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RET/PTC translocations and clinico-pathological features in human papillary thyroid carcinoma

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Thyroid carcinoma is the most frequent endocrine cancer accounting for 5–10% of thyroid nodules. Papillary histotype (PTC) is the most prevalent form accounting for 80% of all thyroid carcinoma. Although much is known about its epidemiology, pathogenesis, clinical, and biological behavior, the only documented risk factor for PTC is the ionizing radiation exposure. Rearrangements of the Rearranged during Transfection (*RET*) proto-oncogene are found in PTC and have been shown to play a pathogenic role. The first *RET* rearrangement, named *RET*/PTC, was discovered in 1987. This rearrangement constitutively activates the transcription of the *RET* tyrosine-kinase domain in follicular cell, thus triggering the signaling along the MAPK pathway and an uncontrolled proliferation. Up to now, 13 different types of *RET*/PTC rearrangements have been reported but the two most common are *RET*/PTC1 and *RET*/PTC3. Ionizing radiations are responsible for the generation of *RET*/PTC rearrangements, as supported by *in vitro* studies and by the evidence that *RET*/PTC, and particularly *RET*/PTC3, are highly prevalent in radiation induced PTC. However, many thyroid tumors without any history of radiation exposure harbor similar *RET* rearrangements. The overall prevalence of *RET*/PTC rearrangements varies from 20 to 70% of PTCs and they are more frequent in childhood than in adulthood thyroid cancer. Controversial data have been reported on the relationship between *RET*/PTC rearrangements and the PTC prognosis. *RET*/PTC3 is usually associated with a more aggressive phenotype and in particular with a greater tumor size, the solid variant, and a more advanced stage at diagnosis which are all poor prognostic factors. In contrast, *RET*/PTC1 rearrangement does not correlate with any clinical–pathological characteristics of PTC. Moreover, the *RET* protein and mRNA expression level did not show any correlation with the outcome of patients with PTC and no correlation between *RET*/PTC rearrangements and the expression level of the thyroid differentiation genes was observed. Recently, a diagnostic role of *RET*/PTC rearrangements has been proposed. It can be searched for in the mRNA extracted from cytological sample especially in case with indeterminate cytology. However, both the fact that it can be present in a not negligible percentage of benign cases and the technical challenge in extracting mRNA from cytological material makes this procedure not applicable at routine level, at least for the moment.

Keywords: *RET*, *RET*/PTC, papillary thyroid cancer, oncogene

INTRODUCTION

Thyroid nodules are a very common clinical finding; the prevalence of palpable nodules ranges from 4 to 7% in general population (Mazzaferri, 1992; Gharib, 2004). Although only less than 5% of palpable nodules are malignant lesions, thyroid cancers are the most frequent endocrine malignancy accounting for about 5–10% of thyroid nodules (Braverman and Utiger, 2005). Epidemiological studies in USA and in Europe demonstrated a relevant increased incidence of thyroid cancer and, in particular, thyroid cancer rate of incidence has been the highest among all human tumors during the last decades (Farahati et al., 2004; Davies and Welch, 2006; Kent et al., 2007; Enewold et al., 2009).

About 95% of malignant lesions are derived from thyroid follicular cells and are distinguished into well differentiated, either papillary (PTC) or follicular (FTC) histotype, and anaplastic thyroid carcinoma (ATC; Cardis et al., 2006). As shown in **Figure 1**, PTC is the most prevalent form accounting for about 80% of cases, while FTC represent only 15%. PTC and, to a lesser extent, FTC have a good prognosis if adequately treated (Elisei et al., 2010). Very rare (5%), but also very aggressive and almost invariably lethal, is ATC. Another relatively small percentage of thyroid carcinomas (7.5–10%; Schlumberger and Pacini, 1999) are derived from parafollicular C cells and are called medullary thyroid carcinoma (MTC; De Lellis et al., 2003; Nikiforov, 2009).

In the last 25 years, many studies have been conducted to identify the genetic alterations related to the pathogenesis of these tumors. Several oncogenes have been analyzed for mutations and

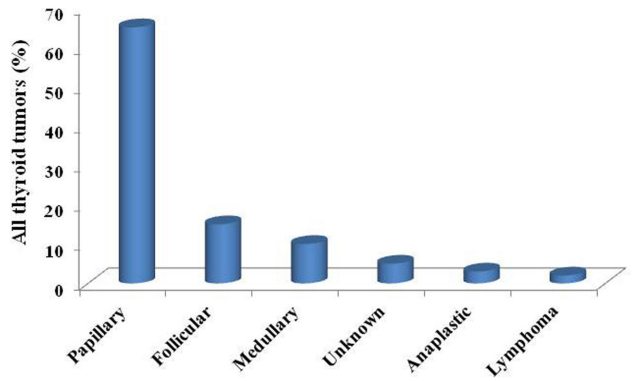

FIGURE 1 | The prevalence of different histotypes among all thyroid tumors: a clear higher prevalence of papillary thyroid cancer (about 80%) is usually reported in all series.

Table 1 | Different prevalences of different oncogenes reported to be involved in thyroid carcinogenesis.

Oncogene	Mean prevalence (%)*
BRAF	48
RET/PTC	20
APC	15
SMAD4	14
CTNNB1	12
IDH1	10
NTRK1	10
CDKN2A	9
EGFR	8
NRAS	4
HRAS	2
KRAS	2
PIK3CA	2

**Data derived from: http://www.sanger.ac.uk/genetics/CGP/cosmic/*

some of them have been found to be strictly correlated with a specific thyroid carcinoma histotype (**Table 1**).

In this review we will focus on PTC and in particular on the relationship between the presence of *RET*/PTC rearrangements, that have been defined to be specific for PTC development and the clinical and pathological features of PTC. The putative role of *RET*/PTC rearrangements in the diagnosis and in the prediction of prognosis will be discussed.

PAPILLARY THYROID CANCER

The annual incidence of thyroid cancer per 10^5 individuals ranges from 1.2 to 2.6 in men and from 2.0 to 3.8 in women and tumor mortality is very low (Franceschi et al., 1993). Thyroid cancer is two to four times more frequent in females than in males. It is rare in children below 16 years of age while in adults the incidence increases with age and the median age at diagnosis is between 45 and 50 years. Differences in the incidence of thyroid cancer according to ethnic origin have been also reported. These differences may be due to environmental factors and dietary habits (Spitz et al., 1988).

Although the etiology of PTC is not well understood, there are some risk factors which are known to put an individual at higher risk of developing the disease. Radiation exposure significantly increases the risk for thyroid malignancies, particularly PTC. This finding was observed in children exposed to radiation after the nuclear bombings in Hiroshima and Nagasaki during the Second World War (Nagataki et al., 1994). Additional evidence was gathered after atomic bombs were tested in the Marshall Islands (Cronkite et al., 1995), after the accident at the Chernobyl nuclear power plant (Williams, 2002; Nikiforov, 2006), and in patients who received low-dose radiation therapy for benign disorders of the head, neck, and thorax (Duffy and Fitzgerald, 1950; Winship and Rosvoll, 1970).

Among other risk factors female gender play an important role in fact it has been shown (Ron et al., 1987) that the sex ratio approaches 1 before puberty and after menopause while during the fertile woman age it is between two and four times higher than in the correspondent men age period. A heavier body weight have been shown also to increase the risk of thyroid cancer (Kitahara et al., 2011).

An important role is also played by the iodine exposure. Areas with low iodine intake usually show higher prevalence of FTC than area with sufficient iodine intake where, conversely, the PTC histotype is more represented (Belfiore et al., 1987). Furthermore the high prevalence of thyroid cancer in regions where the iodine intake is high suggests that iodine intake may play role in thyroid tumorigenesis (Vejbjerg et al., 2007; Guan et al., 2009) as well as other factors not related to iodine like volcanic activity (Pellegriti et al., 2009).

RET/PTC REARRANGEMENTS

The *RET* proto-oncogene is located on chromosome 10q11.2 and encodes for a transmembrane tyrosine-kinase receptor involved in the control of cell differentiation and proliferation. Four different ligands have been reported up to now: glial derived neurotrophic (GDN) factors, Neurturin (NRTN), Artimin (ARTN), and Persepin (PSPN), respectively (Arighi et al., 2005). All these ligands induce *RET* activation through the binding to specific coreceptors. The *RET* gene is expressed in tissues deriving from the neural crest including thyroid C cells and adrenal medulla but it is not expressed in normal thyroid follicular cells (Santoro et al., 1990).

In 1987 the first finding of a new oncogene activated in human PTC was reported (Fusco et al., 1987). Interestingly, the tumoral tissue where the oncogene was firstly described was derived from an irradiated PTC. After 3 years, this oncogene was molecularly cloned: it was a chimeric gene generated by the fusion of the *RET* tyrosine-kinase domain (Wirtschafter et al., 1997) with the 5′ terminal region of a new gene denominated CCD6 (formerly called H4; **Figure 2**; Grieco et al., 1990). This oncogene was named *RET*/PTC.

After the first identification, several types of *RET*/PTC rearrangements have been described (Greco et al., 2009; **Table 2**). At the present 13 different types of *RET*/PTC rearrangements have been reported and all of them are the result of the fusion of the

RET tyrosine-kinase (TK) domain with different genes, which are characterized by the presence of nucleotide sequences coding for proteins with an extremely high probability of forming coiled-coil domains, thus allowing constitutive dimerization of the *RET*-TK domain. This constitutive dimerization determines an uncontrolled proliferation of the follicular cells harboring the *RET*/PTC rearrangement and the development of malignancy. The presence of *RET*/PTC rearrangement in microcarcinoma strongly support the hypothesis of a driving role of this oncogene in the tumoral transformation (Viglietto et al., 1995).

So far, *RET*/PTC rearrangements have been identified almost exclusively in thyroid lesions, and in particular in PTC (Santoro et al., 1993; Tallini and Asa, 2001; Nikiforov, 2002). To our knowledge, the only other human tumor harboring *RET*/PTC rearrangements is primary peritoneal carcinoma (Flavin et al., 2009). However these rearrangements are supposed to be "*passenger*" mutations reflecting RET instability in tumor subclones more than true pathogenetic events. *RET*/PTC rearrangements more frequently found in PTC are *RET*/PTC1, given by the fusion with the CCDC6 (formerly H4) gene and *RET*/PTC3, given by the fusion with the NCOA4 (formerly ELE1) gene (Santoro et al., 1994).

The reported *RET*/PTC prevalence in thyroid tumors varies greatly in different series (Zou et al., 1994; Lam et al., 1998; Mayr et al., 1998; Chua et al., 2000; Cinti et al., 2000; Fenton et al., 2000; Sheils et al., 2000; Puxeddu et al., 2003; Rhoden et al., 2004, 2006; **Table 3**). This difference can be attributed to ethnical and geographic variations as well as to the different sensitivities of detection methods (Zhu et al., 2006). It has been carefully demonstrated that the method used has an important effect on the efficacy of *RET*/PTC rearrangement determination and thus on the reported prevalence (Marotta et al., 2011). Tumor heterogeneity is another factor that can affect the evaluation of *RET*/PTC prevalence. The distribution of *RET*/PTC rearrangement within the same tumor may be heterogeneous, varying from the involvement of most neoplastic cells (i.e., clonal *RET*/PTC) to the presence of

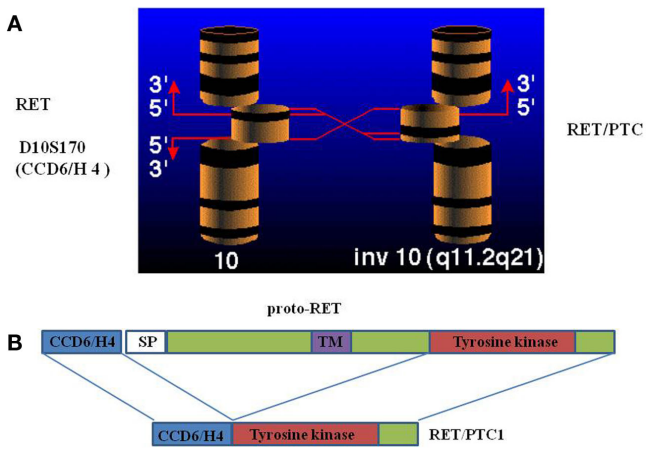

FIGURE 2 | Schematic representation of *RET*/PTC1 rearrangement: a centromeric inversion of chromosome 10 (A) generates a chimeric gene through the fusion of the *RET* tyrosine-kinase domain with the 5′terminal region of a new gene denominated CCD6, formerly called H4 (B).

Table 2 | Different types of RET/PTC rearrangements in thyroid tumors.

Oncogene	Donor gene	Chromosomal location
RET/PTC1	CCD6 (formerly H4)	10q21
RET/PTC2	PRKAR1A	17q23
RET/PTC3	NCO4 (formerly Ele 1)	10q11.2
RET/PTC4	NCO4 (formerly Ele 1)	10q11.2
RET/PTC5	Golgas	14q
RET/PTC6	TRIM24	7q32–34
RET/PTC7	TRIM33	1p13
RET/PTC8	KTN1	14q22.1
RET/PTC9	RFG9	18q21–22
ELKS–RET	ELKS	12p13.3
PCM1–RET	PCM1	8p21–22
RFP–RET	TRIM27	6p21
HOOK3–RET	HOOK3	8p11.21

Table 3 | Prevalence of RET/PTC rearrangements in sporadic and irradiated PTC.

Reference	Post-Chernobyl *n* (%)	Spontaneous *n* (%)
Guerra et al. (2011)**	nd	36%
Hieber et al. (2011)	16/22 (72)	nd
Hamatani et al. (2008)	11/50 (22)*	nd
Rhoden et al. (2006)	nd	25/34 (73)
Zhu et al. (2006)	nd	26/75 (34)
Unger et al. (2006)	10/13 (77)$^{\circ}$ 9/32 (28)$^{+}$	nd
Di Cristofaro et al. (2005)	11/17 (65)	9/21 (43)
Rhoden et al. (2004)	nd	18/25 (72)
Puxeddu et al. (2003)	nd	13/48 (27)
Elisei et al. (2001)	19/25 (76)	11/47 (23)
Cinti et al. (2000)	nd	13/69 (19)
Sheils et al. (2000)	nd	12/50 (24)
Fenton et al. (2000)	nd	15/33 (45)
Chua et al. (2000)	nd	44/62 (71)
Thomas et al. (1999)	37/67 (55)	nd
Smida et al. (1999)	25/51 (49)	nd
Mayr et al. (1998)	nd	8/99 (8)
Tallini et al. (1998)	nd	81/201 (40)
Lam et al. (1998)	nd	17/40 (43)
Sugg et al. (1999)	nd	51/86 (59)
Nikiforov et al. (1997)	33/38 (87)	12/17 (70)
Klugbauer et al. (1995)	9/15 (60)	nd
Fugazzola et al. (1995)	4/6 (66)	nd
Zou et al. (1994)	nd	1/40 (2.5)
Ishizaka et al. (1991)	nd	1/11 (9)

**Atomic bomb survivors.*

$^{+}$Long latency period.

$^{\circ}$Short latency period.

***Data obtained on cytological samples.*

a small fraction of tumor cells (i.e., non-clonal *RET*/PTC) in the sample (Unger et al., 2004; Zhu et al., 2006).

Clonal *RET*/PTC rearrangements occur in about 20% of PTC and are specific for this tumor (Nikiforov, 2002, 2011; Zhu et al., 2006). Non-clonal *RET*/PTC rearrangements have been found not only in PTC but also in 10–45% of thyroid adenomas and other non-neoplastic thyroid lesions (Ishizaka et al., 1991; Wirtschafter et al., 1997; Sheils et al., 2000; Elisei et al., 2001; Chiappetta et al., 2002; Sapio et al., 2011) and Hashimoto's thyroiditis (Rhoden et al., 2006).

As shown in **Table 3**, *RET*/PTC rearrangements are more frequently found in thyroid cancers following radiation exposure (50–80%; Fugazzola et al., 1995; Nikiforov et al., 1997; Thomas et al., 1999; Di Cristofaro et al., 2005; Unger et al., 2006; Hamatani et al., 2008; Hieber et al., 2011). In particular *RET*/PTC3 has been found to be more frequent than *RET*/PTC1 in post-Chernobyl radiation exposed thyroid cancer especially in those with a short latency period (Williams, 2008). *RET*/PTC rearrangements have been also found to be more prevalent in children than in adults both in irradiated and non-irradiated PTC (Nikiforov et al., 1997; Elisei et al., 2001).

Over the time, the proportion of post-Chernobyl thyroid tumors with a *RET*/PTC rearrangement has declined, and in the *RET*/PTC-positive tumors the percentage of those with *RET*/PTC1 has increased while the proportion of those with *RET*/PTC3 has in parallel decreased (Unger et al., 2006). The hypothesis to explain this variation is that with the increase of latency period the effect of radiation is becoming less significant and most recently developed PTC around Chernobyl are more similar to non-irradiated cases. This hypothesis is at least in part supported by the evidence that also the histological features are changing according to the latency period (Williams, 2008).

The high prevalence of *RET*/PTC rearrangements found in post-Chernobyl thyroid tumors and in atomic bomb survivors exposed to high-dose radiation (Hamatani et al., 2008) strongly supports a direct role of radiation exposure in *RET*/PTC generation (Fugazzola et al., 1995; Klugbauer et al., 1995; Bounacer et al., 1997; Nikiforov et al., 1997). *RET*/PTC rearrangements were also found after high-dose radiation to human undifferentiated thyroid carcinoma cells (Ito et al., 1993) and to fetal human thyroid tissue transplanted into SCID mice (Mizuno et al., 2000). The generation of *RET*/PTC rearrangements has been also demonstrated in normal thyroid cultured cells after *in vitro* exposure to radiation (Gandhi et al., 2010a,b). Furthermore, the strong relationship between ionizing radiation exposure and *RET*/PTC rearrangements have been shown by a COMET assay that demonstrated that *RET* oncogene is very susceptible to ionizing radiation (Volpato et al., 2008). Moreover, the spatial contiguity of *RET* and H4 genes within the chromatin may provide a structural basis for generation of *RET*/PTC1 rearrangement by allowing a single radiation track to produce a double-strand break in each gene (Nikiforova et al., 2000; Gandhi et al., 2006, 2010a).

Over the last few decades, significant progress has been achieved in the understanding of the biological mechanisms of radiation carcinogenesis. It has been shown that damage to cellular DNA is responsible for mutagenesis and carcinogenesis and that double-strand breaks is the most important event for the direct generation of gene translocations and rearrangements. In particular there are several *in vitro* evidences demonstrating that thyroid cells exposed to X-Ray develop *RET*/PTC rearrangements (Ito et al., 1993; Goodhead, 1994; Ward, 1995; Mizuno et al., 2000; Caudill et al., 2005). Other than ionizing radiations, other putative carcinogens, like caffeine, ethanol, hypoxia, and others, are able to induce DNA double-strand breaks and generate *RET*/PTC rearrangements (Gandhi et al., 2010a,b). Recently, a direct relationship between ionizing radiation exposure, intracellular hydrogen peroxidase (H_2O_2) generation, double-strand induction, and *RET*/PTC1 rearrangements development was also demonstrated (Ameziane-El-Hassani et al., 2010). After this observation, it can be hypothesize that other agents able to initiate biological production of superoxidase anions and H_2O_2 (Narayanan et al., 1997) can induce *RET*/PTC rearrangements.

RET/PTC REARRANGEMENTS AND CLINICO-PATHOLOGICAL FEATURES OF PTC

A correlation with a more aggressive phenotype and a more advanced stage has been reported for *RET*/PTC rearrangements, especially *RET*/PTC3 (Nikiforov et al., 1997; Powell et al., 1998). In particular, in post-Chernobyl childhood thyroid cancer the *RET*/PTC3 rearrangement was more frequently associated with the solid variant of PTC which is considered a more aggressive variant and the most prevalent among these irradiated tumors. As matter of fact, with the increase of the latency period both the solid variant and the RET/PTC rearrangements prevalence have declined suggesting a strong relationship between radiation exposure, solid variant, *RET*/PTC3 rearrangements, and a more rapid development of the tumor as indicated by the short latency period (Williams, 2008).

In a previous study on sporadic PTC we also demonstrated a positive correlation between the presence of *RET*/PTC3 rearrangement, but not of *RET*/PTC1, with a bigger size of the tumor and a more advanced stage at diagnosis. However, in the same study the levels of expression of thyroid differentiation genes (i.e., thyrotropin stimulating hormone receptor, thyroglobulin, sodium-iodide symporter etc.) was shown to be not significantly different in PTC with or without *RET*/PTC rearrangements, thus suggesting that these genetic alterations should not play a major role in the de-differentiation process (Romei et al., 2008).

Controversial data have been also reported about the correlation of the presence of *RET*/PTC rearrangements and clinical and epidemiological features of patients with PTC. Although there is a general agreement that *RET*/PTC rearrangements, particularly *RET*/PTC1, are more frequent in young patients, also in non-irradiated cases (Elisei et al., 2001) there are other studies that did not show any correlation between *RET*/PTC rearrangements and age, sex, tumor size, staging, number of neoplastic foci, and histological subtype (Puxeddu et al., 2004).

So far no consensus concerning the clinical prognostic value of the presence of a *RET*/PTC rearrangement, either *RET*/PTC3 or *RET*/PTC1, has been reached. Some evidences exists suggesting that PTC with *RET*/PTC1 rearrangement are associated with a more favorable behavior (Saad et al., 2004) while those harboring *RET*/PTC3 rearrangement may be more prone to de-differentiation and a more aggressive behavior (Sugg et al., 1999;

Mochizuki et al., 2010). Initial reports on this specific issue claimed a role in metastatic spread (Jhiang and Mazzaferri, 1994; Sugg et al., 1999) and more recently, it has been suggested that *RET*/PTC-positive cases show higher rates of local extension and lymph node involvement than RET/PTC negative cases (Adeniran et al., 2006). At variance, several other studies were unable to find any relationship between RET/PTC rearrangements and classical prognostic factors (Tallini et al., 1998; Musholt et al., 2000; Basolo et al., 2001; Romei et al., 2008).

In our experience, *RET*/PTC rearrangements do not seem to be correlated with any clinical and pathological feature of aggressiveness either by studying the expression of the *RET*/PTC protein by immunohistochemistry (Basolo et al., 2001) or by studying the mRNA expression of the *RET*/PTC rearrangements by real time RT-PCR (Romei et al., 2008).

DIAGNOSTIC ROLE OF *RET*/PTC REARRANGEMENTS

Fine needle aspiration cytology (FNAC) is the first choice method to distinguish between benign and malignant thyroid nodules (Pacini et al., 2006; Baloch and LiVolsi, 2008; Cooper et al., 2009). However, about 30% of FNAC yields uncertain results because of inadequate sampling (i.e., only few cells or great blood contamination) or because cytological features do not clearly indicate the nature of the lesion (i.e., follicular neoplasia; Gharib et al., 1984; Mazzaferri, 1993). Whenever a follicular neoplasia is diagnosed, surgical treatment, and histological examination are required to differentiate the malignant from the benign nature of the nodule. Since only 20–30% of these nodules turn out to be malignant (Rago et al., 2007), about 80% of patients with a follicular neoplasia undergo an unnecessary thyroidectomy.

The rapidly expanding knowledge of molecular genetics of thyroid cancer has started to translate into clinical practice, offering significant improvement in accuracy of the preoperative diagnosis of thyroid cancer. Several studies have been already published on the possibility to improve the diagnostic power of FNAC by looking for thyroid cancer specific oncogenic alterations (Nikiforova and Nikiforov, 2009). Most studies have explored the diagnostic role of *BRAF* mutation (Jin et al., 2006; Xing et al., 2009; Adeniran et al., 2011; Marchetti et al., 2012). In a large prospective study recently published, the detection of *BRAF* mutations in FNA showed a very high positive predictive value (PPV). However, the biggest diagnostic impact can be achieved only by testing FNA samples for a panel of mutations (i.e., *BRAF*, *RET*/PTC, *RAS*, *TRK*) rather than for a single mutation (Cantara et al., 2010; Guerra et al., 2011). Indeed, *RET*/PTC detection can improve the preoperative diagnosis of thyroid nodules, particularly in samples that are indeterminate by cytology or have an insufficient amount of cells for cytologic evaluation (Cheung et al., 2001; Salvatore et al., 2004; Pizzolanti et al., 2007). Nevertheless the PPV of the detection of *RET*/PTC rearrangements is not as high as the detection of *BRAF* mutations because a low, but not negligible, percentage of nodules positive for RET/PTC rearrangements on FNA which turned out to be benign at histology (Cantara et al., 2010; Guerra et al., 2011). This is not unexpected since, have previously said, there are several reports showing that 5% of benign thyroid nodules and several cases of Hashimoto's thyroiditis are positive for *RET*/PTC rearrangements. Last but not least, the search for *RET*/PTC rearrangements requires the mRNA extraction form the cytological smears that is a much more challenging techniques than the extraction of DNA that is required for the search of *BRAF*. As matter of fact, at the present the search for *RET*/PTC rearrangements in cytologically indeterminate thyroid nodule is still not considered a diagnostic routine tool.

CONCLUSION

In the last years important achievements have been reached in the understanding of the molecular basis of PTC. Although different oncogenes have been found to be altered in PTC, *BRAF* mutations, and *RET*/PTC rearrangements are the most frequently involved. A lot has been discovered between the relationship of *RET*/PTC rearrangements and PTC clinical, pathological, and epidemiological features. Although present also in non-irradiated cases, *RET*/PTC rearrangements are related to radiation exposure and are more frequent in patients with radio induced PTC. Among all *RET*/PTC rearrangements, *RET*/PTC1, and *RET*/PTC3 are in general the most frequent. *RET*/PTC3 is much more prevalent in irradiated PTC especially in those with solid variants. Both of them are more prevalent in children than in adults. Despite all these observations there are not yet clear data showing a definitive prognostic role of neither *RET*/PTC1 or *RET*/PTC3. The presence of a *RET*/PTC rearrangement in the RNAs extracted from cytological material aspirated from a thyroid nodule is strongly predictive of malignancy but some cases of benign nodules can also result to be positive.

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