

Thyroid function in survivors of cancer

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SUMMARY Thyroid function was assessed in three selected groups of children who had survived cancer. Children in group 1 had received radiotherapy to the thyroid area, group 2 had radiotherapy to the thyroid area and adjuvant chemotherapy, and group 3 had chemotherapy with or without radiotherapy away from the thyroid area. There were 75 survivors and 63 (40 boys, 23 girls) were available for study. Eighteen (29%) were found to have thyroid dysfunction, and these included all those who had had lymphangiograms or received a radiation dose greater than 40 Gy to the thyroid area. Only nine of the 18 children were already known to have thyroid dysfunction, and only 15 of 44 children who had had irradiation to the thyroid area had had their thyroid function examined.

This study shows that children who have received radiotherapy to the thyroid area should have their thyroid function assessed regularly. Chemotherapy does not appear to be a risk factor but longer follow up of these children is necessary.

The survival rates for childhood cancer have improved consistently over the last two decades and many children are now cured.¹ This improved prognosis follows intensive treatment with cyclical chemotherapy and high dose irradiation, but unfortunately this can also cause a number of side effects including thyroid dysfunction.²⁻⁶

This study reports the prevalence of thyroid dysfunction among the survivors of selected childhood cancers in the South West region of England. To evaluate its aetiology we have included children who had received various treatment schedules involving chemotherapy or radiotherapy, either alone or in combination.

Patients and methods

The children were the survivors of selected childhood cancer treated in the South West region of England. The population of this region is approximately 3 million and about 70 new patients with cancer are treated annually at the Bristol Children's Hospital Regional Oncology Centre.

Three groups were included in the study. Group 1 had received radiation fields that included the thyroid gland, but had not been treated with any chemotherapy; group 2 had received chemotherapy in addition to radiation involving the thyroid gland; and group 3 had received chemotherapy but any radiation field excluded the thyroid area.

There were 75 survivors of the cancers selected

for this study but only 63 children (40 boys and 23 girls) were included as four had left the area and in eight information on thyroid function could not be obtained.

Clinical data were extracted from the notes. Thyroid function was assessed by measuring serum thyroxine and thyroid stimulating hormone concentrations. Thyroxine was measured by radioimmunoassay and thyroid stimulating hormone by specific double antibody immunoradiometric assay. The normal range in our laboratory for thyroxine concentration is 65–170 nmol/l and for thyroid stimulating hormone <6 mU/l. Thyroid dysfunction was defined as either compensated hypothyroidism (raised thyroid stimulating hormone, normal thyroxine), primary hypothyroidism (raised thyroid stimulating hormone, low thyroxine), or secondary hypothyroidism (normal thyroid stimulating hormone, low thyroxine).

Most patients were treated with a cobalt machine, although a few were treated using a linear accelerator and some by electrons. Estimates of the irradiation dose to the thyroid gland were determined by reviewing the treatment plans and dose prescriptions. The absorbed dose outside the radiation beam was estimated using data from measurements of total scattered and leakage radiation in a water phantom.

Results

Eighteen (29%) children had evidence of thyroid

dysfunction: 10 (16%) with compensated hypothyroidism, and eight (13%) with primary hypothyroidism. None had secondary hypothyroidism. At the time of the study only nine of the 18 children were recognised as having thyroid dysfunction. The clinical data are listed in table 1.

Only 15 of 44 children at risk of developing thyroid dysfunction after radiotherapy to the thyroid area or lymphangiography, or both, had had their thyroid function assessed. Their mean age of follow up was 4.73 years (range 1.2–14.8).

RADIOTHERAPY GROUP

There were 11 children in this group: eight with medulloblastoma and three with Hodgkin's disease. The irradiation dose to the thyroid area varied from 30–40 Gy. Five (46%) children had thyroid dysfunction (table 1). There was no apparent difference in the age at diagnosis, irradiation dose, fractions of dose, or follow up between those who developed thyroid dysfunction compared with those with normal thyroid function.

CHEMOTHERAPY GROUP

There were 20 children in this group. They included four children with Hodgkin's disease, three with rhabdomyosarcomas, seven with Ewing's tumours, three with osteosarcomas, and three with acute myeloid leukaemia. The chemotherapy used included a combination of at least three of the following cytotoxic drugs: vincristine, cyclophosphamide,

doxorubicin, lomustine, actinomycin D, cytarabine, etoposide, ifosfamide, vinblastine, cisplatin, carboplatin, procarbazine, teniposide, dacarbazine, hydroxyurea, epirubicin, chlorambucil, mustine, daunorubicin, prednisolone, and methotrexate. All these children had normal thyroid function apart from one with Hodgkin's disease who had had a diagnostic lymphangiogram (table 1).

CHEMOTHERAPY AND RADIOTHERAPY GROUP

There were 32 children in this group. They included six children with medulloblastoma, three with cerebral tumours, six with rhabdomyosarcomas, six with Hodgkin's disease, three with acute myeloid, and eight with acute lymphoblastic leukaemia with central nervous system relapse resulting in thyroid radiation. The irradiation dose to the thyroid area ranged from 4 to 56 Gy. The chemotherapy used varied from a single agent to intensive combination chemotherapy. Twelve (38%) children had thyroid dysfunction and 11 of them had received an irradiation dose to the thyroid area in excess of 20 Gy, the remaining child had received total body irradiation (11 Gy) (table 1).

DIAGNOSIS, TREATMENT AND THYROID FUNCTION (TABLE 2)

(A) *Medulloblastoma patients (n=14)*

All these children had similar irradiation dose involving the thyroid area averaging 35 Gy (range

Table 1 *Clinical data on 63 survivors of childhood cancer*

Treatment	No of patients	Mean (range) age at diagnosis (years)	Mean (range) follow up (years)	No with thyroid dysfunction
Radiotherapy	11	9.0 (3.0–14.7)	5.5 (2.9–11.2)	5
Chemotherapy	20	6.1 (0.2–14.0)	3.8 (0.8–11.9)	1
Radiotherapy and chemotherapy	32	8.0 (0.2–13.2)	7.0 (1.4–14.8)	12
Whole group	63	7.5 (0.2–14.7)	5.6 (0.8–14.8)	18

Table 2 *Clinical data on tumour type and thyroid function in 63 patients*

Diagnosis	No of patients	Mean (range) age at diagnosis (years)	Mean (range) follow up (years)	Thyroid dysfunction	Raised thyroid stimulating hormone/normal thyroxine	Raised thyroid stimulating hormone/low thyroxine
Medulloblastoma	14	8.0 (3.2–13.3)	6.2 (2.9–11.6)	5	3	2
Hodgkin's disease	13	9.2 (3.4–13.3)	5.3 (1.4–10.5)	6	3	3
Bone tumour	10	10.2 (6.3–14.0)	3.3 (0.8–7.7)	0	0	0
Rhabdomyosarcoma	9	7.6 (1.0–13.0)	5.9 (1.0–11.9)	3	0	3
Acute lymphoblastic leukaemia	8	5.3 (1.2–10.9)	7.3 (2.3–14.8)	2	2	0
Acute myeloid leukaemia	6	5.9 (0.2–12.2)	3.5 (0.8–6.9)	2	2	0
Brain tumour	3	1.9 (1.0–3.7)	5.6 (1.4–10.0)	0	0	0

30–40). Five (36%) patients had thyroid dysfunction in this group; two had irradiation alone, one had irradiation with vincristine, and two had irradiation with vincristine and lomustine. There was no apparent difference in age at treatment, follow up period, chemotherapy used, irradiation dose, or fractions between those who did or did not develop thyroid dysfunction.

(B) Hodgkin's disease patients (n=13)

Five patients had chemotherapy alone or chemotherapy plus radiotherapy away from the thyroid area and all but one had normal thyroid function; the exception was a child who had a diagnostic lymphangiogram. Four patients had chemotherapy plus mediastinal irradiation of 35 Gy and one had thyroid dysfunction. Four patients had radiotherapy in excess of 24 Gy (mean 35 Gy) involving the thyroid area and all had thyroid dysfunction. A total of four patients had lymphangiograms (three also had radiotherapy in excess of 38 Gy to the thyroid area) and all have developed hypothyroidism.

(C) Leukaemia patients

Acute myeloid leukaemia (n=6)—Three patients had chemotherapy alone and all had normal thyroid function. Two patients had chemotherapy plus total body irradiation (a mean dose of 10.7 Gy in one fraction) and one of them had thyroid dysfunction. The sixth patient had spinal irradiation (12 fraction of 2 Gy in 30 days) and he had thyroid dysfunction.

Acute lymphoblastic leukaemia (n=8)—All received radiotherapy involving the thyroid area in 12 fractions during brain or whole central nervous system irradiation for meningeal disease. Only two had thyroid dysfunction having received 23 and 30 Gy to the thyroid respectively. The remaining six patients' radiotherapy dose was 10–18.1 Gy.

(D) Rhabdomyosarcoma patients (n=9)

Five patients received radiotherapy involving the thyroid gland (20–56 Gy). Three who received 50–56 Gy became hypothyroid; the other two patients received 20 Gy to the thyroid area and both had normal thyroid function. Four patients received radiotherapy away from the thyroid gland and they had normal thyroid function.

(E) Bone tumours (n=10)

All had received intensive chemotherapy alone or in combination with radiotherapy not involving the thyroid gland area. All had normal thyroid function.

(F) Cerebral tumours (n=3)

All had received intensive chemotherapy and a

very small dose of irradiation to the thyroid area (40–240 cGy). All had normal thyroid function.

Discussion

The improved survival of children with neoplastic disease has been accompanied by an increase in the side effects of treatment and this includes endocrine disease.^{2 3 7 8} In particular children who have had external beam irradiation to the neck may become hypothyroid^{3 9} and develop thyroid neoplasms.⁶ Although the thyroid gland is relatively radioresistant, its sensitivity is influenced by mitotic activity so that the gland is more vulnerable during its growth in childhood.¹⁰

We have found a prevalence of thyroid dysfunction after external irradiation to the neck of 40%; other reports vary from 16.5¹¹ to 97%.¹⁰ These wide differences reflect variables such as dose of irradiation, age of the patient, length of follow up, and possibly the sensitivity of the laboratory tests. Some authors have made a distinction between compensated and true hypothyroidism,^{12 13} and they report the prevalence of compensated hypothyroidism to be between 29–44%.^{12–14} Our figure of 25% is similar in this respect.

The mechanism by which hypothyroidism develops after irradiation to the neck—whether due to vascular damage, impairment of regeneration, or immunologic reaction—is not clear.¹⁵ Rubin and Casarrett suggested that thyroid irradiation damages both capillaries and endothelium, and that with small doses regeneration takes place.¹⁶ They suggested that with larger doses, however, the residual vascular damage is responsible for a second phase of degeneration of the follicular epithelium and subsequent decrease of thyroid function. In our series the dose of irradiation was important and all those who had had an irradiation dose to the thyroid gland of 40 Gy have developed thyroid dysfunction.

The association between lymphangiography and an increased incidence of hypothyroidism has been documented a number of times.^{14 17} The fat soluble organic iodide used in the lymphangiogram remains in the body for several months, and with its slow and continuous release from lymph nodes it leads to chronic iodide load to the thyroid gland (Wolff-Chaikoff block) causing hypothyroidism.¹⁷ Hodgkin's patients are particularly at risk of hypothyroidism if their disease involves the cervical nodes because they are exposed to both irradiation and lymphangiography. Our study confirms earlier reports that there is an increased incidence of thyroid dysfunction in Hodgkin's disease patients, 46% (six out of 13 patients) when compared with

24% (12 out of 50 patients) in non-lymphomatous extrathyroidal neoplasia.

There are relatively few studies on the effects of chemotherapy on thyroid function. Coffey reported two patients who had become hypothyroid after cyclophosphamide treatment.¹⁸ Sutcliffe *et al* examined two groups with advanced Hodgkin's disease treated solely with chemotherapy.¹⁹ The retrospective group (mean follow up of 35 months) had a modest rise in concentration of thyroid stimulating hormone in 44% but in the prospective group all the patients had normal thyroid function. Iodine based investigation and the total amount of treatment were similar in both groups. They commented that this difference may have been due to the longer length of follow up in the retrospective group.

Schimpff *et al* found no increase in thyroid dysfunction when chemotherapy was given as an adjuvant to irradiation, but they do not mention the follow up period.²⁰ In our study cytotoxic chemotherapy does not appear to have caused any clinical or biochemical evidence of hypothyroidism but the mean follow up is still relatively short. Longer follow up studies should clarify this.

Thyroid dysfunction is a major complication of neck irradiation and requires early detection to minimise potential sequelae. The immediate morbidity is relatively benign with a decrease in height velocity once thyroxine concentrations fall below the normal range. Long term complications may be serious, however, because raised thyroid stimulating hormone concentrations appear to have a permissive role in the development of thyroid neoplasia.²¹ There are a number of reports on the development of thyroid carcinoma after irradiation to the neck,^{21, 22} and it is possible that a damaged gland continuously stimulated by raised concentrations of thyroid stimulating hormone may be at a greater risk of adenomatous and carcinomatous changes.

We believe that all patients who have received irradiation to the neck should have their thyroid function assessed annually for an indeterminate period, and that those with persistently raised thyroid stimulating hormone concentrations (which may rise transiently immediately after irradiation to the neck) should receive thyroid hormone replacement. As the peak incidence of thyroid carcinoma occurs 20 to 30 years after radiation exposure²² indefinite follow up is essential and palpation of the thyroid gland included at every examination.

Our study and others suggest that the thyroid gland appears to be relatively immune to the common cytotoxic agents used for cancer treatment, but this can only be clarified by long term studies.

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