Acta Radiologica Oncology 21 (1982) Fasc. 5

FROM THE DEPARTMENTS OF CLINICAL ONCOLOGY, ENDOCRINOLOGY, OTORHINOLARYNGOLOGY AND CHEMICAL PATHOLOGY, UNIVERSITY HOSPITAL LEIDEN, 2333 AA LEIDEN, THE NETHERLANDS.

PRIMARY HYPOTHYROIDISM AS A COMPLICATION AFTER TREATMENT OF TUMOURS OF THE HEAD AND NECK

J. M. A. DE JONG, W. A. J. VAN DAAL, J. W. F. ELTE, G. J. HORDIJK and M. FRÖLICH

Hypothyroidism is a well-documented complication after treatment with ^{131}I or external irradiation applied locally (MAXON et coll. 1977). The incidence of hypothyroidism after external radiation therapy for head and neck tumours, either with or without surgery, varies widely in the literature. After irradiation followed by laryngectomy and hemithyroidectomy, SHAFER et coll. (1975) reported hypothyroidism in about 50 per cent of the cases, whereas KOULUMIES et coll. (1964) found no distinct dysfunction of the thyroid gland in patients only irradiated. During follow-up of patients treated for a head and neck tumour in this hospital, hypothyroidism has not been considered as a complication. In order to establish the frequency of thyroid gland dysfunction, and in particular hypothyroidism, 100 patients treated for a tumour of the head or neck were investigated.

Material and Methods

In March and April of 1980, thyroid gland function was evaluated on the basis of the levels of thyroid stimulating hormone (TSH) and thyroxine (T_4) in the serum in 100 successive patients being followed up in the combined out-patient clinic of the Departments of Otorhinolaryngology and Radiation Therapy of this hospital. The determinations were made with commercially available kits (TSH: Serono; T_4: Clinical assays; normal values: TSH < 8.0 mU/l and T_4 70–160 nmol/l). Deviating values were redetermined and none of the values had to be changed. Patients with a T_4 value < 70 nmol/l and TSH > 8.0 mU/l, or only TSH > 8.0 mU/l, were referred to the Department of Endocrinology for further analysis. An endocrinologist participated in the evaluations of all patients. The series comprised 88 men and 12 women aged between 14 and 94 years (mean 65 years) with a follow-up period of between 3 and 137 months (mean 40 months). In 34 patients the duration of follow-up was less than one year (Figure). The primary tumour was located in the larynx in 78 patients, the nasopharynx in 5, the oropharynx in 5, the hypopharynx in 5, and in other sites in 7 patients. In no case had the tumour extended to the thyroid gland, and no patient had been previously treated for abnormalities of the thyroid. At follow-up, no recurrences were found, and no anomalies of the thyroid gland were found at palpation of the neck.

All patients had been irradiated. The primary treatment was irradiation alone in 60, 40 of them only irradiated cranially from the caudal side of the cricoid cartilage and the other 20 also below that level. In 4 cases with recurrent tumour after irradiation laryngectomy had been needed for cure, leaving the thyroid gland intact; only one of these 4 was irradiated caudal to the cricoid. Thirty-six patients

Accepted for publication 18 May 1982.

Table 1

Relevant data on 8 patients with hypothyroidism

Sex and age at irradiation (years)	Follow-up (months)	Thyroxine (nmol/l)	Triiodo-thyronine (nmol/l)	Thyroid stimulating hormone (mU/l)	Triiodothyronine resin uptake (per cent)
M 56	15	59	2.8	24	26.7
M 65	27	54	1.9	39	26.6
M 58	16	30	2.9	32	20.8
F 50	58	23	2.5	200	21.6
M*39	72	14	1.6	150	22.3
M 76	66	46	1.9	30	Not done
M 71	36	66	2.7	170	15.2
M 63	43	50	2.5	36	18.3

* No surgical removal of part of the thyroid gland.

Table 2

Form of treatment and occurrence of thyroid dysfunction

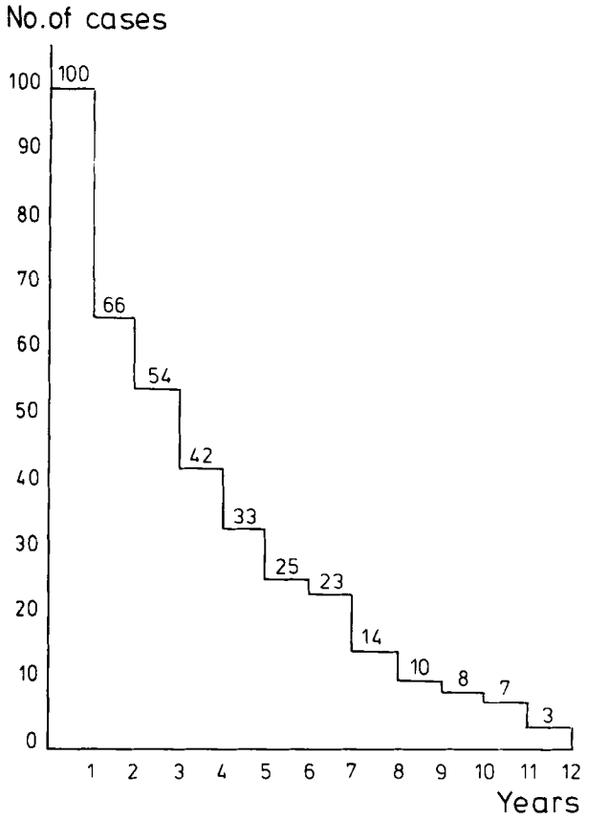
Treatment	No. of cases	Normal thyroid function	Solitary elevated TSH	Hypo-thyroidism
Irradiation alone, above cricoid	40	40	0	0
Irradiation alone, above and below cricoid	20	19	1	0
Irradiation, laryngectomy (thyroid intact)	4	4	0	0
Irradiation and primary surgery (thyroid intact)	11	10	0	1
Irradiation, surgery and removal of part of thyroid	25	15	3	7
Total	100	88	4	8

Table 3

Duration of follow-up and occurrence of thyroid dysfunction

Treatment	Follow-up (years)	No. of cases	Normal thyroid function	Solitary elevated TSH	Hypothy-roidism
Irradiation and surgery (thyroid intact, n=11)	<1	1	1	0	0
	>1	10	9	0	1
Irradiation, surgery and removal of part of thyroid (n=25)	<1	8	8	0	0
	>1	17	7	3	7

were treated with a combination of surgery and irradiation, in 27 cases according to the sandwich method, i.e. 20 Gy in 2 weeks—surgery— 40 Gy in 4 weeks (HORDIJK 1977). In this group a hemithyroidectomy was performed in 17 cases. The other 9 patients received radiation therapy either pre- or postoperatively, and 8 of them underwent hemithyroidectomy. The total dose was 60 Gy in 6 weeks for 94 patients, 45 Gy in 4.5 weeks for 5 patients, and 30 Gy in 2 weeks for one patient. Irradiation was performed with megavolt apparatuses and normal fractionation, usually 2 opposing lateral fields being used. The dose was specified in the midline. Dose planning was done for each patient individually. All fields were checked by simulation. Fixation by a mould was used in most of the cases.



Duration of follow-up.

Results

Primary hypothyroidism was found in 8 of the 100 patients (Tables 1, 2). The hypothyroidism had not led to any complaints, except for fatigue and chilliness, which were improved by substitution therapy with desiccated thyroid (Thyranon, Organon, Holland) or thyroxine (Thyrax, Organon, Holland). Four patients had a single elevated TSH value (Table 2). Irradiation exclusively above the cricoid level (40 patients) caused no functional disturbances. One of the 20 patients also irradiated caudal to the cricoid had an elevated TSH level. Irradiation alone did not cause hypothyroidism. Laryngectomy for recurrent tumour leaving the thyroid gland intact and performed after irradiation did not lead to functional disturbances in the 4 patients. Primary combination of irradiation and surgery led to hypothyroidism in 8/36 (22%) and additionally in 3/36 (8%) to a solitary increased TSH value. When hemithyroidectomy was performed as well, these figures were 7/25 (28%) and 3/25 (12%), respectively (Table 2).

All cases of dysfunction concerned patients with a follow-up of more than one year (Table 3), none being detected within the first year. Of the patients with a hemithyroidectomy and a follow-up period of more than one year, 7/17 (41%) developed hypothyroidism and 3/17 (18%) had a solitary elevated TSH value (Table 3); thus, a functional disturbance was found in 10/17 (59%). For the combination of surgery and irradiation, with the thyroid gland left intact, this rate is distinctly lower after at least one year of follow-up, i.e. 1/10 hypothyroidism. A relationship between the severity of the hypothyroidism and the duration of follow-up was not found.

For patients treated according to the sandwich method and also operated upon with hemithyroidectomy, a difference was found between the duration of the interval between the operation and postoperative irradiation on the one hand and the occurrence of hypothyroidism on the other. This concerns patients with a follow-up period of more than one year. The mean interval for patients who developed hypothyroidism was 31 days (median 22 days). In cases with a normal thyroid function, the mean interval was 49 days (median 40 days).

Discussion

According to the literature, thyroid gland function is not reduced after irradiation of small laryngeal carcinomas (HORST-MEYER & VOLLMAR 1964, KOULUMIES et coll., GREIG et coll. 1965). This was confirmed in the present 40 patients irradiated only above the cricoid level, most of them for a small laryngeal carcinoma.

In view of the position of the thyroid gland, the bulk of which lies on an average at the level of the second and third tracheal rings (DELAND & WAGNER 1972), and the techniques currently used for irradiation, treatment of small laryngeal tumours will rarely lead to exposure of a large part of the thyroid gland to radiation. Thus, functional disorders are not to be expected. Under exposure of a large proportion of the thyroid gland during local irradiation, however, disturbances of function have been described. GLATSTEIN et coll. (1971) and MCHARDY-YOUNG (1969) found a slight reduction of the thyroid gland reserve without distinct hypothyroidism after the treatment of tumours of the head and neck. The present results seem to agree with theirs. Mantle irradiation in Hodgkin's disease, on the contrary, leads to a high percentage of functional disturbances: 4 to 25 per cent hypothyroidism and 13 to 44 per cent solitary TSH elevation (GLATSTEIN

et coll., FUKS et coll. 1976, SLANINA et coll. 1977, SCHIMPFF et coll. 1980). In view of the role of lymphangiography in the genesis of the dysfunction in this last group of patients (SMITH et coll. 1981), these findings are not comparable with those in patients with a head and neck tumour.

According to the literature, the combination of irradiation and surgery leads to hypothyroidism in 50 to 60 per cent of the cases when part of the thyroid gland is removed (MURKEN & DUVALL 1972, SHAFER et coll.). In the absence of excision of thyroid gland tissue, this percentage is about 20 (SHAFER et coll.). The higher rate of dysfunction cannot be ascribed to the operation only. Hemithyroidectomy in a euthyroid patient is followed by hypothyroidism in less than 7 per cent of the cases (YOUNG & MACLEOD 1972, GRIFFITHS et coll. 1974). However, the TSH level rises temporarily as a sign of stimulation (VEEN 1980). GREIG et coll. (1969) showed in rats that stimulation of the thyroid gland leads to cell division, which rarely occurs in the absence of a stimulus. Furthermore, GREIG et coll. (1969) and CROOKS et coll. (1964) found in the rat that an irradiated thyroid gland that is stimulated does not increase in weight due to reduced cell division, a dose-effect relationship was demonstrated. PHILP & MCINTOSH (1970) showed that this effect is still present after 12 months. O'CONNOR et coll. (1980) found, in addition, that in vitro, sheep thyroid gland cells are sensitive to radiation during division, in contrast with non-dividing cells. The increase in the incidence of dysfunction after radiation therapy combined with hemithyroidectomy might be explained by the assumption that injury inflicted by the preoperative irradiation occurs due to stimulation of the remaining part of the thyroid gland which results in loss of function of the gland. At postoperative irradiation, a certain amount of dividing cells and therefore sensitive thyroid gland tissue will be exposed, the amount depending on the duration of the delay after the operation. The difference found between the postoperative interval and the development or non-development of hypothyroidism in the present series seems to support this hypothesis.

Within the first year after treatment no functional disorders were found, whereas SHAFER et coll. reported that all cases with dysfunction occurred within 6 months. This discrepancy might be explained by the differences in the application of irradiation, i.e., only preoperative irradiation versus the sandwich method, which seems likely in terms of the hypothesis mentioned.

The administration of thyroxine during radiation therapy to prevent hypothyroidism, as proposed by SMITH et coll. for patients with Hodgkin's disease is questionable for this group of patients. Although postoperative irradiation of dividing thyroid gland cells will be avoided, stimulation of the remaining part of the gland would at most be postponed and damage would still occur.

In conclusion, it may be said that after only external irradiation for a head and neck tumour, with exposure of only a small part of the normal thyroid gland, hypothyroidism need not be expected, and also after irradiation of a large proportion of the thyroid gland only a small risk for hypothyroidism exists. On the other hand, when irradiation is combined with hemithyroidectomy, the rate of thyroid gland dysfunction increases to about 50 or 60 per cent. For prevention of side effects in the form of hypothyroidism, hemithyroidectomy is only acceptable when well indicated and postoperative irradiation should be performed with a considerable delay after the operation if part of the thyroid gland has been removed, contrary to common oncologic principles. Because of the difficult clinical diagnosis of hypothyroidism (WINTROBE et coll. 1974), particularly in a patient who has undergone laryngectomy, the thyroid gland function should be regularly evaluated during the follow-up of patients treated with combined irradiation and surgery.

SUMMARY

In 100 successive patients treated for tumour in the head and neck region, the function of the thyroid gland was evaluated during follow-up by determination of the serum levels of thyroid stimulating hormone and thyroxine. Radiation therapy alone did not lead to hypothyroidism, 4 patients had no dysfunction after laryngectomy for recurrent tumour after irradiation. Ten of 17 (59%) patients treated with irradiation and surgery including hemithyroidectomy and with a follow-up period of more than one year developed functional disturbance; in the absence of hemithyroidectomy one of 10. In patients who underwent hemithyroidectomy and developed hypothyroidism, the interval between surgery and postoperative irradiation was shorter than in those who did not develop functional disturbance (31 versus 49 days).

ACKNOWLEDGEMENTS

The authors would like to acknowledge the help of J. M. van de Linden-Waals and J. C. Rodenburg for preparing the manuscript.

REFERENCES

CROOKS J., GREIG W. R., MACGREGOR A. G. and MCINTOSH J. A. R.: A quantitative method of measuring the effects of X-irradiation on the growth and function of the rat thyroid gland. Brit. J. Radiol. 37 (1964), 380.

DELAND F. H. and WAGNER H. N.: Reticuloendothelial system, liver, spleen and thyroid. *In:* Atlas of nuclear medicine. Volume 3, p. 235. W. B. Saunders Company, Philadelphia 1972.

FUKS Z., GLATSTEIN E., MARSA G. W., BAGSHAW M. A. and KAPLAN H. S.: Long term effects of external radiation on the pituitary and thyroid glands. Cancer 37 (1976), 1152.

GLATSTEIN E., MCHARDY-YOUNG S., BRAST N., ELTRINGHAM J. R. and KRISS J. P.: Alterations in serum thyrotropin (TSH) and thyroid function following radiotherapy in patients with malignant lymphoma. J. clin. Endocr. 32 (1971), 833.

GREIG W. R., BOYLE J. A., BUCHANAN W. W. and FULTON S.: Clinical and radiobiological observations on latent effects of X-irradiation on the thyroid gland. J. clin. Endocr. 25 (1965), 1009.

— SMITH J. F. B., DUGUID W. P., FOSTER C. J. and ORR J. S.: Assessment of rat thyroid as a radiobiological model. The effects of X-irradiation on cell proliferation and DNA synthesis in vivo. Int. J. Radiat. Biol. 16 (1969), 211.

GRIFFITHS N. J., MURLEY R. S., GULIN R., SIMPSON R. D., WOODS T. F. and BURNETT D.: Thyroid function following partial thyroidectomy. Brit. J. Surg. 61 (1974), 626.

MCHARDY-YOUNG S.: Radiation-induced thyroid disease. Guy's Hosp. Rep. 118 (1969), 353.

HORDIJK G. J.: Behandeling van het larynxcarcinoom. (In Dutch.) Thesis, Leiden 1977.

HORST-MEYER H. ZUR und VOLLMAR R.: Kontrolle der Schilddrüsenfunktion unter hoher Tumorbestrahlung beim Larynxkarzinom mit Hilfe des Radiojodfunktionstestes. Rad. Biol. Ther. 5 (1964), 457.

KOULUMIES M., VOULTILAINEN A. and KOULUMIES R.: Effects of X-irradiation in laryngeal cancer on the function of the thyroid gland. Ann. Med. intern. Fenn. 53 (1964), 89.

MAXON H. R., THOMAS S. R., SAENGER E. R., BUNCHER C. R. and KEREIAKES J. G.: Ionizing irradiation and the induction of clinically significant disease in the human thyroid gland. Amer. J. Med. 63 (1977), 967.

MURKEN R. E. and DUVALL A. J.: Hypothyroidism following combined therapy in carcinoma of the laryngopharynx. Laryngoscope 82 (1972), 1306.

O'CONNOR M. K., MALONE J. F., MORIARTY M. and CULLEN M. J.: The radiobiological response of the thyroid. Brit. J. Radiol. 53 (1980), 135.

PHILP J. R. and MCINTOSH J. A. R.: The long term effects of X-radiation on the goitrogenic response of and iodide trapping by the rat thyroid. Amer. J. Roentgenol. 108 (1970), 386.

SCHIMPFF S. C., DIGGS CH. H., WISWELL J. G., SALVATORE P. C. and WIERNIK P. H.: Radiation-related thyroid dysfunction. Implications for the treatment of Hodgkin's disease. Ann. intern. Med. 92 (1980), 91.

SHAFER R. B., NUTTAL F. Q., POLLAK K. and KUISK H.: Thyroid function after radiation and surgery for head and neck cancer. Arch. intern. Med. 135 (1975), 843.

SLANINA J., MUSSHOFF K., RAHNER T. and STIASNY R.: Long-term side effects in irradiated patients with Hodgkin's disease. Int. J. Radiat. Oncol. Biol. Phys. 2 (1977), 1.

SMITH R. E. JR, ADLER R. A., CLARK P., BRINCK-JOHNSON T., TULLOH M. E. and COLTON TH.: Thyroid function after mantle irradiation in Hodgkin's disease. J. Amer. med. Ass. 245 (1981), 46.

VEEN H. F.: De schildklier na strumectomie. (In Dutch.) Thesis, Rotterdam 1980.

YOUNG H. B. and MACLEOD N.: The fate and function on the thyroid remnant. Brit. J. Surg. 59 (1972), 726.

WINTROBE M. M., THORN G. W., ADAMS R. D., BRAUNWALD E., ISSELBACHER K. J. and PETERSDORF R. G.: Harrison's principles of internal medicine. Seventh edition. McGraw-Hill, New York 1974.