„CAROL DAVILA" UNIVERSITY
OF MEDICINE AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL
MEDICINE

Diagnostic and prognostic markers in papillary thyroid cancer

DOCTORAL THESIS ABSTRACT

Doctoral supervisor:
PROF. UNIV. DR. CORIN BADIU

Doctoral student:
RUXANDRA DOBRESCU

2022

Thesis content

Introduction – background of the doctoral thesis

General section – Thyroid cancer derived from the follicular epithelium

1. **Definition and etiological classification**
2. **Epidemiology, world trends**
3. **Etiopathogenesis of differentiatd thyroid cancer - Molecular biology**
   - 3.1. Genetical alterations
   - 3.2. Environmental factors
   - 3.3. Epigenetic modulators
4. **Clinical presentation**
5. **Diagnosis**
   - 5.1. Biological diagnosis
   - 5.2. Thyroid ultrasound
   - 5.3. Fine needle aspiration biopsy
   - 5.4. Molecular markers in the diagnosis of indeterminate thyroid nodules
6. **Staging systems – principles, clinical relevance**
   - 6.1. Tumor Node Metastasis (TNM) staging system for risk of cancer mortality
   - 6.2. American Thyroid Association (ATA) staging system for risk of recurrence
   - 6.3. Perspectives – The Cancer Genome Atlas (TCGA) – Molecular classification of differentiated thyroid cancer
7. **Treatment – principles, tailoring according to risk groups**
   - 7.1. Surgical treatment – indications, type of surgical intervention
   - 7.2. Radioiodine therapy – indications, risk groups
   - 7.3. Thyroid hormone replacement/ suppressive therapy
8. **Follow-up and dynamic stratification of risk of recurrence**
   - 8.1. Thyroglobulin and anti-thyroglobuline antibodies
   - 8.2. Ultrasound

8.3. I^{131} Whole-body scan

8.4. High resolution imaging: Computer Tomography, Magnetic Resonance Imaging

8.5. Positron emision tomography (PET-CT)

8.6. Long term follow-up – principles, dinamic stratification of risk of recurrence

9. **Persistent and recurrent disease – therapeutic options**

10. **Radioiodine resistence. Sistemic therapy with tyrozin kinaze inhibitors**

11. **Therapeutic perspectives – precision oncology**

12. **Matrix metalloproteinase-9 (MMP-9) and cancer – future directions and perspectives**

Personal contributions – The doctoral research

1. **Seric MMP-9 seric as a diagnostic and prognostic marker in differentiated thyroid cancer**

1.1. Introduction

1.2. Patients and methods

1.3. Results

1.4. Discussion

1.5. Conclusion

2. **The 1562 C/T functional polymorphism of MMP-9 promoter and the susceptibility to develop thyroid cancer**

2.1. Introduction

2.2. Patients and methods

2.3. Results

2.4. Discussion

2.5. Conclusion

3. **BRAF and TERT promoter mutations in differentiated thyroid cancer – relevance, clinico-pathologic correlations, clinical implications**

3.1. Introduction

3.2. Patients and methods

3.3. Results

3.4. Discussion

3.5. Conclusion

4. **Conclusions and personal contributions**

Bibliography

Annexes

Introduction

Differentiated thyroid cancer (DTC) arising from the follicular epithelium of the thyroid gland is the most frequent endocrine neoplasia (1, 2). In general, the prognosis of patients with DTC is good, especially due to the efficacy of radioiodine therapy, but the spectrum of disease presentation is wide, ranging from micropapillary thyroid carcinomas (MPTCs), often clinically insignificant (3), to cancers with an aggressive clinical behaviour characterised by invasion and metastases, sometimes radioiodine resistance (4) and death.

Differentiated thyroid cancer – Current management guidelines. Dilemmas and challenges

The management of differentiated thyroid cancer is based on the concept of risk of recurrence stratification which allows for a tailored treatment for each patient, with the purpose of avoiding over-treatment of low risk patients, at the same time providing prompt, efficient and aggressive therapy to those patients at high risk of recurrence who have a poor prognosis (5-7).

In order to optimise this algorithm, biomedical research has focused, during the last decades, on the quest to identify new markers useful for establishing diagnosis, refining prognosis estimates and optimising treatment of DTC. International guidelines for the management of patients with DTC are periodically re-evaluated and updated (7-11) as new data related to the mechanisms of tumorigenesis, tumour evolution and response to treatment are uncovered.

However, we still face ***the following dilemmas concerning the diagnosis and treatment of DTC:***

- We over-diagnose *clinically insignificant micropapillary thyroid carcinomas (MPTCs)*. Most of these MPTCs have an indolent clinical course even in the absence of surgical intervention (3), but are often treated more aggressively than it is needed – total thyroidectomy, sometimes even radioiodine therapy.
- In those clinically significant thyroid nodules for which fine needle aspiration biopsy is performed, the cytological evaluation reveals, in a high percentage of patients – *indeterminate results (Bethesda III, IV)*. The traditional therapeutic attitude in these

cases is to recommend a diagnostic lobectomy, which will prove to be excessive for those patients with a benign histological result and insufficient for a lot of patients with a histological diagnosis of cancer, who will require completion thyroidectomy.

- The post-surgical management of patients with DTC is based on the concept of risk stratification (8), which takes into account *clinical, imaging and pathology tumour characteristics* and uses these to stratify patients based on their risk of disease mortality and risk of recurrence. On the other hand, new studies show that a molecular classification of thyroid cancer may better predict the clinical course of the disease and the response to treatment (12).
- Patients with *radioiodine resistant DTC* represent a distinct subgroup, with a generally aggressive clinical course and difficult management. Those patients with rapidly progressive metastatic disease are treated with tyrosine-kinase inhibitors, which can slow disease progression but do not affect survival. Therapy is often limited by the numerous adverse events which can be severe (13, 14). The accumulation in the last years of data related to the genetic background of thyroid neoplasia has led to a change of paradigm toward **precision oncology**, which involves using targeted therapies for the specific genetic alterations involved in tumorigenesis (15-17).

The objectives of the doctoral research. Methodological approach

In this context, the objective of the doctoral research was to identify new markers useful for thyroid cancer diagnosis, prognosis and treatment.

The accumulated data related to the genetic background of DTC have shown that the widely variable clinical course reflects, in fact, distinct tumour genetic signatures, leading to predictable phenotypical consequences (12). The initiation and progression of follicular-derived thyroid cancer requires the occurrence and accumulation of various genetic anomalies which will determine tumour behaviour (12, 14, 18, 19). In this *genetic setting*, the process of tumorigenesis is influenced, in the course of an individual's life, by a series of *environmental factors* (ionising radiations, chemical compounds, iodine status), as well as by the *personal genetic background* (18), including certain susceptibility genes or genomic variants which can influence a person's risk to develop thyroid cancer. Moreover,

the process of tumorigenesis in the thyroid tissue is intimately linked to factors that act in the *tumour microenvironment*: adhesion molecules, growth factors and cytokines.

This complex etiopathogenic and clinical context has allowed us to use several research approaches:

i) To investigate the role of serum Matrix Metallo-Proteinase 9 (MMP-9) in benign and malignant thyroid nodular disease as a diagnostic marker, and to evaluate its role as a prognostic marker in papillary thyroid cancer (20).

ii) To evaluate the impact of MMP-9 promoter genotype on the risk to develop papillary thyroid cancer and the correlation between promoter genotype and clinical and pathological features of tumour aggressiveness (21).

iii) To evaluate the BRAF V600E and TERT promoter C228T, C250T tumour mutational status in DTC and to determine the implications for future clinical practice (22, 23).

The doctoral research was conducted as part of the research programs taking place in the "CI Parhon" National Institute of Endocrinology. In the Genitir project, developed and conducted in partnership with the "Nicolae Simionescu" Institute of Cellular Biology and Pathology and the "Ștefan S. Nicolau" Institute of Virology (grant UEFISCDI PN-II-PT-PCCA-2011-3.2 no.135/2012) we evaluated the impact of serum Matrix Metalloproteinase -9 (MMP-9) as a diagnostic and prognostic marker (20), MMP-9 promoter polymorphisms (21), BRAF mutational status, RET/ PTC rearrangements, DNA methylation profiles (24, 25). Based on the accumulated data, we developed a project investigating the genetic background of thyroid tumours in Romania: "Evaluation of BRAF V600E and TERT promoter C228T, C250T mutational status in patients with follicular epithelium derived thyroid cancer". The project is financed by a "CI Parhon" National Institute research grant, having won the 2nd place in the project competition in 2020. The preliminary results of the project have recently been presented (22).

Personal contributions. The doctoral research

1. Serum MMP-9 as a diagnostic and prognostic marker in papillary thyroid cancer (20)

Introduction: Matrix metalloproteinase 9 (MMP-9) has been extensively investigated due to its important role in tumorigenesis, both in the initial stages and during tumour progression, invasion and metastasis (26, 27). High serum or plasma MMP-9 levels have been identified in numerous types of cancer (28-35), but so far there are few studies concerning thyroid cancer (36-39). In this context our objective was to evaluate the role of serum MMP-9 in the diagnosis of papillary thyroid cancer (PTC) and in estimating patient prognosis.

Materials and methods: We enrolled 185 patients with nodular thyroid disease, 88 of these with benign nodular goitre and 97 with PTC. In all the patients blood was drawn before surgery and serum MMP-9 was determined using an immunometric method.

Results: We discovered no significant differences in MMP-9 serum levels in patients with benign vs malignant thyroid disease (*p=0.3*). In PTC there were no significant differences between patients with different histological subtypes, TNM stages, presence or absence of invasion; however, high risk patients according to the ATA classification, presenting with multiple features of tumour aggressiveness, had significantly higher serum MMP-9 levels compared to low-intermediate risk patients (767.5 ± 269.2 ng/ml vs 563.7 ± 228.4 ng/ml, *p=0.019*). A cut-off of 806 ng/ml can differentiate high risk patients with a 60% sensitivity and 87.36% specificity, p=0.018. In patients with available follow-up data (N=78), serum MMP-9 was significantly higher before surgery in patients who required ≥2 ^{131}I doses (*p=0.009*) and in those with biochemical disease persistence or who required additional therapy in order to reach no evidence of disease status (*p=0.017*).

Conclusion: Serum MMP-9 measured before surgery is not useful as a diagnostic marker in PTC, but high levels of MMP-9 can help identify patients with a high risk of persistent disease who will require intensive treatment and careful follow-up.

2. MMP-9 promoter 1562 C/T functional polymorphism and the susceptibility to develop thyroid cancer (21)

Introduction: In the context of the established role of Matrix metalloproteinase-9 (MMP-9) in tumorigenesis (26, 27), and in light of previous studies that have shown that the functional 1562 C/T polymorphism leads to an important increase in gene expression (40), our hypothesis was that patients carrying the T allele would have a higher risk to develop more aggressive cancer, leading to more advanced tumour stages (21).

Material and methods: We evaluated 236 patients with nodular thyroid disease scheduled to undergo thyroid surgery, 119 with benign multinodular goitre and 117 with papillary thyroid cancer. Genomic DNA was isolated from peripheral blood and the -1562C/T genotype was evaluated using PCR-RFLP analysis.

Results: We discovered a significantly higher frequency of the T allele in cancer patients vs patients with benign goitre (17.5% vs 10.1%), p=0.019. Patients with the CT or CT+TT combined genotype had a significantly higher risk to develop papillary thyroid cancer, but this risk was limited to developing micropapillary thyroid carcinoma (genotype CT: OR=6.467, p=0.00006; CT+TT: OR=6.859, p=0.00002), and not more advanced tumour stages (CT: p=0.094; CT+TT: p=0.157). No significant correlations were identified between the -1562C/T genotype and the histological subtype of PTC, degree of invasion or TNM stage.

Conclusion: the presence of the T allele in position 1562 of the MMP-9 promoter significantly increases the risk to develop papillary thyroid cancer. This risk is limited to incipient tumour stages (intra-thyroidal micropapillary thyroid cancer) and not more advanced stages, which suggests that the CT+TT genotype is important for tumour initiation, not progression. Larger studies are needed to confirm these observations at a population level (21).

3. BRAF and TERT promoter C228T, 250T mutations in differentiated thyroid cancer (22)

Introduction: Precision oncology is based on using molecular markers to guide cancer management. In differentiated thyroid cancer, multiple studies have shown that BRAF V600E and TERT promoter tumour status can help refine prognosis estimates and evaluate the risk of disease recurrence and mortality (41, 42), however, so far there are no available data from the Romanian population. In this context our objective was to optimise the protocol for the detection of tumour mutational status and to evaluate the association between mutational status and clinical and pathological features used in current risk stratification algorithms.

Materials and methods: We evaluated 68 tissue samples from 58 patients with differentiated thyroid cancer. Genomic DNA was extracted from paraffin embedded tumour tissue and BRAF V600E and TERT promoter C228T and C250T mutations were evaluated using Sanger sequencing.

Results: BRAF V600E mutation was identified in 21.2% of patients, without significant differences related to patient age or sex. TERT promoter mutations were present in 17.3% 17.3% (9/ 52) of patients, predominantly in the ≥45 year age group ($\chi2$=3.352, p=0.06). The presence of BRAF V600E mutation is significantly associated with aggressive histological subtypes and classical papillary thyroid carcinoma ($\chi2$=11.29, p=0.023), but not with other features of aggressiveness (presence of invasion, TNM stage or ATA risk group). TERT promoter mutations are associated with aggressive histological subtypes ($\chi2$=9.04, p=0.060) and with advanced local tumour stages ($\chi2$=4.121, p=0.042). Patients with co-existent BRAF+TERT mutations (N=5) presented with aggressive disease (ATA high risk) ($\chi2$=6.019, p=0.049) and 4 of the 5 had radioiodine resistance. Moreover, our data indicate a lower prevalence of BRAF V600E mutations compared to the reported average, similar to other European studies, possibly as a consequence of yet incompletely known environmental factors, including iodine status. This is an important element, because these differences can reflect certain particularities of thyroid cancer evolution in the Romanian population (22).

Conclusion: BRAF V600E mutation status is not significantly associated with clinical and pathological features of tumor aggressiveness, which limits its use as a prognostic marker, when assessed independently. TERT promoter mutations are associated with aggressive histologies and locally advanced tumour stages, and the presence of concomitant BRAF

V600E mutations can help identify patients with aggressive clinical disease (ATA high risk, radioiodine resistance) who will require intensive treatment.

Conclusions. Practical implications of the doctoral research

The evaluation of ***serum MMP-9*** before surgery can help identify patients with aggressive forms of thyroid cancer and is a rapid and cheap method, but the result is influenced by numerous biological factors (the presence of alternative secretion sources, such as inflammatory disorders, including autoimmune thyroidis) and pre-analitical factors (storage conditions, sample manipulation), which limits its use in current clinical practice.

The evaluation of the ***1562 C/ T MMP-9 promoter polymorphism*** has shown that the presence of the T allele significnatly increases the risk to develop micropapillary thryoid carcinoma, but not more aggressive cancer stages. It is an interesting observation which might suggest that some micropapillary tumors with an indolent clinical course could in fact represent a distinct clinical cathegory of thyroid cancer. As for any susceptibility factors, larger studies are required to confirm these results at the population level.

The evaluation of the ***tumor mutation status*** in differenciated thyroid cancer has important practical implications, both immediately and for future practice.

Firstly, we have managed to *optimise the detection protocol for tumor mutation status in thyroid tumors*. It is an extremely important element, not only from a research perspective but also from the perspective of current clinical practice, if we consider the *therapeutic implications of these markers*. BRAF V600E status assessment is essential in order to establish the opportunity of treatment with BRAF and MEK inhibitors (dabrafenib and trametinib) in patients with anaplastic thyroid cancer, according to recent recommendations of the American Thyroid Association (43).

From the perspective of future medical practice, as *prognostic markers,* the identification of TERT promoter mutations in thyroid tumour tissue, especially when associated with BRAF V600E mutations, will help identify immediately after surgery those patients with aggressive thyroid cancer who will require intensive treatment.

From a *diagnostic perspective*, molecular testing for BRAF V600E and TERT promoter mutations in fine needle aspirate samples in patients with indeterminate thryoid nodules is easily accessible, with a reduced cost, and can help identify thyroid cancer before surgery.

Selective bibliography

1. Davies L, Welch HG. Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg. 2014;140(4):317-22.

2. Wiltshire JJ, Drake TM, Uttley L, Balasubramanian SP. Systematic Review of Trends in the Incidence Rates of Thyroid Cancer. Thyroid. 2016;26(11):1541-52.

3. Ito Y, Miyauchi A, Kihara M, Higashiyama T, Kobayashi K, Miya A. Patient age is significantly related to the progression of papillary microcarcinoma of the thyroid under observation. Thyroid. 2014;24(1):27-34.

4. Schlumberger M, Brose M, Elisei R, Leboulleux S, Luster M, Pitoia F, et al. Definition and management of radioactive iodine-refractory differentiated thyroid cancer. Lancet Diabetes Endocrinol. 2014;2(5):356-8.

5. Dobrescu R, Badiu C. Papillary, follicular and anaplastic thyroid carcinoma and lymphoma. In: Wass JAH, Arlt W, Semple R, editors. Oxford Textbook of Endocrinology and Diabetes. Oxford: Oxford University Press; 2022.

6. Haugen BR. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: What is new and what has changed? Cancer. 2017;123(3):372-81.

7. NCCN Clinical Practice Guidelines in Oncology - Thyroid carcinoma (Version 1.2021) 2021 [May 8, 2021]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf.

8. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133.

9. Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard Ba G, et al. Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf). 2014;81 Suppl 1:1-122.

10. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol. 2006;154(6):787-803.

11. Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, et al. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-updagger. Annals of oncology : official journal of the European Society for Medical Oncology. 2019;30(12):1856-83.

12. Cancer Genome Atlas Research N. Integrated genomic characterization of papillary thyroid carcinoma. Cell. 2014;159(3):676-90.
13. Dobrescu R, Badiu C. An Expanding Class in the Treatment of Thyroid Cancer: Tyrosine Kinase Inhibitors. Acta Endocrinologica-Bucharest. 2015;11(4):536-9.
14. Tirro E, Martorana F, Romano C, Vitale SR, Motta G, Di Gregorio S, et al. Molecular Alterations in Thyroid Cancer: From Bench to Clinical Practice. Genes (Basel). 2019;10(9).
15. Ho AL, Grewal RK, Leboeuf R, Sherman EJ, Pfister DG, Deandreis D, et al. Selumetinib-enhanced radioiodine uptake in advanced thyroid cancer. N Engl J Med. 2013;368(7):623-32.
16. Rothenberg SM, McFadden DG, Palmer EL, Daniels GH, Wirth LJ. Redifferentiation of iodine-refractory BRAF V600E-mutant metastatic papillary thyroid cancer with dabrafenib. Clin Cancer Res. 2015;21(5):1028-35.
17. Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, et al. Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic BRAF V600-Mutant Anaplastic Thyroid Cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2018;36(1):7-13.
18. Acquaviva G, Visani M, Repaci A, Rhoden KJ, de Biase D, Pession A, et al. Molecular pathology of thyroid tumours of follicular cells: a review of genetic alterations and their clinicopathological relevance. Histopathology. 2018;72(1):6-31.
19. Dobrescu R, Badiu C. Actualities in genetics of differentiated thyroid cancer. Acta Endocrinol (Buchar). 2020;16(1):118-20.
20. Dobrescu R, Picu C, Caragheorgheopol A, Manda D, Ioachim D, Goldstein A, et al. Serum Matrix metalloproteinase-9 (MMP-9) can help identify patients with papillary thyroid cancer at high risk of persistent disease: Value and limitations of a potential marker of neoplasia. Cancer biomarkers : section A of Disease markers. 2020;29(3):337-46.
21. Dobrescu R, Schipor S, Manda D, Caragheorgheopol A, Badiu C. Matrix metalloproteinase-9 (MMP-9) promoter -1562C/T functional polymorphism is associated with an increased risk to develop micropapillary thyroid carcinoma. Cancer biomarkers : section A of Disease markers. 2022.
22. Dobrescu R, Schipor S, Muresan A, Ioachim D, Goldstein A, Manda D, et al. BRAF V600E and TERT promoter mutations in differentiated thyroid cancer in Romania - clinical and pathological correlations. 30th National Congress of the Romanian Society of Endocrinology; Bucharest, Romania2022.

23. Dobrescu R, Schipor S, Muresan A, Ioachim D, Manda D, Vladoiu S, et al. BRAF V600E and TERT promoter mutations in differentiated thyroid carcinoma: relevance, clinical implications. Ziua Institutului CI Parhon2021.

24. Botezatu A, Iancu IV, Plesa A, Manda D, Popa O, Bostan M, et al. Methylation of tumour suppressor genes associated with thyroid cancer. Cancer biomarkers : section A of Disease markers. 2019;25(1):53-65.

25. Iancu IV, Botezatu A, Plesa A, Huica I, Fudulu A, Albulescu A, et al. Alterations of regulatory factors and DNA methylation pattern in thyroid cancer. Cancer biomarkers : section A of Disease markers. 2020;28(2):255-68.

26. Farina AR, Mackay AR. Gelatinase B/MMP-9 in Tumour Pathogenesis and Progression. Cancers (Basel). 2014;6(1):240-96.

27. Barillari G. The Impact of Matrix Metalloproteinase-9 on the Sequential Steps of the Metastatic Process. International journal of molecular sciences. 2020;21(12).

28. Sbardella D, Fasciglione GF, Gioia M, Ciaccio C, Tundo GR, Marini S, et al. Human matrix metalloproteinases: an ubiquitarian class of enzymes involved in several pathological processes. Mol Aspects Med. 2012;33(2):119-208.

29. Patel S, Sumitra G, Koner BC, Saxena A. Role of serum matrix metalloproteinase-2 and -9 to predict breast cancer progression. Clin Biochem. 2011;44(10-11):869-72.

30. Turpeenniemi-Hujanen T. Gelatinases (MMP-2 and -9) and their natural inhibitors as prognostic indicators in solid cancers. Biochimie. 2005;87(3-4):287-97.

31. Jung K, Lein M, Laube C, Lichtinghagen R. Blood specimen collection methods influence the concentration and the diagnostic validity of matrix metalloproteinase 9 in blood. Clin Chim Acta. 2001;314(1-2):241-4.

32. Provatopoulou X, Gounaris A, Kalogera E, Zagouri F, Flessas I, Goussetis E, et al. Circulating levels of matrix metalloproteinase-9 (MMP-9), neutrophil gelatinase-associated lipocalin (NGAL) and their complex MMP-9/NGAL in breast cancer disease. BMC Cancer. 2009;9:390.

33. Wilson S, Damery S, Stocken DD, Dowswell G, Holder R, Ward ST, et al. Serum matrix metalloproteinase 9 and colorectal neoplasia: a community-based evaluation of a potential diagnostic test. Br J Cancer. 2012;106(8):1431-8.

34. Hurst NG, Stocken DD, Wilson S, Keh C, Wakelam MJ, Ismail T. Elevated serum matrix metalloproteinase 9 (MMP-9) concentration predicts the presence of colorectal neoplasia in symptomatic patients. Br J Cancer. 2007;97(7):971-7.

35. Wu CY, Wu MS, Chiang EP, Chen YJ, Chen CJ, Chi NH, et al. Plasma matrix metalloproteinase-9 level is better than serum matrix metalloproteinase-9 level to predict gastric cancer evolution. Clin Cancer Res. 2007;13(7):2054-60.
36. Komorowski J, Pasieka Z, Jankiewicz-Wika J, Stepien H. Matrix metalloproteinases, tissue inhibitors of matrix metalloproteinases and angiogenic cytokines in peripheral blood of patients with thyroid cancer. Thyroid. 2002;12(8):655-62.
37. Zhou SF, Hu SY, Ma L, Miao L, Mao WZ. Correlations between papillary thyroid cancer and peripheral blood levels of matrix metalloproteinase-2, matrix metalloproteinase-9, tissue inhibitor of metalloproteinase-1, and tissue inhibitor of metalloproteinase-2. Chinese medical journal. 2013;126(10):1925-9.
38. Lin SY, Wang YY, Sheu WH. Preoperative plasma concentrations of vascular endothelial growth factor and matrix metalloproteinase 9 are associated with stage progression in papillary thyroid cancer. Clin Endocrinol (Oxf). 2003;58(4):513-8.
39. Maruyama S, Kawata R, Shimada T, Shinomiya T, Hirata Y, Yamamichi I, et al. [Study of matrix metalloproteinase-2 and -9 in thyroid papillary cancer]. Nihon Jibiinkoka Gakkai Kaiho. 2000;103(5):499-505.
40. Zhang B, Ye S, Herrmann SM, Eriksson P, de Maat M, Evans A, et al. Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. Circulation. 1999;99(14):1788-94.
41. Moon S, Song YS, Kim YA, Lim JA, Cho SW, Moon JH, et al. Effects of Coexistent BRAF(V600E) and TERT Promoter Mutations on Poor Clinical Outcomes in Papillary Thyroid Cancer: A Meta-Analysis. Thyroid. 2017;27(5):651-60.
42. Liu R, Bishop J, Zhu G, Zhang T, Ladenson PW, Xing M. Mortality Risk Stratification by Combining BRAF V600E and TERT Promoter Mutations in Papillary Thyroid Cancer: Genetic Duet of BRAF and TERT Promoter Mutations in Thyroid Cancer Mortality. JAMA oncology. 2017;3(2):202-8.
43. Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ, Jr., et al. 2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. Thyroid. 2021;31(3):337-86.

List of publications

Book chapters:

1. Papillary, follicular and anaplastic thyroid carcinoma and lymphoma. **Dobrescu R**, Badiu C. In Oxford Textbook of Endocrinology and Diabetes 3rd Edition, 2022. ISBN: 9780198870197.
2. Efectul pandemiei SARS-CoV-2 asupra managementului afecțiunilor tiroidiene benigne sau maligne. **Dobrescu R**, Stănescu L, Chiriac I, Stancu AM, Badiu C. In Antropologie și tradiții. Colecția Zilele Rainer, 2022. ISBN 978-973-27-3200-7.
3. Patologia tiroidiană în România – de la gușa endemică la secvențierea genetică în cancerul tiroidian. **Dobrescu R**, Chiriac I, Gheorghiu M, Badiu C. In Antropologie și tradiții. Colecția Zilele Rainer, 2021. ISBN 978-973-27-3376-9.

Articles:

1. Matrix metalloproteinase-9 (MMP-9) promoter -1562 C/T functional polymorphism is associated with an increased risk to develop micropapillary thyroid carcinoma. Dobrescu R; Schipor S; Manda D; Caragheorgheopol A; Badiu C. Cancer Biomarkers, 2022. **IF 4.388**
2. What is Hidden in a Cystic Lesion after Extensive Surgery for Medullary Thyroid Carcinoma? Dobrescu R, Stanescu B, Ioachim D, Badiu C. Acta Endo (Buc) 2021 17(2): 280-281 doi: 10.4183/aeb.2021.280. **IF 0.877**
3. Serum MMP-9 can help identify patients with papillary thyroid cancer at high risk of persistent disease: value and limitations of a potential marker of neoplasia. **Dobrescu R**, Picu C, Caragheorgheopol A, Manda D, Ioachim D, Goldstein A, Badiu C. Cancer Biomarkers, Cancer Biomarkers 2020;29(3):337-346. **IF 3.436**
4. Actualities in genetics of differentiated thyroid cancer. **Dobrescu R**, Badiu C. Acta Endocrinologica, Jan-Mar 2020;16(1):118-120. doi: 10.4183/aeb.2020.118. **IF 0.55**
5. Alterations of Regulatory Factors and DNA Methylation Pattern in Thyroid Cancer, Iancu IV, Botezatu A, Plesa A., Huica I., Fudulu A., Albulescu A., Bostan M., Mihaila M., Grancea C., Manda D., **Dobrescu R.**, Vladoiu S., Anton G., Badiu C. Cancer Biomarkers, vol. 28, no. 2, pp. 255-268, 2020. **IF 2.859**

6. Methylation of tumour suppressor genes associated with thyroid cancer. Botezatu, A; Iancu, IV; Plesa, A; Manda, D; Popa, O; Bostan, M; Mihaila, M; Albulescu, A; Fudulu, A; Vladoiu, SV; Huica, I; **Dobrescu, R**; Anton, G; Badiu, C. Cancer Biomarkers 2019;25(1):53-65. **IF 2.859**

Cumulative impact factor: 14.969

Scientific papers presented at national and international conferences

1. BRAF V600E and TERT promoter mutations in differentiated thyroid cancer in Romania - clinical and pathological correlations. **Dobrescu R,** Schipor S, Muresan A, Ioachim D, Goldstein A, Manda D, Vladoiu S, Badiu C. The 30th National Congress of the Romanian Endocrine Society, Jun 2022, Bucharest, Romania.
2. Differentiated thyroid cancer in pregnancy. **Dobrescu R,** Bojoga A, Badiu C. Feb 2022, AECR Symposium, Online Meeting.
3. MMP-9 promoter -1562 C/T functional polymorphism is associated with an increased risk to develop micropapillary thyroid carcinoma. **Dobrescu R,** Schipor S, Manda D, Caragheorgheopol A, Badiu C. The 29th Congress of the Romanian Endocrine Society, Jun 2021, Online Meeting.
4. The effect of the SARS-CoV-2 pandemic on the addressability of patients with benign or malignant disorders. **Dobrescu R**, Stănescu L, Chiriac I, Stancu AM, Badiu C. "Francisc I Rainer" Symposium, May 2021, Bucharest, Romania.
5. Differentiated thyroid cancer in pregnancy – Management challenges. **Dobrescu R**, Badiu C. AECR Symposium "Endocrinology in COVID-19 era", Mar 2021. Online Meeting.
6. MMP-9 1562 C/T polymorphism may be associated with an increased susceptibility to develop micropapillary thyroid cancer but not more advanced tumours. **Dobrescu R**, Schipor S, Picu C, Manda D, Caragheorgheopol A, Badiu C. European Congress of Endocrinology, Apr 2020, Online Meeting.
7. Targeted therapies in advanced differentiated thyroid cancer: efficacy, quality of life, perspectives. **Dobrescu R**, Baetu M, Dyachenko K, Hortopan D, Dumitrascu A, Goldstein A, Badiu C. The 22-nd Symposium of the Romanian Society of PsychoNeuroEndocrinology, Nov 2020, Timisoara, Romania,

8. Thyroid disorders in romania – from endemic goiter to genetic sequencing in thyroid cancer. **Dobrescu R,** Chiriac I, Gheorghiu M, Badiu C. "Francisc I Rainer" Symposium, Oct 2020, Bucharest, Romania.
9. Differentiated thyroid cancer in pregnancy – DO's and DON'Ts. **Dobrescu R,** Badiu C. The 36th Balkan Medical Week, Sep 2020, Bucharest, Romania.
10. Telomerase biology involvement in thyroid neoplasia: from aging clock to aggressive cancers. Badiu C, Dobrescu R. The 55-th Congress of the European Societies of Toxicology, Sep 2019, Helsinky, Finland.
11. Value of serum MMP-9 as a circulating marker in thyroid cancer is highly dependent on sampling and collection conditions. **Dobrescu R**, Picu C, Caragheorgheopol A, Manda D, Ioachim D, Goldstein A, Badiu C. European Thyroid Association Meeting, Sep 2019, Budapest, Hungary.
12. Pre-surgical molecular diagnosis of thyroid nodules. **Dobrescu R**, Badiu C, Romanian Association of Clinical Endocrinology, Sep 2019, Sinaia, Romania – *The AECR prize*.
13. Changes in nutritional status in endocrine disease, **Dobrescu R.** The Romanian Nutrition Congress, Bucharest, Jul 2019.
14. Value and limitation of serum MMP-9 in thyroid nodular disease. **Dobrescu R**, Picu C, Manda D, Caragheorgheopol A, Badiu C. The 21st European Congress of Endocrinology, May 2019, Lyon, France.
15. Clinical variability, diagnostic and therapeutic challenges in medullary thyroid carcionoma. The 6-th National Neuroendocrinology Congress, Oct 2018, Bucharest, Romania. **Dobrescu R**, Baetu M, Dumitrascu A, Ioachim D, Caragheorgheopol A, Badiu C – *3rd prize of the Romanian Neuroendocrinology Society*
16. The thyroid - beyond the anatomo-pathologic exam. Is immunohistochemistry a useful ancillary technique in the diagnosis? The XIII-th Congress of the Romanian Clinical Endocrinology Association, Sep 2018. Stancu C, Dobrescu R, Ioachim D, Manda D, Caragheorgheopol A – *The AECR prize*.