International Journal of Medical Science and Clinical Research Studies

ISSN(print): 2767-8326, ISSN(online): 2767-8342

Volume 03 Issue 01 January 2023

Page No: 80-85

DOI: https://doi.org/10.47191/ijmscrs/v3-i1-16, Impact Factor: 5.365

Role of BRAF V600E Mutation in Papillary Thyroid Cancer

Gloria Nataly Perez Serrano[1], Andrea Minerva Rodríguez Moreno[2], Héctor Gabriel Rodríguez[3]

[1,2,3] Universidad Autonoma de Guadalajara

ABSTRACT

Talking about thyroid carcinomas leaves a fairly wide slope, in which it should be considered not only the variants and their clinical frequency, but the mutant genetic finding that gives preamble to the malignancy, its clinical variability, histological as well as the prognosis. It is important to note that the most frequent thyroid carcinoma in the population is papillary, with an index greater than 80% of all cases, being rare in pediatrics. The papillary thyroid subtype is the result of one of two possible alterations affecting the genes encoding tyrosine kinase, either in the RET gene of chromosome 10q11 or in the BRAF gene, by an early mutation in the MAP kinase signaling pathway. Statistically, it is known that the mutation in the BRAF gene represents most of the alterations that give rise to papillary thyroid carcinoma, and in turn, this BRAF gene presents an alteration in the amino acid 600, which gives rise to the BRAF 600E gene. That is why, in this research work focuses on the role BRAF V600E and papillary thyroid carcinoma, from the pathogenic mechanism that gives rise to the mutation, the genetic location of the mutation. Clinical and histopathological relationship with the BRAF mutation as well as prognosis and certain related complications are mentioned.

ARTICLE DETAILS

Published On:
23 January 2023

Available on:
https://ijmscr.org/

INTRODUCTION

Thyroid carcinomas are infrequent, representing 1.5% of all cancers, with a predominance in the female sex and in patients at the beginning or in mid-adulthood. However, when the carcinoma appears in childhood or late adulthood the ratio between males and females is equalized. [23]

Among thyroid carcinomas, four variables stand out and the frequency is relative: [23].

- Papillary carcinoma (>85% of cases).
- Follicular carcinoma (5 - 15% of cases).
- Anaplastic (undifferentiated) carcinoma (<5% of cases).
- Medullary carcinoma (5% of cases)

Most thyroid carcinomas (except medullary carcinomas) are derived from thyroid follicular epithelium and the vast majority are well differentiated. [23]

Papillary thyroid carcinoma (PTC) has been identified as a malignant epithelial tumor evidencing follicular cell differentiation typically with both papillary and follicular structures, as well as characteristic nuclear changes. [23]
The key to its diagnosis is the nuclear features, whereas the presence of vascular or capsular invasion, is not a necessary requirement. nuclear features have become the equivalent of papillae in the diagnosis of PTCC and tumors that in the past were designated as "mixed papillary-follicular carcinoma" should be reclassified as PTCC. [23]
Variants of papillary carcinoma have been described, considering its anatomopathological particularities, such as size (papillary microcarcinoma); the nature of its boundaries (encapsulated); its architecture (modular-cribiform, solid, micro and macro papillary, etc.); cellular characteristics (tall, columnar, oncocytic, clear cells, etc.); additional tumor components (focal insular component, with squamous cell carcinoma); stromal characteristics (stromal-type fasciitis) [12].

These variants are: conventional papillary thyroid carcinoma (CPTC), papillary thyroid carcinoma follicular variant (PPTVF), papillary thyroid carcinoma high cell thyroid carcinoma (PPTCA).
Approximately 70% of papillary thyroid cancers have mutually exclusive genetic mutations encoding RET or NTRK1 growth factor receptors, the three isoforms of RAS (N, H, K) and BRAF. [6]
BRAF encodes an intermediate signal transmission component in the MAP kinase pathway.
Patients with papillary thyroid cancer who have the BRAF V600E gene mutation very frequently develop lymph node

metastases as well as recurrent tumors.[22] In addition, patients with papillary thyroid cancer who have the BRAF V600E gene mutation often develop lymph node metastases as well as recurrent tumors.

Framework:

Papillary thyroid cancer is the most common malignant endocrine neoplasm cancer; it accounts for 85 - 90 % of all thyroid cancers. [16, 23]. Most papillary carcinomas (70%) have gain-of-function mutations affecting genes encoding tyrosine kinases, RET receptor, NTRK1, or in the BRAF serine/threonine kinase, located in the MAPK pathway. [6, 23]

The histologic peculiarity of these conventional thyroid cancers is characterized by papillary architecture and nuclear features, nuclear enlargement, crowding, clearing and irregular nuclear contours resulting in the formation of nuclear grooves and, in extreme cases, nuclear pseudoinclusions. As previously mentioned, histologic features exhibit different types of papillary cancers, among these are: 1. conventional papillary thyroid carcinoma (CPTC), 2. papillary thyroid carcinoma follicular variant (PTCVF), 3. papillary thyroid carcinoma of tall cells (PTCCA), 4. papillary columnar cell carcinoma (PTCCC), 5. papillary carcinoma of diffuse cells sclerotic type (PTCDCS). [6]

Papillary carcinomas invade lymph nodes and cause lymph node metastasis and multifocality. Venous invasion is seen less frequently (5-7%) and causes lung and bone metastases. [6]

Taking into account the existence of papillary carcinoma variables it can be determined that among these there is a more aggressive behavior one from another and prognosis; conventional papillary thyroid carcinoma (CPTC) has better prognosis, however the tall cell variant, columnar cell variant and diffuse sclerotic type and in stratifications are generally classified in high risk groups. [6]

BRAF V600E mutation is the most frequent alteration found in PTC, with a prevalence of approximately 45%. [20]

Epidemiology:

Papillary thyroid cancer is the most common neoplasm in the endocrine system. The survival rate of patients with this affectation is estimated to be about 5 years in an average of 95 to 97%[5]. There are several risk factors that lead to present the disease such as age since it is a neoplasm that tends to occur in older people, cervical lymph node metastasis, extra-thyroid invasion, etc [4].

This type of thyroid cancer is the most common type of thyroid cancer, characterized by its papillary appearance, accounting for approximately 80% of all thyroid carcinomas[13]. Radiation exposure during childhood is a well-established risk factor for thyroid cancer, it is conceivable that the rising incidence may reflect the increasing use of medical radiation procedures such as computed tomography. Other possible risk factors include smoking, chemicals, environmental etc. [19]

Along with the development of molecular technologies, changes have been found in the practice of thyroid FNA cytology. The central event marking this recent change was the National Cancer Institute's State of Thyroid Science and Aspiration Conference (in October 2007 in Bethesda, Maryland) of pathologists, cytopathologists, radiologists, endocrinologists, and surgeons to standardize the various aspects of thyroid cytology.[2]

A large number of studies have addressed the application of BRAF mutation testing in thyroid cytology specimens. However, only a subset of these studies correlated BRAF mutation results with indeterminate diagnoses that were stratified into ≥ 2 subcategories and only 6 studies used the BSRTC or a comparable system; in addition, the vast majority of studies involving thyroid cytology specimens specifically examined the V600E mutation only.[2] In addition, the vast majority of studies involving thyroid cytology samples specifically examined the V600E mutation only.[2]

The incidence of this BRAF mutation in the pediatric population is thought to be lower than in adults with rates of 0% to 37%, although a recent series revealed a rate of 63% lower than in adults with rates of 0% to 37%, although a recent series revealed a rate of 63%.[18] According to a publication in the Archives of Pathology and Laboratory Medicine by Ryan J. Gertz, the rate of pediatric BRAF mutation is still significantly lower than that in the adult population [18].

As described, patients with tumors positive for the V600E mutation were more likely to have a family history of cancer (p 1⁄4 .04) but this association was not significant when advanced age was taken into account. Patients who were mutation positive were less likely to have Hashimoto's thyroiditis and had a smaller tumor diameter (2.1 cm). [18]

Pathogenesis:

Thyroid carcinomas originating from follicular epithelium, present genetic alterations of the three malignant processes derived from follicular cells and can be activated in two pathways of oncogenesis: the MAPK (mitogen-activated kinase) pathway and the PI-3K/AKT (phosphatidylinositol 2-cyanase) pathway. [23]

In the papillary variable of thyroid carcinomas, activation of the MAPK pathway is characteristic in most papillary carcinomas, and can occur by two main mechanisms; either by gene rearrangement of RET or NTRKI, these genes encoding transmembrane receptor tyrosine kinases. Or mutation of BRAF, which is involved in a potent intermediate signaling component of the MAPK kinase pathway. [23]

The frequency of the RET gene rearrangement-related mechanism is significantly higher in papillary cancers associated with a history of radiation exposure, in 20-40% of papillary carcinomas. [23]

Between 30 - 50% of carcinomas associated with a gain-of-function mutation of the BRAF gene, of which the majority consist of BRAFV600E. A study conducted at the University of Cincinnati in Ohio showed that a somatic mutation in the BRAF gene, V009E is the most common genetic alteration in papillary thyroid carcinoma. [21, 23]

The BRAF gene is a member of the RAF family of kinases that promotes signaling through the RAS-RAF-MAPK signal transduction cascade. [4] An activating mutation located in exon 15 of isoform B of the Raf kinase gene results in a valine-glutamate acid substitution at amino acid 600 (BRAF V600E). [20]

This mutation leads to destabilization of the gene-encoded kinase, promotion of a constitutively activated state, increased BRAF kinase activity towards MAPK kinase and promotion of tumorigenesis through the MAPK pathway. [20]

Mutations in BRAF exon 15 other than V600E are rarely seen in PTC. Some of these rare BRAF exon 15 (r-BRAF) alterations have also been described in thyroid neoplasms other than PTC (i.e., follicular carcinoma and follicular adenoma). [20]

BRAF is a gene that encodes for a protein kinase belonging to the MAPK cascade. Activating mutations in the BRAF gene frequently occur in various solid tumors [5]. BRAF V600 mutations have been found in approximately 50% of cutaneous melanomas and result in constitutive activation of signaling through mitogen-activated protein kinase (MAPK). In more than half of the nonmelanoma cancers with BRAF V600 mutations that have been identified, the incidence of mutations is less than 5% [13].

Papillary thyroid carcinoma can present mutations in different genes, however the most frequently found mutation is in the BRAF gene, which is present in approximately 70% of papillary thyroid cases, according to a study performed in the department of pathology at the University of Pittsburgh, followed by mutations in the PIK3CA, TP53 and NRAS genes. Mutations in the TERT C228T gene have also been found, it is important to note that this mutation is less likely to occur once there is a mutation in the BRAF or RAS genes. [10]

A variant of papillary thyroid carcinoma has been found in children, developed after the Chernobyl and Fukushima accident, with RET/PTC rearrangements [14]. The columnar variant is a rare tumor, affecting at least 0.2% of all cases of papillary thyroid cancer, originating from a metastasis of endometrial adenocarcinoma in which pseudo stratifications of elongated cells containing reminiscent vacuoles are observed, where BRAF gene mutation can be found in one third of cases. [15]

Clinicopathological findings:

Papillary thyroid carcinoma, being the most common variable of the most frequent endocrine neoplasia, has a favorable prognosis, with a 5-year survival rate of 97.8%. In some patients, recurrent or progressive disease after surgery or disease refractory to radioactive iodine therapy may occur. [22]

It is important to know that papillary carcinomas are not functional neoplasms, so they manifest as a goiter, painless with the variant of being inside the gland or as metastasis in cervical lymph node. [23]

It appears that isolated cervical lymph node metastases do not have an important influence on the prognosis, which is usually good, except in patients older than 40 years. [23]

In papillary thyroid carcinoma, mutation in the BRAF V600E gene is known to be the most frequent alteration found in PTC [20].

Many studies have demonstrated a statistically significant association between BRAF V600E mutation and high-risk clinicopathologic features of PTC, including extrathyroidal extension, lymph node metastasis, distant metastasis, recurrent tumors, and advanced stages of PTC at diagnosis. Finding high predictive value between BRAF V600E mutation and PTC recurrence and mortality. [20, 22]

Histopathologic findings:

Most thyroid carcinomas (except medullary carcinomas) are derived from thyroid follicular epithelium and the vast majority are well differentiated. [12, 23]

The manifestation of papillary thyroid carcinomas can vary from single or multifocal lesions within the thyroid gland. It may be delimited and encapsulated or it may infiltrate the adjacent parenchyma with diffuse, poorly defined borders. [12, 23]

The lesions may have regions of fibrosis and calcification, they may even have the characteristic of being cystic. On the cut surface they may appear granular and sometimes contain papillary foci that are macroscopically distinguishable. [12, 23]

To make the clinical diagnosis of papillary carcinoma, the nuclear characteristics or lack of papillary structure are taken into account. [23]

The nuclei of papillary carcinoma cells are characterized by very finely dispersed chromatin that acquires an appearance of transparency with light microscopy, giving the appearance of a ground-glass nucleus or pathologically known as <<Anita the orphan>>. [23]

Within the papillae are concentric calcified structures called psammoma bodies. [23]

A cross section often has the variability of giving an appearance of intranuclear inclusions which receives the name of pseudoinclusions. [23]

Returning to what was stated in previous segments; histologic features exhibit different types of papillary cancers, among these are: 1. conventional papillary thyroid carcinoma (CPTC), 2. papillary thyroid carcinoma follicular variant (PTCVF), 3. papillary thyroid carcinoma of tall cells (PTCCA), 4. papillary carcinoma of columnar cells

(PTCCC), 5. papillary carcinoma of diffuse cells sclerotic type (PTCDCS). [6, 12,]

Prognosis:

This study identified the coexisting BRAF V600E and TERT C228T mutations as a genetic basis for the most aggressive subgroup of papillary thyroid cancer (PTC), whereas the occurrence of only one of these mutations has a much smaller impact on the aggressiveness of PTC. These genetic patterns, in separating patients with PTTC into different risk groups and particularly in defining the group with the most aggressive disease, have important prognostic and therapeutic implications. [3]

It was proposed that the MAPK pathway could promote TERT expression through positive regulation of ETS factors binding the consensus DNA binding site created by TERT promoter mutations. The coexistence of BRAF V600E and TERT promoter mutations was shown to be associated with increased TERT expression in thyroid cancer. [3]

Recent studies have indicated an important role of TERT in tumor growth and aggressiveness of various cancers in animal models. This provides a molecular mechanism that explains the close link between BRAF V600E and TERT promoter mutations in promoting CPT lethality. Because BRAF V600E and TERT promoter mutations are among the most common and prominent oncogenes in human cancers. [1]

Patients with coexisting BRAF V600E promoter mutations and TERT likely received more aggressive treatments due to their more aggressive initial disease. Because such treatments generally improve the clinical outcomes of patients with aggressive thyroid cancer. [1]

According to the American Joint Committee on Cancer (AJCC), the staging system is comprised of the sum of several tumor characteristics, such as size, node status and distant metastasis, which is occasionally considered aggressive. Stage III/IV cancers are those associated with a worse prognosis in terms of recurrence and overall survival than stage I/II tumors. Mutations in the BRAF gene are more frequent in stage III/IV [17].

Complications related to BRAF gene mutation:

PTC, which usually possesses a prognosis, but can progress clinically aggressively to poorly differentiated thyroid cancer with rapid growth and worse outcome. According to the article by David G. McFadden, in research involving the Department of Biology at the Institute of Technology and the Department of Pathology and Medicine at Massachusetts General Hospital. A high proportion of anaplastic thyroid carcinomas (ATC) are associated with the BRAF oncogene and the tumor protein p53, and above all, associated with a previous cancer, originally papillary thyroid carcinomas (PTC). That is, p53 restricts the progression from PTC to CAT. [7]

BRAF mutation as an initiating somatic genetic event and P53 inhibition as a consequence of MAPK pathway activation may lead to the development of highly malignant and lethal CAT involving embryonic transcriptional program and PI3K activation, thus suggesting that MAPK pathway inhibitors are promising for the treatment of advanced thyroid carcinoma. [7]

As explained, a papillary thyroid carcinoma with Trp53 allele crossover to accelerate the progression of the cancer to a more aggressive one revealed that the deterioration was rapid, showing neck masses and development of audible respiratory stridor. Pathologically, a differentiated thyroid carcinoma with highly pleomorphic cells and evidence of necrosis, tracheal invasion and extrathyroidal extension was confirmed. The predominant histologic pattern of ATC, with pleomorphic giant cell pattern also frequently observed. There were no regional lymph node metastases, only pulmonary metastases. [7]

Potent MAPK blockade may be sufficient for a robust initial antitumor response. The combination of PLX4720 (selective BRAF inhibitor) and the mapk / Erk kinase (MEK) inhibitor PD0325901 completely suppressed MAPK pathway activation in human CTA cell lines with PTC. Combined MEK / BRAF inhibition enhances the efficacy of the mATC-targeted MAPK pathway. [7]

Thus, it was concluded that blockade of the more complex MAPK pathway enhances therapeutic responses in cultured ATC cell lines and BRAF-mutant autocrine tumors. Strong in vivo evidence is provided for the important role of p53 loss and PI3K pathway activation during progression to AT. [7]

Among the different variants of papillary cancer, there is genetic variability which demonstrates how the same cancer can have a variety in prognosis. The mutation in the BRAF gene can influence prognosis as the original carcinoma as well as metastasis. According to a publication in the New England Journal of Medicine by Alan L. Ho, MD, cancer metastasis can be refractory to radioactive iodine treatment, so increases in iodine uptake were achieved in patients with papillary thyroid cancers and those with poorly differentiated carcinomas. Of the 20 patients who could be evaluated, 4 of 9 with BRAF mutations had selumetinib-induced increases in iodine uptake-12, however, only a single patient with the BRAF gene mutation had an increase that exceeded the threshold for radioactive iodine treatment, having dramatic increases in iodine uptake in a right cervical lymph node and lung metastasis that was refractory to iodine in early stages. [6]

The results show that inhibition of the MAPK pathway can renew the therapeutic efficacy of radioiodine by enhancing uptake in patients with radioiodine-refractory thyroid cancer whose mutation is in the BRAF gene. [6]

CONCLUSION

Papillary thyroid cancer is the most common malignant endocrine neoplasm cancer; it accounts for 85 - 90 % of all

thyroid cancers. Papillary carcinomas have a pattern of lymph node metastasis. Venous invasion is seen less frequently (5-7%) and causes metastases to the lungs and bones. The BRAF V600E mutation is the most frequent alteration found in PTC, with a prevalence of approximately 45%.as described throughout the article, patients with positive markers for the V600E mutation were more likely to have a family history of cancer. The BRAF gene is a member of the RAF family of kinases that induces signaling through the RAS-RAF-MAPK signal transduction cascade.

A mutation of this gene induces destabilization of the kinase encoded by the gene, promotion of a constitutively activated state, increased BRAF kinase activity toward MAPK kinase, and promotion of tumorigenesis via the MAPK pathway. BRAF mutation as an initiating somatic genetic event and inhibition of P53 as a consequence of MAPK pathway activation may lead to the development of highly malignant CAT, thus MAPK pathway inhibitors proposed as a treatment scheme in highly advanced thyroid cancer.

REFERENCES

I. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4145183/pdf/zlj2718.pdf

II. N. Paul Ohori, MD1; Rashi Singhal, MD, MPH1; Marina N. Nikiforova, MD1; Linwah Yip, MD2;Karen E. Schoedel, MD1; Christopher Coyne, MD3; Kelly L. McCoy, MD2; Shane O. LeBeau, MD3;Steven P. Hodak, MD3; Sally E. Carty, MD2; and Yuri E. Nikiforov, MD, PhD. (Julio, 2015). BRAFMutation Detection in Indeterminate ThyroidCytology Specimens. sep, 2018, de Cancer Cytopathology Sitio web: https://onlinelibrary.wiley.com/doi/epdf/10.1002/cncy.21229

III. https://sci-hub.tw/10.1001/jamaoncol.2016.3288

IV. Dario de Biase, Valentina Cesari, Michela Visani, Gian Piero Casadei, Nadia Cremonini, Greta Gandolfi, Valentina Sancisi, Moira Ragazzi, Annalisa Pession, Alessia Ciarrocchi, and Giovanni Tallini. (April 29, 2014). High-Sensitivity BRAF Mutation Analysis: BRAF V600E Is Acquired Early During Tumor Development but Is Heterogeneously Distributed in a Subset of Papillary Thyroid Carcinomas. Advances in Genetics Endocrine Research, 9.

V. Mingzhao Xing, MD, PhD; Ali S. Alzahrani, MD; Kathryn A. Carson. (April 10, 2013). Association Between BRAF V600E Mutation and Mortality in Patients With Papillary Thyroid Cancer. JAMA Network, 309, 9.

VI. https://www.nejm.org/doi/pdf/10.1056/NEJMoa1209288

VII. http://www.pnas.org/content/pnas/111/16/E1600.full.pdf

VIII. David M. Hyman, M.D., Igor Puzanov, M.D., Vivek Subbiah, M.D., Jason E. Faris, M.D., Ian Chau, M.D., Jean-Yves Blay, M.D., Ph.D., Jürgen Wolf, M.D., Ph.D., Noopur S. Raje, M.D., Eli L. Diamond, M.D., Antoine Hollebecque, M.D., Radj Gervais, M.D., Maria Elena Elez-Fernandez, M.D., Antoine Italiano, M.D., Ph.D., Ralf-Dieter Hofheinz, M.D., Manuel Hidalgo, M.D., Ph.D., Emily Chan, M.D., Ph.D., Martin Schuler, M.D., Susan Frances Lasserre, M.Sc., Martina Makrutzki, M.D., Florin Sirzen, M.D., Ph.D., Maria Luisa Veronese, M.D., Josep Tabernero, M.D., Ph.D., and José Baselga, M.D., Ph.D.. (2015). Vemurafenib in Multiple Nonmelanoma Cancers with BRAF V600 Mutations. sep, 2018, de The new england journal o f medicine Sitio web: https://www.nejm.org/doi/pdf/10.1056/NEJMoa1502309

IX. Iñigo Landa, Ian Ganly, Timothy A. Chan, Norisato Mitsutake, Michiko Matsuse, Tihana Ibrahimpasic, Ronald A. Ghossein, and James A. Fagin. (2013). Frequent Somatic TERT Promoter Mutations in Thyroid Cancer: Higher Prevalence in Advanced Forms of the Disease. Agosto 2018, de Human Oncology and Pathogenesis Program (I.L., T.A.C., J.A.F.) and Departments of Medicine (J.A.F.), Surgery (I.G., T.I.), Radiation Oncology (T.A.C.), and Pathology (R.A.G.), Memorial Sloan-Kettering Cancer Center, New York, New York 10065; and Nagasaki University Research Center for Genomic Instability and Carcinogenesis (N.M., M.M.), Department of Radiation and Medical Sciences, Atomic Bomb Disease Institute, Nagasaki University, Nagasaki 852– 8523, Japan Sitio web: https://watermark.silverchair.com/jcem1562.pdf?token=AQECAHi208BE49Ooan9kkhW_Ercy7Dm3ZL_9Cf3qfKAc485ysgAAAh4wggIaBgkqhkiG9w0BBwagggILMIICBwIBADCCAgAGCSqGSIb3DQEHATAeBglghkgBZQMEAS4wEQQMxS094zvQrG0MEIV9AgEQgIIB0e2ZtSFod6wfQ_U50AivTvvyd4mX-k7htCEDbUD96xq6fIaNM-xrhPCWzVaXNjlrM17gG9OGEvWLezFaMt_98MIApcHKf8fp8DT5saz-vNGjxiU3Wy-E_aVJCnhamzFpmHXFqHaxZVmQJi9en1h36Y5R20q72vAigAPBBQmq9Ymm8CxTW0OX5AL960iH_SCIuhFPDkh7ehEYHkHS-IuMjNb9sHQ4mLR9XJ1X6os_mDlmsvXQauG1E_jpfqAprVAFdPFfEA7LgxC903jAIOJmshjg3TVh_91tYHSSammEq3cStoDHN3dkwHkwozL0-N4_dvR0KwFtN8zq6hVQJ3urUZFF9R9gxk7EjC9hYy4ultJMmnh8BsSg_O3LuBtezCNv_x8C333UAbsl93r5tR2ce9gOujKZQAA6nfFcSc3DuWEpEXw_ZOsK-x1sRfIJGAugRKHSsZLv_3s86vypZoQgUEX-OEhe89FRnUKVDm5x0QeyPZbpkjDUNS5fKA9

uwCLanI-l42NTBXv2H03b4tSkHS3uBbqDG4IsmfFuMMZ5bfRINUvkZPeEcK_kvwkdoRTx_BvN9cczeM0bpNcOsDaWYELjzrToLYhtUVJY4Tap8hCsKA

X. Marina N. Nikiforova, Abigail I. Wald, Somak Roy, Mary Beth Durso, and Yuri E. Nikiforov. (2013). Targeted Next-Generation Sequencing Panel (ThyroSeq) for Detection of Mutations in Thyroid Cancer. Septiembre 2018, de Division of Molecular and Genomic Pathology, Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania 15261 Sitio web: https://www.ncbi.nlm.nih.gov/pubmed/23979959

XI. YONG WANG1*, QINHAO GUO2*, YAN ZHAO1 , JIEJING CHEN1 , SHUWEI WANG1 , JUN HU1 and YUEMING SUN1. (2014). BRAF activated long non coding RNA contributes to cell proliferation and activates autophagy in papillary thyroid carcinoma. Septiembre 2018, de Department of General Surgery, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210000; 2 Department of Obstetrics and Gynecology, Northern Jiangsu Province Hospital, Clinical Medical College, Yangzhou University, Yangzhou, Jiangsu 225001, P.R. China Sitio web: https://www.spandidos-publications.com/ol/8/5/1947

XII. Sang Ryung Lee,1 Chan Kwon Jung,corresponding author1 Tae Eun Kim,1 Ja Seong Bae,2 So Lyung Jung,3 Yeong Jin Choi,1 and Chang Suk Kang1. (Junio, 2016). Molecular Genotyping of Follicular Variant of Papillary Thyroid Carcinoma Correlates with Diagnostic Category of Fine-Needle Aspiration Cytology: Values of RAS Mutation Testing. 2018, de Mary Ann Liebest, Inc Publishes Sitio web: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3822389/

XIII. Serpil Dizbay Sak . (2015). Variants of Papillary Thyroid Carcinoma: Multiple Faces of a Familiar Tumor. 2018, de Department of Pathology, Ankara University, Faculty of Medicine, Ankara, Turkey Sitio web: http://www.turkjpath.org/pdf/pdf_TPD_1746.pdf

XIV. Noboru Takamura, Makiko Orita, Vladimir Saenko et al.. (Agosto, 2016). Radiation and risk of thyroid cancer: Fukushima and Chernobyl. The Lancet updates, 4, 647. Sitio web: https://www.thelancet.com/journals/landia/article/PIIS2213-8587(16)30112-7/fulltext#articleInformation

XV. M.R.PelizzoaG.PennellibM.ZaneaF.GaluppinibP. M.CollettidI.Merante BoschinaD.Rubello. (August, 2015). Papillary thyroid carcinoma (PTC) in Lynch syndrome: Report of two cases and discussion on Lynch syndrome behaviour and genetics. 2018, de Department of Oncological Surgery and Gastroenterology (DiSCOG), Clinica Chirurgica II, University of Padova, Padova, Italy Sitio web: https://www.sciencedirect.com/science/article/abs/pii/S0753332215001419

16. Xiaoguang Shi Rengyun Liu Fulvio Basolo Riccardo Giannini Xiaopei Shen Di Teng Haixia Guan Zhongyan Shan Weiping Teng Thomas J. Musholt Khawla Al-Kuraya Laura Fugazzola Carla Colombo Electron Kebebew Barbara Jarzab Agnieszka Czarniecka Bela Bendlova Vlasta Sykorova Manuel Sobrinho-Simões Paula Soares Young Kee Shong Tae Yong Kim Sonia Cheng Sylvia L. Asa David Viola Rossella Elisei Linwah Yip Caterina Mian Federica Vianello Yangang Wang Shihua Zhao Gisele Oler Janete M. Cerutti Efisio Puxeddu Shen Qu Qing Wei Huixiong Xu Christine J. O'Neill Mark S. Sywak Roderick Clifton-Bligh Alfred K Lam Garcilaso Riesco-Eizaguirre Pilar Santisteban Hongyu Yu Giovanni Tallini Elizabeth H. Holt Vasily Vasko Mingzhao Xing. (Junio, 2016). Differential Clinicopathological Risk and Prognosis of Major Papillary Thyroid Cancer Variants . 2018, de The Journal of Clinical Endocrinology & Metabolism Sitio web: https://academic.oup.com/jcem/article/101/1/264/2806832

XVI. Chunping Liu, Tianwen Chen and Zeming Liu. (06 september 2016). Associations between BRAF V600E and prognostic factors and poor outcomes in papillary thyroid carcinoma: a meta-analysis. World Journal of Surgical Oncology, 12. web:https://wjso.biomedcentral.com/track/pdf/10.1186/s12957-016-0979-1

XVII. http://www.archivesofpathology.org/doi/pdf/10.5858/arpa.2014-0612-OA

19. https://academic.oup.com/jcem/article/99/2/E276/2537161

20. https://academic.oup.com/jcem/article/101/11/4413/2765032

21. http://cancerres.aacrjournals.org/content/63/7/1454.full-text.pdf

XVIII. Eun Kyoung Choi Ari Chong Jung Min Ha Chan Kwon Jung Joo Hyun O Sung Hoon Kim. (2017). Clinicopathological characteristics including BRAF V600E mutation status and PET/CT findings in papillary thyroid carcinoma. 12 de Octubre del 2018, de Korean Society of Nuclear Medicine Sitio web:https://onlinelibrary.wiley.com/doi/full/10.1111/cen.13335

XIX. Robbins y Contran. (2015. 9na edición). Patología estructural y funcional . Madrid: ELSEVIER SAUNDERS. Pag: 1094 - 1097