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Long-term Effects in Skin and Thyroid after Radiotherapy for Skin Angiomas: a French Retrospective Cohort Study

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To evaluate the long-term effects of skin angioma irradiation, a recall programme was established which included the systematic recalculation of the radiation dose to the skin and the thyroid. 22% of the 6229 patients contacted had a dermatological examination which revealed cutaneous dystrophy in 81% of the 1137 exposed angiomas and in 39% of the 208 unexposed angiomas. The risk of dystrophy (telangiectasia, hypopigmentation, superficial and subcutaneous atrophy) was 12.1 higher ($P < 0.0001$) among patients who had received a surface skin dose above 30 Gy than among those who had received a dose of 10 Gy or less. The relative risk for each dystrophy component increased significantly ($P < 0.001$) with surface skin dose. Furthermore, 14 basal cell carcinomas (BCC) were observed in 12 patients from the exposed group for all quantities of radiation, with a mean latency period of 22 years. No BCC was observed for a surface skin dose below 10 Gy. Thyroid testing was done on a subgroup of 431 patients whose thyroid gland had been particularly exposed during angioma irradiation. After recalculation, the dose delivered to the gland was below 1 Gy in 98% of patients. Only 13 thyroid nodules were discovered (1 hot and 12 cold). 1 patient with a cold nodule had a malignant thyroid tumour 21 years after irradiation. He belonged to the group of 7 patients who had received a thyroid dose above 1 Gy. Although no morphological abnormality was found in 98% of the tested patients, most (92%) had a thyroid iodine content below 15 mg (the standard French value), while a raised serum thyroglobulin level (> 30 ng/ml) was observed in 17%. This might confer a higher risk of subsequently developing thyroid nodules.
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INTRODUCTION

THE STUDY of the late effects of radiotherapy is of major clinical interest, because radiation treatment may be responsible for various complications such as skin dystrophy, infertility, growth disorders and second primary malignant neoplasms [1]. However, such studies require large populations of exposed individuals adequately followed up over a long period of time, as well as accurate information on treatment administered sometimes several decades ago, in order to estimate doses delivered to the target organs. These two conditions are generally met in the evaluation of thyroid complications following ionising irradiation to the head and neck during childhood for an enlarged thymus gland, hypertrophic tonsils and sinusitis; a correlation has been found between the dose and the risk of thyroid tumour [2]. For other forms of radiotherapy such as the local application of radioactive plaques used to treat skin angiomas, it is more difficult to evaluate the dose received. Despite large cohort population studies, there has been no evaluation of possible dose response relationships for malignant tumours observed in different sites after irradiation of skin angiomas [3].

Ionising radiation was one of the treatments for haemangiomas until the 1960s when it was demonstrated that the majority resolve spontaneously in early childhood [4, 5]. Haemangiomas of infancy have been the subject of many studies at the Institut Gustave-Roussy (IGR) including a randomised therapeutic trial conducted between April 1961 and February 1963 to investigate

the results of irradiation versus no treatment [6]. We here report the results of a study of an IGR cohort population which responded to a recall programme established in order to evaluate the long-term skin and thyroid sequelae after angioma irradiation according to the doses received. These doses have been recalculated.

PATIENTS AND METHODS

Patients

A retrospective study for a long-term evaluation of patients treated by radiotherapy for angioma was performed at IGR between January 1985 and December 1987. Information was abstracted from the IGR registration book only for patients treated from 1941 until December 1973, in order to have at least 12 years of follow-up. All patients whose treatment had not been entirely performed at IGR were excluded. A total of 6229 patients (5032 irradiated and 1197 non-irradiated) were considered. The medical history and photographs of the initial angioma and detailed radiotherapy data (date and dose of each treatment, site and number of treatments with a diagram of the radiotherapy field at each session) were available for all the patients.

After a preliminary study performed on 68 patients in 1984, a letter was sent to each patient requesting his/her participation in the survey; 2541 calling notices were returned because the person had moved and 2406 notices were ignored. Among the 1350 addressees who had the proposed medical examination, 73% had received irradiation treatment and 27% were untreated ($P < 0.001$).

The final analysis was performed on 1345 patients: 1137 irradiated angiomas (i.e. exposed) and 208 non-irradiated angiomas (non-exposed). The data on size of angioma were unknown in 5 subjects, who were excluded. The cohort population was predominantly female (72%), and caucasian with (96%) sun reactive skin types III or IV (74%). 22% of the patients reported a family history of angioma. About 95% of the patients were examined or treated between 1960 and 1973 and 83% of patients were below 2 years of age at the time of their first medical visit and first treatment.

Dermatological examination

The location of the different angiomas for each patient was coded into 26 different areas according to a division of the body surface. In cases of multiple angiomas, separate forms were completed for each angioma. Angiomas were separated into haemangiomas or vascular malformations according to Mulliken's classification [7]. Initial characteristics of angiomas are given in Table 1. 46% of treated angiomas were found in the facial area. Tuberous and mixed haemangiomas represented 86% of the treated group. Subcutaneous haemangiomas and port wine stains were more often left untreated.

Cutaneous evaluation based on initial description and photographs of the angioma area was recorded separately, as telangiectasia, hypopigmentation and hyperpigmentation, cutaneous and subcutaneous atrophy, keratosis, dry skin, alopaecia, acne or necrosis with the aim of differentiating persistent angioma or sequelae from chronic radiation dermatitis (CRD). A biopsy was obtained for all suspect nodules in and around the angioma area or elsewhere and submitted to a pathological examination.

Table 1. Characteristics of the 1345 studied angiomas

	Exposed (n=1137)	Unexposed (n=208)
Location of angiomas		
Scalp	11.9	8.2
Face (except eyelids)	31.4	22.6
Eyelid	3.0	2.4
Neck	7.4	8.2
Trunk (except breast)	25.3	26.9
Breast	0.8	2.9
Upper limbs	9.5	11.5
Lower limbs	6.7	13.0
Types of angiomas		
Haemangioma		
Tuberous	41.1	23.1
Mixed	44.6	26.0
Subcutaneous	6.4	18.7
Vascular malformations		
Port wine stain	7.0	22.1
Venous and arteriovenous malformations	0.9	6.7
Stellar	0.1	3.4
Thickness (mm)		
≤ 2	36.2	49.7
3–4	20.7	10.6
≥ 5	43.1	36.0
Largest diameter (mm)		
≤ 15	38.1	30.0
16–30	34.3	34.0
≥ 30	27.6	36.0
Surface skin dose (Gy)		
≤ 10	16.0	
]10–20]	26.4	
]20–30]	29.9	
> 30	27.6	
Dose at 10 mm in depth (Gy)		
Negligible	57.7	
< 2	15.9	
[2–10[	14.0	
≥ 10	12.4	

% of patients.

Thyroid examination

In order to check the effect of angioma irradiation on thyroid nodule occurrence, a thyroid gland examination was proposed to a subgroup of 441 exposed patients because their angioma was either located less than 5 cm from the thyroid gland and treated by different irradiation modes—phosphorus (^{32}P), strontium (^{90}Sr) or yttrium (^{90}Y)—or elsewhere and treated by radium (^{226}Ra) or by X-ray therapy. All these patients were evaluated in the IGR nuclear medicine unit. A senior member of the unit explained the reason for the thyroid examination and outlined the functional and morphological method evaluation. Consent was obtained in 431 patients. They were predominantly female (77%) and had been treated below 2 years of age (87%).

After clinical examination, radioimmunoassay methods were used for the following analyses: total thyroxine (T4; Abbott T4-TDX, normal range 60–160 nmol/l), FT4 (clinical assay one-step FT4 kit, range 7–27 pmol/l) triiodothyronine (T3, Behring

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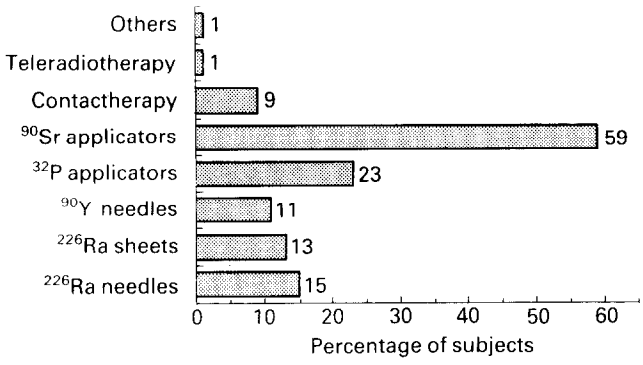

Fig. 1. Percentage of subjects who received at least one type of radiation at Institut Gustave-Roussy (1941–1973).

T3 kit, range 1.1–2.8 nmol/l). During 1985, thyroid-stimulating hormone (TSH) was measured by a non-sensitive method (CEA kit, minimum detectable value 1 mU/l, upper limit of normal range 8 mU/l). Thereafter, a more sensitive method was introduced in clinical routine (RIA gnost TSH Behring kit, lowest detectable value 0.03 mU/l, upper limit of normal range 5 mU/l). The serum level of thyroglobulin (Tg) was measured by a double antibody method (normal range 2.5–30 ng/ml). Serum with positive anti-thyroglobulin antibodies even at low titre (1/10 dilution) were excluded [8]. Antibodies were measured by haemagglutination techniques using thymine T (Wellcome) for antithyroglobulin antibodies and thymine M (Wellcome) for antimicrosomial antibodies. Sera were considered positive for antithyroglobulin antibodies if the titre was greater than 1000, and positive for antimicrosomial antibodies if the titre was greater than 400.

After thyroid palpation, 378 patients underwent a scintigraphic examination of the thyroid gland with 37 mBq ^{99m}Tc. Thyroid iodine content was also measured by X-ray fluorescence in 215 patients (normal range 2.5–27.5 mg) [9].

Dose re-evaluation

Most patients were treated by local irradiation but with different qualities of radiation. Haemangiomas were initially considered as an indication for ^{226}Ra sheets or needles. Later, in order to eliminate the potentially hazardous gamma irradiation emitted by radium, betatherapy was mainly used and consisted of either ^{90}Sr and ^{32}P flat applicators, or interstitial betatherapy with ^{90}Y needles [10]. A few haemangiomas were also treated by teleradiotherapy or contactherapy. The type of radiotherapy was determined by the thickness and surface of the angiomas [11]. Angiomas between 1 and 5 mm in thickness were treated with ^{32}P and ^{90}Sr applicators, whatever the surface. ^{90}Y needles were used for angiomas greater than 10 mm in thickness except when surface area was less than 5 cm^2 (contactherapy) or greater than 25 cm^2 (teleradiotherapy). 83% of exposed patients received at least two treatment sessions. The mean duration of treatment was 1.1 years and the mean number of sessions 3.6. The same method, e.g. ^{90}Sr, could be used several times or different qualities or radiation could be used in sequence. Figure 1 shows percentages of subjects who received one type of radiation treatment at least once; ^{32}P or ^{90}Sr applicators were mainly used. Since the late 1970s radiation treatment for angiomas has no longer been performed at the IGR.

Dose recalculations which took into account the radiation quality were performed for all patients. The doses were calculated for each angioma location at the skin surface and at 10 mm depth, for two main reasons. Firstly, some of the radioisotopes used are only beta emittors (^{32}P and ^{90}Sr) with low energy (< 1 MeV), and therefore electrons penetrate very superficially in the tissues (a few mm). Other radioisotopes are beta and gamma emittors (^{226}Ra) and penetration in this case is deeper due to the relatively high energy of the photon (2.5 MeV). Secondly, a large number of patients had a combination of different types of radionucleides. All these characteristics were implicitly taken into account in the expression of the doses at these two different depths. Doses were estimated for each radiation treatment delivered to the angioma and summed. For angiomas treated in different sectors, because the field was too big to be treated at one time, doses retained correspond to the sector which had received the maximum dose.

The dose delivered to the thyroid was also estimated. A mathematical phantom of a child or adult was used to yield anatomical information relative to distances between the angioma and the thyroid [12, 13].

Statistical analysis

Some difficulties arose in the analysis of the study. Firstly, the percentage of treated patients was significantly higher than that of untreated patients among individuals who underwent the dermatological examination. In order to verify whether the reasons for non-response were similar in the two groups, we performed a complementary study on a randomised sample of the total population. A mailed questionnaire was sent to 595 patients in each group. The proportion of patients who completed the questionnaire, but did not attend the examination because of the complete regression of the angioma, was significantly higher ($P < 0.0001$) among non-irradiated patients (76%) than among patients treated by radiation (29%). This complementary study showed that the group of unexposed patients was not a suitable control group. However, we felt that cutaneous long-term results were informative in the 208 untreated patients and that among treated patients the relationship between the occurrence of chronic radiation dermatitis and/or cutaneous skin epitheliomas and doses of radiation was worth the study. The reference category was defined as the group of patients with the lowest surface skin dose delivered to the angioma i.e. $\leq$ 10 Gy. This arbitrary limit was fixed in order to have enough patients in the reference group.

Secondly, for patients with multiple angiomas (23%), only the largest one and the treatment related to it were considered in the dermatological evaluation, because it was felt that several angiomas in one person were not equivalent to one angioma in several persons. The data were analysed using the PIGAS programme [14]. Percentages were compared by the χ^2 test and means by the Student's t test. Relative risk (RR) and 95% confidence intervals (CI) were estimated by the Mantel–Haenszel method [15].

Thirdly, no control group was constituted for thyroid evaluation: for ethical reasons, it was not possible to propose a thyroid scan to all people whose thyroid gland had not been particularly exposed during angioma irradiation. Only a descriptive analysis was performed on the subgroup of 431 exposed patients tested for thyroid function.

RESULTS

Dermatological results

The delay between the diagnosis of angioma and recall examination was less than 20 years in 57% of the subjects and over 25 years in only 10%. Dose recalculations at the angioma locations are summarised in Table 1. At the skin level, 56% of angiomas received doses between 10 to 30 Gy and 28% of angiomas received doses higher than 30 Gy. Doses calculated at 10 mm depth were at least 2 Gy for 26% of angiomas, whereas the evaluation showed no significant penetration for 58%.

Dermatological examination focused on two main evaluations: the presence of dystrophy and the search for cutaneous carcinomas. Dermatological examination revealed cutaneous dystrophies in a large number of patients of both groups: 81% of the exposed patients and 39% of the unexposed patients. These cutaneous dystrophies were persistent angioma, angioma sequelae and CRD. Most persistent angiomas were port wine stains, which accounted for 21% of angiomas in the unexposed patients and 7% in exposed patients. Angioma sequelae in the unexposed group consisted mainly of hypopigmentation (50%), telangiectasias (47%), cutaneous (44%) and subcutaneous (32%) atrophy and less frequently, hyperpigmentation (27%). These components are also part of CRD which explains the difficulty encountered in the clinical assessment of the latter condition in treated patients.

Table 2. Relative risks (RR) of radiodystrophy according to skin dose

	Surface skin dose (Gy)				
	≤ 10	]10–20]	]20–30]	> 30	*P*
Dystrophy					
No	56	63	41	11	
Yes	125	234	296	298	
RR	1.0*	1.7	3.2	12.1	0.0001
(95% CI)		(1.1–2.6)	(2.0–5.2)	(5.9–25.6)	
Telangiectasia					
No	134	167	151	117	
Yes	47	130	186	192	
RR	1.0*	2.2	3.5	4.7	0.0001
(95% CI)		(1.5–3.4)	(2.3–5.3)	(3.1–7.2)	
Hyperpigmentation					
No	129	170	194	139	
Yes	52	127	195	195	
RR	1.0*	1.9	3.4	4.3	0.0001
(95% CI)		(1.2–2.8)	(2.3–5.1)	(2.8–6.5)	
Hypopigmentation					
No	131	196	194	139	
Yes	50	99	143	169	
RR	1.0*	1.3	1.9	3.2	0.0001
(95% CI)		(0.9–2.0)	(1.3–2.9)	(2.1–4.8)	
Superficial atrophy					
No	106	144	123	92	
Yes	68	153	214	216	
RR	1.0*	1.7	2.7	3.7	0.0001
(95% CI)		(1.1–2.5)	(1.8–4.0)	(2.4–5.5)	
Subcutaneous atrophy					
No	127	191	206	156	
Yes	68	106	131	152	
RR	1.0*	1.3	1.5	2.3	0.0001
(95% CI)		(0.9–2.0)	(1.0–2.2)	(1.5–3.4)	

*Reference category.
CI = confidence interval.

Table 3. Relative risks (RR) of radiodystrophy according to dose at 10 mm depth

	Dose at 10 mm (Gy)				
	Negligible	< 2	]2–10[	≥ 10	*P*
Dystrophy					
No	93	42	24	12	
Yes	559	137	133	124	
RR	1.0*	0.5	0.9	1.7	NS
(95% CI)		(0.4–0.8)	(0.6–1.5)	(0.9–3.4)	
Subcutaneous atrophy					
No	436	114	77	53	
Yes	215	65	80	83	
RR	1.0*	1.2	2.1	3.2	0.0001
(95% CI)		(0.8–1.7)	(1.5–3.0)	(2.1–4.7)	
Sclerosis					
No	584	162	123	93	
Yes	67	17	34	43	
RR	1.0*	0.9	2.4	4.0	0.0001
(95% CI)		(0.5–1.6)	(1.5–3.9)	(2.5–6.4)	
Alopaecia					
No	624	174	141	120	
Yes	27	5	14	16	
RR	1.0*	0.7	2.3	3.9	0.001
(95% CI)		(0.2–1.8)	(1.1–4.7)	(1.5–6.2)	

*Reference category.

RR in exposed patients are given in Table 2, according to surface skin doses and in Table 3 according to doses at 10 mm depth. The risk of dystrophy was 12.1 higher ($P < 0.0001$) among patients who had received a surface skin dose above 30 Gy than among patients who had received a surface skin dose of 10 Gy or less. For each dystrophy component (telangiectasia, hyperpigmentation, hypopigmentation, superficial and subcutaneous atrophy), RR increased significantly ($P < 0.0001$) with surface skin dose. For a dose recalculated at 10 mm depth, the risk of dystrophy was 1.7 times higher, although not significantly so, among patients who had received a dose above 10 Gy than among patients who had received a negligible dose. The RR increased significantly ($P < 0.001$) with doses at 10 mm depth for deep dystrophy components (subcutaneous atrophy, sclerosis and alopaecia). Moreover, the relationships between dystrophy and surface skin doses or doses at 10 mm depth were not modified after adjustement for type of angiomas.

Of cutaneous carcinomas, 14 pathologically confirmed basal cell carcinomas (BCC) were observed in 12 patients (3 males and 9 females), and were exclusive to the exposed group. 10 out of 12 patients had haemangioma (4 tuberous and 6 mixed) and 2 patients had a port wine stain. 3 of these 12 had been treated for 4 BCC at IGR before the recall programme. Thus, 10 BCC were discovered and treated during the recall programme.

1 patient developed a BCC on a verrucous linear nevus located on the shoulder between 2 haemangiomas: one on the forehead treated by ^{226}Ra flat application and the other on the arm treated by ^{90}Sr flat application. The dose delivered at the site of this BCC was estimated to be 2 mGy. This BCC was excluded from the analysis since verrucous linear nevus is a predisposing condition for BCC. The other 11 patients developed 13 BCC (2

Table 4. Description of cutaneous carcinomas and thyroid nodules

Basal cell carcinomas in treated areas ($n=11$)*	
Skin dose to the angioma (Gy)	
≤ 10	0
]10–20]	1
]20–30]	2
> 30	8
Dose at 10 mm in depth (Gy)	
Negligible	5
< 2	2
[2–10[	2
≥ 10	2
Delay between first treatment and occurrence of BCC (yr)	
≤ 10	1
]10–20]	3
]20–30]	6
> 30	1
Types of angiomas	
Haemangiomas	9
Port wine stain	2
Thyroid nodules (n = 13)†	
Delay between first treatment and nodule diagnosis (yr)	
< 20	4
20–29	7
≥ 30	2
Pathology of the 11 excised cold nodules	
Benign	11
Malignant	1
Dose received by thyroid (mGy)	
≤ 100	8
]100–500[	2
[500–1000]	0
> 1000	1

*2 patients had 2 BCC on the same angioma, discovered at the same examination.

†12 nodules were cold (1 recovered spontaneously) and 1 was hot.

patients had 2 BCC) in the treated area, essentially at the borderline, with sizes varying from 3–40 mm. Most BCC diagnosed during the recall programme were small (about 5 mm) and none had been noticed by the patients.

The qualities of radiation used, latency period, location on the body surface and associated risk factors were studied.

Patients were treated with different qualities of radiation. 5 had been treated with ^{226}Ra sheets or needles. 3 of these 5 patients had in addition ^{90}Sr (1 patient), ^{32}P (1), ^{32}P and 200 KV (1). For betatherapy, 1 patient was treated with ^{32}P, 2 with ^{90}Sr, 2 with ^{32}P and ^{90}Sr and 1 with ^{90}Y, ^{90}Sr and ^{32}P. In this series no patient treated by ^{90}Y alone developed BCC. Table 4 indicates the occurrence of BCC according to the dose delivered to the angioma. No BCC was observed for surface skin doses below or equal to 10 Gy and 8 BCC were observed for doses exceeding 30 Gy. On the contrary, 5 BCC were observed for a negligible dose at 10 mm depth.

8 patients were less than a year of age at the time of first treatment. 3 patients were treated at the ages of 4, 16 and 29 years, respectively. The mean age at the time of BCC diagnosis was 27 years (range 17–41). The latency period between treatment and development of BCC was short (4 years) in only 1 patient, treated at the age of 29.

In 6 out of 11 patients, the site of the treated angioma was the head and neck and in 5 patients the trunk. The distribution of angioma found in head and neck areas versus the trunk was not significantly different between patients with or without BCC.

Chronic radiodermatitis was present in 4 patients. In the 2 patients with a port wine stain vascular dystrophy persisted without signs of CRD. In the other 5 patients a cutaneous dystrophy with epidermal atrophy was present at the site of angioma and the clinical examination alone could not determine whether this dystrophy was either related to angioma sequelae or to radiation treatment. None of the patients had a history of intense chronic sun exposure. 2 patients had been treated by cryotherapy prior to radiotherapy. In addition, in 1 of these 2 patients BCC developed on a scar following an injury which had occurred 22 years previously.

Thyroid examination

The delay between thyroid examination and treatment of angioma was over 20 years in 65% of the subjects. Since ^{32}P and ^{90}Y were the most frequently used type of irradiation, the dose delivered to the thyroid gland was below 1 Gy in 98% of the patients (Table 5).

Thyroid function diseases were observed in only 5 patients (1 hyperthyroidism and 4 hypothyroidism) while total (S.E.) T4 [103 (28) nmol/l] and free T4 [19.2 (4.8) pmol/l], total T3 [2 (1) nmol/l] and TSH [TSH – NS 4.41 (4.5) mU/l, TSH – US 1.41 (0.91) mU/l] were within the euthyroid range for the 431 other patients. Anti-thyroglobulin and anti-microsomial antibodies were negative in 98% and 94%, respectively, of the euthyroid patients. Although no correlation was found between thyroid iodine content and thyroid dose, 93% of the patients had a value below 15 mg (Table 5), which is the mean value of the French population [15 (5) mg] [9]. Serum Tg level was also found to be above the upper limit of the normal value (30 ng/ml) in 17% of the patients. This high serum Tg level was also found in patients without morphological thyroid disease.

After clinical palpation and thyroid scan, thyroid abnormalities were detected in 38 patients. Simple goitre was the most frequent abnormality (28 cases) and a thyroid nodule was

Table 5. Results of thyroid examination (%) (n=431)

Total radiation dose received by thyroid (mGy)	
< 10	52.2
[10–500[	43.7
[500–1000[	2.5
[1000–7230]	1.6
Thyroid scan (n = 378)	
Normal	89.2
Cold nodules	1.8
Goitres	7.1
Hot nodules	0.3
Thyroglobulin (ng/ml) (n = 394)	
≤ 10	12.7
]10–20]	48.5
]20–30]	21.8
]30–40]	8.8
]40–50]	3.6
> 50	4.6
Thyroid iodine content (mg) (n = 215)	
< 5	19.0
[5–10[	48.8
[10–15[	24.7
[15–30[	7.0
≥ 30	0.5

observed in 9 patients. A further 4 nodules were discovered and treated before the time of examination. Of these 13, there were 1 hot and 12 cold nodules. In most of these paients, the dose received by the thyroid gland was below 100 mGy (70%) and the delay between first treatment and nodule discovery was above 20 years (70%) (Table 4). 1 patient out of 12 with a cold nodule recovered spontaneously. The remaining 11 patients were treated by surgery which revealed 10 benign tumours and 1 papillary thyroid carcinoma. The latter was diagnosed in a female patient 21 years after radiation treatment to the head and neck area for a large haemangioma. This patient belonged to a group of 7 having received a thyroid dose above 1 Gy (range 1.2–8).

Mortality and malignancies

Mortality data were available in the IGR registration book for 15 patients. Additional mortality data for 12 patients were obtained from the replies to calling notices. The cause of death was obtained for 16 out of these 27 patients. It was neither related to angioma nor to treatment in 9 cases. Among the 7 other patients, angioma complications such as haemorrhage (Kasabach and Merritt syndrome), respiratory distress (subglottic haemangioma) or disseminated intravascular coagulation (DIC) led to death in 5 cases. Furthermore, 2 patients died of malignancy: ovary malignancy in a 14-year-old girl previously treated by three sessions of radium sheet application for forehead haemangioma and acute leukaemia (LAM) in an 8-year-old boy previously treated by a combination of radium and radioactive phosphorus applicator on a malar haemangioma.

Among the 1350 patients examined at IGR, 2 were treated for a haematological malignancy: 1 for Hodgkin's disease and 1 for Burkitt's lymphoma. They were both in the radiation-treated group.

DISCUSSION

This study has two main characteristics. First, it was not a registry-based study but a recall programme which included the examination of each patient who responded to a recall letter. It is noteworthy that 22% of the 6229 patients who were sent a recall letter accepted to return to the IGR for evaluation of angioma treated 12–30 years earlier; these results are encouraging for other long-term treatment evaluations which now appear necessary in medicine. However, this response rate is low and we cannot exclude a recall bias in that participants had more severe long-term effects and were therefore more willing to participate. Nevertheless, our data were obtained on the largest population with angiomas (1345 patients) reported so far [16, 17].

Secondly, the radiation dose delivered to two organs (skin and thyroid) was systematically recalculated. Even dated medical records at IGR allowed an accurate recalculation of doses as in the study of De Vathaire *et al.* [18] which seemed to be difficult in other series [19].

To our knowledge the development of CRD after low-dose radiation treatment of angiomas has been the subject of only two reports. Braun Falco *et al.* [16] reported radiation sequelae in 23% of 495 irradiated haemangiomas examined 2 years after contact radiation therapy. They found radiation sequelae in patients who had received a dose below 10 Gy and the risk of radiation sequelae increased with higher doses. Bekerus [17] reported radiation sequelae in 38% of 200 haemangiomas followed up for at least 8 years after ^{90}Sr radiation treatment. The percentage of cutaneous dystrophy in our exposed group (81%) is higher and may be explained by a longer follow-up (> 12 years) since cutaneous radiation sequelae are well known to increase with time. Dose recalculation confirmed that the risk of superficial components of CRD (telangiectasia, hypopigmentation and hyperpigmentation, epidermal atrophy) and overall risk of dystrophy increased with incremental surface skin doses starting from the defined reference dose (i.e. 10 Gy). Likewise the risk of developing the three deep components of CRD (subcutaneous atrophy, sclerosis, alopaecia) was accentuated by an increased dose at 10 mm in depth starting from the defined reference dose (i.e. negligible dose). Among the 181 patients treated with surface skin doses of 10 Gy or less, 31% had all CRD components, which is in agreement with the results of Braun Falco *et al.* [16]. These results differ from the conclusion of Sulzberger *et al.* [20] and Rowell [21, 22] that there is a cumulated threshold dose of 10–14 Gy for fractionated superficial Roentgen ray therapy resulting in CRD for higher doses and no sequelae for lower doses.

Since 1902, skin cancers have been reported within treatment sites after radiation treatments for neoplasia or benign conditions [23]. These tumours were mainly cutaneous carcinomas, either squamous cell carcinomas (SCC) or BCC, which are predominant in several reports [24–28]. At least 13 out of the 14 BCC in the present series seemed to be related to radiation therapy when three factors are considered: (1) the young age of the patients: at least 11 of 1137 treated patients between 25 and 34 years of age developed a BCC during the follow-up. (2) Location in treated sites, whether on sun-exposed skin or on covered areas: BCC did not occur predominantly in the sun-exposed areas (i.e. head and neck). This suggests the lack of a significant additional influence of ultraviolet radiation which was discussed by Shore *et al.* [26], whose patients were irradiated for ringworm of the scalp. Moreover, there was no difference between sun-reactive skin types in treated patients with or without BCC. These results differ from other studies demonstrating that fair-skinned persons could be at increased risk of developing skin carcinomas after low-dose radiation treatment [19, 27]. (3) 2 patients had two BCC in the same treated area: the incidence of multiple BCC has been mentioned by other authors [19, 26] as an indicator of radiogenic skin carcinoma.

Most types of radiation seemed to increase the risk of developing cutaneous carcinomas. This increased risk was initially reported with X-rays, but later low energy radiation and grenz rays [29] were also incriminated. In this respect patients who received betatherapy were considered to be at low risk of secondary carcinoma [10]. The present series demonstrates that all qualities of radiation, ^{90}Y perhaps excluded, confer a risk of cutaneous carcinoma. Rowell [21] reported that the most important risk factor in patients with radiation-induced skin cancer was the total accumulated dose. However, according to Albert and Shore [30] no diminution in the effect was found for doses below 4 Gy. In our series, doses at skin level had the highest value. No BCC was observed for doses of 10 Gy or less whereas 8 BCC occurred for doses higher than 30 Gy. On the other hand, no relation could be found with increasing doses at 10 mm in depth.

As this series also showed that risk of CRD increased with higher doses, it is noteworthy that some BCC were observed without clinical evidence of CRD. Chronic radiodermatitis was long thought to be a prerequisite for the induction of skin cancer, but documentation now exists that BCC may occur in skin with little or no evidence of radiation skin damage (namely after multiple chest X rays) [30].

The interval between irradiation and evaluation seems to be of crucial importance. Some studies have concluded that there is an absence of excess skin cancers after short intervals of follow-up: 9 years, according to Sulzberger *et al.* [20]. In the present series, 8 patients had BCC between 20 and 30 years after irradiation treatment. However, the mean delay of follow-up for the exposed patients was only 19 years. Greater number of cutaneous carcinoma are to be expected in our patients in future because the median latency period between the last treatment exposure and the development of skin cancer has been estimated to be 31 [17], 33 [26] or 43 years [25].

Most of the 431 patients of the thyroid subgroup had received a radiation dose below 1 Gy. Among these patients, 99% were euthyroid and 12 developed a cold nodule, one of which was malignant. No thyroid cancer was observed in the 11 patients with cold nodules who received a dose below 1 Gy for a follow-up period of 20 years. The only case of thyroid cancer was found in the group of 7 patients who had received a thyroid dose above 1 Gy. This is in contrast with other studies. Following thymus irradiation, Shore *et al.* [31] found 30 thyroid cancers and 59 benign thyroid adenomas in 2650 irradiated patients, 62% of whom had received a thyroid dose below 500 mGy, while 1 thyroid cancer and 8 thyroid adenoma were observed in 4800 sibling controls. As suggested by these authors, it is possible "that the mean large radiation doses to the thymus during infancy may have diminished immunocompetence, thereby increasing susceptibility to cancer induction". For an estimated dose as low as 91 mGy, Ron *et al.* [32] found a 4-fold increase in the risk of thyroid cancer among 10 804 persons irradiated for scalp tinea during childhood as compared to control groups. However the dosimetry of this series is based on a mean retrospective evaluation and questionable with regard to head size, accurate positioning of the ports, squirming of the child and or shield slippage during treatment. More recently Holm *et al.* [33] did not find any increased risk for thyroid cancer after small doses of ^{131}I which delivered to the thyroid gland a mean dose of about 500 mGy. Although no morphological abnormality was found in 98% of our patients, most of them (92%) had a decrease of their thyroid iodine content, and a raised serum Tg level was observed in 17%. This may confer a high risk of subsequently developing thyroid nodules [34]. These patients should be carefully followed because the length of follow-up for our population is short (21 years) compared to other studies (30 years).

In conclusion, there is a risk of radiogenic epithelial skin carcinomas after radiation treatment of cutaneous hemangiomas even after betatherapy. These results confirm that radiation therapy should systematically be avoided for these benign vascular cutaneous diseases. A lifelong follow-up of this cohort population should be recommended, given that cutaneous carcinomas tend to be characterised by a long period of latency. Furthermore, additional information on the significance of the increase of serum Tg level and decrease of thyroid iodine content in the thyroid nodule development will be obtained in the thyroid-exposed group.

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Phase I Study of Vintriptol, a Tryptophan Ester of Vinblastine

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Vintriptol, a tryptophan ester of vinblastine, is a new vinca alkaloid derivative. Preclinical studies have demonstrated its antitumour activity in a large variety of animal models. In this phase I study, 47 patients with advanced cancer were exposed to escalating doses of vintriptol, starting at 6 mg/m² and following a modified Fibonacci schedule. The drug was administered as an intravenous push on a weekly schedule. Myelosuppression was the dose-limiting toxicity and the maximum tolerated dose was 45 mg/m². Other toxicities consisted of mild nausea and vomiting and the occurrence of fever and dryness of the mouth immediately after drug administration. Neurotoxicity, a major side-effect of other vinca alkaloids, was insignificant. 1 partial remission in a patient suffering from colorectal cancer and 1 minor response in a patient with a metastatic tumour of the cutaneous appendagous glands were documented. Pharmacokinetics of vintriptol were evaluated at the highest dose levels. A dose schedule of 40 mg/m² vintriptol per week is recommended for phase II studies.
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INTRODUCTION

VINCA ALKALOIDS rank among the main groups of anticancer agents because of their broad spectrum of activity and their unique mechanism of action. Vintriptol N-(deacetyl-0-4-vinblastinoyl-23)-L-ethyl tryptophanate methane sulphonate was synthesised in order to increase the therapeutic ratio of vinca alkaloids by diminishing myelosuppression and neurotoxicity. It is the ethyl ester of L-tryptophan and the sulphate of an alkaloid, vincaleukoblastine or vinblastine.

Vintriptol (MW base 969) is obtained by preparation of a monohydrazide of vinblastine, the formation of an acid and then the coupling of the tryptophan ethyl ester at the C23 position.

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Preclinical studies [1–3] have demonstrated that the overall toxicity of the compound is at least five times less than vinblastine. When compared at optimal doses, vintriptol was at least as effective as vinblastine against murine tumours such as F388 and L1210 leukaemias, B16 melanoma, Lewis lung carcinoma and C26 colon carcinoma.

In a phase I study, Ceulemans *et al.* [4] treated 20 patients with advanced cancer with doses ranging from 2.5 mg/m² to 30 mg/m². Main side-effects were dryness of the mouth occurring immediately after administration of the drug and myelosuppression. Leucopenia seemed to be the dose-limiting factor, emerging at a dose of 20 mg/m². At 30 mg/m², the maximum dose reached, white blood count values lower than 2×10^9/l were not observed. Neurotoxicity was insignificant. 2 cases of disease stabilisation were observed in patients with non-small cell lung cancer.

In this study, the maximum tolerated dose (MTD) had not been reached and we therefore performed a further phase I study to determine this.