

# Thyroid cancer after external or internal ionizing irradiation

## Abstract

It has been known for 50 years that thyroid exposure to high doses of ionizing radiation in childhood and adolescence induces an appreciable cancer risk. Epidemiological studies in children treated with external radiotherapy for benign or malignant lesions in the head and neck have also shown the induction of thyroid cancer. The World Health Organization (WHO) has reported that the risk for developing thyroid cancer due to the Chernobyl accident is greatest in newborns and children below the age of 5, less in adolescents and negligible in adults. As reported, during the first 15 years after the accident, the increase in thyroid cancer cases in Belarus was 87.8 fold in children, 12.7 fold in adolescents and 4.5 fold in adults more than expected. Papillary thyroid cancer with a relative risk incidence of approximately 80% per se is typical in childhood and adolescence. We refer to the differences between adult and childhood papillary thyroid cancers. Gene mutations in thyroid tumors induced after Chernobyl accident have been studied extensively. The treatment comprises thyroid surgery, suppressive doses of thyroxine and radioiodine. It is noteworthy that the thyroid gland can be protected from the intake of radioactive iodine by oral administration of potassium iodide.

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## External exposure

### a. External radiotherapy

It has been known for 50 years that exposure of the thyroid to ionizing radiation in childhood and adolescent induces an appreciable cancer risk [1]. Thyroid gland and bone marrow are considered the most radiosensitive tissues [2]. About 80% of the tumors occurring after external irradiation to the thyroid during childhood are benign and 20% are malignant [2, 3]. Concerning thyroid cancer, many epidemiological studies on children treated by external radiotherapy benign or malignant lesions in head and neck region have been published [1-6]. The indications for treatment included, hemangioma, enlarged thymus and tonsils, lymphoid hyperplasia, tuberculosis adenitis, acne and tinea capitis. Practically all thyroid carcinomas (70% to 97% of cases) are papillary carcinomas. Their biological behavior is similar to that of other thyroid carcinomas with an overall favorable long term prognosis [7, 8]. Radiation-related thyroid carcinomas are often preceded by or arise simultaneously with benign thyroid adenomas [4, 9, 10], and hypothyroidism frequently occurs after high dose radiation to the neck [11]. A pooled analysis [3], using data from cohort studies of individuals exposed to acute external ionizing radiation before the age of 20 years, found an average excess relative risk of 7.7 per Gy, while the excess absolute risk was 4.4 per  $10^4$  person-year Gy [3]. A linear dose-response function was found to fit the data well. Risk was about 30% lower for fractionated doses [3]. In the pooled analysis of seven studies, the risk of thyroid carcinoma increased after a mean dose as low as 100mGy to the thyroid gland [12]. At lower doses, the relative risk cannot be calculated because of uncertainties regarding the absorbed dose. For higher absorbed doses (up to 15Gy), a linear relation exists between the dose and the risk of carcinoma. At doses higher than 15Gy, the risk per Gray decreases, probably because of cell killing, but the overall risk remains elevated [4, 8]. Almost no thyroid cancers prior to 5 years after irradiation have been reported [2-4]. The pooled analysis suggested that the excess relative risk per Gy was the greatest about 15 years after exposure but was still elevated 40 or more years after irradiation [2].

### b. Atomic bomb explosion of Hiroshima and Nagasaki

The situation after the atomic bomb explosions of Hiroshima, and Nagasaki was similar. Data from the Japanese atomic bomb study have been used to estimate age-related excess

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relative risk coefficients per Gy amounting to 9.5, 3.0, 0.3 and -0.2 at ages 0-9, 10-19, 20-39 and >40, respectively [12]. Females are approximately two to three times more likely than males to develop both benign and malignant thyroid nodules after irradiation during childhood [8, 11]. It has been claimed that malignant thyroid tumors after external irradiation typically appear as papillary cancer in approximately 85% of the exposed children and adolescents [2, 5, 13-15]. The papillary histology findings per se are typical of thyroid cancer in childhood and adolescence. Bilateral lobe involvement was significantly more common in radiation induced thyroid cancer [16].

### c. The Chernobyl accident - Internal exposure

In this chapter we will briefly review the most significant events that environmental factors affect thyroid gland after the Chernobyl accident on April 1986. Over  $10^{19}$  Bq of radionuclides were released into the atmosphere including radioactive iodine [ $^{131}\text{I}$ ]. Radioiodine-131 has a half life of 8.09 days [13, 14] and is mixed with short lived isotopes, including iodine-133 ( $^{133}\text{I}$ ) and tellurium 132 (half life of 3.26 days which decays to  $^{132}\text{I}$  half life of 2.3h). These radionuclides were deposited to various countries according to the direction of the wind and other meteorological conditions. Being volatile, these radionuclides were inhaled considerably, entered the milk chain, and ingested through contaminated food and water [14, 15] (Fig. 1).

The level of contamination, and especially the thyroid gland dose was higher in children than in adults because the thyroid mass increases with age. In the newborns, the thyroid mass is 1gr and increases to 15-20gr in adults. The thyroid absorbed dose is therefore extremely higher in newborns and young children [17]. In children who remained at the contaminated territory after the accident and drank locally produced milk, 85% of the radiation dose to the thyroid was due to  $^{131}\text{I}$  and 15% to short-lived radionuclides [15]. The mean thyroid effective dose in children living in the most contaminated countries was estimated to be near 700mSv in Belarus and 100 to 200mSv in Ukraine and in Russia [14]. In western European countries, the mean thyroid dose ranged from a fraction of 1mSv to a few mSv in children and was 5-10 fold lower in adults. In France the mean radiation dose was 2.4mSv per year [14, 15].

External radiation from these short lived radionuclides must also be taken into account. The estimated radiation doses delivered to the thyroid are only an approximation. The World Health Organization (WHO) has recently, 2006, reviewed the health impacts of the accident, and specific attention has been paid to internal exposure of the thyroid gland and its close relationship to childhood thyroid cancer [18].

### Health consequences

To date more than 1.500 cases of thyroid cancer have been recorded that concern approximately 2 million children younger than 15 years who were exposed to the radioactive



**Figure 1.** Increase in the number of thyroid carcinoma after 1986, starting in 1990, in subjects who were below 15 years of age at the time of diagnosis and were living in southern Belarus, and northern Ukraine, and after 1994 in children living in southern Russia.

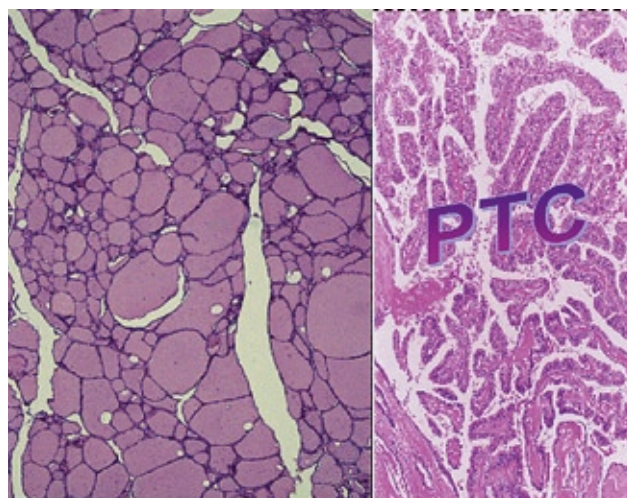
fallout [6, 19, 20]. In Belarus the incidence between 1986 and 2000 was 13.5 per 100000 children per year, compared to a normal incidence < 1 per year [9, 20, 21]. As reported during the 15 years after the accident compared to the 15 years before the accident, the increase in thyroid cancer cases in Belarus was 87.8 fold in children, 12.7 fold in adolescents and 4.5 fold in adults [22-24]. It is noteworthy that the male/female sex ratio was 1 to 5 in adults, while it was close to 1 in children and adolescents [21-24].

Papillary thyroid cancer with a relative risk incidence of approximately 80 % per se is typical for thyroid cancer in childhood and adolescence however, after exposure to radioiodine this relative frequency is increased close to 100% [24, 25]. Latency times between radiation exposure and development of thyroid cancer, range between a minimum of 3-7 years and a maximum of 40-50 years. Risk decreases significantly with increasing age of exposure with little risk apparent after the age of 20 years. Linearity best describes the dose response in children exposed to radiation before the age of 15 years [23, 25-27]. A high frequency of lymphocyte infiltration of the thyroid gland and of circulating thyroid antibodies was reported in exposed children from Belarus and was attributed to radiation exposure [9, 17]. As already referred, after exposure to external radiation, benign thyroid nodules occur more frequently (80%) than carcinomas (20%) [17]. The incidence of other malignancies, including leukemia did not increase after 1986 either in children or in adults in Belarus, Ukraine or Russia. Furthermore, in European Union countries after the Chernobyl accident the number of thyroid cancer cases, increase by 5%-10% annually, which may be due to better detection of spontaneous thyroid cancers, after using fine needle biopsy aspiration (FNBA) and ultrasound tests and not linked to thyroid irradiation [17, 25]. Post-Chernobyl gland thyroid cancer in children in Belarus and Ukraine appeared unexpectedly early, only four years after the accident, and in unexpectedly high rate [23, 24]. After external irradiation to the neck, the incidence of thyroid cancer increases after a latency period of at least five years. Such an increase cannot be attributed to reinforced screening of thyroid cancer in children because only a few thyroid tumors were microcarcino-

mas, whereas the majority were very advanced lesions [4, 16]. Thyroid carcinomas occurred in the most contaminated regions of Belarus, Ukraine and Russia. The radiation dose to the thyroid, based on available estimates, seems to be lower than initially thought. In Ukraine, 79% of the children received a thyroid effective dose below or equal to 300mSv, 10.5% received from 300mSv to 1Sv and 10.5% received more than 1Sv. In children exposed to external radiation, the excess relative risk of thyroid cancer was significant for thyroid absorbed doses as low as 100mGy. In Ukraine, a correlation was found between the mean thyroid dose in children and the incidence of thyroid cancers [25]. This finding supports the etiological role of radioactive iodine isotopes in the occurrence of thyroid cancer [17, 27]. In contrast, the studies on many subjects exposed to diagnostic or therapeutic doses of  $^{131}\text{I}$  failed to show an increased risk of thyroid cancer [17, 27]. Post-Chernobyl thyroid cancer occurred mainly in children who were below 10 years of age at the time of the accident. This is in keeping with finding in Japanese atomic bomb survivors and in subjects submitted to external radiation, in which the risk was maximal for those younger than 5 years of age and increased with age. Thus means that children and pregnant women must be the priority target population for prophylactic measures when atmospheric contamination occurs [28].

### Comparison with naturally – occurring thyroid tumors

A comparison of clinical and epidemiological features of thyroid carcinoma diagnosed in Belarus before 1996 with those of 369 children and adults followed up after thyroid carcinoma in Italy and in France [9] showed that the influence of gender on the post-Chernobyl thyroid carcinomas was much lower and the female to male ratio was significantly higher in Italy and in France. Furthermore, thyroid carcinomas were diagnosed before the age of 15 years, while the number of cases in Italy and in France increased progressively with age, with the majority of tumors (57%) being diagnosed in patients who were older than 14 years [17]. Over 90% of the post-Chernobyl thyroid carcinomas were papillary, few being of the follicular type. However, only a minority (about 10%) of these tumors were of the classic papillary type. Most cancers were classified as solid (one third) and follicular variants (one third). The diffuse sclerotic variant accounted for about 10% of these carcinomas. Their features were those of aggressive tumors as demonstrated by the histological appearance, the large size, frequent multifocality, extra-capsular extension, lymph node metastases and lung metastases at the time of diagnosis [17, 28-30]. Post-Chernobyl tumors more frequently associated with abundant lymphocyte infiltrations of the thyroid gland and humoral thyroid autoimmunity were also reported [5, 9, 17, 31-33]. We emphasize that another possible consequence of the ionizing radiation is the development of benign nodular hyperplasia, which must be discriminated from the cancer based on clinical and fine needle biopsy aspiration findings [34-36] (Fig. 2).



**Figure 2.** The differences between normal thyroid tissue and papillary thyroid cancer are illustrated in the above histology specimens.

### Studies of thyroid tumor genes

In theory, it is possible to correlate the potential tumorigenic impact of  $^{131}\text{I}$  on the thyroid gland with the growth of thyroid cells [6, 37] that in young children are in the process of active replication. In contrast, adult thyroid follicular cells exposed to radiation have already completed their replication program. The more vigorous growth potential of follicular cells in children exposed to radiation may facilitate the development of thyroid cancer while the limited growth potential of adult follicular cells will hamper the development of cancer [17].

Gene mutations in Chernobyl thyroid tumors have been studied extensively. The frequency of point mutation of ras gene was low, restricted to follicular tumor or absent. No Gs protein gene (gsp) or TSH-R mutations were found. On the contrary a high frequency of ret gene rearrangement (55% - 85%) mainly PTC1 and PTC3 was detected in several series of thyroid cancer in children after the Chernobyl in Ukraine [29]. Ret/PTC3 oncogene was associated with the aggressive behavior of these tumors, and it was the main rearrangement found in papillary carcinoma that occurred a few years after the accident. Ret/PTC1 was more frequently found in papillary carcinomas that occurred later and in those of the classic histological type [29, 30]. P53 mutations were very rare but may explain the aggressiveness of some papillary thyroid cancers [31]. Genetic predisposition to radiation-induced tumors has been hypothesized to explain the epidemic of thyroid cancer after Chernobyl. It is possible related to a defect in DNA repair mechanisms; it also might be associated with other factors such as dietary iodine deficiency or other environmental agents [32-36].

### Response to conventional treatment

The conventional treatment comprises near or total thyroidectomy,  $^{131}\text{I}$  treatment and suppressive doses of L- thyrox-



ine [36]. A study [37] included 249 Ukrainian children and adults initially treated with near-total thyroidectomy followed by  $^{131}\text{I}$ . Thyroid ablation occurred in only 52% of the patients and among them only 24% required a single dose of  $^{131}\text{I}$ . These results indicate that thyroid ablation was difficult in this population, due to the young age of the patients, the particular features of post-Chernobyl thyroid carcinomas or to sub-optimal surgical procedures. Another study [38] analyzed the outcome of 64 Belarus children, who received post-surgical treatment and follow-up in Pisa. Initial treatment consisted of total thyroidectomy in all patients, followed by  $^{131}\text{I}$  treatment and L-thyroxine suppressive treatment. After a mean follow-up of 39 months, based on serum thyroglobulin levels and on the results of a  $^{131}\text{I}$  total body scan, 59% of patients were free of disease and 38% had persisted disease, including 14 with lymph-node metastases and 7 with lung metastases. Two patients developed lung metastases during follow-up.

A study was performed in the Nuclear Medicine department in Wartburg, Germany, on 209 children, aged 7-18 years who had advanced disease at the time of diagnosis [36]. They were treated with  $^{131}\text{I}$  for distant metastases (16%) or for lymph-node metastases (97%). At the end of the observation period, 84% achieved a complete remission, including normalization of serum thyroglobulin. In the remaining cases, a partial response was obtained and treatment was repeated. These results indicate that patients with radiation-induced papillary thyroid carcinoma treated with a combination of surgery,  $^{131}\text{I}$  and hormonal treatment respond favorably to treatment in a comparable manner to that observed in age-matched series of patients with naturally-occurring thyroid carcinomas [17, 39-42].

## Iodine prophylaxis

In case of contamination with radioactive iodine, the thyroid is the critical organ likely to sustain damage. Administering potassium iodide (KI) orally can protect the thyroid. Potassium iodide inhibits uptake of  $^{131}\text{I}$  by the thyroid, thus blocking irradiation of the gland. The effect of KI is dependent on the dose administered and on the pre-existing iodine equilibrium. The rationale using KI is to dilute the minimal amount of  $^{131}\text{I}$  ingested with a very large amount of stable iodine and in so doing, to reduce the likelihood of radioactive uptake by the thyroid [17]. Two other mechanisms are at work: the iodine transport machinery is saturated and incorporation of the iodine in the thyroglobulin molecule is blocked (Wolf-Chaikof effect). This effect is very rapid, 30min after iodine ingestion; the maximal inhibition of radioiodine uptake is obtained. Daily iodine intake regulates  $^{131}\text{I}$  uptake: when iodine uptake is adequate, i.e. around  $150\mu\text{g}$ , average 24h uptake of  $^{131}\text{I}$  is 20%, and will increase to 40%-60% if thyroid is iodine deficient [8]. It is noteworthy that the inhibition is maximized after the administration of 130mg of KI (100mg of iodine), regardless of the uptake status before KI. Lower doses are required in children to achieve optimal blockade [17].

The individual doses recommended are: a) 100mg of iodine: adult subjects- including pregnant women, b) 50mg of iodine: children below 13 years of age and c) 25mg of iodine: children below 3 years of age.

The tablets of KI must be diluted in water or fruit juice to attenuate their unpleasant taste. Administration should be avoided on an empty stomach. The iodine should be administered, ideally before radioactive contamination and if this is not possible at the time of contamination or immediately after. A single dose should suffice. Whether this is repeated depends upon the predicted radiation doses to the thyroid and the duration of the contamination. After all these, the radiation dose to the thyroid may be reduced by 92%. Iodine prophylaxis requires that the KI tablets be available immediately. Preventive distribution of KI tablets to people living around nuclear power station is the mainstay for effective iodine prophylaxis [17, 40, 44]. We must emphasize that thyroid uptake will be increased significantly within 1 to 2 days following a single dose of KI. Daily administration of KI is therefore advisable in case of prolonged contamination. Treatments exceeding 1 or 2 weeks may, however, increase the side effects of KI. The usefulness of KI prophylaxis has been demonstrated in Poland. It was administered in 10.5 million children out of 7 million adults, where the thyroid radiation dose reduced by 4%-25% in subjects treated on April 29 and April 30, respectively. The administration of KI has been harmless and may not induce thyroid dysfunction, congenital hypothyroidism, hypothyroidism, and iodine induced thyrotoxicosis [41]. Extra thyroidal side effects-nausea, vomiting, abdominal pain and skin eruption- were mild and transient. They occurred in 0.35% of children and in 0.2% of adults treated with one or two doses of KI. Only two subjects with known hypersensitivity to iodine were hospitalized.

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