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The natural history of thyroid function abnormalities after treatment for childhood cancer

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ABSTRACT

The aim of the study was to find out which of childhood cancer survivors are at higher risk of thyroid dysfunction, and the timeframe for its development. The consequences of different treatments, particularly chemotherapy, were of interest.

Follow-up data for 291 patients from a cohort of 360 patients were available and analysed in this retrospective study.

Impaired thyroid function occurred in 71/291 (24%) patients: brain tumours 30/65 (46%), Hodgkin's disease (HD) 10/21 (48%), leukaemia/non Hodgkin's lymphoma (NHL) 19/140 (14%) and others 12/65 (18%). Patients with brain tumours had a higher hazard ratio (HR) over leukaemia/NHL (HR 7.47) but not over HD (HR 1.57). These patients also developed thyroid hypofunction earlier than patients with HD or leukaemia/NHL. Age at diagnosis did not have an effect on the occurrence or timeframe of development of thyroid hypofunction. Radiotherapy (HR 4.68) and radiotherapy combined with chemotherapy (HR 2.90) were associated with a higher risk than chemotherapy alone. Chemotherapy added to radiotherapy tended to increase risk (HR 2.42 95% confidence interval (CI) 1.00–5.87). Craniospinal irradiation did not differ significantly from total body irradiation (TBI) (HR 1.09 95%CI 0.25–4.76) or direct thyroid irradiation (HR 0.81 95%CI 0.32–2.06), but cranial irradiation (CIR) (HR 0.18 95%CI 0.08–0.38) was less harmful to thyroid function. Girls were more prone to effects of irradiation (HR 2.10 95%CI 1.15–3.82).

All treatments, excluding surgery, predispose to thyroid dysfunction. Suggestions for follow-up of thyroid function are made.

1. Introduction

The improvement of chemo- and radiotherapy regimens has decreased mortality and increased cure rates of childhood malignancy. As a result of this positive development, the focus of many clinicians and researchers has, in the past decade, shifted to describing, optimally anticipating, and treating the late-effects of the treatments themselves.[1,2]

In a recent study, it was estimated that one third of young adult survivors of childhood cancer experience moderate to severe long-term effects of treatment.[3] Among the clinically well recognised late-effects of cancer therapy, growth retardation,[4–6] infertility[7] and cardiac toxicity[8,9] are of particular importance.

During the last decade, in addition to cognitive late-effects,[10,11] endocrine sequelae[12,13] have been of particular interest. The common factor in these two is that the treatment of the malignancy involved the central nervous system (CNS). The endocrine effects of radiotherapy in the treatment of brain tumours[12,14,15] and tumours of the head- and neck

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region[16] are among the well documented effects of cancer therapy in young adult survivors of childhood malignancy.

In addition to problems in growth hormone and gonadotrophin production, thyroid function has been of interest among researchers. In infants, untreated hypothyroidism results in stunted growth and can even lead to mental retardation. Later on in childhood and adolescence it may cause neuropsychological symptoms such as chronic tiredness, mental fatigue, and learning difficulties.

Whilst the effects of direct and indirect radiotherapy on thyroid function are indisputable and have been confirmed by several studies,[17–19] there are only a few articles documenting the effects of chemotherapy. Moreover, the existing studies have yielded contradictory results. Some studies have included chemotherapy, addressing it as a possible additional risk in patients receiving radiotherapy,[15,20,21] while few focused on the thyroid toxicity of chemotherapy alone.[22,23] Also the reported time span for development of abnormal thyroid hormone levels is often a range which varies from one study to another. A study on medulloblastoma patients[15] reported a time span ranging from less than 6 months to 6.5 years after therapy, whereas in another study including a large variety of malignancies[24] hypothyroidism appeared between 4.8 and 5.5 years post diagnosis. On the other hand, a recent study on Hodgkin's disease (HD) patients[25] reported a time span ranging from as early as 0.7 to 11.3 years post-diagnosis.

Chemotherapy was found to increase the incidence of thyroid dysfunction in two studies involving patients with brain tumours[26,27] Both studies showed combination therapies to be more damaging to the hypothalamo-pituitary-thyroid axis (HPTA) than radiation alone. However, chemotherapy was not found to pose an additional negative effect on the function of the HPTA in investigations by Van Santen[20] or Schmiegelow[21] with their co-workers. In a more generalised study reported by Rose et al., chemotherapy was found to be associated with an increased risk of hormonal deficiency, which was defined as one of the triad of growth hormone deficiency, hypothyroidism or pubertal abnormality.[28] Nygaard and co-workers pioneered a study in which acute leukaemia patients were treated exclusively by chemotherapy.[29] Their cytotoxic regimen, which included relatively intensive intravenous and intrathecal methotrexate dosing, was not found to cause thyroid dysfunction.

In Finland, all patients diagnosed with a paediatric malignancy are followed-up by visits to paediatric units and laboratory tests taken at increasing intervals for a period of 10 years after completion of cancer treatment or even longer if adulthood is not reached by that time. However, there are as yet no general guidelines for an optimal endocrine follow-up surveillance program. Recommendations are study- and hence malignancy specific and vary from annual pubertal surveillance in non-CNS tumour survivors[28] to lifelong surveillance in head and neck tumour survivors.[16]

The aims of this study were a) to find out which patients are at increased risk of developing impaired thyroid function, b) to analyse whether chemotherapy poses an increased risk of hypothyroidism in comparison to radiotherapy alone, c) to determine whether and to what extent chemotherapy increases the risk of survivors developing hypothyroidism, d) to determine at what time point after cancer diagnosis thyroid dysfunction arises, and e) to evaluate the need and optimal timing for regular surveillance of thyroid function in childhood cancer patients.

2. Patients and methods

2.1. *Patients*

The study included all patients diagnosed and treated for a paediatric malignancy at Turku University Hospital, covering a population of nearly one million inhabitants. Patients were diagnosed from October 1974 to December 2002 and aged up to 16 years at the time of diagnosis of the primary malignancy/tumour. The last follow-up date was 31.07.2004. With the approval of the Ministry of Health and Social Affairs as well as the local ethical committee, data of 360 patients fulfilling the inclusion criteria were collected from medical records. Sixty-nine patients (19%) were excluded from the analysis due to a lack of records of TSH and fT4 testing, mainly because of early death. The data on 291 patients with adequate follow-up were analysed and are presented here.

Patients were subgrouped into diagnostic and treatment groups. The diagnostic division resulted in four groups formed according to the type of malignancy and similarity of the treatment protocol: HD, non Hodgkin's lymphoma (NHL)/acute leukaemias, brain tumours, and others. For the purpose of this study NHL and leukaemia patients were considered together due to very similar treatment regimens used in our institution during the study period. The second grouping was based on treatment modalities, resulting in four groups: surgery only, chemotherapy with or without surgery, irradiation with or without surgery, and chemotherapy and irradiation together with or without surgery.

The surgery group was taken as a baseline group, as surgery is not in itself thought to correlate with an increased risk for developing thyroid dysfunction, unless the tumour affects the hypophyseal area or thyroid gland. The group treated by chemotherapy alone was studied in view of previous contradictory answers to the question of whether or not chemotherapy by itself poses an increased risk and to explore whether alkylating agents were associated with increased risk. In the irradiation group, it was expected that the effect on thyroid function would be clearly demonstrated as the brain tumour patients, treated with the highest radiation doses, form the majority in this group. The last group including patients who had received both chemotherapy and irradiation was created in order to explore whether or not chemotherapy acted as an additional risk factor for thyroid dysfunction. Details of the patients are listed in Table 1, and description of their status at the end of the study in Table 2. There were no cases of thyroid malignancy among the study patients.

2.2. *Treatment*

Radiotherapy data were collected from patients' medical records including: time of treatment, dose and field of irradiation. Patients were grouped by field of irradiation as follows: cranial irradiation (CIR), craniospinal irradiation (CSIR), total body irradiation (TBI), direct thyroid, and other. The majority

Table 1 – Description of the study patients

Participants	N	Age at diagnosis		Follow-up time	
		Median	(Q1–Q3)	Median	(Q1–Q3)
All subjects	291	5.26	(2.81–11.13)	6.13	(2.43–11.38)
Male	164	5.34	(3.10–10.91)	6.24	(2.30–11.38)
Female	127	5.19	(2.41–11.15)	5.94	(2.55–11.85)
Diagnostic groups					
Brain	65	6.42	(3.38–11.13)	2.20	(1.19–5.20)
Leukaemia/NHL	140	4.71	(3.12–8.96)	8.16	(4.25–13.49)
HD	21	12.41	(11.52–15.25)	5.83	(3.46–9.90)
Others	65	4.54	(1.83–8.81)	7.98	(2.60–12.15)
Treatment groups					
Surgery only	12	4.55	(3.93–7.17)	3.07	(0.99–8.96)
Chemotherapy (+/− surgery)	142	4.7	(2.53–10.72)	6.46	(3.28–11.26)
Irradiation (+/− surgery)	17	12.21	(7.54–14.08)	4.99	(1.45–8.65)
Chemotherapy + irradiation (+/− surgery)	118	6.07	(3.13–11.10)	5.93	(2.20–12.19)
Missing data	2	2.32	(0.01–4.46)	3.62	(0.01–7.24)

Q1–Q3 = interquartile range covering 50% of findings around the median, HD = Hodgkin's disease, NHL = non-Hodgkin lymphoma.

Table 2 – Detailed description of the study patients at the end of study

	Patients in final analysis			
	Dead before the end		Alive at the end	
	Total	With event	Total	With event
Brain	14	5	51	25
Leukaemia/NHL	6	0	134	19
HD	1	0	20	10
Others	5	2	60	10
Total	26	7	265	64

of patients with malignant brain tumours (excluding children below the age of 2–3 years at diagnosis) were irradiated. According to the protocols, prophylactic CSIR was given to patients with certain malignant infratentorial tumours, as well as to patients with spinal metastases. According to the NHL protocols in use at the time, some NHL patients received local radiotherapy to the region of the primary tumour and/or prophylactic CIR. Also if lymphoma cells were found in the CNS at the time of diagnosis, CIR was given. Among leukaemia patients, CIR was given in overt CNS-leukaemia as well as prophylactically for those patients treated according to high-risk protocols. In this study population, there were some leukaemia patients from the 1970s to early 1980s, during which period, prophylactic CIR was also included in the protocols for non-high-risk patients. TBI was used in conditioning for allogenic stem cell transplantation. CIR dosage in brain tumour patients varied from 35 to 55 Gy, in leukaemia patients doses were 18 or 24 Gy. The dose of CSIR was 24 Gy and the dose of TBI either 10 or 12 Gy. The effect of thyroid irradiation was analysed in patients treated with irradiation to the neck and/or the mediastinum. These patients received doses varying from 20 to 40 Gy.

Chemotherapy data was collected noting: regimen used, date of initiation, and termination of treatment, whether or not alkylating agents were given, as well as any changes or modifications to the standard treatment regimens. The main alkylating agents given to study patients were: cyclophosphamide, ifosfamide, CCNU, BCNU, dacarbazine, procarbazine and nitrogen mustard. The patients had been treated according to Nordic or other international protocols. The distribution of treatments among patients is presented in Table 3.

2.3. *Laboratory methods*

In our department, thyroid function is measured at the time of diagnosis, at the end of treatment, and then every 6 months for 2 years and thereafter usually annually, or more frequently if there is evidence of thyroid dysfunction. For the purpose of this study, thyroid dysfunction, or in statistical terms an event, was defined as either the time point of the initiation of thyroxin therapy, or either a fT4 value below or a TSH value exceeding the defined normal range, both on

Table 3 – The details of treatment modalities

	Radiotherapy					Alkylators	Surgery
	CIR	CSIR	TBI	Direct thyroid	Other local	Given	
Diagnostic groups							
Brain	30/65 (46.2%)	14/65 (21.5%)	0/65	0/65	1/65 (2.0%)	26/65 (40.0%)	57/65 (87.7%)
Leukaemia/NHL	32/140 (22.9%)	5/140 (3.6%)	10/140 (7.1%)	0/140	5/140 (3.6%)	109/140 (77.9%)	12/140 (8.6%)
HD	0/21	0/21	0/21	11/21 (52.4%)	0/21	19/21 (90.5%)	2/21 (9.5%)
Others	1/65 (1.5%)	1/65 (3.4%)	0/65	0/65	19/65 (29.2%)	40/65 (61.5%)	56/65 (86.2%)

two consecutive measurements. Hence, by this definition an event will include clinical, subclinical and central cases of thyroid dysfunction. This way of considering fT4 levels allowed for the identification of so-called hidden central hypothyroidism, which has been shown to be underdiagnosed.[24] Mildly elevated TSH was regarded as an important factor because prolonged elevated TSH levels have been suggested to contribute to the development of pathological serum lipid profiles[30] as well as cardiovascular problems,[31] thus adding to the pre-existing risk of metabolic disturbances.[32] Furthermore, not only has therapeutic radiation been associated with thyroid neoplasms,[33] but also one animal study suggests a link between prolonged elevated TSH levels[34] and thyroid neoplasms.

Due to the retrospective nature of the study, it was not possible to consider TRH-testing as this was not one of the standard methods used to screen for thyroid dysfunction. In primary hypothyroidism, the TRH test is useful as it shows an increased response, yielding a difference between peak and basic levels of TSH. However, in pituitary/hypothalamic hypothyroidism, the TSH response is low or normal, thus not particularly diagnostic in these situations. It is also known that several drugs can interfere with the TRH test and reduce and thus confound the TSH response. The use of the TRH test has greatly decreased due to the development of sensitive TSH-testing. There is also evidence for the redundancy of TRH-testing in the diagnosis of primary and central hypothyroidism.[35]

The assay method for fT4, which began in 1984, has changed three times during the study period (Amerlex-M, Spectria, Amerlex-MAB, and since 4/1996 AutoDELFIA). Regression equations have been provided by the laboratory for the above measurements. However, these correlations were shown to be imprecise and were thus not used to unify the fT4 data. Instead, the data were considered as deviant or normal values according to the time specific normal range. The TR-IFMA method was used for TSH measurement, and the data were considered as deviant or normal values.

2.4. *Statistical methods*

The statistical analyses were carried out using SAS/STAT® software, Version 9.1.3 SP1 of the SAS System for Windows (SAS Institute Inc., Cary, NC, USA). For descriptive statistics, medians, ranges and interquartile ranges (Q1–Q3) were calculated. Interquartile ranges were thought to be especially informative in reporting the time frame of events as they indicate the time points between which the middle 50% of observations are located. The data were analysed with statistical survival analysis.[36] The log-rank test was used to indicate statistically significant differences between the event-free curves in the plots.

More detailed analyses were performed according to our study aims, in relevant patient/treatment groups. In these calculations, Cox proportional hazard models with prognostic variables were used as well as models with only the primary explanatory variable. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported and considered statistically significant if the p-value was less than 0.05.

2.5. *General population data*

In Finland, all patients receiving hormone substitution are entitled to reimbursement by the government social insurance agency. From their reimbursement database, we were able to obtain data on the numbers of patients receiving reimbursement in each age-group in the year 2004. Combining this data with population data of 2004 obtained from Statistics Finland enabled us to calculate valid approximations of the prevalence of hypothyroidism in Finland. In the age-group 0–4 yrs, the percentage was 0.03%, this being a good estimate of congenital hypothyroidism, whereas the corresponding value for the youth population aged 4 to 19 years was 0.12%, this being a good estimate of juvenile hypothyroidism in Finland. In the whole Finnish population, the total prevalence of hypothyroidism was around 1.6%.

3. Results

Regarding thyroid function, there were 71 study events (24.4%) indicating decreased function in the analysed patients. Out of these study events, 47 were patients already on thyroxin treatment. Of these patients, 16 (36%) had been tested for plasma thyroid antibodies. These were found to be elevated in five patients, who did not display homogeneity with regard to diagnosis (2 ALL, 2 HD, 1 NHL and 1 CNS tumour). In Table 4, the study events and their timing are presented by diagnostic and treatment groups.

In the brain tumour group, 30/65 (46.2%) patients were found to have decreased thyroid function, while corresponding figures in the leukaemia/ NHL, HD, and other group were 19/140 (13.6%), 10/21 (47.6%) and 12/65 (18.9%), respectively. Timing of the study events is presented by diagnostic groups in Fig. 1 and by treatment groups in Fig. 2.

From Fig. 1, it can be seen that the risk of thyroid dysfunction was highest in patients with brain tumours and the events occurred after a shorter interval than in other diagnostic groups. From the interquartile ranges (Q1–Q3) presented in Table 4, it is apparent that 75% of study events had occurred by 3.8 years. However, the plateau was not reached until just after 6 years post cancer diagnosis. In HD patients, thyroid dysfunction was as common, but there were several patients in whose case the event appeared more than 5 years after diagnosis, and the interquartile range stretched from 1.5 to 8 years. In the group of leukaemia/NHL patients, events started occurring later than in other groups, and though events were rare, no clear plateau was reached. It took 9.7 years before 75% of events had occurred. The log-rank test indicated that there were differences among the event-free curves of treatment groups ($p < 0.001$). To quantify the differences between diagnostic groups, hazard ratios were calculated in a model without covariates. Patients with brain tumours had a significant hazard ratio over leukaemia/NHL patients 7.47 (95% CI 4.11–13.57; $p < 0.0001$) and over the group Other 4.53 (95% CI 2.30–8.93; $p < 0.0001$), but not over HD patients 1.57 (95% CI 0.76–3.22; $p = 0.221$).

Fig. 2 shows that radiotherapy poses a higher risk to thyroid dysfunction than other treatment modalities. The time elapsed to the study event ranged from about 7 months to

Table 4 – The study events within diagnostic and treatment groups

	Event		Time from diagnosis to event (yr)		
	Yes/total	%	Median	Q1–Q3	Min–max
Diagnostic groups					
Brain	30/65	46.2	1.7	1.2–3.8	0.01–8.6
Leukaemia/NHL	19/140	13.6	5.5	2.9–9.7	1.7–19.6
HD	10/21	47.6	5.7	1.5–8.0	0.8–14.9
Other	12/65	18.5	2.1	1.0–5.7	0.07–14.6
Total	71/291	24.4	2.5	1.5–5.9	0.01–19.6
Treatment groups					
Surgery only	2/12	16.7	1.1	0.03–2.1	0.03–2.1
Chemotherapy (+/− surgery)	18/142	12.7	2.9	1.6–8.2	0.07–19.6
Irradiation (+/− surgery)	8/17	47.1	2.12	1.4–5.8	0.6–8.7
Chemotherapy+ irradiation (+/− surgery)	42/118	35.6	2.8	1.6–5.9	0.3–14.9
Missing data	1/2	50.0	0.01	0.01–0.01	0.01–0.01
Total	71/291	24.4	2.5	1.5–5.9	0.01–19.6

Q1–Q3 = interquartile range covering 50% of findings around the median.

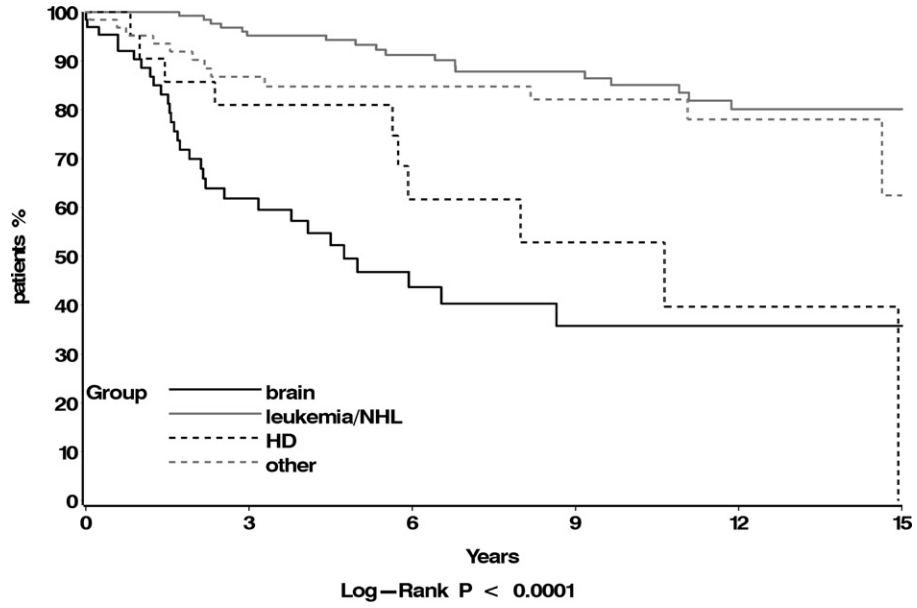

Fig. 1 – The proportion of patients with normal thyroid function by time from diagnosis in different diagnostic groups.

8.7 years, and was clearly shorter than among the other treatment modalities. The combination of chemotherapy and radiotherapy showed proportionally less study events than radiotherapy alone. However, thyroid dysfunction also started to appear early in this group of patients, and 75% of study events were detected by 5.9 years post cancer diagnosis. Even in the group of patients treated with only surgery, there were two study events. This, however, was explained by the location of the tumour in the hypophyseal area in both patients. Also in the group of patients treated with only chemotherapy, thyroid dysfunction was seen. The study events appeared gradually over the years, but by 8.2 years post diagnosis 75% of them were detected. The log-rank test indicated a significant difference between the event-free curves of treatment groups ($p < 0.001$). To quantify the differences between treatment groups, hazard ratios were calculated in a model without covariates. Radiotherapy as well as combination therapy had a significant hazard ratio over chemotherapy alone, 4.68 (95% CI 2.04–10.78; $p = 0.0003$) and 2.90 (95% CI 1.67–5.05; $p = 0.0002$), respectively.

In an analysis of the effect of chemotherapy as an additional variable to radiotherapy, the brain tumour group was considered, as the number of patients receiving combination therapy was greatest in this group. There were a total of 20 events among brain tumour patients receiving both radiotherapy and chemotherapy ($N = 37$), and seven events in the brain tumour group receiving only radiotherapy ($N = 18$). In an adjusted analysis, where gender, age at diagnosis, and radiation dose were viewed as additional variables, the effects of these variables were not statistically significant. The adjusted hazard ratio calculated for chemotherapy (used in addition to radiotherapy) was, however, 2.54 (95%CI 0.93–6.93; $p = 0.07$). This hazard ratio can be interpreted to indicate a tendency. When the variables lacking

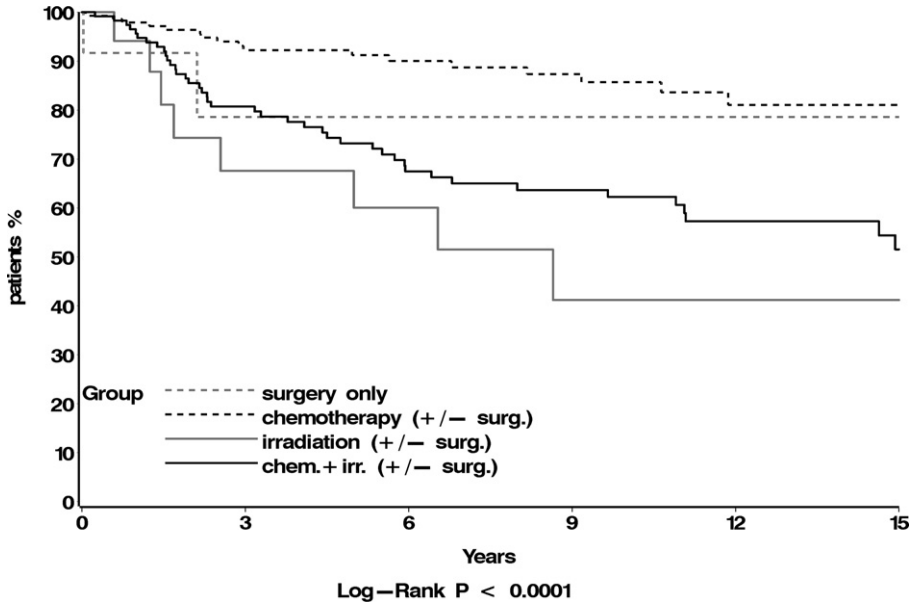

Fig. 2 – The proportion of patients with normal thyroid function by time from diagnosis in different treatment groups.

statistical association were eliminated from the model, the variable chemotherapy in addition to radiotherapy yielded an unadjusted HR of 2.42 (95%CI 1.00–5.87; $p = 0.05$), which supports the above mentioned tendency.

To analyse alkylating agents as an explaining chemotherapy variable, the treatment groups leukaemia/NHL and Other were viewed, as this combination had the highest number of patients receiving chemotherapy including alkylators but no irradiation. There were 12 events among the patients receiving alkylators but no radiotherapy ($N = 81$), and 14 events among those who got both treatments ($N = 66$). In an adjusted analysis, the following variables were considered: alkylating agents, irradiation in addition to chemotherapy, gender, and age at diagnosis. This calculation yielded an adjusted HR 1.85 (95%CI 0.69–4.99; $p = 0.23$) for treatment with alkylating agents. When the other variables lacking statistical association were eliminated from the model, the variable alkylating agents gave an unadjusted HR 2.00 (95%CI 0.77–5.22; $p = 0.16$). Thus, alkylating agents seemed not to be an independent risk factor for the development of thyroid dysfunction.

To observe the effect of radiotherapy as an additional risk factor in combination with chemotherapy, the leukaemia/NHL group was observed as, in this diagnostic group, the number of patients receiving only chemotherapy was comparable with the number of patients receiving additional radiotherapy. There were nine events among 87 patients receiving

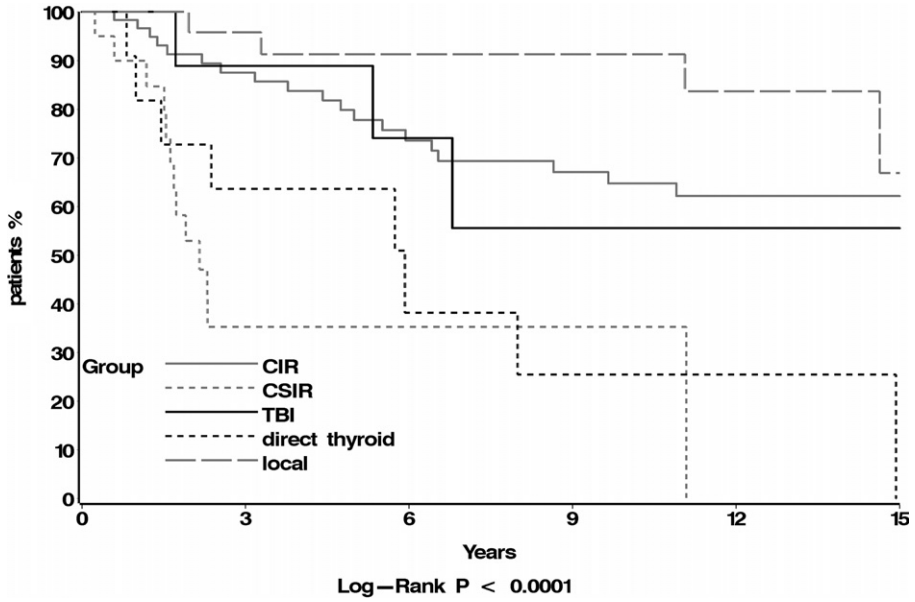

Fig. 3 – The proportion of patients with normal thyroid function by time from diagnosis in different localisations of irradiation.

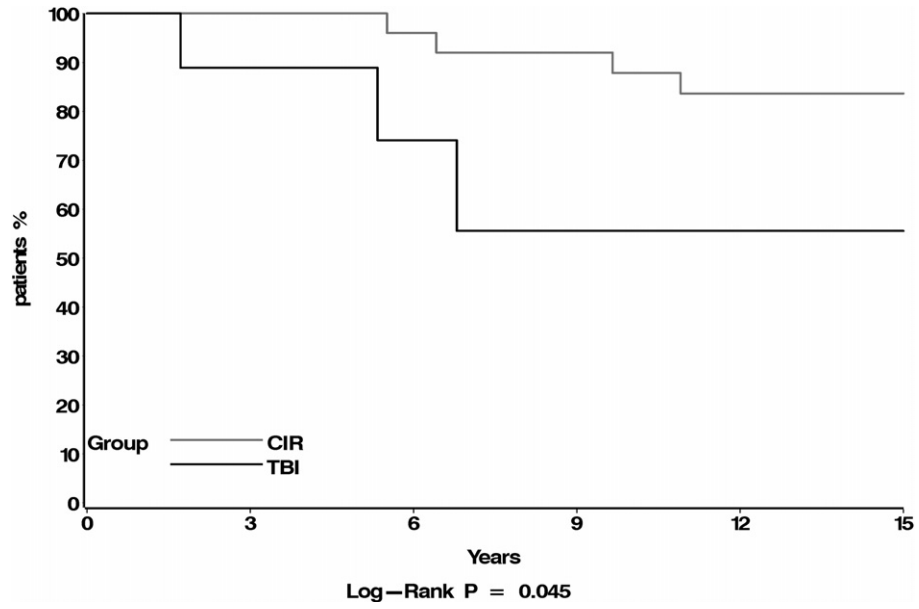

Fig. 4 – The proportion of leukaemia patients with normal thyroid function by time from diagnosis according to the mode of irradiation.

only chemotherapy, and ten events among 53 patients receiving combined therapy. In an adjusted analysis, which also included gender and age at diagnosis, an adjusted HR 1.25 (95%CI 0.50–3.15; $p = 0.63$) was found for the effect of radiotherapy in addition to chemotherapy. Thus, there was no significant difference in the probability of events in either of the treatment groups.

The occurrence of events in the different radiation groups as a function of time is shown in Fig. 3. The log-rank test indicated differences among the event-free curves ($p < 0.0001$). From this figure, it is apparent that the CSIR group stands out as the group developing thyroid dysfunction at an earlier timepoint than other groups. Age at diagnosis was not found to be statistically significant. In an adjusted analysis, with gender and radiation dose as covariates, the hazard ratio of CSIR did not differ from that of TBI (HR 1.09 95%CI 0.25–4.76, $p = 0.90$) or thyroid irradiation (HR 0.81 95%CI 0.32–2.06, $p = 0.66$). However, CIR (HR 0.18 95%CI 0.08–0.38, $p < 0.0001$), and other local irradiation (HR 0.09 95%CI 0.03–0.31, $p < 0.0001$) proved to be less harmful. Although age at diagnosis was not found to be statistically significant, an unexpected effect of gender was found, females (HR 2.10 95%CI 1.15–3.82, $p < 0.015$) being more prone to the harmful effects of irradiation.

Though the number of leukaemia patients who had undergone a stem cell transplant was low, we wanted to analyse the effect of TBI in comparison with CIR within this subgroup. The event-free curve of those receiving TBI differed significantly from that of the CIR group ($p = 0.04$) (Fig. 4). In a multivariate analysis, including the dose of irradiation ($p = 0.06$), gender ($p = 0.26$), and age at diagnosis ($p = 0.75$), the hazard ratio of TBI over CIR was statistically significant (HR 21.07, 95%CI 2.02–219.39, $p = 0.01$). When gender and age at diagnosis were eliminated from the model as not significant variables, TBI compared to CIR yielded a HR of 18.5 (95%CI 1.80–189.98; $p = 0.01$).

4. Discussion

Recognition and prediction of late consequences of cancer therapy is the most clinically applicable aspect of the study of late-effects. The goal of this study was to find basis for a tailored surveillance of thyroid dysfunction. This would allow paediatric oncologists involved in post-cancer surveillance to identify the patients at risk of developing thyroid dysfunction, and if need be, refer them to the paediatric endocrinologist for further evaluation. As our aim was to identify all the cases of clinical, subclinical and central hypothyroidism, without exploring the mechanism behind diminished thyroid function, we relied on the adequacy of TSH and fT4 testing.

We found that cancer survivors are at a higher risk of developing hypothyroidism than the general Finnish population (see methods). Juvenile hypothyroidism, which by definition includes hypothyroidism in the age group of >2 years, has several etiological factors, including cases due to an ectopic thyroid, a lack of iodine intake, lack of TSH (often linked to hypopituitarism) as well as those cases due to cancer treatment. The majority of cases are, however, due to autoimmune processes.

When juvenile hypothyroidism in our population is considered, our study shows the incidence to be increased among cancer patients compared with that in the healthy population (0.12%) both when looking at thyroid hormone replacement (16%) and thyroid hypofunction (24.4%). Our results were in keeping with those in a study with a similar variation in patient material, in which the corresponding percentages were 18% and 26.8%, respectively.[20]

When viewing diagnostic groups, thyroid hypofunction was found to exceed that of the general population (1.6%) in all groups. This increment was particularly obvious in the brain tumour and HD groups. A recent study by Metzger and co-workers reported the same level of hypothyroidism in white HD patients.[24] Van Santen and co-workers found

patients with lymphoma to have the highest risk for thyroid damage.[20] However, in their analysis, the proportion of brain tumour patients was lower than in our study. We found nearly as much impaired thyroid function among HD patients as in the brain tumour group. The effect of radiation fields probably explains the finding in both groups.

When viewing treatment modalities, our results confirmed those of the previous studies, indicating the significance of radiotherapy as a risk factor for hypothyroidism.[17–19] CSIR and direct thyroid irradiation were the most deleterious in this context. It was also interesting to note the gender difference in the risk inflicted by radiotherapy on the thyroid axis. Female patients were more vulnerable. A recent study by Sklar and co-workers also found female sex to be an independent risk factor for hypothyroidism and thyroid nodules in radiated HD patients.[18]

Chemotherapy yielded a lower percentage of thyroid hypofunction than irradiation alone, or the combination of chemotherapy and irradiation. When viewing the whole study population, it also seemed that chemotherapy does not pose an additional risk factor to radiotherapy in impairing thyroid function. On the contrary, our result would raise the idea that chemotherapy reduces the risk of hypothyroidism when used in conjunction with radiotherapy. However, as the radiation dose was most probably lower and radiation field probably less harmful to the thyroid gland in the groups receiving combination therapy, conclusions should be drawn with caution. Furthermore, it must be noted, that the incidence of thyroid hypofunction in the group receiving only chemotherapy exceeded that in the normal population.

By studying the patients by treatment group, we aimed to evaluate the effect of chemotherapy on thyroid function, both as a sole treatment and as a part of combination therapy. In brain tumour patients, the largest group receiving combination therapy, a trend was found showing increase in thyroid hypofunction when chemotherapy was added to radiotherapy. This result was in agreement with the findings of Ogilvy-Stuart and co-workers[27] and Livesey and co-workers.[26] However, in a study by Van Santen and colleagues, which involved a large variety of malignancies, no additional effect of chemotherapy on radiotherapy was found.[20] It must be noted that Van Santen's study did not involve continued follow-up of survivors, but rather registered thyroid values at a single timepoint.[20] Contrary to our results, no additional effect of chemotherapy was seen in a small series of patients with medulloblastoma reported by Heikens et al.[12] In their series, the incidence of thyroid dysfunction was lower though median follow-up time was longer. In the light of the previous studies on greater numbers of brain tumour patients, it appears that chemotherapy may add to the risk of thyroid hypofunction already present in patients receiving radiotherapy.

In the reverse analysis, conducted in the leukaemia/NHL group, whose treatment was based on chemotherapy accompanied by smaller doses of radiotherapy, chemotherapy alone was associated with an elevated risk for thyroid hypofunction. This risk was not accentuated by radiotherapy. One may pose the question: is there a critical dose after which radiotherapy begins to add to the thryoid toxicity of chemotherapy? The evaluation of a critical threshold of the thyroid gland or hypothalamo-pituitary axis reached by different ratios of combination therapy is a question for further research.

The relevance of the aforementioned results is highlighted with regard to the current trend of searching for new regimens which aim to reduce radiation doses.[10] The finding that chemotherapy may play its own part when used in conjunction with radiotherapy should be taken into consideration and the negative effects of the combined therapy should be considered as the summation of both components. The observation of a significant effect from chemotherapy was of particular relevance as the dose of cranial irradiation did not seem to be an independent factor contributing to the toxicity of radiotherapy in the leukaemia/NHL group.

Contrary to the reports concerning patients with testicular cancer[23] and HD,[22] we did not find alkylating agents to be the causative factor for chemotherapy-induced thyroid hypofunction. However, the inability to demonstrate a detrimental effect of alkylating agents may have been a reflection of the relatively small numbers in the study. Whether or not a particular subgroup of chemotherapeutic agents is responsible for the harmful effects of chemotherapy is a question for further research.

The thyroid function of leukaemia patients who had undergone stem cell transplantation was also of particular interest. Despite the smaller dose of radiation, TBI proved more harmful than CIR with regard to the thyroid axis. This could be explained by the larger direct thyroid dose resulting from TBI compared to the scatter from CIR. It is thus noteworthy, that after stem cell transplantation with TBI conditioning, a child patient is at considerable risk for the development of thyroid hypofunction.

We found three studies which reported the timeframe of the occurrence of hypothyroidism. One focused on the timeframe for the occurrence of different types of hypothyroidism in different diagnostic groups,[24] while the others reported the timescale to the development of thyroid hypofunction in general in medulloblastoma[15] and HD[25] patients respectively. Results of the first study cannot be compared to ours as the basic setup of the study focused on central hypothyroidism. In the second study, abnormal thyroid function developed between below 6 months to 6.5 years after therapy. Their findings were in agreement with our results in the brain tumour group. It must be considered that our study involved a larger variety of brain tumours, some located further away from the hypothalamo-pituitary axis, and that in our study, time was measured from diagnosis instead of the end of therapy. The study on HD patients showed a similar profile for timeframe as the corresponding group in our study.

The results of our study confirm the opinion that all children with malignancy treated with radiation to the head, neck and mediastinum are at risk of developing hypothyroidism and thus should be monitored with regular thyroid function test surveillance up to around 10 years post-diagnosis. In leukaemia and NHL patients without radiation therapy, annual thyroid follow-up could be proposed beyond 10 years. Patients receiving only surgical treatment (excluding tumours of the hypothalamo-pituitary and thyroid regions) are not at an increased risk and do not require programmed thyroid surveillance. The patients treated with CSIR and TBI are at greatest risk of hypothyroidism and thus patients with brain

tumours and leukaemia treated by CSIR and patients conditioned with TBI for stem cell transplantation, need regular thyroid function tests, possibly at 3-month intervals up to 2 years post-diagnosis. Thereafter the interval can gradually be prolonged to annual surveillance. Patients with HD, who have received radiation to the neck and mediastinum, probably need thyroid function testing at 6-month intervals up to 6 years post diagnosis, after which annual surveillance is suggested. New regimens which aim at reducing radiotherapy doses and increasing chemotherapy may not solve the problem of late-effects on the thyroid function.

Conflict of interest statement

None declared.

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