Eur J Cancer Clin Oncol, Vol. 19, No. 8, pp. 1081–1086, 1983.
Printed in Great Britain.

0277-5379/83$3.00+0.00

Radiation-induced Head and Neck Tumours: Is the Skin as Sensitive as the Thyroid Gland?*

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Abstract—*Six hundred and five persons, randomly selected from a cohort of* 2400 *patients who had been irradiated* 16–46 yr *previously for benign diseases in the head and neck region, were traced, recalled and examined for radiation-associated tumours. Three hundred and sixty-seven patients were alive,* 179 *had died and* 66 *had emigrated. Two hundred and fifty-seven patients were clinically examined,* 87 *refused or were not able to participate and* 16 *could not be contacted. Eighteen of the clinically examined patients had been or were being treated for* 20 *skin carcinomas with a mean latency of* 37 yr. *In this group only* 7 *carcinomas of the thyroid gland were observed, with a mean latency of* 38 yr. *Eleven carcinomas of the skin and* 3 *of the thyroid gland were reported in the group which was examined by means of questionnaires. The observed number of carcinomas of the skin is higher than expected according to the dose-effect relationship of UNSCEAR, whereas the number of carcinomas of the thyroid gland is lower. It is concluded that there might be less difference in susceptibility for the induction of tumours by ionizing radiation between the skin and the thyroid gland than is commonly assumed.*

INTRODUCTION

QUANTITATIVE data on human radiation-induced carcinomas have recently become available. The thyroid gland is reported to be the most susceptible organ in the head and neck region [1, 2]. Within the first 25 yr after exposure 50–150 carcinomas/10^4 persons/Gy would be expected in this organ.

For the skin of the head and neck region, UNSCEAR has reported 2–10 carcinomas/10^4 persons/Gy [1]. Forty years ago the main indications for radiotherapy of the head and neck region were tuberculous lymphadenitis, enlarged tonsils, laryngeal papillomas and other benign diseases. A pilot study was undertaken to assess the risk of these patients for late effects and particularly radiation-induced cancer. We were able to initiate this study at the Department of Radiotherapy of the University Hospital in Leiden since all the irradiation records from 1920 were available. This paper reports the differences in the rates of induced carcinomas in the skin and thyroid gland and those expected on the basis of the UNSCEAR data [1].

MATERIALS AND METHODS

Between 1920 and 1963 about 5000 patients were irradiated in the Department of Radiology for benign diseases in the neck and head region. Nearly all patients had been treated with orthovolt X-rays of approximately 1 mm Cu h.v.l. The irradiation fields measured mostly 6×8 or 8×10 cm^2. Some patients with a hemangioma had been irradiated with softer X-rays (1.2 mm AL h.v.l.) or with radium needles. The fraction doses ranged from 0.7 to 4.0 Gy. The dose and number of fractions depended on the effect of the treatment. The period between consecutive pairs of fractions lasted 3–4 weeks. The median overall treatment time was about 150 days. For this study

Accepted 17 February 1983.
*This study was financially supported by the Koningin Wilhelmina Fonds, Netherlands Cancer Research Fund.

the treatment method was reconstructed and the dose distribution recalculated for each patient as precisely as possible. Because the thyroid gland is a paired organ the dose in the reference point R (Fig. 1) was used. The mean dose in Sr was the same as in R. The mean dose in Sl was 0.5 Gy higher than in R. Because the enlarged tuberculous lymph nodes changed the diameter of the neck and the dose distribution, a standard correction factor was applied to these cases (Fig. 1).

The irradiation apparatus was calibrated for the first time in 1932. Therefore the patients irradiated between 1920 and 1932 were excluded from the study since it was not possible to estimate the applied dose in this group. Furthermore, about 1600 patients who had been irradiated for arthrosis of the cervical spine were excluded because of their advanced age and correspondingly high mortality. A cohort of about 2400 patients remained available for the study. From these patients a random sample of 605 patients (279 males and 326 females) was selected, traced and, if possible, recalled for examination. Table 1 shows some characteristics of these 605 patients, subdivided according to indication for irradiation and whether we could trace them for examination.

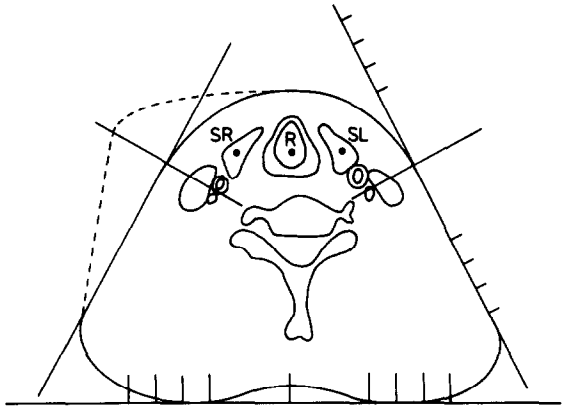

Fig. 1. Cross-section at the level of the thyroid gland with reconstruction of the treatment fields.

Three hundred and sixty patients were still alive and still in the Netherlands. One hundred and seventy-nine patients had died and 66 had emigrated. The last group has not been traced. Two hundred and fifty-seven of the 360 living patients consented to participate in a clinical examination and 87 refused. Only 16 patients did not respond to our invitation letter or phone call. These 16 patients form together with the 66 emigrated persons the group of 82 non-contacted patients (Table 1). The 257 patients who participated in the clinical examination were seen separately by a radiotherapist, a dermatologist, an endocrinologist and an otorhino-laryngologist. All patients underwent a scintigraphic examination of the thyroid gland with 5 mCi 99-Tc pertechnetate. One anterior and two oblique views were interpreted without knowledge of the result of the palpation.

Patients were advised to have a subsequent examination if signs of a malignant tumour were observed. In case of lesions in the skin, the mouth and the throat, a biopsy was taken. Palpable nodules or cold lesions on the scintigram bigger than 1 cm were considered to be an indication for detailed examination in the Department of Endocrinology. If cold lesions on the scintigram did not correspond with palpable nodules, the examination was repeated after 6 months. The patients were referred after this second examina-

Table 1. Irradiation data per indication and tracing-group

	No. of patients	Dose in point R* (Gy)†	Age at irradiation (yr)	Follow-up period (yr)‡
Tuberculous lymphadenitis	410	11.7 (8.3)	24 (20)	34 (37)
Hyperthyroidism	73	20.1 (18.0)	35 (33)	35 (37)
Haemangioma	33	1.3 (0.5)	3 (0.3)	31 (32)
Enlarged tonsils	22	1.7 (0.7)	16 (14)	32 (31)
Others	67	5.3 (2.2)	28 (25)	27 (31)
Clinically examined	257	10.2 (7.0)	15 (14)	39 (37)
Refused	87	10.4 (6.0)	22 (20)	40 (41)
Non-contacted	82	9.1 (6.1)	22 (18)	39 (37)
Died	179	13.6 (9.3)	40 (39)	22 (22)
All patients	605	11.1 (7.1)	25 (22)	33 (36)

*R(eference) point in the midline at the level of the vocal cords (Fig. 1).

†Mean values, median values in parentheses.

‡For the dead patients the number of years from the first irradiation until the year of death, and for the other patients until 1979.

tion if the lesions had grown. The same indications for explorative surgery of the thyroid gland were applied in these patients as for non-irradiated patients with thyroid nodules. At explorative surgery only the lobe with macroscopic abnormalities was removed. If the nodule proved to be a carcinoma, total thyroidectomy followed. If papillary carcinomas smaller than 1 cm were found in one lobe and the other lobe was normal on palpation, surgery was confined to hemithyroidectomy, this being a safe procedure. All biopsies and surgically removed tissues were examined by the same pathologist.

Patients who refused or who were not able to participate in the clinical examination were asked to answer a questionnaire concerning their state of health and tumours in the head and neck region. Relevant data were verified in hospital records. Causes of death were traced in the records of the University Hospital or the Central Registry of Death Certificates.

RESULTS

The clinically examined patients

Ten of the 257 clinically examined patients had been treated for skin carcinomas in the past. The mean latency between the irradiation and skin cancer treatment was 35 yr (range 21–43 yr). All these tumours were basal cell carcinomas except one (squamous cell carcinoma, Table 2). During the present examination new tumours were observed in 8 other patients. The mean latency for these tumours was 43 yr (range 23–47 yr). The diameter ranged from 3 to 10 mm. Three patients with a skin carcinoma had a slight, 5 a moderate and 3 a severe röentgen dermatitis. The skin of two patients showed no signs of dermatitis. Five patients had undergone a skin transplantation. The tumours appeared in the skin of the main treatment field and not in the skin of the exit beams. Twenty-five patients had been operated upon for thyroid nodules previously. The mean latency between the irradiation and the operation was almost 30 yr (range 13–43 yr). In three patients the nodule had been extirpated; in 10 patients a hemithyroidectomy and in 8 patients a near-total thyroidectomy had been performed. Four patients had undergone a total thyroidectomy. Histological slides were not available for revision in 7 cases. In 3 of these 25 patients a carcinoma had been observed, 2 of the papillary and 1 of the follicular type (Table 2). In almost all removed thyroid glands nodular hyperplasia was present. In 10 of the previously operated patients nodules were observed once again during the present examination. In 52 patients nodules were detected for the first time. All 62 patients with nodules at this examination were referred to the Department of Endocrinology. Not included in this group are 26 persons with nodules which were active or smaller than 1 cm, which could not be palpated and had not grown within 6 months. Twenty-nine of the 62 referred patients were operated upon, of which 4 had previous surgery. The mean latency was 42 yr (range 26–47 yr). In 17 patients a hemithyroidectomy, in 5 patients a near-total thyroidectomy and in 6 patients a total thyroidectomy was performed. In 1 patient no nodule was found in the thyroid gland, but there proved to be an adenoma of one of the parathyroid glands. The remaining 33 patients with thyroid nodules were not operated upon because of their advanced age (>70 yr, 3), refusal (14) or lack of indication (16), e.g. after cytologic examination. Only 4 of the 29 operated patients proved to have a carcinoma; in 2 cases this was smaller than 0.5 cm and of the papillary type. One patient had a multicentric follicular carcinoma (largest diameter 1.5 cm) and in a fourth patient a diffusely growing papillary carcinoma was observed. In three cases an adenoma and in the remaining 22 patients mainly nodular hyperplasia was seen. Eight patients with

Table 2. Numbers of patients with malignant tumours in the irradiated region

	257 clinically examined patients		49 questionnaires
	<1979	≥1979	
Skin			
Squamous cell carcinoma	1		
Basal cell carcinoma	9 (10)	7 (8)	6 (11)
m. BOWEN		1	
Thyroid gland carcinomas ≥1 cm	3	2	
<1 cm		2	3
Ear-nose-throat carcinomas	2		1

Some patients had more than one skin tumour. The total number of tumours is given in parentheses.

Two patients who developed tumours in more than one organ are mentioned 2 or 3 times.

thyroid nodules had a skin malignancy simultaneously. Three patients had been treated for tumours of the salivary glands or larynx after a mean latency of 38 yr. There were no malignancies detected in this region as a result of the present examination. In Table 3 some relevant characteristics of the patients with a malignancy of the thyroid gland or the skin are compared with the group without such a tumour. In the groups with tumours we saw more females, younger patients, higher doses and a longer follow-up period than in the other groups.

The non-examined patients

Forty-nine of the 87 patients who refused the clinical examination provided us with useful information. Six of them had been treated because of skin malignancies in the irradiated field. One patient had been treated consecutively for 6 basal cell carcinomas between 31 and 47 yr after the exposure.

Ten patients in this group were known to have diseases of the thyroid gland. Seven had been operated upon after a mean latency of 32 yr (range 26–40 yr). Revising the slides, the pathologist detected 3 papillary carcinomas smaller than 0.5 cm which were not diagnosed at the original examination (Table 2). In this group 2 benign tumours of one of the parotid glands were observed. The previously mentioned patient with 6 basal cell carcinomas had also been treated for an epidermoid carcinoma of a minor salivary gland. We succeeded in tracing the cause of death of 149 of the 179 patients (Table 4). The 30 remaining patients had died before 1950, the year the central registration of causes of death started. Between the irradiation and death a mean time elapsed of 22 yr, and of 24 yr for 10 patients who died of a malignant tumour in the head and neck region. In most cases no slides were available for revision.

Table 4. Causes of death

Malignant tumour	
Outside irradiated region	37
Inside irradiated region	
Larynx-pharynx	3
Thyroid gland	2
Bone	2
Parotic gland	1
Unknown origin	2
Other diseases	102
Unknown	30
Total	179

DISCUSSION

Two divergent problems have been identified in this study, namely that the incidence of irradiation-induced thyroid carcinoma is lower and that of skin cancer is higher than reported.

The prevalence of carcinomas of the thyroid gland, salivary glands and the skin in the neck region is so low that we should expect less than one of each of these carcinomas in the examined group of 257 people [3, 4]. An exception would have to be made for papillary thyroid carcinomas smaller than 1 cm. The prevalence of these tumours in healthy persons can amount to 9%, or even to 17 and 24% in Japan and Hawaii, if the glands are examined exhaustively [5]. Two of the 7 thyroid carcinomas in the clinically examined group of the present study were smaller than 1 cm, which may be considered a normal prevalence. The remaining 5 thyroid carcinomas and the other carcinomas may be attributed to the irradiation. On the basis of the dose–effect relationships published by UNSCEAR [1], we would expect to find in the group of 257 examined patients about 10–30 carcinomas of the thyroid gland, 1–5 carcinomas of the skin and about the same number of carcinomas of the salivary

Table 3. Characteristics of the patients with and without carcinomas of the skin or the thyroid gland in the clinically examined group

	Skin		Thyroid gland	
	With tumour ($n = 18$)	Without tumour ($n = 239$)	With tumour ($n = 7$)	Without tumour ($n = 250$)
Sex: female/male	1.6	1.0	2.5	1.0
Age at irradiation (yr)	20.5 (12)*	15.5 (15.0)	10.4 (9.0)	15.6 (15.3)
Dose point R (Gy)	19.5 (12)	10.0 (7.2)	20.7 (25.7)	10.4 (7.3)
Dose skin (Gy)	32.8 (25)	19.2 (15.2)	40.5 (47.3)	19.4 (15.2)
Latency (yr)	37 (41)		38 (41.0)	
Follow-up (yr)	43 (44)	38 (37.0)	43 (44.0)	38 (37.0)

*Mean values, median values in parentheses.

glands. The numbers of 7 carcinomas of the thyroid gland (of which two were smaller than 1 cm) and 18 patients with 20 skin carcinomas are not in accordance with these expectations. This is especially true if we take into account the length of the follow-up period. The dose–effect relationship of UNSCEAR holds true for the first 25 yr after exposure. After this period an equal number of carcinomas per unit time would be expected. In the present study the mean latency of the thyroid carcinomas was 37 yr. Only one carcinoma was detected within 25 yr after the irradiation. The numbers of 2 salivary gland carcinomas and 1 larynx carcinoma are too small to draw conclusions.

Possible explanations for the differences between the observed and the expected numbers of carcinomas should be mentioned. Firstly, the dose–effect relationships of UNSCEAR for thyroid carcinomas are based upon studies with a wide divergence in patient selection and methods of examination. Sometimes doses could not be calculated or estimated. In one study only nodules larger than 2 cm were surgically explored [6], while in other studies thyroidectomy was performed for slight cold spots on the scintigram. More than 80% of the carcinomas reported by Favus *et al.* were smaller than 1.5 cm [7], whereas all the tumours reported by Parker *et al.* were larger than 2 cm [6]. If we only considered tumours in excess of 1.5 cm, our number of 5 of 257 patients (1.9%) would exceed the number of 11 of 1056 (1.1%) found by Favus *et al.* [7]. The chance of finding small carcinomas increases if a greater part of the gland is removed. Most of our patients had only a hemithyroidectomy whereas, for instance, nearly all the patients reported by Refetoff *et al.* underwent a total thyroidectomy [8].

Another explanation for our low number of thyroid carcinomas might be found in the selection of patients. Less than half of the sample of 605 persons were clinically examined. Therefore it cannot be excluded that many tumours have accumulated in the groups of non-contacted and deceased patients. Furthermore, only 29 of the 62 patients referred with thyroid nodules were operated upon. This means that some carcinomas have probably been missed. But even if we assume that in these 33 patients as many carcinomas have been induced as in the operated group, our total number of carcinomas larger than 1 cm does not exceed the lowest expected number of 10.

If we compare our patients and irradiation data with those of other studies, some differences are striking. The mean age of first irradiation in the clinically examined group was 15 yr and in the sample 25 yr. In Japan and on the Marshall Islands a higher risk has been calculated for persons between 10 and 18 yr at exposure compared to other ages [9]. It is clear that this could not be the cause of our low number of thyroid carcinomas. We can find more plausible explanations in the irradiation data. The mean dose in the thyroid gland of the clinically examined patients was about 10 Gy and the median dose 7 Gy. These doses were applied in 7–10 fractions. In most cohorts studied for radiation-induced tumours the dose ranged from 5 to 15 Gy [10]. In this respect, our patients do not differ from those from other studies. But unlike elsewhere, the overall treatment time for our patients was rather long. The mean treatment period exceeded 200 days and the median time was about 150 days. Mostly, 3–4 weeks elapsed between 2 pairs of fractions. The induction of tumours must take place in the cells damaged at the sublethal level. This damage can be repaired in the interval between fractions. Our low number of thyroid carcinomas could be explained if we assume that with larger time intervals between fractions the risk of tumour induction decreases because of increasing repair of sublethal damage. This mechanism has been postulated for human thyroid carcinomas by Hempelmann [11]. Finally, we should consider the possibility that the thyroid gland has not always been in the direct beam. In most patients we could check the position of the irradiation fields with the scar of the lymphadenitis or the röentgen dermatitis, but in some patients this check was impossible.

The above-mentioned possible reasons for the low number of induced thyroid carcinomas cannot explain the high number of skin carcinomas we observed. It is evident that the skin is easier to examine than the thyroid gland. All newly discovered skin carcinomas were smaller than 1 cm. In this respect we should compare the number of tumours in the thyroid gland and in the skin with restraint. If we compare our number of skin tumours with those of other studies it is difficult to believe that the differences could be explained by the methods of examination. UNSCEAR suggests that the skin might be less sensitive for the induction of tumours or that the latency for these tumours could be longer than the follow-up periods in most studies. Spittle observed a very long latency of 41.5 yr after treatment for tinea capitis [1]. No studies have been published with as many irradiation-associated tumours as we found. Only the number of 5 carcinomas in 100 patients reported by Rowell approximates our finding of 18 patients with 20 carcinomas in 257 examined patients [12]. Our mean latency of 37 yr seems to confirm the suggestion of UNSCEAR that the latency for skin

carcinomas could be longer than for induced carcinomas in other organs. But on the other hand, the latency for our thyroid carcinomas was as long as for the skin tumours. If we consider the tumours in the clinically examined group of 257 persons and we use the median doses of 15.5 Gy in the main skin field and of 7.0 Gy in the thyroid gland, then the number of 20 skin carcinomas and of 7 thyroid carcinomas would correspond with a dose–effect relationship of 50 and 40 carcinomas/10^4 persons/Gy respectively for a follow-up period of 39 yr.

These figures are not comparable without the mentioned limitations. However, we can conclude that there is less difference in susceptibility for radiation-induced tumours between the thyroid gland and the skin than suggested by UNSCEAR in 1977.

As a conclusion, we can say that (1) the observed differences in dose–effect relationship for induced thyroid gland carcinomas between the studies in Leiden and elsewhere may be attributed to differences in patient selection, methods of study and overall treatment time; and (2) there might be less difference in susceptibility for the induction of tumours by ionizing radiation between the thyroid gland and the skin than suggested by the dose–effect relationships of UNSCEAR.

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