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Review

Thyroid cancer after radiation exposure

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1. Introduction

Studies conducted among atomic bomb survivors and patients exposed to radiation for benign and malignant conditions have clearly shown that external irradiation to the neck during childhood increases the risk of thyroid tumours. Among these thyroid tumours, 80% are benign adenomas, and approximately 20% are carcinomas, the most frequent being the papillary thyroid carcinoma (PTC) [1].

2. Epidemiological data

In children, the thyroid gland appears to be extremely sensitive to the carcinogenic effects of radiation exposure, the excess risk of thyroid cancer in a pool of seven studies published in 1995 being 7.7 per Gy delivered to the thyroid [2], and more than 85% of thyroid cancers in these subjects being attributable to radiation. This risk estimation was confirmed by subsequent studies [3–5]. In contrast, the excess risk is much lower in adults or is even not significant [1,2].

The latency period is at least 5 years [1,2]. The relative risk increases 5–10 years after radiation exposure, is maximal at 15–30 years, and then declines, although an excess risk is still apparent at 40 years [2].

The risk is significantly increased after a mean dose to the thyroid as low as 100 mGy [2,5]. Above this dose, there is a linear relationship between the dose and the risk of carcinoma [1,2]. At doses higher than 1500 cGy, the risk per Gray decreases, probably because of cell killing, but the overall risk remains elevated [1–3]. There is no lower dose limit below which the risk can be totally excluded.

After exposure to external radiotherapy, the risk of thyroid carcinoma is only slightly decreased when the fractionation is increased, but the statistical power of these studies was low [3,6].

Three subject-related factors (the age at exposure, the gender and the individual susceptibility) may greatly modify the risk. A young age when exposure to radiation occurs is a major risk factor: in children, the risk is maximal when radiation exposure occurs below the age of 5 years, this risk decreases with older age, and above the age of 15–20 years the risk is only slightly or even not significantly increased. No study has evidenced an increased risk of PTC following radiation exposure after the age of 45 years [1,2]. After radiation exposure during childhood, thyroid cancer incidence is 2–3 times higher in females than in males [1,2]. Because the incidence of spontaneous thyroid cancer is also 2–4 times higher in females than in males, the additional risk of thyroid cancer due to radiation was estimated to be 4–12 times higher in females than in males.

Individual or familial susceptibility is suggested by the occurrence of several cases of thyroid carcinomas among irradiated children in some families, by the occurrence in some individuals of several radiation-induced tumours (thyroid, parathyroid, salivary, neural and depending on the irradiation fields, breast and brain) [1,2]. A higher risk was found in children irradiated for a primary cancer than in children from the general population exposed to radiation for other reasons, and in children irradiated for a neuroblastoma or Hodgkin's disease than in those irradiated for another primary cancer [3,7]. A defect in DNA repair mechanisms may be responsible for this higher susceptibility, but environmental factors such as the iodine diet and subject-related factors (body weight, fertility history) may also play a role [8].

There is no evidence that the risk of thyroid cancer is increased in adults and adolescents exposed to [^{131}I] radioactive iodine for diagnosis (mean thyroid dose: 1

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Gy) or as therapy for thyrotoxicosis (mean thyroid dose: 100 Gy) [9–11]. This may simply be related to a radiation exposure at an age when the sensitivity of the thyroid gland to the carcinogenic effects of radiation is low. Data in children are still too scarce to exclude such a risk in young children, but in two cohort studies, performed on approximately 2500 and 5000 young subjects, respectively, who received [^{131}I] for diagnosis or as therapy for thyrotoxicosis, there was no evidence of any excess risk, but most of these subjects were adolescents at the time of exposure [10,11].

3. Consequences of the Chernobyl accident

A tumorigenic effect of radioactive iodine isotopes on the thyroid has been strongly suggested by the increased incidence of PTC in heavily contaminated children in the Marshall Islands after the atomic bomb testing in 1954 [12], and more recently in Belarus and Ukraine, as a consequence of the Chernobyl accident in 1986 [13]. This was confirmed by a recent study on children who lived within a 150 km radius of Chernobyl: no thyroid cancer was observed in 9472 children born in 1987–1989, whereas 1 case was recorded among 2409 children born between 27 April 1986 and 31 December 1986 (i.e. during the months following the accident), and 31 cases in the 9720 children born between 1 January 1983 and 27 April 1986 [14]. Thyroid carcinomas were likely to have been caused by exposure to radioactive iodine isotopes. They occurred mostly in children who were aged less than 10 years and particularly in those aged less than 5 years [15], and who lived in the most contaminated areas at the time of the accident. In these areas, the mean thyroid dose was several Grays. The incidence of thyroid carcinoma in young children increased less than 5 years after the accident, and these thyroid cancers were aggressive, similarly to those occurring at a young age (<10 years) in the absence of previous radiation exposure [16–18].

In the case of a contamination with radioactive isotopes of iodine, the radiation dose to the thyroid gland is higher in young children. It is 1000–10 000 times higher than that to any other organ [19]. It is therefore not surprising that the incidence of tumours at other sites and of leukaemia did not increase even in highly contaminated children [20].

The increased incidence of thyroid carcinomas observed in Western countries in the last 25 years does not appear to be related to the Chernobyl fallout, the excess radiation dose to the thyroid gland being low, in the order of magnitude of the annual natural radiation dose. A more extensive thyroid screening in the general population is likely to be the cause and during the same period of time, the thyroid cancer-related mortality was stable or even decreased [21].

4. Molecular carcinogenesis

The mechanisms through which radiation induces thyroid tumours are still poorly understood. The frequency of activating point mutations of the *RAS* genes is similar to that found in tumours occurring in the absence of previous radiation exposure, activating point mutations of the G-protein or of the thyroid-stimulating hormone (TSH)-receptor, and inactivating mutations of the *TP53* gene are rarely found. Gene rearrangements may frequently be involved: *RET*/PTC rearrangements are found in 60–80% of radiation-associated PTC and in 45% of radiation-associated adenomas; in the absence of previous radiation exposure, *RET*/PTC rearrangements were found in only 5–15% of PTC and were not found in adenomas [22–25]. In addition, *RET*/PTC3 rearrangement was found more frequently in aggressive PTC that occurred less than 10 years after the accident, and *RET*/PTC1 in PTC that occurred later and in those occurring after external radiation exposure [23–26].

5. Clinical management of radiation-related thyroid tumours

All subjects exposed to radiation during childhood should be submitted to a life-long follow-up [1,2,16]. Risk factors for developing a thyroid carcinoma should be identified, including a high radiation dose, a young age at radiation exposure, female gender and personal or familial history of radiation-associated tumours. Most subjects are euthyroid, with a normal serum TSH level. There is no evidence in humans that thyroxine treatment may decrease the risk of thyroid carcinoma. Neck palpation and neck ultrasonography should be performed every 1–3 years, depending on the risk factors. A micronodule (less than or equal to 1 cm in diameter) only needs to be controlled with ultrasonography 6–12 months later. Any thyroid nodule of more than 1 cm in diameter warrants a complete work-up including a fine-needle aspiration biopsy, and treatment may then be based on the results of the cytology. However, nodules are often multiple and, for this reason, surgery is frequently the only option.

Initial characteristics and outcome of PTCs occurring after exposure to radiation are similar to those occurring in the absence of previous radiation exposure. The only difference found in a case–control study was a higher frequency of multifocality, and this is a strong argument in favour of a routine near-total thyroidectomy [17]. However, PTCs that appeared early (less than 10 years) after the Chernobyl accident were more aggressive, and this may be related to the young age at occurrence of the disease [15].

The initial treatment includes in all patients with a clinical tumour a near-total thyroidectomy and dissec-

tion of the central neck compartment, and radioiodine ablation in those at a high risk of recurrence and tumour-related death. Thyroxine treatment and follow-up are similar to those of PTC patients with no history of neck irradiation [27].

Surgery for a benign nodule should consist of a bilateral thyroid resection and be followed by thyroxine treatment.

In conclusion, exposure to radiation should be avoided in children. Exposure to radiation for the treatment of benign lesions should no longer be performed, radioiodine should not be used in young children for diagnosis or therapy for thyrotoxicosis and in cases of atmospheric contamination, children should receive as a priority prophylaxis treatment with potassium iodide.

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