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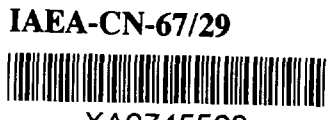

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THYROID TUMOURS FOLLOWING FRACTIONATED IRRADIATION IN CHILDHOOD

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Abstract

Results of a cohort study designed to evaluate the long term risk of thyroid tumours after fractionated high doses of external beam radiotherapy received by the thyroid are reported. In this cohort study, doses have been estimated for each child.

INTRODUCTION

Thyroid tissue is one of the more radiosensitive organs of the human body *(1)*. After irradiation, the excess of relative risk (ERR) of thyroid tumour per dose unit decreases with increasing age at time of irradiation *(1,2)*. During the first decades, following a dose of 1 Gy delivered during childhood in one or a very few number of fractions, both the risk of differentiated carcinoma and that of adenoma was found to range between 5 and 10 *(2-4)*. After 20 years following the irradiation, the ERR decreases with time since irradiation *(2,3,5)*. At the opposite, the absolute excess of risk (AER) increases during at least 40 years *(2,3,5)* following irradiation. The dose-response relationship is essentially linear for dose up to a few Gy *(2,4)*. Very few studies have been published concerning thyroid tumours occurring among patients who received external radiotherapy for a cancer in childhood *(6,7)*, although they constitute one of the population at higher risk of thyroid cancer in western countries. In the absence of available cohort of children who received high dose radio-iodine *(6)*, the study of thyroid tumour after first cancer in childhood is the only way to improve the epidemiological knowledge about thyroid tumours occurrence after high radiation dose to thyroid in childhood. As Chernobyl disaster showed, such a knowledge could be an important issue in radioprotection *(8)*. We report here the results of a cohort study designed to evaluate the long term risk of thyroid tumours after fractionated high doses of external beam radiotherapy received by the thyroid. In this cohort study, doses to have been estimated for each child.

PATIENTS

A retrospective cohort of 4096, of which 2827 received external beam radiotherapy, children treated in 8 centres in France and in the UK was established comprising patients who were alive 3 years after the first cancer, diagnosed before the age of 15 and before 1986. The diagnoses of first and second thyroid tumours were confirmed by histology. Only clinical thyroid tumour that needed surgery were taken into account.

RADIATION DOSIMETRY

For each of the 2827 patients who received radiotherapy, the radiation doses were estimated at the middle of the 2 lobes and at the isthmus of the thyroid. A computer program called "Dos_EG" has been developed for these calculations *(9)*. The mean radiation thyroid dose received by the 2827 patients who received external radiotherapy was 7.0 Gy (range : <0.001 to 75).

STATISTICAL METHODS

In the absence of available reference rate, we analyse thyroid adenoma incidence using patients who did not received radiotherapy as the reference category.

Both the Standardised Incidence Ratio (SIR) of thyroid cancer and the Relative Risk (RR) of thyroid adenoma was modelled assuming that the number of thyroid cancers followed a Poisson

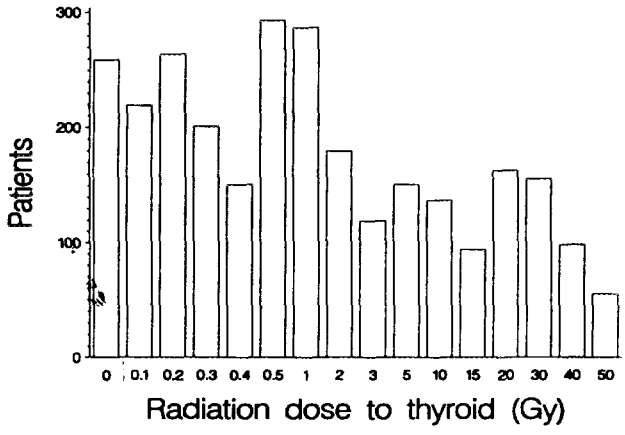

Figure : Radiation dose thyroid in a cohort of 2827 children treated by external radiotherapy for a cancer in childhood

distribution. Statistical tests were performed by comparing the deviance of nested models *(11)*. We modelled the variation of the thyroid tumour risk with time since irradiation, as a power function of the time since irradiation, as done by previous authors *(5)*.

RESULTS

From 3 to 29 years after 1st cancer, 58 patients developed a clinical thyroid tumour, which needed surgery, 44 adenomas and 14 differentiated carcinomas. All these patients but one had received radiotherapy. The cumulative incidence of differentiated thyroid carcinoma 30 years after radiotherapy was 1.5%, with a standard deviation (sd) equal to 0.5%, and that of thyroid adenoma was 5.4% (sd=1.1%).

Overall, the 2827 patients who received radiotherapy had a 88-fold higher risk (95%CI : 50-143) of developing a thyroid carcinoma than expected from the general population.

No thyroid cancer and only one thyroid adenoma occurred between 3 and 5 years after Rx. The temporal pattern of occurrence of adenomas was similar to that of carcinomas (table I). No significant decrease of the excess of SIR of c per Gy nor in the annual incidence of thyroid adenoma par Gy was shown.

The In our cohort, radiation dose to thyroid increased with age at radiotherapy, because of the increasing proportion of CNS and Hodgkin's disease as a first cancer, with increasing age. Both the excess of SIR of thyroid cancer per Gy and the annual incidence of adenoma per Gy strongly decreased with age at radiotherapy (table II).

No decrease of thyroid tumour risk for doses higher than 10 Gy was shown (table III). According to the adjustments, the SIR of thyroid carcinoma and the Relative risk of thyroid adenoma was found to range between 5 and 10 for 1 Gy. As compared to a purely linear model, the addition of a negative exponential term for cell killing due to high doses to thyroid improves the fit of the model (χ^2 = 4.3, df=1, p=0.04 for the carcinoma, and χ^2 = 4.8, df=1, p=0.03 for the adenomas). No modification of effect of the total dose to thyroid according to the number of fractions was found.

DISCUSSION

Based on a cohort of 2827 3-year survivors of a cancer in childhood who received fractionated external radiotherapy (mean number of fractions = 27) leading to a very large range in the dose to thyroid (from 0.05 to 50 Gy), we found the dose-response relationship between the dose to thyroid and the risk of thyroid tumour (adenoma and carcinoma) was linear up to a few Gy. Our estimation of the relative risk of thyroid cancer for a dose of 1 Gy (5 to 10 according to the adjustments) was similar to that observed after irradiation in one or a few number of fractions *(1-4)*. For higher doses, the risk increased, but slower.

Table I - Thyroid tumours occurrence according to time since radiotherapy in a cohort of 2827 patients which received external radiotherapy during childhood.

Years after Rt	Patients still followed	Differentiated thyroid carcinomas				Thyroid adenomas	
		n	Annual incidence x 10^5	Annual excess* of incidence x 10^5	SIR*	n	Annual incidence x 10^5
3-9	2827	2	12	11	55	3	17
10-14	2001	3	36	36	80	15	181
15-19		6	120	119	179	15	229
≥ 20	746	3	63	61	56	10	206
≥ 3	2827	14	39	39	88	43	121

** as compared to general population*
Rt : Radiotherapy
SIR : Standardised Incidence Ratio

Table II - Thyroid tumours according to age at radiotherapy in a cohort of 2827 patients which received external radiotherapy during childhood.

Age at Rt in years	Patients	Differentiated thyroid carcinomas				Thyroid adenomas	
		n	Annual incidence x 10^5	Annual excess* of incidence x 10^5	SIR*	n	Annual incidence x 10^5
0-1	642	4	42	42	159	13	137
2-4	673	3	34	34	92	13	149
5-9	781	3	33	33	77	12	132
≥ 10	731	4	49	49	69	5	63

SIR : Standardized Incidence Ratio
* as compared to general population

Table III - Thyroid tumours according to the radiation dose to thyroid in a cohort of 2827 patients which received external radiotherapy during childhood.

	Dose to thyroid (Gy)					
	No Ct	< 0.24	0.25 to 0.99	1 to 9.9	10 to 29	>= 30
N subjects	1269	743	773	680	411	216
Rx dose to thyroid (Gy)	0	0.11	0.52	3.5	19	40
Adenomas	1	2	5	13	13	10
RR*	1+	2.2	4.7	20	54	94
Carcinomas	0	1	3	5	3	2
SIR	-	11	63	129	151	169
Adjusted SIR *	-	1+	4.0	11	11	23

a : Excluding the first 3 years of follow-up.
** stratified for first cancer type, age at 1st trt, sex, country and follow-up*
+ reference category

Although our study deal with a relatively low number of irradiated patients (2827), the range of the doses available for investigation of dose-response relationship was very large : 20% of patients received less than 0.2 Gy and the 10% higher received more than 26 Gy. No other published study deals with such a range of radiation dose to thyroid. The only other study concerning thyroid tumours after radiotherapy for a 1st cancer, a case-control study in which the lowest dose received by a case of thyroid cancer was 1 Gy, was enable to investigate the shape of the dose-response relationship for doses lower than 2 Gy *(7)*. In the three other large studies concerning thyroid tumours after irradiation in childhood, the problem was inverse, i.e. it was difficult to investigate the shape of dose-response relationship for doses higher than a few Grays : amongst the 2650 children irradiated for thymus enlargement in USA, only 55 children had received more than 5 Gy *(4)*. In the same way, the highest dose received to thyroid by any of the 10834 children in the Israeli study on tinea capitis was 0.5 Gy *(10)*. Only very few of the 14351 infants who received radiotherapy for skin hemangioma in the Swedish study had received more than 5 Gy to thyroid *(3)*

We found a increase of the risk by a factor 3.8 for children aged under 2 years of age at time of irradiation as compared to those more than 5 years. This role of age is also in agreement with the findings of all the other studies on thyroid irradiation effects *(7)*.

We were not able to find a significant quadratic term in the dose-response relationship between dose to thyroid and the ERR of thyroid adenoma. This result agrees with that of Ron *(4)*, but not with those of Shore who has found a significantly supra linear dose-response relationship for adenomas *(3)*. All the studies on thyroid carcinomas after irradiation in childhood, also failed to show evidence of a significant non linear term *(7)*.

Despite the large range of number of fractions per patient (2 to 97) in our study, we failed to demonstrate a clear effect of the dose fractionation.

CONCLUSION

The pattern of the risk for thyroid cancer after fractionated external radiotherapy for a cancer in childhood was found to be similar to that observed by other authors after irradiation delivered during one or a few fractions. This failed to show any evidence for reduction of the risk of thyroid tumour with the fractionation of the dose.

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