THYROID CARCINOMA: DIAGNOSTIC AND THERAPEUTIC APPROACH; GENETIC BACKGROUND (REVIEW)

1A. LEWINSKI, 2T. FERENC, 3 S. SPORNY, 4B. JARZAB

1Department of Thyroidology, Institute of Endocrinology and 3Department of Pathomorphology, Chair of Pathomorphology, Medical University of Łódz; 2Department of Biology and Medical Genetics, Military Medical University, Łódź; 4The Oncology Center, M. Sklodowska-Curie Memorial Institute, Gliwice, Poland
E-mail: alewin@psk2.am.lodz.pl

This paper reviews the state-of-the-art on the management of thyroid cancer in humans, including the following thyroid carcinomas: papillary, follicular, poorly differentiated (insular), undifferentiated (anaplastic), and medullary (sporadic and inherited forms). Also metastatic (secondary) neoplasms of the thyroid gland have been approached. The rules of treatment (surgical, with use of ¹³¹I and suppressive therapy with L-thyroxine) of particular types of thyroid cancers have been presented – both descriptively and by schemes. Furthermore, the role of genetic background in the pathogenesis of thyroid neoplasms has carefully been reviewed for papillary, follicular and medullary carcinoma. The paper constitutes a compendium of current views with respect to cytological and histopathological diagnostics of thyroid cancers.

Key words: Thyroid cancer – Pathomorphology – Cytology – Treatment – Genetic background

1. Clinical and pathological classification

Thyroid cancer is a disease of a complex course, thus it should be approached – at each stage of diagnostics and treatment – by consultant with an established endocrinological and oncological experience.

From the practical point of view, the primary malignant neoplasms of the thyroid can be divided into three categories (CHAN 1995):

1. low malignancy: A. papillary carcinoma, B. minimally-invasive follicular carcinoma;
2. moderate malignancy: A. widely-invasive follicular carcinoma, B. medullary carcinoma, C. malignant lymphoma, D. poorly differentiated thyroid carcinoma;
3. high malignancy: A. undifferentiated carcinoma, B. malignant haemangioendothelioma (angiosarcoma).

Three main types of thyroid cancer – originating from the follicular cell of this gland – are distinguished: papillary, follicular and undifferentiated (anaplastic), set in order from the highest incidence rate (FONSECA and SOBRINHO-SIMÕES 1995). In addition, medullary thyroid carcinoma, originating from the C cell of the gland, should be discussed, this type of cancer being the most rarely met (FRANC et al. 1998).

Any suspicion of thyroid cancer is the consequence of clinical examination and of the result of fine-needle aspiration biopsy (FNAB). The data from ultrasonography (US) and scintigraphy are to be regarded as auxiliary in the diagnostic protocol, keeping in mind that all the FNABs should be performed under US-guidance (KULIG et al. 1996).

1.1. Papillary thyroid carcinoma

The following microscopic variants of papillary thyroid carcinoma (PTC) are reported: 1. classic; 2. follicular; 3. tall-cell; 4. columnar-cell; 5. with diffuse sclerosis; 6. trabecular/solid; 7. clear-cell; 8. oxyphilic; 9. lipomatous; 10. with fascitis-like stroma; 11. cribriform (CHAN 1995).

Three forms of PTC are distinguished in clinical pathology:
THYROID CARCINOMA MANAGEMENT: REVIEW

1. microcarcinoma (diameter <1.0 cm, non-palpable): A. minute (diameter <0.5 cm); B. tiny (diameter 0.5-1.0 cm); 2. intrathyroidal (usually of diameter >1.5 cm, encapsulated or without connective tissue capsule, dominating as a diagnostic problem); 3. extrathyroidal (diameter >5.0 cm, extending the thyroid capsule and infiltrating the neighbouring tissues).

The most significant traditional prognostic factors of the classic form of PTC include (CHAN 1995):

A. age (mortality below the age of 40 is exceptional);
B. sex (some data indicate worse prognosis in men);
C. tumour size (mortality from PTC is proportional to the extent of malignant process);
D. infiltration into perithyroid tissues results in much worse prognosis;
E. encapsulation of tumour is a positive prognostic factor;
F. metastases (distant metastases significantly deteriorate the prognosis, while these in lymphatic nodes do not significantly affect the survival time).

Cytological picture of PTC is highly characteristic and fully corresponds to the final diagnosis (SPORNY 1999). Essential cytological findings constituting the “minimal criteria” for diagnosis may be summarized as follows: 1. syncytial type tissue fragments with or without any architectural pattern; 2. enlarged pale nuclei with very fine dusty or powdery chromatin; 3. multiple micro- and/or macronucleoli (may not be clearly seen in MGG smears); 4. intranuclear cytoplasmic inclusions and linear chromatin ridges/folds/grooves (all variants of PTC).

1.2. Follicular thyroid carcinoma

The following histopathological types of follicular thyroid carcinoma (FTC) are distinguished (CHAN 1995): minimally-invasive; widely-invasive; oncocytic; clear-cell; trabecular hyalinizing; with cribriform and fusocellular patterns (Tab. 1 and 2).

The features of FTC, associated with poor prognosis, include (JORDA et al. 1993): advanced age of patient (above the 60th year of life); big size of tumour (above 4 cm); extrathyroid invasion of tumour at the time of diagnosis; highly expressed intravascular invasion (angioinvasion); domination of trabecular and solid patterns in texture; aneuploidy (a number of researchers do not regard it as affecting the chance of survival).

Unfortunately, FNAB does not allow any unequivocal differentiation between the thyroid adenoma and highly differentiated follicular carcinoma. In such cases, cytological picture allows to draw only a differential diagnostic circle remaining within the term: “follicular neoplasm/tumour” (KULIG et al. 1996).

Cytological features of “follicular neoplasm” include: numerous cell arrangements being the equivalents of microfollicular structures (rosettes, clusters of syncytial structure); cellular or nuclear monomorphism; lack of signs of oncocytic metaplasia; lack of or very scarce colloid.

The formulation of final diagnosis is possible only after histopathological examination of the excised thyroid tissue (postoperative diagnosis). Only after that it is possible to evaluate the infiltration of the tumour cap-

<table>
<thead>
<tr>
<th>TYPE OF TUMOUR</th>
<th>WITH TYPICAL APPEARANCE OF CELLS</th>
<th>WITH ATYPICAL APPEARANCE OF CELLS</th>
<th>WITH ATYPICAL STROMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>Normofollicular (simple)</td>
<td>Atypical</td>
<td>Adenolipoma</td>
</tr>
<tr>
<td></td>
<td>Macrofollicular (colloid)</td>
<td>With bizarre nuclei</td>
<td>Adenochondroma</td>
</tr>
<tr>
<td></td>
<td>Microfollicular (fetal)</td>
<td>Oncocytic*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trabecular/solid (embryonal)</td>
<td>Clear-cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signet-ring-cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lipid-rich</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trabecular hyalinizing</td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Minimally-invasive</td>
<td>Oncocytic*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Widely-invasive</td>
<td>Clear-cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trabecular hyalinizing</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>With cribriform and fusiform</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>cellular patterns</td>
<td></td>
</tr>
</tbody>
</table>

*According to certain researchers, oncocytic neoplasms (of Hürthle cells) stand for a separate category of pathologic changes of the thyroid.

Table 1
Classification of follicular neoplasms of the thyroid gland (SPORNY 1999)

1. According to certain researchers, oncocytic neoplasms (of Hürthle cells) stand for a separate category of pathologic changes of the thyroid.
sule and the vascular embolisms with neoplastic cells. The diagnosis of “follicular neoplasm” of the thyroid by FNAB provides a definite indication for the surgery, so as to obtain the final diagnostic confirmation in the postoperative histopathological study (SPORNY 1999).

### 1.3. Undifferentiated and poorly differentiated (insular) thyroid carcinoma

The cytological picture of undifferentiated (anaplastic) carcinoma is highly characteristic and fully corresponds to the final diagnosis (the same as in case of PTC) (CHAN 1995).

Cytologic types of undifferentiated carcinoma include: epithelioid; spindle-cell carcinoma (pseudosarcomatous); giant-cell carcinoma; giant-cell carcinoma with osteoclast-like cells; (?) malignant haemangiendothelioma; (?) squamous (planoepithelial).

Most of authors also distinguish so called insular carcinoma which is an intermediate form between differentiated (papillary, follicular) and undifferentiated (anaplastic) carcinomas.

The cytological findings in insular carcinoma may be summarized as follows: highly cellular smears, scanty or no colloid; cells – single and in syncytial, irregular aggregates with nuclear crowding and overlapping, solid trabecular, rounded clusters, poorly formed microfollicles; high nuclear/cytoplasmic ratio; moderate anisokaryosis and nuclear atypia, including hyperchromasia and chromatin coarseness, prominent nucleoli; mitotic figures and necrotic background seen occasionally.

### 1.4. Medullary thyroid carcinoma

In the medullary thyroid carcinoma (MTC), the cytological picture is usually not fully characteristic but, when correlated with clinical data and immunohistochemical examinations, it speaks for a precise diagnosis (WEIDNER 1996).

Functional variants of MTC are as follows: rich in amyloid; without calcitonin; mucinous; without amyloid; multihormonal; producing melanin.

Cytological findings in MTC (ORELL and PHILIPS 1997) include: cellular, often bloody smears of mainly dispersed epithelial cells; clusters, syncytia and, sometimes, semicircular rows of rosettes of cells, rarely true microfollicular groups; plasmacytoid cells with a moderate amount of cytoplasm and eccentric nucleus; dense clusters of cells with scanty cytoplasm, ovoid nuclei and nuclear moulding, often scattered spindle cells; moderate anisokaryosis, single cells with very large nuclei, common bi- and multinucleate cells; uniform nuclear hyperchromasia, stippled chromatin; a few cells with intranuclear cytoplasmic inclusions are commonly found; a variable number of single cells with coarse, brightly red cytoplasmic granulation (MGG staining); colloid absent, amyloid found in about half of the cases; cells stain positively for calcitonin and carcino-embryonic antigen (Tab.3).

### 1.5. Metastatic (secondary) neoplasms in the thyroid

Among metastatic neoplasms into the thyroid should be mentioned: 1. clear-cell carcinoma of kidney; 2. breast cancer (women); 3. lung cancer (men); 4. malignant melanoma; 5. digestive tract cancers; 6. cervical carcinoma; 7. ovarian cancer; 8. prostatic cancer; 9. adrenocortical carcinoma; 10. chorioncarcinoma.

A negative result of FNAB should not be regarded as an argument against surgical treatment, if clin-

---

**Table 2**

Characteristics of various types of follicular thyroid carcinoma (FTC) (CHAN 1995)

<table>
<thead>
<tr>
<th></th>
<th>MINIMALLY INVASIVE</th>
<th>WIDELY INVASIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mean age of patients</td>
<td>47 – 50 years</td>
<td>53 – 59 years</td>
</tr>
<tr>
<td>Haematogenic metastases</td>
<td>2 – 14%</td>
<td>29 – 60%</td>
</tr>
<tr>
<td>Metastases in lymphatic nodes</td>
<td>3 – 4%</td>
<td>13 – 24%</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 – 16%</td>
<td>18 – 86%</td>
</tr>
<tr>
<td>Prognosis</td>
<td>Good. Recurrence and metastases are rare, after many years from surgery</td>
<td>Uncertain. A tendency towards recurrence and metastases 3-5 years after surgery</td>
</tr>
</tbody>
</table>
### Table 3
**Characteristics of medullary thyroid carcinoma (MTC) (SPORNY 1999)**

<table>
<thead>
<tr>
<th></th>
<th>Sporadic MTC (75%)</th>
<th>Inherited MTC (25%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>The mean age of patients (years)</strong></td>
<td>44 – 50</td>
<td>41 – 43</td>
</tr>
<tr>
<td></td>
<td>21 – 38</td>
<td>12 – 23</td>
</tr>
<tr>
<td><strong>Sex (M:F)</strong></td>
<td>1:1.3</td>
<td>1:1</td>
</tr>
<tr>
<td></td>
<td>1:1</td>
<td>1:1</td>
</tr>
<tr>
<td><strong>Type of inheritance</strong></td>
<td>Autosomal Dominating</td>
<td>Autosomal Dominating</td>
</tr>
<tr>
<td></td>
<td>Autosomal Dominating</td>
<td>Autosomal Dominating</td>
</tr>
<tr>
<td><strong>Mutations in the RET protooncogene</strong></td>
<td>918 (exon 16)</td>
<td>918 (exon 16)</td>
</tr>
<tr>
<td>DNA of tumour cells:</td>
<td>609, 611, 618,</td>
<td>609, 611, 618,</td>
</tr>
<tr>
<td>Codons:</td>
<td>883 (exon 15),</td>
<td>883 (exon 15),</td>
</tr>
<tr>
<td></td>
<td>766 (exon 13)</td>
<td>766 (exon 13)</td>
</tr>
<tr>
<td></td>
<td>620 (exon 10),</td>
<td>620 (exon 10),</td>
</tr>
<tr>
<td></td>
<td>634 (exon 11)</td>
<td>634 (exon 11)</td>
</tr>
<tr>
<td><strong>Concomitant lesions</strong></td>
<td>Pheochromocytoma localised – the most frequently - in the adrenal medulla (50%), adenoma or hyperplasia of parathyroid glands (30–40%)</td>
<td>Pheochromocytoma localised – the most frequently - in the adrenal medulla (40-50%), neurofibromas of the skin and mucosa, marphanoid silhouette, ganglioneuromas in the digestive tract (Hirschsprung’s disease clinical picture)</td>
</tr>
<tr>
<td><strong>Proliferation of C cells beyond neoplasm</strong></td>
<td>Usually absent</td>
<td>Usually absent</td>
</tr>
<tr>
<td></td>
<td>Usually absent</td>
<td>Usually present</td>
</tr>
<tr>
<td></td>
<td>Usually present</td>
<td>Usually invasive</td>
</tr>
<tr>
<td><strong>Proliferation rate – prognosis</strong></td>
<td>Varies, uncertain</td>
<td>Usually a slow growth</td>
</tr>
<tr>
<td></td>
<td>Rather slow increase</td>
<td>Usually invasive</td>
</tr>
<tr>
<td><strong>Other features</strong></td>
<td>Frequent metastases into lymphatic nodes, rarely hematogenic</td>
<td>Pheochromocytoma appears in about 10 years after MTC diagnosis</td>
</tr>
<tr>
<td></td>
<td>Rapid metastases in lymphatic nodes of the neck and mediastinum, hematogenic metastases in the liver, lungs and bones</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4
**Structural aberrations of chromosomes in papillary thyroid carcinoma (PTC) (n=70) (PIEROTTI et al. 1996)**

<table>
<thead>
<tr>
<th></th>
<th>n = 51 (73%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Casual aberrations of the number and structure</strong></td>
<td>n = 10</td>
</tr>
<tr>
<td>Clonal structural aberrations</td>
<td>n = 5</td>
</tr>
<tr>
<td>Inv(10)(q11.2; q21.2)</td>
<td>HERRMANN et al. 1991b</td>
</tr>
<tr>
<td>t(10;17)(q11.2;q23)</td>
<td>JENKINS et al. 1990; PIEROTTI et al. 1992</td>
</tr>
<tr>
<td>Der(1)</td>
<td>SOZZI et al. 1992; unpublished – 1 case</td>
</tr>
</tbody>
</table>

Clinical examination justifies to suspect a malignant tumour. In such cases, the difference between the clinical picture and the cytologic result should “possibly” be explained, even by an intraoperative examination (KULIG et al. 1996).

2. **Treatment of thyroid cancers**

**Surgical treatment** is a procedure of choice. In case of differentiated thyroid cancer, the surgical treatment includes a radical thyroidectomy, complet-
Figure 1. Scheme of treatment of suspected and/or diagnosed differentiated carcinoma of the thyroid gland.
ed – if metastases to lymphatic nodes are found – by a uni- or bilateral modified dissection of the neck lymphatic system. Only the papillary cancer of the thyroid, in the pT1aN0M0 stage (unifocal papillary cancer of a diameter <1 cm, without infiltration into the capsule of the gland or any metastases into the lymphatic nodes or distant metastases) can be treated by a subtotal thyroidectomy. In practice, this indication refers exclusively to the cessation of repeated surgery (radicalisation) after an unexpected discovery of micro-cancer in a postoperative examination of the thyroid tissue after subtotal thyroidectomy, performed for other indications.

Radioiodine treatment (with $^{131}$I) is applied only in cases of differentiated carcinoma of the thyroid and is regarded as: complementary treatment after radical surgery or as a radical treatment itself in cases of non-operative local recurrence and distant metastases, provided they demonstrate iodine uptake. In cases of non-operative primary tumour, $^{131}$I-treatment may be regarded as a palliative approach.

Patients with differentiated thyroid cancer must receive L-thyroxine – through the whole life – in doses providing for a suppression of TSH secretion (suppressive treatment), as TSH stimulates the growth of neoplastic cells. In patients with diseases of the heart and of the circulatory system, the doses of L-thyroxine should be balanced to be possibly the highest but still not causing any side-effects. In patients with medullary and anaplastic cancers, L-thyroxine doses are determined at the level appropriate to balance the deficiency of thyroid hormones (substitutive treatment).

The schemes of the recommended complex treatment of differentiated thyroid cancers, undifferentiated thyroid carcinoma and medullary thyroid carcinoma are presented in Fig. 1, 2 and 3, respectively.

3. Genetic background in the pathogenesis of thyroid neoplasms

Participation of genetic factors in the formation and development of various types of thyroid neoplasms is presented in Fig. 4.

3.1. Papillary thyroid carcinoma

In PTC, the activation or overexpression of three tyrosine kinase oncogenes – the rearrangement of $RET$ and $TRK$ and the overexpression of $met$ – are usually observed (Farid et al. 1995).

A. $RET$ protooncogenes

Products of $RET$ (locus in 10q11.2 region) and $TRK$ (locus in 1q32-41 region) protooncogenes have an activity of tyrosine kinase (Pierotti et al. 1996). The activation of $RET$ and of $TRK$ protooncogenes was found in 33% and 17% of the examined cases of PTC, respectively.

Four oncogenic sequences $RET/PTC^*$ ($RET$/papillary thyroid carcinoma) are known (Tab. 4, Fig. 5):

1. $RET/PTC1$ sequence, denoted also as $RET/H4$. This sequence results from a paracentric inversion in chromosome 10, inv(10) (q11.2 q21). This type of inversion leads to a fusion of the 3' end of tyrosine kinase domain of $RET$ protooncogene with the 5' end of gene labelled with H4 probe (locus D10S170) (Pierotti et al. 1992).

2. $RET/PTC2$ sequence results from the translocation between chromosomes 10 and 17, t(10;17)(q11.2; q23). This type of translocation leads to a fusion of the 3' end of tyrosine kinase (catalytic) domain of $RET$ protooncogene with the 5' terminal sequence of gene in chromosome 17, encoding the RIfα regulatory subunit of protein kinase A (Bongarzone et al. 1993).

3. $RET/PTC3$ sequence – results from a fusion of the 3' end of tyrosine kinase domain of $RET$ protooncogene with the 5' terminal sequence of another gene located in chromosome 10 – $ELE1$, denoted also as $RET$ Fused Gene (RFG). It is also an inversion (Santoro et al. 1994).

4. $RET/PTC4$ sequence results from a fusion of the 3' end of tyrosine kinase domain of $RET$ protooncogene with the 5' end of the $ELE1$ gene (an inversion in chromosome 10). The rearrangement between the tyrosine kinase domain of $RET$ protooncogen and $ELE1$ occurred in the other region than it was in the case of $RET/PTC3$ (Fugazzola et al. 1996; Klugbauer et al. 1996). The $RET/PTC4$ sequence was identified in cells of PTC patients who had been at risk of radiation after the Chernobyl accident (Fugazzola et al. 1996; Klugbauer et al. 1996).

The same authors reported on another oncogenic sequence, namely $RET/PTC6$, also resulting from the rearrangement between $RET$ protooncogene and $ELE1$ gene, identified in cells of post-Chernobyl papillary
thyroid tumours in children. However, the most frequent Sequences, identified as a result of the above mentioned irradiation in children were RET/PTC3 (58%) and RET/PTC1 (16%) (NIKIFOROV et al. 1997).

B. TRK protooncogene

*NTRK1 protooncogene – in its unchanged (wild) form – encodes a protein from the nerve growth factor (NGF) receptor family. In humans, NTRK1 gene loci are located in two regions of chromosome 1 (1q23-24, 1q32-41) (MORIS et al. 1991).

Trk oncogenic sequence proceeds as an outcome of an intrachromosomal inversion within the long arms (q) of chromosome 1, including the NTRK1 gene, what favours the formation of a new hybrid gene. In result of this chromosomal aberration, a fusion takes place of the 3' end of tyrosine kinase domain of the NTRK1 gene with the 5' end of the gene for tropomyosin (nonmuscular tropomyosin gene), located in the 1q31 region. The oncogenic Trk sequence is the most frequent one, being also the most characteristic for the “spontaneous” forms of papillary thyroid carcinomas, i.e., tumours, the genesis of which remains without any relation to previous irradiation (PIEROTTI et al. 1996).

GRECO et al. (1992, 1997) and PIEROTTI et al. (1996) have reported three new oncogenic sequences from the Trk family (Trk-T1, Trk-T2, Trk-T3), identified in cells of PTC (Fig. 6).

The Trk-T1 and Trk-T2 oncogenic sequences, which differ by molecule size between each other, result from a fusion of the 3' end of tyrosine kinase domain of NTRK1 protooncogene (as it has already been mentioned, a part of this gene is included in the Trk oncogene structure) with the 5' end of TPR gene (translocated promoter region) (PIEROTTI et al. 1996; GRECO et al. 1992, 1997). The TPR gene, localised within the 1q25 region, encodes a protein which, most probably, is a component of the cytoskeleton (MIRANDA et al. 1994; BYRD et al. 1994). It has been postulated that deletions, inversions, and mutual translocations, occurring between a pair of chromosomes 1, lead to a revealing of these oncogenic sequences (GRECO et al. 1997).

The Trk-T3 oncogenic sequence results from the fusion of 3' end of tyrosine kinase domain of the

---

**Figure 2. Scheme of treatment of undifferentiated (anaplastic) carcinoma of the thyroid gland.**
MEDULLARY THYROID CARCINOMA (MTC)

Preoperatively diagnosed (FNAB, high concentration of calcitonin) or genetic identification

Diagnosed in histopathological study after operation of goitre for other performed indication

Before operation it is necessary to exclude pheochromocytoma of the adrenals

reoperation

Total thyroidectomy and cervical lymphadenectomy (pre- and paralaryngeal nodes)
- biopsy of deep cervical nodes
- when positive, the modified resection of cervical lymphatic

Examination to find the inherited forms of MTC

Study of ret oncogen mutation in peripheral blood lymphocytes

+ diagnostic imaging of the abdominal cavity to look for pheochromocytoma of the adrenals, determination of methoxy catecholamines and catecholamines in 24-hour urine collection, other studies in 24-hour urine collection, other studies to look for MEN 2

In patient’s family:

Study of germinal mutation of ret oncogen in peripheral blood lymphocytes

Postoperative determination of calcitonin concentrations: basal and pentagastrin-stimulated

Follow up: every 3-6 months:
- clinical examination
- US imaging of basal calcitonin concentration (test of stimulation with pentagastrin once a year)
- US examination of the chest
- US examination of the abdominal cavity
- in case of MEN 2, also determination of catecholamines in 24-hour urine collection (every year) and of serum Ca** concentration (every two years)

Neoplastic focus:
US, CT, NMR, scintigraphy (Tc-V-DMSA, MIBI, anti-CEA, octreotid)

+ Other therapeutical approaches:
Telerradiotherapy* of the cervical region and mediastium or directed into metastases, therapy with 131I-MIBG, chemotherapy, treatment with somatostatin analogues

Surgical treatment

*Therapy with 131I is not recommended

Figure 3. Scheme of treatment of medullary thyroid carcinoma.
Figure 5. Schematic illustration of the RET protooncogene product and its oncogenic variants RET/PTC1, -2, -3 and -4. SP – signal peptide; TM – transmembrane domain; TK – tyrosine kinase domain; D10S170 – locus of gene labelled with H4 probe; Riα – regulatory subunit of protein kinase A; ELE1 – another gene located in chromosome 10, denoted also as RET Fused Gene (RFG). Arrows indicate fusion points, following the RET/PTC rearrangements (the detailed description – see text) (after: SUAREZ 1998, modified).
**NTRKI** protooncogene with the 5' end of gene, called **TFG** (Trk-fused gene) (Suarez 1998; Greco et al. 1995) or **TAG** (Trk-activating gene) (Pierotti et al. 1996; Suarez 1998; Greco et al. 1995).

The **TFG** gene (TAG), which codes the production of cytoplasmatic protein of molecular mass of 68 kDa, has been found on chromosome 3 (Fig. 6). Therefore, the oncogenic Trk-T3 sequence occurs in result of a mutual chromosomal translocation t (1;3) (Greco et al. 1995).

### C. Met protooncogene

**Met** protooncogene (*locus in 7q21-q31 region*) encodes for the receptor protein consisting of 2 subunits, α and β, connected by a disulphide bond (Gandino et al. 1991). This transmembrane tyrosine kinase protein has been identified as the receptor for a polypeptide known as hepatocyte growth factor (HGF) or scatter factor (SF) (Bottaro et al. 1991; Naldini et al. 1991)

It has been observed that *met* oncogene undergoes amplification in cells of about 70% of examined papillary thyroid carcinomas, but only in 25% of follicular carcinomas. The hepatocyte growth factor receptor (HGF-R) is a protein product of *met* oncogene.

No expression of *met* oncogene was observed in cells of anaplastic and medullary thyroid carcinomas, as well as in cells of benign tumours and of normal thyroid tissue (Di Renzo et al. 1992).

The overexpression of *met* oncogene was found to be related to high histological and clinical malignancy of papillary carcinoma.

#### 3.2. Follicular thyroid carcinoma

**A. Ras** protooncogene

Studies of thyroid cancers aetiology have revealed differences, with the follicular carcinoma being more common in the areas of dietary iodine deficiency, and the papillary carcinoma – more common in the areas of iodide excess (Williams 1995).

Fairly concordant with these data are the observations by Sun et al. (1991), who have found that the percentages of *ras* mutations (which are predominantly observed in follicular neoplasms) are higher in iodine-deficient areas (85%) than in the areas rich with iodine (16%).

The data, provided by many authors, suggest that *ras* protooncogene activation plays an important role in the initiation and progression of follicular tumours but also, however in a much less degree, of papillary tumours (Tab. 6 and 7).

In cells of thyroid follicular adenomas, *ras* protooncogene mutations occurred more frequently in microfollicular type (Masood et al. 1993).
B. Chromosome 3p

HERRMANN et al. (1991a) showed a cytogenetic and molecular evidence for the loss of genetic material in the short arm of chromosome 3 (3p) in follicular carcinoma cells. The loss of heterozygosity (LOH) was observed in cells of all the 6 examined follicular carcinomas of the thyroid, using a pheA4 probe (region 3p22-24.1) and pH3H2, pHF12-32 probes (region 3p21). LOH was not observed in 3p in follicular adenomas and in papillary thyroid carcinomas.

In the 3p21-24.1 region, a suppressor gene may be present, the mutation of which leads to a transition of follicular adenoma into follicular carcinoma (HERRMANN et al. 1991a; FAGIN 1992).

In the 3p24 region, protooncogene c-erbAβ is localized. Its expression leads to a synthesis of receptor proteins for many hormones, including triiodothyronine (T₃).

3.3. Medullary thyroid carcinoma – RET protooncogene

RET protooncogene is located in chromosome 10 (10q11.2). The gene has 20 exons, 60-287 bp long, and takes more than 60 kb of genomic DNA. RET protooncogene encodes for a protein product consisting of 1114 or 1072 aminoacides (2 isoforms), showing the activity of tyrosine kinase receptor: 1. the extracellular domain of RET protein, encoded by 10 exons, takes part in ligand binding, which is an unidentified growth factor; 2. the transmembrane domain is encoded by 1 exon and, in its neighbourhood, a cystein-reach region is located, belonging to the extracellular domain; 3. the cytoplasmatic domain is encoded by 9 exons. In the terminal part of the moleculc, there is a tyrosine-kinase domain.

If – in case of PTC – genetic changes of chromosome 10, comprising RET protooncogene, are structural aberrations, then the changes of the same protooncogene are point mutations in MTC.

A. Sporadic medullary thyroid carcinoma

With respect to sporadic MTC, mutations in exon 16 (codon 918) were observed in 23-67 % of patients. ATG (encoding methionine) was replaced by ACG (encoding threonine). Rare mutations affected codon 768 (glutamic acid was replaced by aspartic acid) and codon 883 (alanine was replaced by phe-
nnylalanine). Mutations were observed only in DA from tumour tissues.

**B. Familial medullary thyroid carcinoma (FMTC)**

The condition to diagnose familial medullary thyroid carcinoma (FMTC) is finding families with MTC without the accompanying presence of pheochromocytoma and without hyperplasia or adenoma of parathyroid glands (MULLIGAN et al. 1994).

RET protooncogene mutations were identified in the same 5 codons (609, 611, 618, 620, 634), as for MEN 2A (multiple endocrine neoplasia type 2A) syndrome. However, the relative distribution of mutations in the familial form of MTC was nearly the same for codons: 618 (35%), 620 (25%), 634 (30%).

One family with this type of MTC was observed, in which mutation occurred in codon 768 (MULLIGAN and PONDER 1995). Out of the above mentioned mutations, the most important are those in codons 618 and 634; in both cases the mutations are related to the change of cysteine by serine (TGC → TCC).

**C. Multiple endocrine neoplasia type 2A (MEN 2A)**

In more than 95 % of patients with MEN 2A, mutations in exons 10 and 11 were observed.

With respect to exon 10, mutations were observed in codons: 609, 611, 618, and 620, while in exon 11, they occurred in codon 634. In 87% of the patients mutations occurred in codon 634: TGC was changed
into CGC, providing for a replacement of cysteine by arginine; TGC was changed into TAC, causing cysteine replacement by thyrosine.

**D. Multiple endocrine neoplasia type 2B (MEN 2B)**

In the majority of patients (> 90%) with MEN 2B, inherited mutations in exon 16 (codon 918) were identified. Also the mutations, formed in codon 918, are described. Interestingly enough, the de novo occurring mutations were observed only in the paternal allele of RET.

The proposed diagnostic management to differentiate between the sporadic and inherited forms (FMTC, MEN 2A, MEN 2B) of MTC is presented in Fig. 7.

**References**


BYRD DA, SWEET DJ, PANTE N, KONSTANTINOV KN, GUAN T, et al. Tpr, a large coiled coil protein whose amino terminus is involved in activation of oncogenic kinases, is localized to the cytoplasmic surface of the nuclear pore complex. J Cell Biol 127, 1515-1526, 1994


FARID NR, SHI Y, ZOU M. Molecular basis of thyroid cancer. Endocrine Rev 15, 202-232, 1994

FARID NR, ZOU M, SHI Y. Genetics of follicular thyroid cancer. Endocrinol Metab Clin N Am 24, 865-883, 1995


FUGAZZOLA L, PIEROTTI MA, VIGANO E, PACINI F, VORONTSOVA TV, BONGARZONE I. Molecular and biochemical analysis of RET/PTC4, a novel oncogenic rearrangement between RET and ELE1 genes in a post-Chernobyl papillary thyroid cancer. Oncogene 13, 1093-1097, 1996


GRECO A, MARIANI C, MIRANDA C, LUPAS A, PAGLIARDINI S, POMATI M, PIEROTTI MA. The DNA rearrangement that generates the TRK-T3 oncogene involves a novel gene on chromosome 3 whose product has a potential coiled-coil domain. Mol Cell Biol 15, 6118-6127, 1995


HERRMANN ME, TALPOIS GB, MOHAMED AN, SAXE A, RATNER S, LALLEY PA, WOLMAN SR. Genetic markers in thyroid tumors. Surgery 110, 941-948, 1991b


THYROID CARCINOMA MANAGEMENT: REVIEW


Lemoine NR, Mayall ES, Stringer B, Wynford-Thomas D. High frequency of ras oncogene activation in all stages of human thyroid tumorigenesis. Oncogene 4, 159-164, 1989


Orell SR, Philips J. The Thyroid: fine-needle biopsy and cytological diagnosis of thyroid lesions. In: Mono-


Pierotti MA, Bongarzone I, Borrello MG, Greco A, Pilotti S, Sozzi G. Cytogenetics and molecular genetics of carcinomas arising from thyroid epithelial follicular cells. GEnes Chromosom Cancer 16, 1-14, 1996


Sozzi G, Bongarzone I, Miozzo M, Borrello MG, Butti MG, et al. A t(10;17) translocation creates the RET/PTC2 chimeric transforming sequence in papillary thyroid carcinoma. Genes Chrom Cancer 9, 244-250, 1994


Sporny S. Cytodiagnostics of Thyroid Diseases (in Polish). Studio Graficzne Sobiepanski-Trocha s.c., Łódz 1999


Weidner N. The Difficult Diagnosis in Surgical Pathology. W.B. Saunders, Philadelphia 1996


Corresponding Author: Prof. Andrzej Lewinski, M.D. Department of Thyroidology Medical University of Łódz Dr. Sterling St. No. 5 91-425 Łódz, Poland phone/fax (+48) 42 6322594 E-mail: alewin@psk2.am.lodz.pl

Accepted: March 15, 2000