than in dedicated research studies. Thus, true incidence growth can be related to risk factors such as changes in iodine supplementation, adiposity, oestrogens, parity, pregnancy-related increases in TSH levels, exposure to ionising radiation and chemicals, e.g., polybrominated diphenyl ethers, used as flame retardants.

The final diagnosis of thyroid tumours, dominated by benign follicular adenomas and malignant papillary, follicular and medullary carcinomas, depends on FNA and histopathology. Classic morphology, based on invasion and nuclear features, substantiates the diagnosis in most cases and represents the basis of WHO diagnostic criteria.

A significant innovation is the definition of new entities in the recent WHO classification to designate thyroid tumours with controversial morphological appearance, doubtful invasion or questionable nuclear features. Follicular tumours that definitely lack invasion but exhibit

controversial nuclear structure are classified as non-invasive follicular thyroid neoplasm with papillary-like nuclear features. Follicular-patterned neoplasms with questionable invasion are called either follicular tumours of uncertain malignant potential if the nuclei are of non-papillary type or well-differentiated tumour of uncertain malignant potential in other cases. These new entities provide pathologists with the long-awaited benefit of accurate diagnosis.

Ancillary methods include the widely accessible immunohistochemistry and rapidly developing field of miRNA analysis. HBME-1, TROP-2, CITED1 and CK19 can be helpful in diagnostics of papillary carcinoma, while galectin-3 might serve as second-line marker. Expression of CD20 in PC has been recently reported. Distinction between FA and FC is difficult; HBME-1, p27 and galectin evaluation has been recommended. MC holds neuroendocrine differentiation.

Regarding miRNAs, PC is characterised by upregulation of miR-146b, miR-222, miR-221 and miR-181b and downregulation of miR-145, miR-451, miR-613 and miR-137. FC features downregulated miR-199a-5p and upregulated miR-197 and miR-346. In MC, miR-21 and miR-129-5p are downregulated.

Initial studies suggest that increased SIR can be poor prognostic factor in thyroid cancer.

Acknowledgements

The present work was supported by scientific project No. 1.1.1.2./VIAA/1/16/242 (BS).

Conflict of interest

The authors report no conflicts of interest to disclose.

Author details

Ilze Fridrihsone[1]*, Ilze Strumfa[1], Boriss Strumfs[2], Andrejs Vanags[3], Dainis Balodis[1], Arvids Jakovlevs[1], Arnis Abolins[1] and Janis Gardovskis[3]

*Address all correspondence to: Ilze.Fridrihsone@rsu.lv

1 Department of Pathology, Riga Stradins University, Riga, Latvia

2 Latvian Institute of Organic Synthesis, Riga, Latvia

3 Department of Surgery, Riga Stradins University, Riga, Latvia

References

[1] Ahn HS, Lee JB, Seo M, Park SH, Choi BI. Distinguishing benign from malignant thyroid nodules using thyroid ultrasonography: Utility of adding superb microvascular imaging

and elastography. La Radiologia Medica. 2018;**123**(4):260-270. DOI: 10.1007/s11547-017-0839-2 [Epub ahead of print]

[2] Wilhelm S. Evaluation of thyroid incidentaloma. The Surgical Clinics of North America. 2014;**94**(3):485-497. DOI: 10.1016/j.suc.2014.02.004

[3] Nikiforov YE, Baloch ZW, Belge G, Chan JKC, Derwahl KM, Evans HL, Fagin JA, Ghossein RA, Lloyd RV, Oriola J, Osamura RY, Paschke R, Sobrinho Simoes M. Follicular adenoma. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. pp. 69-72

[4] Choi N, Moon WJ, Kim HY, Roh HG, Choi JW. Thyroid incidentaloma detected by time-resolved magnetic resonance angiography at 3T: Prevalence and clinical significance. Korean Journal of Radiology. 2012;**13**(3):275-282. DOI: 10.3348/kjr.2012.13.3.275

[5] Lim HK, Park ST, Ha H, Choi SY. Thyroid nodules detected by contrast-enhanced magnetic resonance angiography: Prevalence and clinical significance. PLoS One. 2016;**11**(2): e0149811. DOI: 10.1371/journal.pone.0149811

[6] Kim K, Emoto N, Mishina M, Okada S, Isu T, Yoshida D, Kobayashi S, Teramoto A. Incidental detection of thyroid nodules at magnetic resonance imaging of the cervical spine. Neurologia Medico-Chirurgica (Tokyo). 2013;**53**(2):77-81. DOI: https://doi.org/10.2176/nmc.53.77

[7] Farra JC, Picado O, Liu S, Ouyang W, Teo R, Franco AM, Lew JI. Clinically significant cancer rates in incidentally discovered thyroid nodules by routine imaging. The Journal of Surgical Research. 2017;**219**:341-346. DOI: 10.1016/j.jss.2017.06.050

[8] Hoang JK, Nguyen XV. Understanding the risks and harms of management of incidental thyroid nodules: A review. JAMA Otolaryngology. Head & Neck Surgery. 2017; **143**(7):718-724. DOI: 10.1001/jamaoto.2017.0003

[9] Papaleontiou M, Hughes DT, Guo C, Banerjee M, Haymart MR. Population-based assessment of complications following surgery for thyroid cancer. The Journal of Clinical Endocrinology and Metabolism. 2017;**102**(7):2543-2551. DOI: 10.1210/jc.2017-00255

[10] Cannizzaro MA, Lo Bianco S, Picardo MC, Provenzano D, Buffone A. How to avoid and to manage post-operative complications in thyroid surgery. Updates in Surgery. 2017;**69**(2):211-215. DOI: 10.1007/s13304-017-0475-3

[11] Lee YS, Nam KH, Chung WY, Chang HS, Park CS. Postoperative complications of thyroid cancer in a single center experience. Journal of Korean Medical Science. 2010;**25**(4): 541-545. DOI: 10.3346/jkms.2010.25.4.541

[12] Su A, Wang B, Gong Y, Gong R, Li Z, Zhu J. Risk factors of hypoparathyroidism following total thyroidectomy with central lymph node dissection. Medicine (Baltimore). 2017; **96**(39):e8162. DOI: 10.1097/MD.0000000000008162

[13] Francis DO, Pearce EC, Ni S, Garrett CG, Penson DF. Epidemiology of vocal fold paralyses after total thyroidectomy for well-differentiated thyroid cancer in a Medicare population. Otolaryngology and Head and Neck Surgery. 2014;**150**(4):548-557. DOI: 10.1177/0194599814521381

[14] Materazzi G, Ambrosini CE, Fregoli L, De Napoli L, Frustaci G, Matteucci V, Papini P, Bakkar S, Miccoli P. Prevention and management of bleeding in thyroid surgery. Gland Surgery. 2017;**6**(5):510-515. DOI: 10.21037/gs.2017.06.14

[15] Brito JP, Morris JC, Montori VM. Thyroid cancer: Zealous imaging has increased detection and treatment of low risk tumours. British Medical Journal. 2013;**347**:f4706. DOI: 10.1136/bmj.f4706

[16] Schneider R, Machens A, Randolph GW, Kamani D, Lorenz K, Dralle H. Opportunities and challenges of intermittent and continuous intraoperative neural monitoring in thyroid surgery. Gland Surgery. 2017;**6**(5):537-545. DOI: 10.21037/gs.2017.06.08

[17] Yang S, Zhou L, Lu Z, Ma B, Ji Q, Wang Y. Systematic review with meta-analysis of intraoperative neuromonitoring during thyroidectomy. International Journal of Surgery. 2017;**39**:104-113. DOI: 10.1016/j.ijsu.2017.01.086

[18] Adam MA, Thomas S, Youngwirth L, Hyslop T, Reed SD, Scheri RP, Roman SA, Sosa JA. Is there a minimum number of thyroidectomies a surgeon should perform to optimize patient outcomes? Annals of Surgery. 2017;**265**(2):402-407. DOI: 10.1097/SLA.0000000000001688

[19] Huang K, Luo D, Huang M, Long M, Peng X, Li H. Protection of parathyroid function using carbon nanoparticles during thyroid surgery. Otolaryngology and Head and Neck Surgery. 2013;**149**(6):845-850. DOI: 10.1177/0194599813509779

[20] La Vecchia C, Malvezzi M, Bosetti C, Garavello W, Bertuccio P, Levi F, Negri E. Thyroid cancer mortality and incidence: A global overview. International Journal of Cancer. 2015;**136**(9):2187-2195. DOI: 10.1002/ijc.29251

[21] Lukas J, Drabek J, Lukas D, Dusek L, Gatek J. The epidemiology of thyroid cancer in the Czech Republic in comparison with other countries. Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czech Republic. 2013;**157**(3):266-275. DOI: 10.5507/bp.2012.086

[22] Rosai J, Albores Saavedra J, Asioli S, Baloch ZW, Bogdanova T, Chen H, DeLellis RA, Erickson LA, Fagin JA, Franssila KO, Giordano TJ, Hay ID, Katoh R, Lloyd RV, Mete O, Nikiforov YE, Piana S, Prasad ML, Sadow P, Schneider AB, Soares P, Sobrinho Simoes M, Vielh P, Wenig BM. Papillary thyroid carcinoma. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. pp. 81-91

[23] LiVolsi V, Abdulkader Nallib I, Baloch ZW, Bartolazzi A, Chan JKC, DeLellis RA, El Naggar AK, Eloy C, Eng C, Fagin JA, Ghossein RA, Giordano TJ, Kondo T, Lloyd RV, Mete O, Nikiforov YE, Nonaka D, Paschke R, Perren A, Rosai J, Sadow P, Schneider AB, Sobrinho Simoes M, Tallini G, Williams MD. Folicular thyroid carcinoma. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. pp. 92-95

[24] Tormey WP, Byrne B, Hill AD, Sherlock M, Thompson CJ. Should serum calcitonin be routinely measured in patients presenting with thyroid nodule? Minerva Endocrinologica. 2017;**42**(4):306-310. DOI: 10.23736/S0391-1977.17.02566-4

[25] Kilfoy BA, Zheng T, Holford TR, Han X, Ward MH, Sjodin A, Zhang Y, Bai Y, Zhu C, Guo GL, Rothman N, Zhang Y. International patterns and trends in thyroid cancer incidence, 1973-2002. Cancer Causes & Control. 2009;**20**(5):525-531. DOI: 10.1007/s10552-008-9260-4

[26] Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngology. Head & Neck Surgery. 2014;**140**(4):317-322. DOI: 10.1001/jamaoto.2014.1

[27] Uppal A, White MG, Nagar S, Aschebrook-Kilfoy B, Chang PJ, Angelos P, Kaplan EL, Grogan RH. Benign and malignant thyroid incidentalomas are rare in routine clinical practice: A review of 97,908 imaging studies. Cancer Epidemiology, Biomarkers & Prevention. 2015;**24**(9):1327-1331. DOI: 10.1158/1055-9965.EPI-15-0292

[28] Grady AT, Sosa JA, Tanpitukpongse TP, Choudhury KR, Gupta RT, Hoang JK. Radiology reports for incidental thyroid nodules on CT and MRI: High variability across subspecialties. AJNR. American Journal of Neuroradiology. 2015;**36**(2):397-402. DOI: 10.3174/ajnr.A4089

[29] Schmid D, Ricci C, Behrens G, Leitzmann MF. Adiposity and risk of thyroid cancer: A systematic review and meta-analysis. Obesity Reviews. 2015;**16**(12):1042-1054. DOI: 10.1111/obr.12321

[30] Colditz GA, Peterson LL. Obesity and cancer: Evidence, impact and future directions. Clinical Chemistry. 2018;**64**(1):154-162. DOI: 10.1373/clinchem.2017.277376

[31] Derwahl M, Nicula D. Estrogen and its role in thyroid cancer. Endocrine-Related Cancer. 2014;**21**(5):T273-T283. DOI: 10.1530/ERC-14-0053

[32] Rajoria S, Hanly E, Nicolini A, George AL, Geliebter J, Shin EJ, Suriano R, Carpi A, Tiwari RK. Interlinking of hypoxia and estrogen in thyroid cancer progression. Current Medicinal Chemistry. 2014;**21**(11):1351-1360. DOI : 10.2174/09298673216661312011424 34

[33] Zhu J, Zhu X, Tu C, Li YY, Qian KQ, Jiang C, Feng TB, Li C, Liu GJ, Wu L. Parity and thyroid cancer risk: A meta-analysis of epidemiological studies. Cancer Medicine. 2016;**5**(4):739-752. DOI: 10.1002/cam4.604

[34] Zabuliene L, Jasilionis D, Miseikyte-Kaubriene E, Stukas R, Kaceniene A, Smailyte G. Parity and risk of thyroid cancer: A population-based study in Lithuania. Hormones & Cancer. 2017;**8**(5-6):325-329. DOI: 10.1007/s12672-017-0308-3

[35] Wartofsky L. Increasing world incidence of thyroid cancer: Increased detection or higher radiation exposure? Hormones (Athens, Greece). 2010;**9**(2):103-108

[36] Takano T. Natural history of thyroid cancer [review]. Endocrine Journal. 2017;**64**(3):237-244. DOI: 10.1507/endocrj.EJ17-0026

[37] Grani G, Lamartina L, Cantisani V, Maranghi M, Lucia P, Durante C. Interobserver agreement of various thyroid imaging reporting and data systems. Endocrine Connections. 2018;**7**(1):1-7. DOI: 10.1530/EC-17-0336

[38] Prieditis P, Radzina M, Strumfa I, Narbuts Z, Ozolins A, Vanags A, Gardovskis J. Diagnostic value of contrast-enhanced ultrasound evaluation of malignant and benign solitary thyroid nodules. Proceedings of the Latvian Academy of Sciences. Section B. 2016;**70**(1):1-6. DOI: 10.1515/prolas-2016-0001

[39] Lu R, Meng Y, Zhang Y, Zhao W, Wang X, Jin M, Guo R. Superb microvascular imaging (SMI) compared with conventional ultrasound for evaluating thyroid nodules. BMC Medical Imaging. 2017;**17**(1):65. DOI: 10.1186/s12880-017-0241-5

[40] Suh CH, Baek JH, Choi YJ, Lee JH. Performance of CT in the preoperative diagnosis of cervical lymph node metastasis in patients with papillary thyroid cancer: A systematic review and meta-analysis. AJNR. American Journal of Neuroradiology. 2017;**38**(1):154-161. DOI: 10.3174/ajnr.A4967

[41] Moghaddam PA, Virk R, Sakhdari A, Prasad ML, Cosar EF, Khan A. Five top stories in thyroid pathology. Archives of Pathology & Laboratory Medicine. 2016;**140**(2):158-170. DOI: 10.5858/arpa.2014-0468-RA

[42] Agaimy A, Hahn T, Schroeder J, Elhag A. Follicular thyroid adenoma dominated by spindle cells: Report of two unusual cases and literature review. International Journal of Clinical and Experimental Pathology. 2012;**5**(2):143-151

[43] Lloyd RV, Buehler D, Khanafshar E. Papillary thyroid carcinoma variants. Head and Neck Pathology. 2011;**5**(1):51-56. DOI: 10.1007/s12105-010-0236-9

[44] Giordano TJ. Follicular cell thyroid neoplasia: Insights from genomics and The Cancer Genome Atlas research network. Current Opinion in Oncology. 2016;**28**(1):1-4. DOI: 10.1097/CCO.0000000000000248

[45] Romero-Rojas AE, Diaz-Perez JA, Mastrodimos M, Chinchilla SI. Follicular thyroid carcinoma with signet ring cell morphology: Fine-needle aspiration cytology, histopathology, and immunohistochemistry. Endocrine Pathology. 2013;**24**(4):239-245. DOI: 10.1007/s12022-013-9271-x

[46] Squillaci S, Pitino A, Spairani C, Ferrari M, Carlon E, Cosimi MF. Mucinous variant of follicular carcinoma of the thyroid gland: Case report and review of the literature. International Journal of Surgical Pathology. 2016;**24**(2):170-176. DOI: 10.1177/1066896915617026

[47] Chan JKC, Nikiforov YE, Tallini G. Other encapsulated follicular-patterned thyroid tumours. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. pp. 75-80

[48] Range DE, Jiang XS. An update on noninvasive follicular thyroid neoplasm with papillary-like nuclear features. Current Opinion in Oncology. 2018;**30**(1):1-7. DOI: 10.1097/CCO.0000000000000416

[49] DeLellis RA, Al Ghuzlan A, Albores Saavedra J, Baloch ZW, Basolo F, Elisei R, Kaserer K, LiVolsi V, Matias-Guiu X, Mete O, Moley JF, Nikiforov YE, Nose V, Pinto AE. Medullary thyroid carcinoma. In: Lloyd RV, Osamura RY, Kloppel G, Rosai J, editors. WHO Classification of Tumours of Endocrine Organs. 4th ed. Lyon: International Agency for Research on Cancer; 2017. pp. 108-113

[50] Chu YH, Lloyd RV. Medullary thyroid carcinoma: Recent advances including microRNA expression. Endocrine Pathology. 2016;**27**(4):312-324. DOI: 10.1007/s12022-016-9449-0

[51] Baloch ZW, LiVolsi VA. C-cells and their associated lesions and conditions: A pathologists perspective. Turkish Journal of Pathology. 2015;**31**(Suppl 1):60-79. DOI: 10.5146/tjpath.2015.01315

[52] Rossi ED, Martini M, Straccia P, Gerhard R, Evangelista A, Pontecorvi A, Fadda G, Maria Larocca L, Schmitt F. Is thyroid gland only a "land" for primary malignancies? Role of morphology and immunocytochemistry. Diagnostic Cytopathology. 2015;**43**(5):374-380. DOI: 10.1002/dc.23241

[53] Zhang L, Liu Y, Li X, Gao W, Zheng C. Metastases to the thyroid gland: A report of 32 cases in PUMCH. Medicine (Baltimore). 2017;**96**(36):e7927. DOI: 10.1097/MD.0000000000007927

[54] Schmid KW. Lymph node and distant metastases of thyroid gland cancer. Metastases in the thyroid glands (Article in German). Der Pathologe. 2015;**36**(Suppl 2):171-175. DOI: 10.1007/s00292-015-0071-6

[55] Hegerova L, Griebeler ML, Reynolds JP, Henry MR, Gharib H. Metastasis to the thyroid gland: Report of a large series from the Mayo Clinic. American Journal of Clinical Oncology. 2015;**38**(4):338-342. DOI: 10.1097/COC.0b013e31829d1d09

[56] Collins DC, Yela R, Horgan N, Power DG. A rare thyroid metastasis from uveal melanoma and response to immunotherapy agents. Case Reports in Oncological Medicine. 2016;**2016**:6564094. DOI: 10.1155/2016/6564094

[57] Mase T, Funahashi H, Koshikawa T, Imai T, Nara Y, Tanaka Y, Nakao A. HBME-1 immunostaining in thyroid tumors especially in follicular neoplasm. Endocrine Journal. 2003;**50**(2):173-177. DOI: https://doi.org/10.1507/endocrj.50.173

[58] Arcolia V, Journe F, Renaud F, Leteurtre E, Gabius HJ, Remmelink M, Saussez S. Combina tion of galectin-3, CK19 and HBME-1 immunostaining improves the diagnosis of thyroid cancer. Oncology Letters. 2017;**14**(4):4183-4189. DOI: 10.3892/ol.2017.6719

[59] Erdogan-Durmus S, Ozcan D, Yarikkaya E, Kurt A, Arslan A. CD56, HBME-1 and cytokeratin 19 expressions in papillary thyroid carcinoma and nodular thyroid lesions. Journal of Research in Medical Sciences. 2016;**21**:49. DOI: 10.4103/1735-1995.183986

[60] Scognamiglio T, Hyjek E, Kao J, Chen YT. Diagnostic usefulness of HBME1, galectin-3, CK19, and CITED1 and evaluation of their expression in encapsulated lesions with questionable features of papillary thyroid carcinoma. American Journal of Clinical Pathology. 2006;**126**(5):700-708. DOI: 10.1309/044V-86JN-2W3C-N5YB

[61] Murtezaoglu AR, Gucer H. Diagnostic value of TROP-2 expression in papillary thyroid carcinoma and comparison with HBME-1, galectin-3 and cytokeratin 19. Polish Journal of Pathology. 2017;**68**(1):1-10. DOI: 10.5114/pjp.2017.67610

[62] Dunderovic D, Lipkovski JM, Boricic I, Soldatovic I, Bozic V, Cvejic D, Tatic S. Defining the value of CD56, CK19, Galectin-3 and HBME-1 in diagnosis of follicular cell derived lesions of thyroid with systematic review of literature. Diagnostic Pathology. 2015;**10**:196. DOI: 10.1186/s13000-015-0428-4

[63] Prasad ML, Pellegata NS, Huang Y, Nagaraja HN, de la Chapelle A, Kloos RT. Galectin-3, fibronectin-1, CITED-1, HBME1 and cytokeratin-19 immunohistochemistry is useful for the diagnosis of thyroid tumors. Modern Pathology. 2005;**18**(1):48-57. DOI: 10.1038/modpathol.3800235

[64] Nasr MR, Mukhopadhyay S, Zhang S, Katzenstein AL. Immunohistochemical markers in diagnosis of papillary thyroid carcinoma: Utility of HBME1 combined with CK19 immunostaining. Modern Pathology. 2006;**19**(12):1631-1637. DOI: 10.1038/modpathol.3800705

[65] Nechifor-Boila A, Borda A, Sassolas G, Hafdi-Nejjari Z, Borson-Chazot F, Lifante JC, Sturm N, Laverriere MH, Berger N, Decaussin-Petrucci M. Immunohistochemical markers in the diagnosis of papillary thyroid carcinomas: The promising role of combined immunostaining using HBME-1 and CD56. Pathology, Research and Practice. 2013;**209**(9):585-592. DOI: 10.1016/j.prp.2013.06.012

[66] Ozolins A, Narbuts Z, Strumfa I, Volanska G, Gardovskis J. Diagnostic utility of immunohistochemical panel in various thyroid pathologies. Langenbeck's Archives of Surgery. 2010;**395**(7):885-891. DOI: 10.1007/s00423-010-0690-6

[67] Liu YY, Morreau H, Kievit J, Romijn JA, Carrasco N, Smit JW. Combined immunostaining with galectin-3, fibronectin-1, CITED-1, Hector Battifora mesothelial-1, cytokeratin-19, peroxisome proliferator-activated receptor-{gamma}, and sodium/iodide symporter antibodies for the differential diagnosis of non-medullary thyroid carcinoma. European Journal of Endocrinology. 2008;**158**(3):375-384. DOI: 10.1530/EJE-07-0492

[68] Yesil C, Kandemir O, Haksever H, Dabakoglu T. Is BECLIN-1 immunoreactivity more effective than HBME-1 in diagnosis of papillary thyroid cancer? Acta Chirurgica Belgica. 2015;**115**(4):299-305. DOI: 10.1080/00015458.2015.11681116

[69] Addati T, Achille G, Centrone M, Petroni S, Popescu O, Russo S, Grammatica L, Simone G. TROP-2 expression in papillary thyroid cancer: A preliminary cyto-histological study. Cytopathology. 2015;**26**(5):303-311. DOI: 10.1111/cyt.12196

[70] Bychkov A, Sampatanukul P, Shuangshoti S, Keelawat S. TROP-2 immunohistochemistry: A highly accurate method in the differential diagnosis of papillary thyroid carcinoma. Pathology. 2016;**48**(5):425-433. DOI: 10.1016/j.pathol.2016.04.002

[71] Simms A, Jacob RP, Cohen C, Siddiqui MT. TROP-2 expression in papillary thyroid carcinoma: Potential diagnostic utility. Diagnostic Cytopathology. 2016;**44**(1):26-31. DOI: 10.1002/dc.23382

[72] Nakamura N, Erickson LA, Jin L, Kajita S, Zhang H, Qian X, Rumilla K, Lloyd RV. Immu nohistochemical separation of follicular variant of papillary thyroid carcinoma from follicular adenoma. Endocrine Pathology. 2006;**17**(3):213-223

[73] Eldien MMS, Abdou AG, Rageh T, Abdelrazek E, Elkholy E. Immunohistochemical expression of ER-α and PR in papillary thyroid carcinoma. Ecancermedicalscience. 2017;**11**:748. DOI: 10.3332/ecancer.2017.748

[74] Yavropoulou MP, Panagiotou G, Topouridou K, Karayannopoulou G, Koletsa T, Zarampoukas T, Goropoulos A, Chatzaki E, Yovos JG, Pazaitou-Panayiotou K. Vitamin

D receptor and progesterone receptor protein and gene expression in papillary thyroid carcinomas: Associations with histological features. Journal of Endocrinological Investigation. 2017;**40**(12):1327-1335. DOI: 10.1007/s40618-017-0700-4

[75] Al-Sharaky DR, Younes SF. Sensitivity and specificity of galectin-3 and glypican-3 in follicular-patterned and other thyroid neoplasms. Journal of Clinical and Diagnostic Research. 2016;**10**(3):EC06-EC10. DOI: 10.7860/JCDR/2016/18375.7430

[76] Zheng J, Lu W, Wang C, Xing Y, Chen X, Ai Z. Galectin-3 induced by hypoxia promotes cell migration in thyroid cancer cells. Oncotarget. 2017;**8**(60):101475-101488. DOI: 10.18632/oncotarget.21135

[77] Matesa-Anic D, Moslavac S, Matesa N, Cupic H, Kusic Z. Intensity and distribution of immunohistochemical expression of galectin-3 in thyroid neoplasms. Acta Clinica Croatica. 2012;**51**(2):237-241

[78] Arcolia V, Journe F, Wattier A, Leteurtre E, Renaud F, Gabius HJ, Remmelink M, Decaestecker C, Rodriguez A, Boutry S, Laurent S, Saussez S. Galectin-1 is a diagnostic marker involved in thyroid cancer progression. International Journal of Oncology. 2017;**51**(3):760-770. DOI: 10.3892/ijo.2017.4065

[79] Fanfone D, Despretz N, Stanicki D, Rubio-Magnieto J, Fossepre M, Surin M, Rorive S, Salmon I, Vander Elst L, Laurent S, Muller RN, Saussez S, Burtea C. Toward a new and noninvasive diagnostic method of papillary thyroid cancer by using peptide vectorised contrast agents targeted to galectin-1. Medical Oncology. 2017;**34**(11):184. DOI: 10.1007/s12032-017-1042-y

[80] Yamanaka K, Ito Y, Okuyama N, Noda K, Matsumoto H, Yoshida H, Miyauchi A, Capurro M, Filmus J, Miyoshi E. Immunohistochemical study of glypican 3 in thyroid cancer. Oncology. 2007;**73**(5-6):389-394. DOI: 10.1159/000136159

[81] Castellone MD, Celetti A, Guarino V, Cirafici AM, Basolo F, Giannini R, Medico E, Kruhoffer M, Orntoft TF, Curcio F, Fusco A, Melillo RM, Santoro M. Autocrine stimulation by osteopontin plays a pivotal role in the expression of the mitogenic and invasive phenotype of RET/PTC-transformed thyroid cells. Oncogene. 2004;**23**(12):2188-2196. DOI: 10.1038/sj.onc.1207322

[82] Guarino V, Faviana P, Salvatore G, Castellone MD, Cirafici AM, De Falco V, Celetti A, Giannini R, Basolo F, Melillo RM, Santoro M. Osteopontin is overexpressed in human papillary thyroid carcinomas and enhances thyroid carcinoma cell invasiveness. The Journal of Clinical Endocrinology and Metabolism. 2005;**90**(9):5270-5278. DOI: 10.1210/jc.2005-0271

[83] Wu G, Guo JJ, Ma ZY, Wang J, Zhou ZW, Wang Y. Correlation between calcification and bone sialoprotein and osteopontin in papillary thyroid carcinoma. International Journal of Clinical and Experimental Pathology. 2015;**8**(2):2010-2017

[84] Metivier KS, Deitz K, Xu WW, Conzemius M, Wilke VL. Gene expression profiling demonstrates differential expression of osteopontin in follicular thyroid carcinomas compared to normal thyroid tissue in dogs. Veterinary and Comparative Oncology. 2014;**12**(3):181-197. DOI: 10.1111/j.1476-5829.2012.00348.x

[85] Ferreira LB, Eloy C, Pestana A, Lyra J, Moura M, Prazeres H, Tavares C, Sobrinho-Simoes M, Gimba E, Soares P. Osteopontin expression is correlated with differentiation and good prognosis in medullary thyroid carcinoma. European Journal of Endocrinology. 2016;**174**(4):551-561. DOI: 10.1530/EJE-15-0577

[86] Wu G, Zhou Y, Li T, Guo J, Zhou Z. Immunohistochemical levels of matrix metalloproteinase-2 and CD44 variant 6 protein in the diagnosis and lateral cervical lymph node metastasis of papillary thyroid carcinoma. The Journal of International Medical Research. 2013;**41**(3):816-824. DOI: 10.1177/0300060513481923

[87] Calangiu CM, Simionescu CE, Stepan AE, Cernea D, Zavoi RE, Margaritescu C. The expression of CK19, vimentin and E-cadherin in differentiated thyroid carcinomas. Romanian Journal of Morphology and Embryology. 2014;**55**(3):919-925

[88] Ozolins A, Narbuts Z, Strumfa I, Volanska G, Stepanovs K, Gardovskis J. Immunohistochemical expression of HBME-1, E-cadherin, and CD56 in the differential diagnosis of thyroid nodules. Medicina (Kaunas, Lithuania). 2012;**48**(10):507-514

[89] Rendon-Huerta E, Chavarria-Velazquez CO, Montano LF. Claudins, inflammation and epithelial-mesenchymal transition in gastric tissue. Journal of Gastrointestinal and Digestive System. 2013;**3**:149. DOI: 10.4172/2161-069X.1000149

[90] Zwanziger D, Badziong J, Ting S, Moeller LC, Schmid KW, Siebolts U, Wickenhauser C, Dralle H, Fuehrer D. The impact of CLAUDIN-1 on follicular thyroid carcinoma aggressiveness. Endocrine-Related Cancer. 2015;**22**(5):819-830. DOI: 10.1530/ERC-14-0502

[91] Isic Dencic T, Cvejic D, Paunovic I, Tatic S, Havelka M, Savin S. Cytokeratin19 expression discriminates papillary thyroid carcinoma from other thyroid lesions and predicts its aggressive behaviour. Medical Oncology. 2013;**30**(1):362. DOI: 10.1007/s12032-012-0362-1

[92] Lamba Saini M, Bouzin C, Weynand B, Marbaix E. An appraisal of proliferation and apoptotic markers in papillary thyroid carcinoma: An automated analysis. PLoS One. 2016;**11**(2):e0148656. DOI: 10.1371/journal.pone.0148656

[93] Cyniak-Magierska A, Stasiak M, Naze M, Dedecjus M, Brzezinski J, Lewinski A. Patterns of cyclin A and B1 immunostaining in papillary thyroid carcinoma. Annals of Agricultural and Environmental Medicine. 2015;**22**(4):741-746. DOI: 10.5604/12321966.1185787

[94] Chen Z, Liu N, Zhu G, Dralle H, Hoang-Vu C. Targeting of the anti-apoptotic gene survivin in human thyroid carcinoma. International Journal of Molecular Medicine. 2012;**30**(3):465-472. DOI: 10.3892/ijmm.2012.1046

[95] Guerra A, Marotta V, Deandrea M, Motta M, Limone PP, Caleo A, Zeppa P, Esposito S, Fulciniti F, Vitale M. BRAF (V600E) associates with cytoplasmatic localization of p27kip1 and higher cytokeratin 19 expression in papillary thyroid carcinoma. Endocrine. 2013;**44**(1):165-171. DOI: 10.1007/s12020-012-9843-4

[96] Abulkheir IL, Mohammad DB. Value of immunohistochemical expression of p27 and galectin-3 in differentiation between follicular adenoma and follicular carcinoma. Applied Immunohistochemistry & Molecular Morphology. 2012;**20**(2):131-140. DOI: 10.1097/PAI.0b013e318228de00

[97] Pusztaszeri MP, Sadow PM, Faquin WC. CD117: A novel ancillary marker for papillary thyroid carcinoma in fine-needle aspiration biopsies. Cancer Cytopathology. 2014;**122**(8):596-603. DOI: 10.1002/cncy.21437

[98] Bychkov A, Jung CK. Aberrant expression of CD20 in thyroid cancer and its clinicopathologic significance. Human Pathology. 2018;**71**:74-83. DOI: 10.1016/j.humpath.2017.10.015

[99] Sasaki Y, Seto M, Miyoshi H, Okada S, Yokoyama S, Ohshima A, Ohshima K. Papillary thyroid carcinoma expressing CD20. Pathology International. 2017;**67**(7):350-354. DOI: 10.1111/pin.12548

[100] Wuertz FG, Kresnik E, Malle P, Hyden M, Lind P, Rogatsch H, Gallowitsch HJ. Fine-needle aspiration with immunohistochemistry using a modified scrape cell block technique for the diagnosis of thyroid and parathyroid nodules. Acta Cytologica. 2016;**60**(2):118-130. DOI: 10.1159/000446466

[101] Komminoth P, Roth J, Saremaslani P, Matias-Guiu X, Wolfe HJ, Heitz PU. Polysialic acid of the neural cell adhesion molecule in the human thyroid: A marker for medullary thyroid carcinoma and primary C-cell hyperplasia. An immunohistochemical study on 79 thyroid lesions. The American Journal of Surgical Pathology. 1994;**18**(4):399-411

[102] Frank-Raue K, Machens A, Leidig-Bruckner G, Rondot S, Haag C, Schulze E, Lorenz A, Kreissl MC, Dralle H, Raue F, Schmid KW. Prevalence and clinical spectrum of nonsecretory medullary thyroid carcinoma in a series of 839 patients with sporadic medullary thyroid carcinoma. Thyroid. 2013;**23**(3):294-300. DOI: 10.1089/thy.2012.0236

[103] Cappagli V, Potes CS, Ferreira LB, Tavares C, Eloy C, Elisei R, Sobrinho-Simoes M, Wookey PJ, Soares P. Calcitonin receptor expression in medullary thyroid carcinoma. PeerJ. 2017;**5**:e3778. DOI: 10.7717/peerj.3778

[104] Cvejic D, Savin S, Golubovic S, Paunovic I, Tatic S, Havelka M. Galectin-3 and carcinoembryonic antigen expression in medullary thyroid carcinoma: Possible relation to tumour progression. Histopathology. 2000;**37**(6):530-535

[105] Mourra N, Bennis M, Boelle PY, Cochand-Priollet B, Lefevre M, Lepine C, Balaton A, Klijanienko J, Menegaux F, Tissier F. Clusterin expression in medullary thyroid carcinoma is inversely correlated with the presence of lymph node metastases. Human Pathology. 2017;**64**:37-43. DOI: 10.1016/j.humpath.2017.03.009

[106] Werner TA, Tamkan-Olcek Y, Dizdar L, Riemer JC, Wolf A, Cupisti K, Verde PE, Knoefel WT, Krieg A. Survivin and XIAP: Two valuable biomarkers in medullary thyroid carcinoma. British Journal of Cancer. 2016;**114**(4):427-434. DOI: 10.1038/bjc.2016.5

[107] Lodewijk L, van Diest P, van der Groep P, Ter Hoeve N, Schepers A, Morreau J, Bonenkamp J, van Engen-van Grunsven A, Kruijff S, van Hemel B, Links T, Nieveen van Dijkum E, van Eeden S, Valk G, Borel Rinkes I, Vriens M. Expression of HIF-1α in medullary thyroid cancer identifies a subgroup with poor prognosis. Oncotarget. 2017;**8**(17):28650-28659. DOI: 10.18632/oncotarget.15622

[108] Bi Y, Meng Y, Wu H, Cui Q, Luo Y, Xue X. Expression of the potential cancer stem cell markers CD133 and CD44 in medullary thyroid carcinoma: A ten-year follow-up and

prognostic analysis. Journal of Surgical Oncology. 2016;**113**(2):144-151. DOI: 10.1002/jso.24124

[109] Herac M, Niederle B, Raderer M, Krebs M, Kaserer K, Koperek O. Expression of somatostatin receptor 2A in medullary thyroid carcinoma is associated with lymph node metastasis. Acta Pathologica, Microbiologica, et Immunologica Scandinavica. 2016;**124**(10):839-845. DOI: 10.1111/apm.12584

[110] Soudry E, Stern Shavit S, Hardy B, Morgenstern S, Hadar T, Feinmesser R. Heat shock proteins HSP90, HSP70 and GRP78 expression in medullary thyroid carcinoma. Annals of Diagnostic Pathology. 2017;**26**:52-56. DOI: 10.1016/j.anndiagpath.2016.11.003

[111] Melo DH, Mamede RCM, Neder L, Silva WA Jr, Barros-Filho MC, Kowalski LP, Pinto CAL, Zago MA, Figueiredo DLA, Jungbluth AA. Expression of cancer/testis antigens MAGE-A, MAGE-C1, GAGE and CTAG1B in benign and malignant thyroid diseses. Oncology Letters. 2017;**14**(6):6485-6496. DOI: 10.3892/ol.2017.7072

[112] Grimaldi A, Zarone MR, Irace C, Zappavigna S, Lombardi A, Kawasaki H, Caraglia M, Misso G. Non-coding RNAs as a new dawn in tumor diagnosis. Seminars in Cell & Developmental Biology. 2018;**78**:37-50. DOI: 10.1016/j.semcdb.2017.07.035

[113] MacFarlane LA, Murphy PR. MicroRNA: Biogenesis, function and role in cancer. Current Genomics. 2010;**11**(7):537-561. DOI: 10.2174/138920210793175895

[114] Hashemzadeh MR. Role of micro RNAs in stem cells, cardiac differentiation and cardiovascular diseases. Gene Reports. 2017;**8**:11-16

[115] Rodriguez-Montes JA, Menendez Sanchez P. Role of micro-RNA in colorectal cancer screening. Cirugía Española (English Edition). 2014;**92**(10):654-658. DOI: 10.1016/j.ciresp.2014.05.012

[116] Sasanakietkul T, Murtha TD, Javid M, Korah R, Carling T. Epigenetic modifications in poorly differentiated and anaplastic thyroid cancer. Molecular and Cellular Endocrinology. 2018;**469**:23-37. DOI: 10.1016/j.mce.2017.05.022

[117] Chruscik A, Lam AK. Clinical pathological impacts of microRNAs in papillary thyroid carcinoma: A crucial review. Experimental and Molecular Pathology. 2015;**99**(3):393-398. DOI: 10.1016/j.yexmp.2015.08.013

[118] Boufraqech M, Klubo-Gwiezdzinska J, Kebebew E. MicroRNAs in the thyroid. Best Practice & Research. Clinical Endocrinology & Metabolism. 2016;**30**(5):603-619. DOI: 10.1016/j.beem.2016.10.001

[119] Rossi ED, Martini M, Capodimonti S, Cenci T, Larocca LM. The role of miRNAs in the evaluation of follicular thyroid neoplasms: An overview of literature. Journal of the American Society of Cytopathology. 2017;**6**(3):96-104. DOI: https://doi.org/10.1016/j.jasc.2017.02.001

[120] Rodriguez-Rodero S, Delgado-Alvarez E, Diaz-Naya L, Martin Nieto A, Menendez Torre E. Epigenetic modulators of thyroid cancer. Endocrinology, Diabetes, Nutrition. 2017;**64**(1):44-56 . DOI: 10.1016/j.endinu.2016.09.006

[121] Hayashi M, Jono H, Shinriki S, Nakamura T, Guo J, Sueta A, Tomiguchi M, Fujiwara S, Yamamoto-Ibusuki M, Murakami K, Yamashita S, Yamamoto Y, Li JD, Iwase H, Ando Y. Clinical significance of CYLD downregulation in breast cancer. Breast Cancer Research and Treatment. 2014;**143**(3):447-457. DOI: 10.1007/s10549-013-2824-3

[122] Balkwill FR, Mantovani A. Cancer-related inflammation: Common themes and therapeutic opportunities. Seminars in Cancer Biology. 2012;**22**(1):33-40. DOI: 10.1016/j.semcancer.2011.12.005

[123] Strumfa I, Bogdanova T, Kalva A, Strumfs B, Rumba R, Vanags A, Drike I, Mezale D, Abolins A, Jakovlevs A, Balodis D, Gardovskis J. Systemic inflammatory reaction in gastric cancer: Biology and practical implications of neutrophil to lymphocyte ratio, Glasgow prognostic score and related parameters. In: Mozsik G, Karadi O, editors. Gastric Cancer. Croatia: InTech; 2017. pp. 143-197. DOI: 10.5772/intechopen.69723

[124] Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. Future Oncology. 2010;**6**(1):149-163. DOI: 10.2217/fon.09.136

[125] McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. Current Opinion in Clinical Nutrition and Metabolic Care. 2009;**12**(3):223-226. DOI: 10.1097/MCO.0b013e32832a7902

[126] Proctor MJ, Morrison DS, Talwar D, Balmer SM, Fletcher CD, O'Reilly DS, Foulis AK, Horgan PG, McMillan DC. A comparison of inflammation-based prognostic scores in patients with cancer. A Glasgow inflammation outcome study. European Journal of Cancer. 2011;**47**(17):2633-2641. DOI: 10.1016/j.ejca.2011.03.028

[127] Liu CL, Lee JJ, Liu TP, Chang YC, Hsu YC, Cheng SP. Blood neutrophil-to-lymphocyte ratio correlates with tumor size in patients with differentiated thyroid cancer. Journal of Surgical Oncology. 2013;**107**(5):493-497. DOI: 10.1002/jso.23270

[128] Kuo CY, Liu TP, Yang PS, Cheng SP. Characteristics of lymphocyte-infiltrating papillary thyroid cancer. Journal of Cancer Research and Practice. 2017;**4**(3):95-99

IntechOpen