



ONCOLOGY

Thyroid carcinoma associated with other primary neoplasms, a single center study

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Abstract

Background and aims. Thyroid carcinoma is the most frequent endocrine malignancy. It develops following a complex interaction of environmental and genetic factors. Its incidence is on the rise mostly due to the frequent diagnosis of microcarcinomas (tumor <1 cm). In most cases, it has very good prognosis and survival rates. The incidence of a second primary malignancy in thyroid cancer patients is higher than in the general population. In this article, we focus on the role of BRAF V600E mutation in the development of other primary neoplasms associated with thyroid carcinoma.

Methods. This study was conducted in the department of Nuclear Medicine and Genetics of the “Prof. Dr. Ion Chiricuță” Institute of Oncology of Cluj-Napoca. We evaluated patients with thyroid carcinoma, who were diagnosed and treated for other malignancies such as breast, colorectal, lung cancer and malignant melanoma. In addition, we tested for the BRAF V600E mutation using paraffin samples of patients.

Results. We identified 17 patients that had thyroid carcinoma associated with other primary malignancies. Two of the patients included in the study had three associated primary cancers. The time interval between the diagnoses of two primary neoplasms in the same patient was 6.15 years, with a standard deviation (SD) of 5.39 years. The most common primary tumor associated with thyroid carcinoma in this study was breast cancer. We applied genetic testing for the BRAF V600E mutation in 12 patients. The BRAF V600E mutation positivity rate was 26.9% and most of the cancer associations were metachronous (occurring at least 6 months after thyroid cancer).

Conclusions. The BRAF V600E mutation is an important prognostic factor in the neoplasms included in this study, but its presence is not a predictive factor for the appearance of a metachronous or synchronous associated primary neoplasm to thyroid cancer.

Keywords: thyroid, neoplasm, BRAF V600E, multiple primary malignancies

Background and aims

The occurrence of other primary cancers associated with thyroid carcinoma is not as uncommon as we thought. They appear due to environmental risk factors [1], genetic predisposition (mutation of some oncogenes) or due to cancer treatment, the consequence of aggressive diagnostic and therapeutic procedures. The incidence rate of other primary neoplasms associated with thyroid cancer reported in the literature is 13.1% for

males and 13.7% for females [1,2].

Associated primary neoplasms may be synchronous or metachronous. Synchronous primary cancer occurs no later than six months after the diagnosis of the first primary neoplasm, metachronous cancer occurs after a six-month interval.

Thyroid cancers may occur in association with other primary tumors, independently or in syndromes, such as familial adenomatous polyposis, Peutz-Jeghers syndrome, juvenile polyposis and

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syndromes associated with PTEN mutation [3,4].

According to studies by Subramanian et al. [5] and Sawka et al. [6], the appearance of the second primary malignancy in a person with a history of thyroid cancer is more common than in the general population; in patients treated with radioiodine therapy, there are conflicting studies. A study published by Piciu et al. [7] in 2016 assessed the risk of developing a second primary neoplasm after differentiated thyroid cancer treated with medium and low doses of radioiodine therapy. Although the researchers had stated that there was a statistically significant relationship between the association of differentiated thyroid neoplasm and breast cancer, ovarian cancer and uterine cancer, it was shown that radioiodine therapy had no statistically significant correlation with the development of the second primary tumor, which raised the possibility of other etiologic factors.

The occurrence of any type of cancer in patients diagnosed with thyroid cancer is twice as common as in the general population. It most often occurs in the first year after the diagnosis of thyroid cancer, which suggests the possibility of iatrogenic effect of the applied therapy or a possible common or partially common etiology [2,8].

The BRAF V600 mutation constitutes 90% of all BRAF mutations, which results in a ten times stronger activation of the MAPK pathway. The roles of the MAPK pathway are multiple: proliferation, differentiation, migration, cell survival and angiogenesis. Aberrant activation of the MAPK pathway by the mutation of the BRAF gene has been observed in several types of cancers: melanoma, bronchopulmonary cancer, thyroid carcinoma, pancreatic neoplasm, colorectal and ovarian cancer [9,10]. The vast majority, 90% of BRAF mutations, occur in the V600 range, most of them in exons 11 and 15 [11].

Among the cancers mentioned above, our study focuses on the association of thyroid carcinoma with melanoma, bronchopulmonary cancer, breast cancer or colorectal cancer.

Melanoma is a malignant tumor of the skin, mucous membranes and pia mater. Its characteristics are the rapid evolution, high metastatic rate, reserved prognosis and high mortality. In the case of melanoma, the BRAF V600E mutation is an independent marker of negative prognostic value and is more common in the population of Europe and America. According to actual studies, the BRAF mutation itself is not sufficient to activate the MAPK pathway in melanocyte nevi; the mRNA expression of the BRAF gene appears to be a more accurate indicator for the verification of the MAPK pathway activity. According to Kang et al. [11], BRAF status has no effect on survival. The usefulness of identifying BRAF status lies in the application of targeted therapy, BRAF V600E inhibitors, which are used frequently in the treatment of melanoma.

The presence of the BRAF mutation has a negative prognosis in the case of colorectal cancer, by activating the MAPK pathway, reduces the effectiveness of EGR

antibodies (epidermal growth factor), thus determining reserved prognosis. Several studies show that monotherapy with BRAF inhibitors has few advantages; current studies focus on researching the association of BRAF inhibitors with other targeted therapy agents such as EGFR, MEK, PI3K inhibitors. Chemotherapy in case of BRAF mutant tumors has lower efficacy. BRAF is an independent negative prognostic factor in stage two and three colorectal cancers according to Sanz et al. [10], with no impact on relapses or survival. The risk of death is much higher for BRAF mutant colorectal cancers.

Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, with modest survival. Molecular subclasses, depending on the mutant gene are HER2, KRAS, PIK3CA and BRAF. In the study conducted by Cui et al [9], the BRAF mutation rate was 2.6%. The mutation is more common in female patients, with no differences in incidence between smokers and non-smokers, more common in adenocarcinomas, regardless of the stage of the disease.

Globally, breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women [12]. It occurs in both men and women, but is much more common among females. The diagnosis of breast cancer consists by the presence of malignant epithelial cells [13]. So far, we do not know the exact causes of breast cancer. Risk factors that increase the chance of breast cancer are hormonal, constitutional, environmental, demographic and lifestyle factors. Breast cancer develops by a complex interaction between genetic makeup, lifestyle and environmental factors [14]. Incidentally, breast cancer is more frequent than inherited. A number of inherited mutant genes have been identified that may increase the risk of breast cancer, and the most common and well known are the BRCA1 and BRCA2 genes [15]. Treatment consists of surgery, radiation therapy, chemotherapy and hormone therapy depending on the stage of the disease [16].

Patients and methods

The present study is a retrospective analytical study, in the field of oncology, including patients with thyroid neoplasm associated with another primary malignancy such as lung, breast, malignant melanoma or colorectal cancer. The inclusion and exclusion criteria are presented in table I.

The study was carried out within the Department of Nuclear Medicine of "Prof. Dr. Ion Chiricuță" Institute of Oncology of Cluj-Napoca, where the infrastructure, profile and experience in oncological pathology, as well as the large number of cases of thyroid neoplasm created a good scientific base. Genetic testing took place in the genetics department at the same institute.

The ethics committee of the Iuliu Hatieganu Institute and the University of Medicine and Pharmacy Cluj-Napoca evaluated and approved this study. All patients had signed informed consents.

Table I. Study inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Patient diagnosed with thyroid cancer	Lack of access to paraffin slides
Patient with primary neoplasm, one or multiple of: melanoma, bronchopulmonary cancer, colorectal cancer, breast cancer.	Incomplete observation sheets

We collected the data by analyzing the observation files of patients who had their periodic oncological follow-up check during January 2018-August 2018, and also by searching for cases with multiple neoplasms in the admission system of the institution.

We stratified patients into subgroups according to sex, age, time of first neoplasm, type of tumor associated with thyroid carcinoma, identification of periods of risk of synchronous or metachronous cancers, evaluation of factors involved: hormonal suppressive treatment, applied oncological treatments, existence of genetic factors, environmental factors etc., the presence of the BRAF V600E mutation in the available paraffin blocks. The genetic tests were performed on tissue samples properly preserved between 4–47 months.

For the BRAF V600E testing, we used the paraffin blocks of patients. To isolate the genomic DNA, we sliced five sections of 10- μ m thickness from the paraffin-embedded tissues, which were subsequently subjected to the macro dissection technique. Using the Purelink Genomic DNA Mini kit (Invitrogen), we extracted the genomic DNA. A sufficient concentration of intact DNA is essential for the quantification reaction of the BRAF V600E mutations for the real-time PCR technique to take place. As a result, the isolated DNA was

analyzed quantitatively using the NanoDrop® ND-1000 spectrophotometer (Thermo Scientific) which determines the concentration and purity of the isolated genetic material.

Detection of BRAF V600E mutation from the samples under study was performed by real-time PCR technique using the IVD EntroGen BRAF Codon 600 Mutation Analysis kit II and the real-time PCR platform Light Cycler Cobas z 480 (Roche). A concentration of DNA samples of 20 ng/ μ l was used for the PCR reaction. For the positive control, we used the standard positive control in the kit and for the negative control we used RN-free water. We performed the evaluation of the amplification products by reading two fluorochromes: FAM (465-510) for the BRAF V600E mutation, respectively VIC (540-580) for internal control. Ct (cycle treshold) values at which the fluorescent signal of the amplicon was detected were calculated by the Absolute Quantification/Second Derivative Max method.

For the data analysis, we used Microsoft Excel 2010.

Results

Following the data collection, we identified 46 patients with multiple primary malignancies, of which 17 cases had thyroid carcinoma associated with another primary carcinoma from those mentioned above (Table II).

Table II. Cases of primary malignancies associated with thyroid cancer.

Case number	Tumor no. 1	Tumor no. 2	Tumor no. 3	Type of association
1	Invasive ductal carcinoma	Papillary thyroid carcinoma		Metachronous
2	Papillary thyroid carcinoma	Invasive ductal carcinoma		Synchronous
3	Papillary thyroid carcinoma	Invasive ductal carcinoma		Metachronous
4	Invasive ductal carcinoma	Papillary thyroid carcinoma		Metachronous
5	Papillary thyroid carcinoma	Melanoma		Metachronous
6	Melanoma	Papillary thyroid carcinoma		Synchronous
7	Papillary thyroid carcinoma	Melanoma		Synchronous
8	Rectal adenocarcinoma	Papillary thyroid carcinoma		Metachronous
9	Invasive ductal carcinoma	Papillary thyroid carcinoma		Metachronous
10	Lobular breast carcinoma	Papillary thyroid carcinoma		Metachronous
11	Invasive ductal carcinoma	Papillary thyroid carcinoma		Metachronous
12	Papillary thyroid carcinoma	Invasive ductal carcinoma		Metachronous
13	Invasive ductal carcinoma	Papillary thyroid carcinoma		Metachronous
14	Papillary thyroid carcinoma	Invasive ductal carcinoma		Metachronous
15	Papillary thyroid carcinoma	Invasive ductal carcinoma		Metachronous
16	Invasive ductal carcinoma	Papillary thyroid carcinoma	Invasive ductal carcinoma - contralateral	Metachronous
17	Papillary thyroid carcinoma	Melanoma	Colon adenocarcinoma	Metachronous

As shown in table II, we did not identify any association of thyroid and bronchopulmonary carcinoma in our Institution.

The most common type of tumor association identified was metachronous (82.3%) and the most frequent primary tumor association found in this study was thyroid cancer and breast cancer. Figure 1 shows 13 cases out of the 17 cases (76.4%) that identified thyroid cancer associated with breast malignancy.

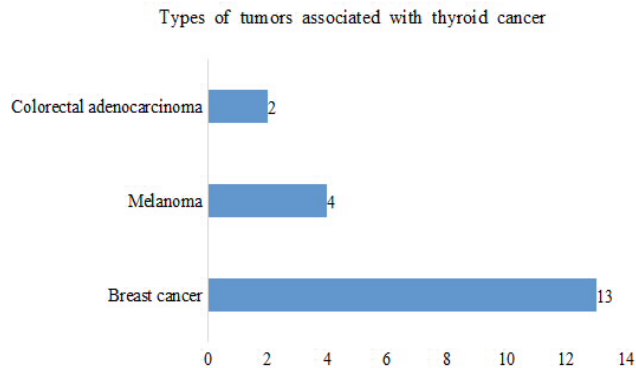


Figure 1. Type and number of primary cancers associated with thyroid cancer.

Two of the patients included in the study had three associated primary malignancies, position 16 and 17 in table II. Of the two, the first patient had thyroid cancer associated with both malignant melanoma and colorectal adenocarcinoma, all three tumors being subsequently tested for BRAF V600E mutation. The second patient had thyroid carcinoma associated with primary breast cancer in both breasts, all three tested for BRAF V600E mutation.

All patients included in the study are female. The mean age for the first primary cancer +/- SD is 47.7 +/- 11.5 years old, and for the second cancer is 53.9 +/- 9 years old. The most common age group is 40-60 years. The interval between the two primary cancers was 6.15 +/- 5.39 years (Figure 2).

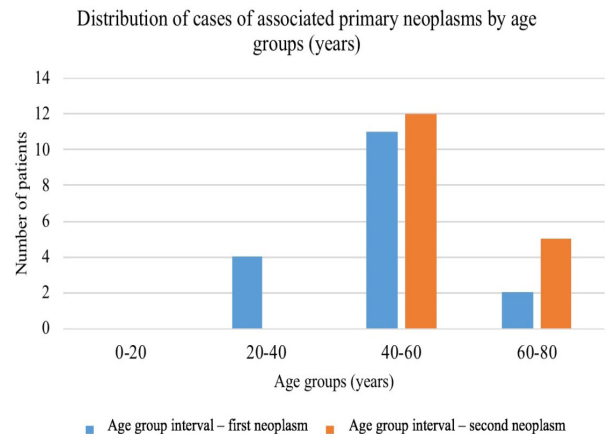


Figure 2. Distribution of multiple neoplasms by age groups.

Of the 17 patients included in our study, five could not be tested for the BRAF V600E mutation, due to lack of biological tissue samples. Thus, we applied genetic testing in the case of 12 patients, shown in table III.

Of the total genetic tests to identify the BRAF V600E mutation applied to the first primary neoplasm, 25% were positive, 75% negative. For the second primary neoplasm, the positivity rate of the genetic testing was 33%. In total, five patients tested positive for the BRAF V600E mutation, two of them being tested positive for both, the first and second primary neoplasms (Table IV).

Table III. BRAF V600E genetic test results.

Patient no.	Tumor no. 1	BRAF V600E – (1)	Tumor no. 2	BRAF V600E – (2)
1	Invasive ductal breast carcinoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	NEGATIVE
2	<i>Papillary thyroid carcinoma</i>	POSITIVE	Invasive ductal breast carcinoma	NEGATIVE
3	<i>Papillary thyroid carcinoma</i>	NEGATIVE	Invasive ductal breast carcinoma	NEGATIVE
4	Invasive ductal breast carcinoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	POSITIVE
5	<i>Papillary thyroid carcinoma</i>	POSITIVE	Melanoma	POSITIVE
6	Melanoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	NEGATIVE
7	<i>Papillary thyroid carcinoma</i>	POSITIVE	Melanoma	POSITIVE
8	Rectal adenocarcinoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	NEGATIVE
9	Lobular breast carcinoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	NEGATIVE
10	Invasive ductal breast carcinoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	NEGATIVE
11*	Invasive ductal breast carcinoma	NEGATIVE	<i>Papillary thyroid carcinoma</i>	NEGATIVE
12*	<i>Papillary thyroid carcinoma</i>	NEGATIVE	Melanoma	POSITIVE

* We identified two patients with triple primary tumor association, highlighted separately.

Table IV. BRAF V600E test positivity depending on tumor types.

Tumor type	BRAF V600E +	BRAF V600E -
Thyroid carcinoma	4	8
Melanoma	3	1
Colorectal adenocarcinoma	0	2
Breast carcinoma	0	8

Table V. BRAF V600E genetic test results in patients with triple tumor association.

	Neoplasm 1	Result BRAF V600E	Neoplasm 2	Result BRAF V600E	Neoplasm 3	Result BRAF V600E
Patient no. 1	Invasive ductal breast carcinoma	NEGATIVE	Papillary thyroid carcinoma	NEGATIVE	Invasive ductal breast carcinoma (contralateral breast)	NEGATIVE
Patient no. 2	Papillary thyroid carcinoma	NEGATIVE	Melanoma	POSITIVE	Colon adenocarcinoma	NEGATIVE

Of the 12 patients who underwent the BRAF V600E test, two patients presented an association of three primary neoplasms, shown in table V.

The type of association between the three primary malignancies in the case of both patients was metachronous. In the case of the first patient, the time interval between the appearance of cancer no. 1 and cancer no. 2 was 11.4 years, and between cancer no. 2 and no. 3 it was 3.19 years. In the case of the second patient, the time interval between neoplasm one and two is 3.66 years, and between neoplasm two and three was 4.58 years.

Discussion

Current studies on primary cancers associated with thyroid neoplasm are insufficient. In the department of Nuclear Medicine of the “Prof. Dr. Ion Chiricuța” Institute of Oncology, we frequently observe patients with thyroid cancer who had other associated primary malignancies. Based on these initial observations, some issues might be interesting to be discussed, such as: Why is thyroid cancer so commonly associated with other malignancies? What is the order of events? What are the possible deterministic factors? What is the role of the BRAF V600E genetic mutation in thyroid cancer and associated primary cancers such as colorectal, bronchopulmonary, melanoma and breast cancer?

The increased incidence of cancers in the general population requires additional studies on genetic and environmental factors, pathophysiological mechanisms involved in tumor pathogenesis and on the development of individual targeted molecular treatments depending on the etiopathogenetic mechanisms.

Researchers discovered the importance of BRAF mutations in oncology in 2002. Since then, BRAF

mutations have been described in a wide range of benign and malignant tumors, including melanoma, colorectal adenocarcinoma, thyroid carcinoma, Langerhans histiocytosis, papillary craniopharyngioma, hairy cell leukemia, biliary carcinomas, gastrointestinal stromal tumors and many others [17].

By studying the medical literature, the lack of articles is obvious on synchronous or metachronous associated primary cancers. Most of the studies in this domain are retrospective observational studies.

Our study is a retrospective observational study, which has limitations such as lack of an institutional multicancer registry, lack of national tumor registry, lack of tumor tissue in some situations. In some cases, we did not have access to biological samples for the BRAF V600E analysis due to the patient being operated on or treated in another hospital.

All the patients included in this study are female, although this was not an inclusion criteria. A possible explanation for this are the tumors themselves and their comparative frequency in males versus females. Thyroid cancer is much more common in the female population. According to a study conducted in the United States over a period of 39 years, the incidence of thyroid cancer among the female population was 75% [18]. Breast tumor pathology is a rarity among the male population. Less than 1% of diagnosed breast cancers occur in males [19]. The incidence of colorectal cancer varies greatly globally and it is closely linked to the Western lifestyle. The incidence is higher in men than in women and increases strongly with age [20]. Malignant melanoma is generally more common in the male population; the incidence of melanoma has significant differences between men and women depending on age and anatomical location [21].

The type of association most frequently observed in the present study is the metachronous type; 82.35% of the cases of associated primary tumors are on this category, with an average occurrence interval between malignancies of 6 years.

The most affected age range is between 40-60 years, both for the first and second primary neoplasms.

BRAF V600E is an important prognostic factor in oncology patients. We performed BRAF V600E testing in 12 patients, two of whom had a triple primary tumor association. The BRAF V600E genetic test positivity percentage in this study is 26.9%. There was no positive test for colorectal adenocarcinoma or breast cancer. Out of four tests performed for malignant melanoma, three came out positive (75%). The frequency of BRAF V600E mutations in melanomas that occur in sites almost completely protected from the sun (i.e. acral and mucosal melanomas) is low [22,23].

We performed twelve tests for thyroid carcinoma, of which four tested positive for the BRAF V600E mutation (33.3%). These results highlight the role of BRAF therapy in malignant melanoma and a possible applicability in thyroid cancer.

The frequency of patients surviving a cancer diagnosis continues to increase due to the increasing incidence of cancer, as well as the improved survival of cancer patients due to advances made in cancer research, diagnosis and treatment [24]. The risk of associated multiple primary cancers also increases due to the growing number of cancer survivors, the long-term side effects of chemotherapy and radiation therapy, increased diagnostic sensitivity, and persistent effects of genetic and behavioral risk factors [25,26]. Thus, even in this small study, we identified two patients with three primary cancers. This underlines the necessity of further research on the topic of multiple associated primary neoplasms.

Conclusions

Thyroid cancer is the most common malignant endocrine tumor, with a rapid increase in incidence in the last two decades.

There is a substantial increase in cases of primary tumors associated with thyroid neoplasm due to improved patient survival and to the higher accuracy of diagnostic protocols. Numerous studies have been done on the effect of radioiodine therapy and the development of other associated primary neoplasms, so far no deterministic relationship being reported for low and medium doses of radioiodine.

The majority of associated primary tumors were metachronous, which emphasizes the importance of monitoring cancer patients not only for a possible recurrence, but also for other newly detected primary neoplasms.

The BRAF V600E mutation is an important prognostic factor in the neoplasms included in this study, but its presence is not a predictive factor for the development of a metachronous or synchronous associated primary neoplasms.

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