

# Chromosomal Rearrangements of RET/PTC in Post-Chernobyl Thyroid Cancer

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DOI: 10.30699/mci.4.2.28

Submitted: 14 December 2019

Revised: 19 January 2020

Accepted: 5 February 2020

e-Published: 1 April 2020

## Keywords:

Radiation, Ionizing  
Chernobyl Nuclear Accident  
Thyroid Neoplasms

## Abstract

A hypothesis is proposed here that RET rearrangements in papillary thyroid cancers are related to the disease duration and tumor progression. The most common RET rearrangements are RET/PTC1 and RET/PTC3. RET/PTC1 is more prevalent in classic papillary thyroid carcinoma (PTC), its diffuse sclerosing variant, and papillary microcarcinoma; while RET/PTC3 is frequently found in less differentiated solid PTC. RET/PTC3 is associated with larger tumor size and multifocality in sporadic pediatric PTC. The RET rearrangements; especially RET/PTC3, which is frequently detected among Chernobyl thyroid cancers is developed after exposure to radiation at an early age, is proposed to be a potential trigger of malignancy. There are many late-stage tumors among the first-wave Chernobyl PTCs that tend to be larger and less differentiated than those detected later. The high proportion of late-stage cases shortly after the accident is explained by the neglected cases in the screening process and also by the fact that some non-exposed patients were registered as radiation-exposed. The screening was productive because of the reservoir of undiagnosed cases in the population: registered incidence of thyroid cancer (TC) among children and adolescents prior to the Chernobyl disaster was low in the Soviet Union; compared to other developed countries. In conclusion, RET rearrangements, especially RET/PTC3, were correlated with the tumor progression. If the hypothesis defended here is correct, a low prevalence of RET/PTC3 among sporadic TC is circumstantial evidence of efficient cancer diagnosis and early detection.

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## INTRODUCTION

The proto-oncogene RET (rearranged during Transfection) encodes a tyrosine kinase receptor. Chromosomal rearrangements that produce fusion genes and activate the proto-oncogene are named RET/PTC after the gene RET and papillary thyroid carcinoma (PTC). The reported frequency of RET/PTC rearrangements (fusions) among all PTCs was estimated to be around 28% [1, 2]. There are different RET rearrangements such as RET/PTC1 and RET/PTC3 as the most prevalent types [2, 3]. RET/PTC3 was associated with the

solid morphologic variant of PTC, larger tumor size, and multifocality in sporadic pediatric PTC [4]. Generally, RET rearrangements are more prevalent in classic PTC than in the follicular type which may be caused by distinct oncogenic pathways and/or by an admixture of true follicular thyroid cancers (TC). Approximately, 9% of poorly differentiated thyroid carcinomas harbor RET/PTC [2]; indicating that some of them are developed from PTC with RET fusions [1]. The potential role of RET mutations in non-papillary

thyroid tumors is beyond the scope of this communication. A hypothesis is proposed here that RET rearrangements in PTC are related to the disease duration and tumor progression. In this regard RET/PTC3 is associated with late-stage tumors as compared with RET/PTC1. PubMed and Russian-language databases were applied for the literature review; using RET/PTC and thyroid cancer as the keywords. Lack of enough data in epidemiological research of low-dose radiation and inter-study heterogeneity i.e. uneven quality of studies analyzed together in reviews and meta-analyses are among the potential biases [5-7]. The reliability of research is sometimes difficult to be evaluated. According to Little et al., studies of questionable reliability “should therefore probably not be used for epidemiologic analysis, in particular [8-12]”. The exaggeration of the medical consequences of the Chernobyl disaster and other radioactive contaminations were previously discussed [13-17]. Overestimated numbers of radiogenic cancers were served as a motive to search for markers of radiation-related malignancies; while RET rearrangements were the main candidates for this role. The core hypothesis presented in this research and preceding papers was that some neglected TCs have been misinterpreted after the Chernobyl accident as rapidly growing radiogenic cancers [13-17]. Accordingly, the supposed markers of radiogenic etiology are in fact associated with longer disease duration and tumor progression. This concept has more general implications: if it is correct, a low percentage of RET/PTC3 among spontaneous TCs could be considered as circumstantial evidence of efficient diagnosis and early tumor detection in different countries.

#### **Association of RET/PTC With Radiogenic and Advanced TCs**

The RET fusions, especially RET/PTC3, are frequently found in PTC of patients who have been exposed to the Chernobyl disaster at an early age [18, 19]. These markers are supposed to be potential indicators of radiation-related TCs [20]. There was an association between RET/PTC3 and a solid histological structure that was prevailed in PTC during the first 10 years after the accident [19, 21]. The years 1986-96 approximately

corresponded to the “first wave” post-Chernobyl TCs [18, 19, 21]. There were many late-stage cancers among the first wave cases. In a study from Belorussia (1986-91, 86 pediatric TC), 61.5% of cases had high or intermediate grades of TC. In another study (1991-92, 84 pediatric TC), the cancers were reportedly aggressive, accompanied by intraglandular tumor dissemination (92%), cervical lymph node metastases (88%), and ingrowth into the capsule and surrounding tissues (89%). In a study from Ukraine (1986-96, 244 pediatric TC), T4 (TNM stage) was found in about 50% of cases with a proportion of 66-71% in adolescents; more references are in the preceding review and the monograph [13, 15]. It can be reasonably assumed that many of these tumors have been developed prior to the Chernobyl disaster. The first wave TCs tended to be larger and less differentiated than those detected later [21], one of the reasons may be the admixture of advanced cases. According to Yablokov et al., as a crucial study, Chernobyl TCs are more aggressive at early stages with high lymphatic invasiveness [22]. The thyroid screening after the Chernobyl disaster was yielding due to the reservoir of late-stage cancers in the population: the detection rate of pediatric TC prior to the accident was lower in the Soviet Union (SU) than in other industrialized nations [23, 24]. Besides, there was an endeavor to be recognized as victims of Chernobyl to avail of compensations). Cases from non-contaminated areas must have been averagely in more advanced stages due to the lack of screening modalities in those areas. The post-Chernobyl pediatric TC were predominantly of papillary type often containing areas with less differentiated solid and follicular patterns, indicating that the “first wave” post-Chernobyl TC was diagnosed averagely at a later stage. The RET/PTC fusions were associated with the T3-4 stages, local recurrence, and distant metastases [25]. These features in children and adolescents tended to correlate with RET/PTC3 rather than RET/PTC1 [20]. RET/PTC3 was associated with aggressiveness, larger dimensions, and later stages at diagnosis [1]. As mentioned above, the presence of RET/PTC3 was often combined with larger tumor size and multifocality in sporadic PTC in pediatrics [4]. It was assumed that RET/PTC1 predispose

the patient to subsequent RET rearrangements, RET/PTC3 being the next frequent one [26]. A majority of the first-wave PTCs after Chernobyl harbored RET/PTC3 fusions; while 63% of the cancers with RET/PTC3 were detected in the first decade after the disaster [19]. Conversely, RET/PTC1 was predominant after 10 years. The first-wave TCs were less structurally differentiated than those found later [21]. With time passing after the accident, the proportion of cancers with RET rearrangements decreased, whereas in RET-positive cases the proportion of RET/PTC1 grew with a decrease in the prevalence of RET/PTC3 [18, 19]. The percentage of late-stage cancers must have been higher among early post-accident cases when the reservoir of neglected tumors was still untapped.

As an exceptional finding, the cohort of pediatric PTC after the Chernobyl disaster with the predominance of RET/PTC3 was deemed unique worldwide [27]. On the contrary to Chernobyl, among sporadic PTC cases, the prevailing RET rearrangement was RET/PTC1 [3]. Of note, post-Chernobyl cancer is unique not for the whole world but for industrialized countries where the diagnosis is generally more efficient. As expected, RET/PTC3 was the most frequent RET fusion type in the studies from the Indian Subcontinent [28, 29]. Conversely, RET/PTC1 prevailed in PTCs that were developed after radiotherapy in France, whereas among sporadic cases both RET/PTC1 and RET/PTC3 were rare [30]. Analogously, pediatric TCs from Japan were considerably more differentiated than their counterparts from Ukraine and Belorussia including the Chernobyl area [31]. The prevalence of RET rearrangements in the Japanese pediatric TCs was relatively low; while RET/PTC1 was more predominant [32, 33]. Of note, the prevalence of RET/PTC3 found by the screening after the Fukushima Daiichi nuclear accident was lower than sporadic Japanese cases [33]. The screening in Japan resulted in the detection of earlier cases, whereas the first wave post-Chernobyl screening found many neglected TCs which certifies the efficient diagnosis in Japan. In addition to the factors discussed here and in previous studies [13-17], the high-resolution ultrasound equipment used in Fukushima that was not available after the Chernobyl accident

made its contribution to the early diagnosis [33]. The in vitro induction of RET fusions after cell irradiation was reported [20], but the doses in experiments were much higher than the averages in Chernobyl victims. The in vitro information on RET/PTC1 induction by doses as low as 0.1 Gy was singular [34]. Certain claims by Nikiforov, a leading co-worker of the research (34), ascribing the global growth of TCs incidence by the nuclear testing or accidents [35] are indicative of a bias discussed in previous papers [14, 15].

## **DISCUSSION**

There is evidence that the frequency of RET/PTC fusions, especially RET/PTC3, tends to correlate with the disease duration and a later stage of the tumor progression in PTC patients. In view of the clustering of rearranged cells, it was assumed that RET fusions are relatively late subclonal phenomenon [36], which agrees with the hypothesis discussed here. The RET/PTC3 were found much more frequently in Ukraine than in France [37]. A worldwide decrease in RET/PTC incidence as well as in developed countries over the last decades [38, 39] along with the growing TC detection rate [32] could be attributed to the improving diagnostic technologies. The decreasing trend may be in fact even stronger in view of the growing sensitivity of RET/PTC detection methods [33].

A relationship between RET/PTC and individual doses of ionizing radiation was noticed among Chernobyl cases [40]. Tuttle et al., found no associations between RET/PTC and different doses [41]. It is known that correlation per se does not prove causality, being possibly resulted from the dependence of diagnostic quality and self-reporting from individual doses [14, 15]. Correlations between individual doses and RET rearrangements among atomic bomb survivors [40] could be caused by a similar bias as well as by higher doses than in Chernobyl victims. Note that acute exposures to low linear energy transfer (LET) radiation are generally more efficient than protracted ones [42]. The enhanced frequency of RET/PTC was noticed in PTC from patients who had undergone radiotherapy during childhood [43]. Many of them were treated for cancer so that the doses were much higher than average

Chernobyl doses. The same fact pertains to the study [30], where the prevalence of RET/PTC in TC after radiotherapy for benign or malignant conditions was higher than that in sporadic cases. Of note, the hypothesis proposed here does not exclude a possibility of RET/PTC induction by radiation but foregrounds the accumulation of mutations with time and their association with certain steps of the tumor progression (RET/PTC3 – with a later step). Despite the referencing of articles [16, 17] and debates at conferences, this hypothesis was not mentioned in the review [44], where it was claimed with the references [45-48] that RET/PTC is more frequent in occult cancers and microcarcinomas than in “mature tumors” [44]. The cited papers are not new (1995–2001); studies with different results and conclusions have been published since then. For example, in the study [48] from 1998, RET/PTC was reportedly not associated with the tumor size, extrathyroidal spread and metastasizing. However, in a later publication from the same institution, an association between high expression of RET/PTC1 and the tumor size was pointed out [26]. Apparently, RET/PTC1 can appear relatively early in the course of the tumor progression whereas RET/PTC3 tends to arise later on.

Furthermore, there was a report on a higher proportion of RET/PTC (not further specified) and some other cytogenetic markers (BRAF, RAS, PAX8-PPAR $\gamma$ ) in T1 compared with T2-4 stages of PTC [25]. In the same paper, it is written that the RET/PTC-positivity was significantly associated with the T3-4 stages. We inquired about this discrepancy by the study published by Yip et al., [25] and received a comment from Yuri Nikiforov declaring that “It’s in a way a moot point since the entire staging system has changed dramatically since 2015. RET/PTC-positive tumors are papillary carcinomas with the propensity to lymph node metastasis but tend to occur more often in younger patients. They are overall considered of intermediate American Thyroid Association (ATA) risk for recurrence” (e-mail communication 19 Sept. 2019). We responded to the following: “The staging system may have changed but any staging system reflects the tumor progression. Do the figures “RET/PTC: T1– 57%, T2–8%, T3–22%, T4–14%” [25]

mean that RET/PTC disappears with the tumor progression? If yes, why do they disappear? Are mutations not supposed to accumulate with the tumor progression? How then RET/PTC can correlate with the ‘propensity to lymph node metastasis’? Is there indeed a discrepancy in the article [25] or maybe there was an artifact?” Yuri replied: “RET/PTC positive tumors rarely undergo dedifferentiation, the fusion (RET/PTC) is virtually never found in anaplastic thyroid carcinoma (ATC), so they rarely kill patients, yet can involve multiple lymph nodes and recur” (e-mail communication 20 Sept. 2019). It is known that malignant tumors generally tend to undergo progression. However, for PTC the progression does not mean a transformation to ATC probably because of different oncogenic pathways. More details and references are in the letter [49] commenting on the article [25]. Theoretically, a disappearance of RET/PTC-positive cells along with the tumor de-differentiation could be caused by a negative clonal selection due to the lower viability of mutation-bearing cells. Further research with reliable detection of both RET/PTC1 and RET/PTC3 is needed. With regard to the data about associations of RET/PTC (RET/PTC3 in particular) with a younger patients’ age [50-52], it could be speculated that TC is detected in young people averagely at a later stage. This can be caused by lower oncological alertness (doctors less often think on cancer examining young patients) or by a more rapid tumor progression in younger individuals.

Many publications about Chernobyl, mentioned it as a matter-of-course that additional TC cases after the disaster were induced by the exposure to ionizing radiation i.e. certain studies looking for markers of radiogenic malignancies [53] were based on the premise that a large part of Chernobyl-related cancers was of radiogenic nature. In fact, some proposed markers of radiogenic post-Chernobyl cancer are probably associated with a more advanced tumor stage [54]. The detection rate of TC in children and adolescents before the Chernobyl disaster was lower in the former SU than in other industrialized parts of the world [13, 23, 24]. The screening in the contaminated territories was productive because many old neglected cases were found. This fact is often

disregarded in the literature. For example, Fridman et al., wrote that the frequency of sporadic TC in the former SU in the period 1971-85 did not differ from global statistics [55] referring to the study of Williams [18], where no such statements were found. Balonov wrote about the background of TC incidence in children  $\leq 10$  years old of 2-4 cases/million/year [56]. However, in Belorussia only 3 pediatric ( $\leq 15$  years old) with TC were diagnosed during 1981-85 (incidence rate  $\sim 0.3$  cases/million/year). For the whole of Ukraine, the statistics were correspondingly 25 and 0.5 and for its northern regions - 1.0 and 0.1 [24]. The above-cited figures are low in comparison with other developed countries [13, 23], which means that there was a reservoir of neglected cancers. It is known that the screening can enhance a registered TC incidence 10-fold or more [5, 57] due to a “reservoir of clinically silent cancers” [58]. Finally, with regard to the cleanup workers (liquidators), it should be considered that many of them underwent regular medical checkups [59, 60] i.e. the surveillance bias has taken place [14, 15].

## CONCLUSION

There is evidence that RET rearrangements in PTC, especially RET/PTC3, tend to correlate with the tumor progression. In the future, relationships between different types of RET/PTC, tumor dimensions, stage, and grade should be tested quantitatively. Further data collection on the frequency of different RET/PTC fusion types in less developed countries may provide more evidence in support of the association between RET/PTC3 and the tumor progression i.e. averagely later tumor detection. If the hypothesis presented here is correct, a low prevalence of RET/PTC3 among sporadic TC cases could be seen as a statistical indicator of efficient TC diagnosis and early detection in a given population.

## ACKNOWLEDGMENTS

Not applicable.

## CONFLICT OF INTEREST

The authors declared no conflict of interest.

## ETHICS APPROVAL

Not applicable.

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