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Long-term endocrine side effects of childhood Hodgkin's lymphoma treatment: a review

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BACKGROUND: Since childhood cancer survival has increased, long-term effects of treatment have gained interest. Childhood Hodgkin's lymphoma has been treated successfully for decades now. We provide an overview of the literature on long-term endocrine side effects, such as gonadal dysfunction and growth retardation, as a result of childhood Hodgkin's lymphoma treatment.

METHODS: A comprehensive search of the Pubmed database was performed.

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RESULTS: We identified 16 studies (10 studies: 298 male survivors and 6 studies: 230 female survivors) about gonadal dysfunction. In survivors treated with alkylating agents or pelvic radiotherapy, severe gonadal damage is described. Recovery was rarely described. Seven studies (481 survivors) about bone mineral density (BMD) and growth were identified. The effects on BMD appear to be small. Data on growth are scarce, but show that radiotherapy in a dose of >30 Gy including the spine, especially in pre-pubertal children, results in reduced height. We included 10 studies (4012 survivors) about thyroid complications. Hypothyroidism is the most common thyroid disorder after radiotherapy. There is also a significant incidence in thyroid carcinoma after low-dose radiation. In survivors treated with chemotherapy only, hypothyroidism and thyroid cancer have not been reported.

CONCLUSIONS: The severity of endocrine toxicity after childhood Hodgkin's lymphoma depends on the type of treatment. Gonadal dysfunction seems to be the most severe endocrine long-term effect, especially after treatment with alkylating agents or pelvic radiotherapy. The knowledge obtained in specific follow-up programmes for paediatric cancer survivors will help to find the optimal balance between curability and long-term side effects.

Key words: childhood Hodgkin's lymphoma / gonadal function / endocrine late effects

Introduction

Childhood cancer has become a curable disease. Currently, two-third of all children with cancer reach long-term survival (Howell and Shalet, 1998; McVie 1999; Levi *et al.*, 2001; Baade *et al.*, 2010; Kaatsch 2010; Smith *et al.*, 2010). Hence, long-term effects of treatment in childhood cancer survivors have been acknowledged to be of major importance. It has been estimated that 70% of survivors have developed at least one of the long-term sequelae resulting from treatment. One-third of these effects have even been classified as severe or life threatening (Oeffinger *et al.*, 2006; Geenen *et al.*, 2007). In Hodgkin lymphoma survivors, 70% reported at least one chronic condition (Castellino *et al.*, 2011).

Hodgkin's lymphoma is a malignancy of the lymph nodes and lymphatic system with possible involvement of other organs. It has two incidence peaks. The first peak occurs between the ages of 15 and 30 years and the second between 45 and 55 years. Hodgkin's lymphoma is very rare in children under 15 years of age (Oberlin, 1998). Paediatric Hodgkin's lymphoma has a very good prognosis: an event-free survival (EFS) up to 93% and an overall survival of even 96% have been reported (Gurney *et al.*, 1995; Schellong, 1996; van den Berg *et al.*, 1997a; Schellong, 1998; Hudson and Donaldson, 1999; Nachman *et al.*, 2002; Hakvoort-Cammel *et al.*, 2004). The treatment of childhood Hodgkin's lymphoma consists of chemotherapy, radiotherapy or a combination of both. In former years, treatment of paediatric Hodgkin's lymphoma often involved extended field high-dose radiation therapy, which was associated with several severe side effects, such as secondary malignancies (Donaldson and Kaplan, 1982; Mauch *et al.*, 1983; Cardous-Ubbink *et al.*, 2007). Currently, most paediatric oncology centres use a risk-adapted treatment schedule consisting of both chemotherapy and low-dose, involved field or even involved node radiotherapy with high EFSs (Donaldson 1981; Weiner *et al.*, 1991; Oberlin *et al.*, 1992; Hudson *et al.*, 1993; Hunger *et al.*, 1994; Schellong *et al.*, 1999; Viani *et al.*, 2006; Donaldson *et al.*, 2007). In a few centres, it was decided to treat childhood Hodgkin's lymphoma with chemotherapy only in order to minimize the risk of severe late effects, such as infertility, while preserving good cure rates (van den Berg *et al.*, 1997a, b; Hakvoort-Cammel *et al.*, 2004).

Both chemotherapy and radiotherapy have serious potential side effects, especially when used in children. In both Canadian and US studies, a high prevalence of self-reported somatic health problems is followed by a higher risk of psychosocial late effects, such as a lower educational level, unemployment, low income and fewer close friends (Hudson *et al.*, 2003; Oeffinger *et al.*, 2006; Pang *et al.*, 2008; Gurney *et al.*, 2009). In a Dutch cohort, there were only small differences in health-related quality of life and the burden of self-reported somatic disease (Langeveld *et al.*, 2004). Several follow-up studies have been performed to investigate the incidence of long-term side effects (such as abnormal cardiac function, auditory dysfunction and endocrine disruption) in all childhood cancer survivors. In general, long-term side effects of chemotherapy depend on the patient characteristics (e.g. age), type of chemotherapy (e.g. alkylating agents, anthracyclines) and cumulative dose, whereas the toxicity of radiotherapy is related to the dosage and extent of the irradiated field (Geenen *et al.*, 2007; de Bruin *et al.*, 2009; Woodward *et al*, 2011).

In this paper, we present the available literature on endocrine late sequelae after childhood Hodgkin's lymphoma treatment with a special focus on gonadal dysfunction, growth, bone mineral density (BMD), body composition and thyroid dysfunction.

Methods

To provide an overview and summary of the known long-term endocrine effects of Hodgkin's lymphoma treatment, a comprehensive search of the Pubmed database was performed for all articles published until February 2011. Search-criteria relevant to childhood cancer survivors and long-term endocrine effects were used: childhood cancer survivors, childhood, adolescent, Hodgkin's lymphoma, endocrine effects, growth, BMD, thyroid function, gonadal function and ovarian reserve. If not included initially, cross-references picked up during the review procedure were also selected. Only articles published in the English language were included. In this way, we identified 188 papers. After carefully reading the abstracts, 166 papers were excluded because they describe the late effects of all childhood cancer treatments instead of the effects of Hodgkin's lymphoma treatment only. The 22 papers remaining and another 11 papers identified through cross-reference searches resulted in a total of 33 papers concerning specific late endocrine effects of the treatment of childhood Hodgkin's lymphoma.

Results

Gonads

An important side effect of both radiotherapy and chemotherapy is gonadal dysfunction or complete loss of gonadal activity. This might

Table I Studies on testicular function in male childhood Hodgkin's lymphoma survivors.

Author	n[a]	Age (range)[b]	Median follow-up	Therapy		Gonadal evaluation						
						Semen analysis			Serum markers			
				CT	RT	n	Azo	Oligo	n	LH	FSH	Inhibin B
Heikens et al. (1996)	19	11 years (5–15 years)	10 years	MOPP	0	18	67%	33%	19	↑	↑	-
Ortin et al. (1990)	20	13 years (2–15 years)	9 years	MOPP	12	15	60%	15%	11	↑	↑	-
Mackie et al. (1996)	46	12.2 years (8.2–15.3 years)	6 years	ChlVPP	0	-	-	-	46	↑	↑	-
Shafford et al. (1993)	30	10 years (4–15 years)	11.8 years	ChlVPP	10	13	91%	9%	30	↑	↑	-
Papadakis et al. (1999)	36	13 years (2–22 years)	6.8 years	MDP	6	2	100%	–	36	↑	↑	-
Ben Arush et al. (2000)	20	2–16 years		MOPP/ABVD COMP MOPP	4	20	40%	40%	20	↑	↑	-
Cicognani et al. (2000)	11	10.3 years (3–15 years)	5.5 years	ABVD MOPP/ABVD COPP/ABVD	0	-	-	-	11	↑	↑	↓[d]
van den Berg et al. (2004)	14	14 years (5–18 years)	5.1 years	MOPP/ABVD	0	-	-	-	14	=[c]	=[c]	-
Gerres et al. (1998)	46	14.9 years	1.9 years	OEPA OEPA/COPP	0	-	-	-	46	↑[d]	↑[d]	-
van Beek et al. (2007a)	56	11.4 years (3.7–15.9 years)	15.5 years	A(or E)BVD MOPP/A (or E)BVD	0	21	53%[d]	6%[d]	56	↑[d]	↑[d]	↓[d]

- , information not available; CT, chemotherapy; MOPP, mechlorethamine*; vincristine, procarbazine*, prednisolone; COPP = MOPP cyclophosphamide* replaces mechlorethamine; COMP = COPP, methotrexate replaces procarbazine; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine*; MDP, doxorubicin, procarbazine*, prednisolone, vincristine, cyclophosphamide*; ChlVPP, chlorambucil*, vinblastine, procarbazine*, prednisolone; OEPA, vincristine, etoposide, prednisolone, doxyrubicin; OPPA = OEPA procarbazine* replaces etoposide. (* = alkylating agent) RT, number of patients with gonadal radiotherapy.
n, number of patients tested; azo, azoospermia; oligo, oligospermia; LH, luteinizing hormone; FSH, follicle-stimulating hormone. Arrows indicate increased (↑), decreased (↓) or normal values (=).
[a]Number of male survivors.
[b]Age at diagnosis (median and range).
[c]Only two male survivors with increased levels of FSH and one with an increased level of LH.
[d]Only in patients treated with MOPP or COPP.

result in reduced fertility or even infertility. Moreover, in women it might also cause a subsequent loss of bone mass due to the depletion of estrogens.

Male survivors

We identified 10 studies, involving 298 male survivors, concerning male gonadal dysfunction after childhood Hodgkin's lymphoma treatment in Table I. Azoospermia and oligospermia are common long-term side effects in male childhood Hodgkin's lymphoma patients after radiotherapy and chemotherapy, especially when alkylating agents, e.g. mustine or procarbazine were used.

Endocrine markers for male fertility. In most follow-up studies of long-term childhood cancer survivors, combinations of testicular volume, semen analysis and/or serum levels of LH, FSH and testosterone are assessed to evaluate gonadal function and fertility. An increase in serum FSH is considered to be the first indirect indicator of testicular dysfunction (Pierik *et al.*, 1998) and is reported more after alkylating chemotherapy when compared with treatment without alkylating chemotherapy (Mackie *et al.*, 1996; Schellong, 1996; Gerres *et al.*, 1998; van den Berg *et al.*, 2004). In general, the levels of LH and FSH are inversely correlated to the cumulative dose of alkylating agents (Bramswig *et al.*, 1990; Schellong, 1996; van Beek *et al.*, 2007a). No LH/FSH changes were found after chemotherapy with low dosages of alkylating agents (Gerres *et al.*, 1998; van den Berg *et al.*, 2004).

Recently, inhibin B has been identified as a good direct marker for assessment of testicular function. This hormone is produced by Sertoli cells of the testis, and inhibits the production of FSH in the pituitary. Inhibin B is strongly correlated with sperm counts (Klingmuller and Haidl, 1997; Pierik *et al.*, 1998; van Beek *et al.*, 2007a). In current medical practice where assisted reproductive technology (ART) is available, lower inhibin B levels do not necessarily mean infertility, but lower levels are associated with lower sperm counts in both healthy and subfertile men (Kingmuller and Haidl; 1997; Pierik *et al.*, 1998). Inhibin B, as a marker for gonadal impairment, was found to be lower in long-term survivors of childhood cancer (van Casteren *et al.*, 2009a, Fig. 1). Only two studies in childhood Hodgkin's lymphoma survivors used inhibin B as a marker for male gonadal function. One small study reported decreased inhibin B levels in childhood Hodgkin's lymphoma survivors treated with mechlorethamine, vincristine, procarbazine and prednisone (MOPP) and adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) or cyclophosphamide, vincristine, procarbazine and prednisolone (COPP) and ABVD compared with healthy controls (Cicognani *et al.*, 2000). We showed in male survivors of childhood Hodgkin's lymphoma that inhibin B was decreased after treatment with MOPP but not after epirubicin, bleomycin, vinblastine and dacarbazine (EBVD).

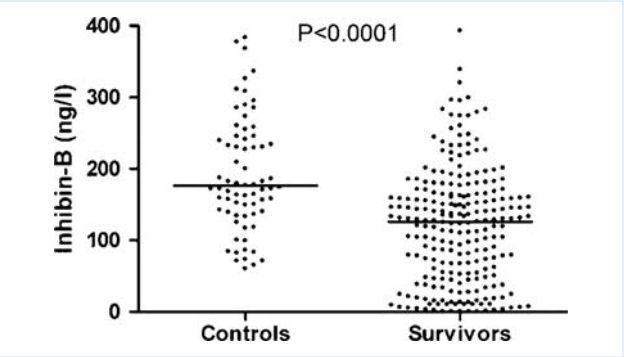

Figure 1 Inhibin B values of controls and childhood cancer survivors. Each dot represents one person. The horizontal lines represent the median values of inhibin B in the normospermic controls (176.5 ng/l) and in the survivors (123.0 ng/l, $P < 0.0001$) (adapted from van Casteren *et al.* 2009a). This material is reproduced with permission of John Wiley & Sons, Inc.

Moreover, inhibin B was a better indicator for spermatogenesis in long-term childhood Hodgkin's lymphoma survivors than FSH (van Beek *et al.*, 2007a).

Sperm quality. Nearly all male Hodgkin's lymphoma survivors treated with alkylating chemotherapy only, suffer from oligospermia or azoospermia. This is the case with both adult Hodgkin's lymphoma survivors (Waxman *et al.*, 1982; Clark *et al.*, 1995; Viviani *et al.*, 1999; Sieniawski *et al.*, 2008) and childhood Hodgkin's lymphoma survivors (Heikens *et al.*, 1996; van Beek *et al.*, 2007a). We showed that in 12 out of 17 (70%) long-term male survivors of childhood Hodgkin's lymphoma, treated without radiotherapy but with MOPP, had azoospermia or severe oligospermia, whereas all survivors treated without alkylating chemotherapy, had normospermia (van Beek *et al.*, 2007a). After 10 years of follow-up in a small group of survivors, no recovery of spermatogenesis was observed (Heikens *et al.*, 1996). In adult Hodgkin's lymphoma survivors, recovery of spermatogenesis after alkylating chemotherapy (such as procarbazine) has only been reported in a small proportion within 5–15 years follow-up, but survivors treated with ABVD appear to be at a significant advantage over survivors treated with MOPP in terms of testicular function, as demonstrated by the return to normal fertility in the vast majority of survivors treated with ABVD (Waxman *et al.*, 1982; Viviani *et al.*, 1985; Marmor and Duyck, 1995; Howell and Shalet, 2005; van der Kaaij *et al.*, 2010). Although animal studies suggest a protection against the cytotoxic effects of chemotherapy before puberty in both males and females (Shetty *et al.*, 2000), recent clinical studies in male patients treated for Hodgkin's lymphoma show no difference in the severity of the gonadal damage (van Beek *et al.*, 2007a) or the chance of recovery of spermatogenesis between boys treated before puberty and those treated during or after puberty (Ortin *et al.*, 1990; Ben Arush *et al.*, 2000). Although semen analysis studies are scarce, reduction of alkylating agents reduces the risk of gonadal damage, as detected by increased serum FSH levels and decreased inhibin B levels (van den Berg *et al.*, 2004). We recently reported, using sperm analysis combined with fertility markers like inhibin B, that gonadal damage was significantly related to the cumulative dosages of alkylating agents in childhood Hodgkin's lymphoma survivors (van Beek *et al.*, 2007a).

Since the testis is one of the most radiosensitive tissues, very low dosages of radiation can cause severe gonadal damage. When treated with testicular irradiation dosages below 0.2 Gy, no significant effect on FSH levels or sperm counts was observed in adult patients treated for Hodgkin's lymphoma. When treated with dosages between 0.2 and 0.7 Gy, a transient dose-dependent increase in FSH and reduction in sperm concentration were observed, with a return to normal values within 12–24 months ($n = 17$; Kinsella *et al.*, 1989). Ten adult Hodgkin's lymphoma patients treated with testicular doses of radiation of 1.2–3 Gy, were all azoospermic following treatment, with no recovery up to 15 months of follow-up. After 15 months, four patients showed recovery and up to 40 months later recovery was observed in another (Speiser *et al.*, 1973). After 17–43 months, no recovery was observed in patients treated with 1.4–2.6 Gy, but a return to fertility was seen in two patients treated with testicular radiation dosages of 1.2 Gy. This may represent a threshold for permanent testicular damage (Centola *et al.*, 1994). In survivors of childhood acute lymphoblastic leukemia treated with total body irradiation (TBI) or testicular irradiation ($n = 7$), severe gonadal damage was observed (van Casteren *et al.*, 2009b). In childhood Hodgkin's lymphoma survivors, pelvic radiotherapy in a small group of adult males caused azoospermia that was reversible in most cases (66–96%) within 2 years after cessation of therapy (Pedrick *et al.*, 1986; Dubey *et al.*, 2000). Ortin *et al.* reported a small group of boys treated with pelvic radiotherapy (30–45 Gy). Recovery of spermatogenesis occurred after longer follow-up, and recovery to normal levels was less frequent (2 out of 12: 17%) than reported in patients treated during adulthood (Ortin *et al.*, 1990).

In childhood Hodgkin's lymphoma survivors in whom radiotherapy and chemotherapy were combined, spermatogenesis was disturbed in up to 75–100% of the male patients, similar to studies with chemotherapy including alkylating agents (Ortin *et al.*, 1990; Shafford *et al.*, 1993; Papadakis *et al.*, 1999; Ben Arush *et al.*, 2000) (Table I).

In conclusion, in male childhood cancer survivors treated with alkylating agents or pelvic radiotherapy, severe gonadal damage is described. In survivors treated without alkylating agents, normal gonadal function was observed. Gonadal damage is significantly related to the cumulative dosages of alkylating agents. Recent studies with a long (>10 years) follow-up have shown recovery of spermatogenesis in a small proportion of childhood Hodgkin's lymphoma survivors. Therefore, prolonged follow-up studies are recommended to investigate recovery and to determine possible fertility treatment in male survivors.

Female survivors

We identified six studies involving 230 female survivors concerning female gonadal dysfunction after childhood Hodgkin's lymphoma treatment (Table II). In female childhood cancer survivors both alkylating agents and abdominal radiotherapy can cause severe ovarian damage, eventually leading to premature ovarian failure (POF) (van Beek *et al.*, 2007b; Green *et al.*, 2009a, b; Lie Fong *et al.*, 2009; Sudour *et al.*, 2010).

Endocrine markers for female fertility. Usually, gonadal function is measured in follow-up studies by analysing serum LH and FSH levels

Table II Studies on ovarian function in female childhood Hodgkin's lymphoma survivors.

Author	*n*[a]	Age (range)[b]	Median follow-up	Therapy		Gonadal evaluation					
				CT	RT	Amenorrhoea irregular cycle[c]	Pregnancies	Serum markers			
								n	LH	FSH	Inhibin B	AMH
Hudson *et al.* (1993)	37	14.6 years (4.3–20.1 years)	4.1 years	COP/ABVD	18	6/37	17 in 10 women	-	-	-	-	-
Ortin *et al.* (1990)	86	13 years (2–15 years)	9 years	MOPP MOPP/ABVD ABVD PAVe VMB	28	11/86	40 in 86 women	-	-	-	-	-
van den Berg *et al.* (2004)	14	14 years (5–18 years)	5.1 years	MOPP ABVD MOPP/ABVD	0	2/14	1 in 14 women	14	=[d]	=[d]	-	-
Mackie *et al.* (1996)	32	13.0 years (9.0–15.2 years)	4.3 years	ChlVPP	0	10/32	11 in 9 women	32	↑[e]	↑[e]	-	-
Papadakis *et al.* (1999)	29	14.1 years (6.1–20.0 years)	5.2 years	MDP	6	-	8 in 6 women	29	↑	↑	-	-
van Beek *et al.* (2007b)	32	11.6 years (5.7–24.5 years)	15.5 years	A(or E)BVD MOPP/A(orE)BVD	0	1/32	17 in 11 women	32	=	↑[f]	↓[f]	↓[f]

-, information not available; CT, chemotherapy; MOPP, mechlorethamine*, vincristine, procarbazine*, prednisolone; COP, cyclophosphamide*, vincristine, procarbazine*; ChlVPP, chlorambucil*, vinblastine, procarbazine*, prednisolone; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine*; PAVe, procarbazine*, alkeran*, vinblastine; VMB, vinblastine, bleomycin, methotrexate. (* = alkylating agent); RT, number of patients with gonadal radiotherapy; *n*, number of patients tested; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AMH, anti-Müllerian hormone. Arrows indicate increased (↑), decreased (↓) or normal values (=).

[a]Number of female survivors.

[b]Age at diagnosis (median and range).

[c]Amenorrhoea or irregular cycle only in female survivors treated with alkylating therapy or pelvic irradiation.

[d]Increased FSH in 17/32 and LH in 15/32 female survivors.

[e]Only two female survivors with increased levels of FSH and one with an increased level of LH.

[f]Only in women treated with MOPP.

(Burger *et al.*, 1995). Both FSH and LH are predictive for ovarian reserve although FSH presumably only increases above the normal range with severe loss of ovarian function (Fauser, 2000; Larsen *et al.*, 2003). In recent years, two new markers to assess ovarian function became available. The first one, inhibin B, which in females is solely produced by granulosa cells of small antral follicles, is decreased in women with known fertility problems (e.g. imminent ovarian failure) and undetectable in post-menopausal women (Yamoto *et al.*, 1997; Petraglia *et al.*, 1998; Burger, 1999). Inhibin B is one of the first endocrine markers to change in perimenopausal women and is the cause for the monotropic rise in FSH which is characteristic of the perimenopausal period (Burger *et al.*, 1999b). The second marker is anti-Müllerian hormone (AMH), which is similarly produced by granulosa cells of early developing (pre-) antral follicles, and levels decrease coinciding with a decrease in the number of developing follicles with age (de Vet *et al.*, 2002; van Disseldorp *et al.*, 2008; Shebl *et al.*, 2011). A strong correlation between irregular cycles (as a surrogate for menopausal transition) and AMH levels randomly measured during the reproductive lifespan in a group of healthy women was observed (van Rooij *et al.*, 2004). In addition, AMH was shown to be a good predictor for the success of ART (Eldar-Geva *et al.*, 2005; Silberstein *et al.*, 2006; Freour *et al.*, 2007; La Marca *et al.*, 2007; Kini *et al.*, 2010). However, results of different studies should be carefully interpreted, because international standards for AMH assays are lacking. Recently, it was reported that long-term ovarian function after chemotherapy can be predicted by pretreatment serum AMH levels in women with early breast cancer (Anderson and Cameron, 2011). We showed that AMH is a good early marker for a decreased ovarian reserve in female Hodgkin's lymphoma survivors, even when LH and FSH are still within normal ranges and menstrual cycles are still regular (van Beek *et al.*, 2007b). These results were recently confirmed in a larger cohort of survivors of other types of childhood cancer in our institute (Lie Fong *et al.*, 2009; Fig. 2).

Ovarian function. A small study showed that 8 out of 10 girls with Hodgkin's lymphoma, treated with pelvic irradiation only, had a preserved normal ovarian function. It is important to note that in that study nine girls did have an oophoropexy prior to irradiation to transfer the ovaries out of the radiation field. None of the girls treated with radiotherapy to other sites than the pelvis suffered from POF (Ortin *et al.*, 1990). AMH levels were not measured in this study. Abdominal radiotherapy can cause decreased levels of AMH, thereby reflecting critically impaired ovarian reserve even in the presence of, as yet, normal menstrual cycles (Lie Fong *et al.*, 2009). Another study showed that exposure to increasing dosages of radiation to the ovaries and a diagnosis of Hodgkin's lymphoma are risk factors for nonsurgical POF (Green *et al.*, 2009a, b). The studies that describe the reproductive status of women after chemotherapy and/or radiotherapy for childhood Hodgkin's lymphoma are reported in Table II. The incidence of POF depends on several factors: chemotherapy regime and dosages, pelvic radiotherapy and age at diagnosis. Several hypotheses have been postulated about the exact mechanisms of chemotherapy-induced ovarian damage, but the exact mechanisms still remain unknown. However it is clear that the damage caused by chemotherapy leads to a relatively poor pregnancy outcome in survivors (Meirow *et al.*, 2010). When treated with pelvic irradiation, the dose of radiation required to destroy 50% of primordial follicles was determined to be <2 Gy (Wallace *et al.*, 2003). One third of the Hodgkin's lymphoma survivors treated during childhood with chemotherapy containing procarbazine suffered from POF or had a high risk of entering menopause before the age of 40 years (Mackie *et al.*, 1996; de Bruin *et al.*, 2008). Recovery of ovarian function was reported rarely (Mackie *et al.*, 1996) and was not seen in patients treated with pelvic irradiation (Papadakis *et al.*, 1999). However Ortin *et al.* reported less than 10% POF after chemotherapy only and that the other survivors had normal menstruation function (Ortin *et al.*, 1990). We showed that ovarian damage occurs in the

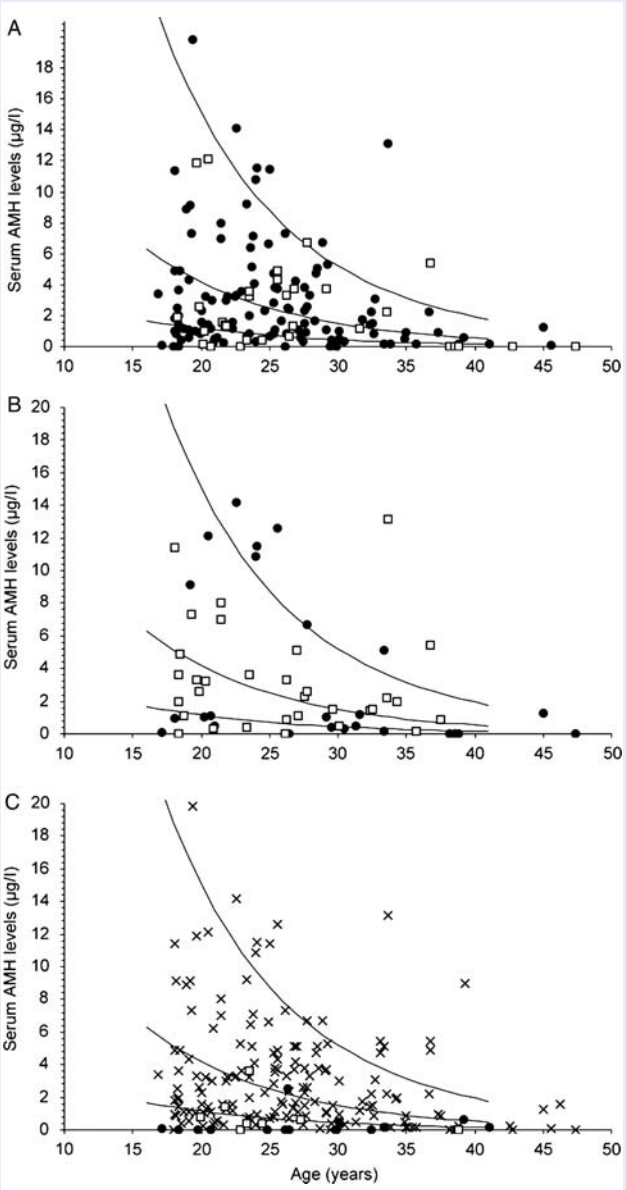

Figure 2 Serum AMH levels in subgroups of survivors compared with the 10th, 50th and 90th percentile of AMH levels in controls (——). (**A**) Survivors treated prior (•) to or after (□) menarche. (**B**) Survivors with regular menstrual cycles (•) or oligo- or amenorrhoea (□). (**C**) Survivors treated with TBI or abdominal radiotherapy (•), more than three MOPP cycles (□) or another treatment regimen (×) (adapted from: Lie Fong *et al.*, 2009).

majority of women treated with MOPP as reflected by severely decreased anti-Müllerian hormone (AMH) serum levels (van Beek et al., 2007b). These childhood Hodgkin's lymphoma survivors had significantly reduced AMH levels when compared with survivors of other types of childhood cancer (Lie Fong et al., 2009). Recently, AMH serum levels were measured prior to, during and after treatment in adult women treated with chemotherapy for lymphoma. Women treated with ABVD showed recovery of AMH levels at 12 months after stopping treatment, while women treated with non-ABVD but with cyclophosphamide showed no recovery of AMH levels at 12 months after stopping treatment (Decanter et al., 2010).

Childhood Hodgkin's lymphoma survivors treated with chemotherapy with a limitation of MOPP therapy to three courses seem to suffer less from gonadal damage compared with six MOPP courses (van den Berg et al., 2004; van Beek et al., 2007b). Cumulative risk of menopause at the age of 40 did not differ between childhood cancer survivors treated at a younger age when compared with those treated at an older age (de Bruin et al., 2008), nor between treatment before and after menarche (Lie Fong et al., 2009).

Several studies reported up to 40% POF in female Hodgkin's lymphoma survivors treated during childhood with both pelvic irradiation and alkylating chemotherapy (mustine and procarbazine) (Ortin et al., 1990; Hudson et al., 1993), while none of the women treated without pelvic irradiation ($n = 18$) had POF (Hudson et al., 1993). Some studies in adult female Hodgkin's lymphoma survivors suggest less POF when patients were treated before the age of 25 years when compared with those patients treated after that age (Kreuser et al., 1987) and a better chance of recovery of ovarian function (Brusamolino et al., 2000). Two large childhood cancer survivor cohorts reported increased risks of premature menopause or ovarian failure within 5 years after cessation of therapy after exposure to procarbazine and pelvic irradiation ($\geq$20 Gy), based on information obtained from questionnaires (Chiarelli et al., 1999; Chemaitilly et al., 2006).

In female childhood cancer survivors, both alkylating agents and abdominal radiotherapy can cause severe ovarian damage. Recovery of the gonadal function was reported rarely.

Pregnancy outcome. Fertility is decreased among female childhood cancer survivors compared with female siblings (RR: 0.81) (Green et al., 2009a) and survivors more frequently deliver preterm compared with their siblings when exposed to radiation. Chemotherapy alone does not appear to have an independent effect on the uterus (Signorello et al., 2006), but radiotherapy may cause damage to the uterus, which may lead to premature labour, low birthweight and a higher incidence of post-partum haemorrhage (Critchley, 1999; Critchley et al., 2002; Signorello et al., 2006; Green et al., 2009a, b; Reulen et al., 2009; Lie Fong et al., 2010). Also, a small increased risk of miscarriage was reported in survivors (Reulen et al., 2009). Recently an increased risk of stillbirth and neonatal death has been reported after uterine and ovarian irradiation (Signorello et al., 2010). Therefore a close monitoring during pregnancy and inpatient labour is warranted in women previously treated with abdominal radiotherapy (Lie Fong et al., 2010; Signorello et al., 2010).

Data about pregnancies in childhood Hodgkin's lymphoma survivors are scarce. The percentage of women becoming pregnant after treatment for Hodgkin's lymphoma in previous studies varies from <10% to almost 50% (Ortin et al., 1990; Hudson et al., 1993; Mackie et al., 1996; Papadakis et al., 1999; van den Berg et al., 2004; van Beek et al., 2007b). It is important to report that a proportion of these survivors are proved to be fertile. Confounders, such as age and fertility of the partner, family planning and the time to pregnancy are not available.

Differences in toxicity between male and female survivors

In the past, it has been suggested that gonadal damage was less frequent in female childhood Hodgkin's lymphoma survivors than in male survivors (Ortin et al., 1990). A reason for the less frequently found gonadal damage in female survivors may be the lack of reliable markers for measuring ovarian function in the past. Recent studies using AMH as a marker of ovarian reserve showed impaired gonadal function in a higher proportion of childhood Hodgkin's lymphoma survivors treated with more than three MOPP cycles, abdominal irradiation or TBI (van Beek et al., 2007b; Lie Fong et al., 2009). The extent of gonadal damage seems to depend mostly on the type of treatment, rather than age at treatment (Lie Fong et al., 2009). Previously, female patients younger than 25 years of age were thought to be protected against the toxic effects of alkylating agents (Kreuser et al., 1987; Brusamolino et al., 2000), but none of these studies used AMH. Therefore, the damage to the ovaries might have been underestimated. Early menopause may have been a disguised problem in female childhood Hodgkin's lymphoma survivors, especially after MOPP and abdominal irradiation, and therefore we proclaim that more attention should be paid to this issue, as it could have a major impact on fertility counselling and family planning of these young female childhood Hodgkin's lymphoma survivors treated with alkylating agents or abdominal irradiation.

Prevention

In some clinical trials, gonadotrophin-releasing hormone-analogues (GnRH-a) were used to prevent gonadal damage in patients treated with alkylating agents, and a possible protected function was observed (Pereyra Pacheco et al., 2001; Blumenfeld et al., 2002; Giuseppe et al., 2007). However, none of these studies were prospective, randomized clinical trials, and hence must be considered inconclusive (Lee et al., 2006). Recently, a prospective randomized study of hormonal co-treatment with oral contraception or GnRH-a during treatment for advanced-stage Hodgkin's lymphoma in young women reported no protection of ovarian reserve (Behringer et al., 2010). It is important to note that these studies have not evaluated long-term outcomes and the group of women was small. Therefore, this treatment should not replace alternative options for the protection of fertility, such as gonadal preservation, which should be offered to young female Hodgkin's lymphoma patients before treatment. Trials with GnRH-a in male patients showed no protection of GnRH-a treatment against cytotoxic damage (Johnson et al., 1985; Waxman et al., 1987; Krause and Pfluger, 1989).

Fertility preservation

Studies to prevent gonadal dysfunction in women still are the subject of research. Hence other options for fertility preservation remain very important. Ovarian cryopreservation in pre-pubertal girls, oophoropexy and oocyte vitrification in adults and embryo cryopreservation in adults with a partner are possible options. However, the success rate of ovarian cryopreservation is unclear since the number of women in whom frozen-thawed ovarian tissue has been reimplanted

is unknown (Wallace and Barr 2010). The American Society of Clinical Oncology guideline recommends that ovarian cryopreservation and transplantation procedures should only be performed in centres with the necessary expertise (Lee *et al.*, 2006). However, in Europe and North America, a small number of research-based ovarian tissue storage facilities can provide the best treatment. To provide success rates of cryopreservation, all procedures should be documented and analysed (Wallace and Barr, 2010).

Growth, osteoporosis and body composition

We identified seven studies involving 481 survivors concerning growth, osteoporosis and body composition after Hodgkin's lymphoma treatment during childhood (Table III).

Growth

In general, reduced growth in children during treatment for cancer is either caused by the malignancy itself, or by treatment-related morbidity, such as recurring infections, malnutrition during treatment and the treatment *per se* (surgery, chemotherapy and radiotherapy) (Sklar *et al.*, 1993; Roman *et al.*, 1997; van Leeuwen *et al.*, 2000). Chemotherapy induced growth impairment might be, at least in part, the result of growth hormone deficiency (Roman *et al.*, 1997) or direct interference with bone turnover (Samuelsson *et al.*, 1997). Irradiation of parts of the spine in children contributes to poor growth by decreasing the growth of individual bones of the spine. This may result in reduced final height, but also in disproportional growth. Most of the loss in height after radiotherapy or chemotherapy affects the upper part of the body, reflected by loss in sitting height (Davies *et al.*, 1994). This is not surprising since the spine contains large numbers of epiphyses and if chemotherapy has a direct effect on the epiphyseal growth plate, it seems likely that this would result in greater loss in sitting height than leg length (Davies *et al.*, 1995).

Most of the data regarding the negative effects of childhood Hodgkin's lymphoma treatment on growth are collected from survivors treated with combined modality treatment (Table III). In a study of 124 childhood Hodgkin's lymphoma survivors, treated at the age of 9–16 years with MOPP with or without ABVD, a height loss of 13 cm (2 SDs) was described more than 2 years after cessation of therapy (Willman *et al.*, 1994). This loss was most severe in pre-pubertal-treated children who had received high dose radiotherapy ($\geq$33 Gy) to the entire spine (Willman *et al.*, 1994). In survivors treated before the age of 14, a small, but significant, loss of final height of 0.4 SD after doxorubicin, procarbazine, prednisone, vincristine, cyclophosphamide (MDP) and radiotherapy ($n = 69$) was observed (Papadakis *et al.*, 1996), which is a quite modest loss of height when compared with losses reported in patients treated for other common paediatric malignancies, such as acute leukaemia and brain tumours. Nevertheless, patients treated with chemotherapy and radiation at younger age and with higher radiation dosages are likely to sustain clinically significant decrements in height potential and therefore should be counselled accordingly. Nysom *et al.* showed a reduced height after radiotherapy to the spine 11 years after diagnosis of childhood Hodgkin disease and non-Hodgkin lymphoma (Nysom *et al.*, 2001).

Scarce data are available on growth in childhood Hodgkin's lymphoma survivors after chemotherapy only. The 11 children reported by Papadakis *et al*. treated with chemotherapy only had normal final height (Papadakis *et al.*, 1996). Our own series of 88 Dutch childhood Hodgkin's lymphoma survivors treated with chemotherapy only, showed that only male survivors treated with MOPP had reduced height (van Beek *et al.*, 2009). This might be explained by the fact that the men were younger at diagnosis and more often treated at or before the time of peak height velocity compared with the women within this study.

From these studies, we can conclude that radiotherapy in a dose of more than 30 Gy including the spine (with or without chemotherapy) results in loss of height, most severe in pre-pubertal children. When lower dosages of radiotherapy are used, the impairment of skeletal growth appears to be minimal. Data on growth after chemotherapy only are scarce. Treatment with MOPP seems to cause a reduction in height as well (van Beek *et al.*, 2009). Therefore, extended follow-up studies are necessary to determine the long-term effects on growth. Overall, when comparing these findings with other common paediatric malignancies (such as leukaemia and brain tumours), the loss of height after treatment for Hodgkin's lymphoma seems to be quite modest.

Osteoporosis and osteopenia

As bone mass is acquired during childhood and adolescence, disturbance of this process can result in a lower peak bone mass which subsequently results in osteoporosis and higher fracture rate in later life. In general, BMD is determined by several factors, such as gender, race, physical activity, calcium intake, smoking and alcohol consumption (Krall and Dawson-Hughes, 1993; Lunt *et al.*, 2001). In young girls, the pubertal stage is the most important determinant of BMD, whereas in boys weight is the most important determinant (Boot *et al.*, 1997).

Corticosteroids, which are frequently used in the treatment for Hodgkin's lymphoma, can cause osteopenia and osteoporosis by interference with both osteoblast and osteoclast function (Boot *et al.*, 1999; van der Sluis *et al.*, 2000, 2002). Apart from these direct effects, also indirect effects of chemotherapy, such as gonadal damage, may affect bone turnover (Redman *et al.*, 1988; Kreuser *et al.*, 1992; Ratcliffe *et al.*, 1992). Gonadal damage may cause impaired estrogen production necessary to stimulate osteoblast activity and bone mass acquisition during puberty in females, but also in males (Morishima *et al.*, 1995; Khosla *et al.*, 1998; Grumbach, 2000). Some chemotherapeutic agents such as cyclophosphamide and cisplatin can cause renal damage. This may cause deregulation of the calcium and vitamin D metabolism resulting in lower BMD (Boot *et al.*, 1998). In addition, it has been described that patients during therapy, but also cancer survivors, are generally physically less active in comparison with healthy controls (Schwartz *et al.*, 1998). In children with cancer, the lack of physical activity can potentially cause decreased BMD (Slemenda *et al.*, 1994; Warner *et al.*, 1998).

A decreased BMD is reported in female survivors of adult Hodgkin's lymphoma with POF as well as in male survivors (Redman *et al.*, 1988; Kreuser *et al.*, 1992; Ratcliffe *et al.*, 1992; Holmes *et al.*, 1994; Howell *et al.*, 1998). Three studies reported a slightly reduced BMD, as measured by Dual-energy X-ray absorptiometry (DXA), in survivors of childhood Hodgkin's lymphoma 9.4–15.5 years after diagnosis (Nysom *et al.*, 2001; Sala *et al.*, 2007; van Beek *et al.*, 2009). Compared with local reference values, the size-adjusted bone mass in one study was normal (Nysom *et al.*, 2001). We have shown that female childhood Hodgkin's lymphoma survivors treated with

Table III Studies on BMD and growth in childhood Hodgkin's lymphoma survivors.

Author	n[a]	Age (range)[b]	Median follow-up	Therapy[c]		Outcome		
				CT	RT	Growth	BMD	Body composition
Willman *et al.* (1994)	124	9–16 years	>2 years	MOPP MOPP/ABVD	124[2]	Loss of height with ≥33 Gy radiotherapy in pre-pubertal children	-	-
Papadakis *et al.* (1996)	80	9.7 years (2.4–14.0 years)	>3 years	MDP	11[1], 58[4]	Reduced final height after radiotherapy. Lowest in children treated youngest	-	-
Nysom *et al.* (2001)	44 (23 HL)	11.1 years (3.9–15.0 years)	10.5 years	Prednisone Methotrexate	1[1], 10[2] 6[3], 27[4]	Reduced height	Normal	Increased percentage fat
Sala *et al.* (2007)	22	14.7 years (5.6–17.4 years)	>1 years	-	17[4]	-	Reduced BMD related to cumulative dose corticosteroids	-
Kaste *et al.* (2009)	109	15.1 years (3.1–20.7 years)	7.5 years	Procarbazine, cyclophosphamide, methotrexate, predisone	39	-	Normal, males increased risk for SDS < −1.5	-
van Beek *et al.* (2009)	88	11.6 years (3.7–17.2 years)	15.5 years	A(or E)BVD MOPP/A(or E)BVD	18[4]	Reduced height in males treated with MOPP	Reduced BMD in females treated with MOPP	Increased percentage fat (female without MOPP) Normal lean body mass
Muszynska-Roslan *et al.* (2009)	35	11.6 years (7.8–15.4 years)	6.3 years	Steroids CT without MTX	35		Normal	

-, information not available; HL, Hodgkin's lymphoma; CT, chemotherapy; MOPP, mustine, vincristine, procarbazine, prednisone; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; MDP, doxorubicin, procarbazine, prednisone, vincristine, cyclophosphamide; EBVD = ABVD, epiadriamycin replaces adriamycin; RT, number of patients with [1] = gonads in radiation field, [2] = lumbar spine in radiation field, [3] = cranial irradiation, [4] = other fields of irradiation.
[a]Number of survivors.
[b]Age at diagnosis (median and range).

alkylating chemotherapy (MOPP) without radiotherapy had a slightly, but significantly reduced BMD of the total body and after correction for bone size, also of the lumbar spine (van Beek *et al.*, 2009). Similarly, Sala *et al*. described a reduced BMD of the lumbar spine in childhood Hodgkin's lymphoma survivors, which was correlated with the cumulative dose of corticosteroids (Sala *et al.*, 2007). Another study in childhood Hodgkin's lymphoma survivors reported negligible BMD deficits overall. However, males diagnosed at 14 years or older, were at 6.5 times higher risk than females for BMD deficits (Kaste *et al.*, 2009). In a small series of children treated with prednisolone, chemotherapy and radiotherapy, anthropometric traits or bone mass did not differ from those in the reference group and mediastinal or abdominal irradiation was not associated with BMD (Muszynska-Roslan *et al.*, 2009).

Overall, the effects of childhood Hodgkin's lymphoma treatment on BMD appear to be small and longer follow-up studies are needed to assess the consequences, especially the incidence of osteoporosis, and subsequent fractures in later life. The real impact of childhood Hodgkin's lymphoma treatment on BMD during the post-menopausal period is not known, since it has only been possible to treat childhood cancer successfully over the last few decades. In addition, genetic variation, as reflected by allelic variation in specific single nucleotide polymorphisms, is an important denominator of bone mass in healthy post-menopausal women and also during therapy in certain types of childhood cancer (Kevenaar *et al.*, 2007; Stolk *et al.*, 2009; te Winkel *et al.*, 2010a, b). As yet, it is unknown whether this allelic variation contributes to a decrease in BMD after the age of 50 in childhood cancer survivors.

Body composition

We and others reported that treatment with prednisolone is a risk factor for an increased percentage of body fat in different groups of childhood cancer survivors, especially in acute lymphoblastic leukaemia (ALL) survivors (Nysom *et al.*, 1999; van Beek *et al.*, 2006). Only scarce data are available on body composition in survivors of childhood Hodgkin's lymphoma (Table III). Knowledge on this is important as higher fat mass and BMI increases the risk of metabolic syndrome and cardiovascular incidents in later life (Nuver *et al.*, 2002; Bogers *et al.*, 2007).

Nysom *et al.* showed an increased percentage body fat in a small series of long-term survivors of childhood Hodgkin's lymphoma who were treated with combined modality treatment (Nysom *et al.*, 2003). Our study in childhood Hodgkin's lymphoma survivors treated with chemotherapy only also revealed an increased percentage body fat (van Beek *et al.*, 2009). The percentage body fat of patients treated with MOPP (a prednisolone-containing regimen) was comparable with that of patients treated without MOPP, indicating that prednisolone is not an important determinant of increased percentage body fat in these patients. The different influences of steroids in Hodgkin's lymphoma survivors when compared with ALL survivors may be due to the fact that the cumulative dose of prednisolone is substantially lower in Hodgkin's lymphoma than in ALL (van der Sluis *et al.*, 2000). In childhood Hodgkin's lymphoma survivors, Nysom *et al.* reported normal BMI, despite an increased percentage fat and explained this by a decreased lean body mass, although the lean body mass was not directly measured (Nysom *et al.*, 2003). In our childhood Hodgkin's lymphoma survivor study, median BMI was increased, while lean body mass was normal, indicating that increased fat mass indeed plays an important role (van Beek *et al.*, 2009). In conclusion, scarce data are available on body composition after treatment for childhood Hodgkin's lymphoma. These survivors tend to have increased fat mass, which might increase the risk of developing the metabolic syndrome.

Thyroid

We identified 10 studies involving 4012 survivors about thyroid complications after Hodgkin's lymphoma treatment during childhood (Table IV). After cervical region irradiation, a large proportion, up to 40%, of the childhood Hodgkin's lymphoma survivors reveal thyroid disorders, such as hypothyroidism, thyroid nodules and thyroid cancer (Hancock *et al.*, 1991; Soberman *et al.*, 1991; Hudson *et al.*, 1993; Healy *et al.*, 1996; Atahan *et al.*, 1998; Brusamolino *et al.*, 2000; Sklar *et al.*, 2000; Solt *et al.*, 2000; Thomson and Wallace, 2002) (Table IV). In most of the protocols, the mean radiation dose on the thyroid region was $\geq$35 Gy. Although hyperthyroidism (mainly Graves' disease) may occur after radiotherapy, it is less frequent than hypothyroidism (Hancock *et al.*, 1991; Atahan *et al.*, 1998; Sklar *et al.*, 2000). Altogether, up to 40% of the childhood Hodgkin's lymphoma survivors treated with chemotherapy have impaired thyroid function (Hancock *et al.*, 1991; Healy *et al.*, 1996; Sklar *et al.*, 2000). In patients under the age of 17, the radiation dose has been shown to be the most important risk factor for developing hypothyroidism (Hancock *et al.*, 1991). Female sex and older age at diagnosis have been reported as independent, predisposing risk factors increasing the risk for hypothyroidism (Sklar *et al.*, 2000).

In contrast, in studies of survivors of childhood Hodgkin's lymphoma treated with chemotherapy only, no hypothyroidism was reported (van den Berg *et al.*, 1997a, b; Hakvoort-Cammel *et al.*, 2004) except for one single case (van Beek *et al.*, 2009). However, when patients received additional radiation to the thyroid or mediastinum, six of seven either had abnormal levels of thyroid-stimulating hormone (TSH) or free T4, or used thyroid hormones (van den Berg *et al.*, 1997a, b; van Beek *et al.*, 2009). In a cohort of 205 childhood cancer survivors (of which 28.5% had either Hodgkin's lymphoma or non-Hodgkin's lymphoma), van Santen *et al.* showed that addition of chemotherapy did not increase the damage to the thyroid axis already caused by radiotherapy (van Santen *et al.*, 2003).

The risk of thyroid cancer after radiotherapy is also markedly increased compared with the otherwise healthy population. A large study in more than 1700 childhood Hodgkin's lymphoma survivors reported 20 cases of thyroid carcinoma (RR 18.3) after a median follow-up of 15 years (Sklar *et al.*, 2000). All these 20 patients received radiotherapy to the cervical region. Hancock *et al.* reported that 6 out of 1677 Hodgkin's lymphoma survivors (both children and adults) after combined modality treatment had thyroid cancer (RR 15.6) after a mean follow-up of 10 years (Hancock *et al.*, 1991; Hancock and Hoppe, 1996). However, this follow-up is relatively short for developing a secondary malignancy (van den Berg *et al.*, 1997a, b; Hakvoort-Cammel *et al.*, 2004; van Beek *et al.*, 2009). Recently, 5 out of 112 cases of thyroid carcinoma were reported in children treated with MOPP/ABVD and lower dose radiotherapy after a median follow-up of 20 years (O'Brien *et al.*, 2010). The significant incidence of thyroid carcinoma in this low-dose radiation group is not surprising given the

Table IV Studies on thyroid complications in childhood Hodgkin's lymphoma survivors.

Author	n[a]	Age (range)[b]	Median follow-up	Therapy		Outcome			
				CT	RT	Hypo thyroidism	Hyper thyroidism	Carcinoma	Ultrasound abnormalities
van den Berg et al., (1997b)	21	14 years (5–18 years)	5.0 years	MOPP/ABVD	1	1/21	0/21	0/21	-
Soberman et al. (1991)	18	14 years	6.4 years	-	18	7/18	-	1/18	16/18
Hancock et al. (1991)	1787[c]	28 years (2–82 years)	9.9 years	MOPP MVP ABVD	1677	513/1677	32/1677	6/1677	44/1671
Healy et al. (1996)	46	12.5 years (4–16 years)	10.3 years	None	46	28/46	-	2/46	46/46
Sklar et al. (2000)	1791	14 years (2–20 years)	>5 years	-	1210	456/1791	82/1791	20/1791	146/1791
Atahan et al. (1998)	46	8.5 years (2–18 years)	10.5 years	COPP COPP/ABVD	46	22/46	1/46	-	-
Hudson et al. (1993)	79	14.6 years (4.3–20.1 years)	4.1 years	COP/ABVD	79	19/79	0/79	2/79	0/79
Solt et al. (2000)	26	10.8 years (2.1–16.4 years)	11.3 years	MOPP MOPP/ABVD	26	14/26	0/26	0/26	14/26
van Beek et al. (2009)	88	11.6 years 3.7–17.2 years	15.5 years	A(or E)BVD MOPP/A (or E)BVD	18	5/88	0/88	0/88	-
O'Brien et al. (2010)	110	11.3 years	20.6 years	ABVD/MOPP or MOPP	110			5/110	

-, information not available; CT, chemotherapy, MOPP, mustine, vincristine, procarbazine, prednisone; COPP, cyclophosphamide, vincristine, procarbazine, prednisone; COP, cyclophosphamide, vincristine, procarbazine; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; EBVD, ABVD, epiadriamycin replaces adriamycin; MVP, melphalan, procarbazine, vinblastine. RT, number of patients with radiotherapy to the cervical region.
[a]Number of survivors.
[b]Age at diagnosis (median and range).
[c]Paediatric patients (<17 year): $n = 272$ (analysis not specified for paediatric patients only).

Table V Recommendations: screening for long-term endocrine effects in childhood Hodgkin's lymphoma survivors.

Recommendations	Patients	Physical examination	Advanced screening
Growth, osteoporosis	Irradiation to the spine	Height, sitting height, weight	Dual-energy X-ray absorptiometry
Thyroid	Neck irradiation TBI	Palpation, TSH and free thyroid hormone	Thyroid ultrasound
Gonads: female	All, especially alkylating agents, pelvic/TBI	Tanner stadium Day 2–5: LH, FSH, inhibin B, AMH	Gynaecologist: antral follicle count
Gonads: male	All, especially alkylating agents, pelvic/TBI	Tanner stadium Sperm analysis, testis volume, LH, FSH, inhibin B	—

nonlinear radiation dose–response, in which the thyroid second malignant neoplasm (SMN) risk increases from 0 to 20 Gy and then decreases, with few cases occurring at dosages above 40 Gy due to extensive cell killing (Ronckers *et al.*, 2006). In childhood Hodgkin's lymphoma survivors treated with chemotherapy only, to our knowledge, no cases of thyroid cancer have been reported so far. We studied 88 childhood Hodgkin's lymphoma survivors not treated with radiotherapy and a median follow-up of 15 years, and no cases of thyroid cancer were found (van Beek *et al.*, 2009). Since the risk of thyroid cancer increases even after longer follow-up of more than 20 years (Oeffinger *et al.*, 2003), prolonged surveillance is necessary.

Altogether, hypothyroidism is the most common thyroid disorder after radiotherapy. There is a significant incidence of thyroid carcinoma in the low-dose radiation group, which is consistent with the hypothesis in which thyroid SMN risk increases from 0 to 20 Gy and then decreases due to cell killing. In survivors treated with chemotherapy only, hypothyroidism does not seem to occur and no cases of thyroid cancer have been reported. However, prolonged follow-up is necessary to evaluate the incidence after 20 years.

Recommendations and perspectives

Screening

No consensus exists yet on how to monitor long-term endocrine side effects after childhood Hodgkin's lymphoma. The identification of

novel markers opens new options for screening. However, there are several ways of detecting long-term endocrine effects (Table V).

Gonads

In male survivors, evaluation of testicular function should consist of assessment of Tanner stage, testicular volume and consistency and sperm analysis as well as assessment of LH, FSH and inhibin B serum measurement. Inhibin B, produced by Sertoli cells, is a direct marker that correlates strongly with spermatogenesis. So far, semen analysis has been the standard. However, inhibin B might be a less invasive and reliable marker for gonadal (dys)function. Inhibin B serum levels $<$150 ng/l might be indicative for gonadal damage. Consequently, a sperm analysis should be performed and the patient should be referred to an andrologist.

In female patients, the evaluation should consist of the Tanner stage and LH, FSH, inhibin B and AMH should be assessed. A transvaginal ultrasound might be performed to determine the antral follicle count. LH, FSH and inhibin B should be determined on day 2–5 of the menstrual cycle. If the patient uses oral contraceptives, these tests should be performed a minimum of 1 week after the last pill was taken to minimize the effects of the pill on the gonadal markers (van Heusden and Fauser, 1999). In contrast to FSH, AMH levels seem to be constant during the menstrual cycle (Cook *et al.*, 2000; Fanchin *et al.*, 2005; Hehenkamp *et al.*, 2006; Somunkiran *et al.*, 2007; van den Berg *et al.* 2010). Serum AMH is currently the most reliable serum marker for ovarian reserve (van Rooij *et al.*, 2002; de Vet *et al.*, 2002; van Beek *et al.*, 2007b). Recently, the correlations between ovarian primordial follicle count and antral follicle count and AMH were described, where the antral follicle count ($r = 0.78$) showed a greater correlation with the ovarian primordial follicle count than AMH (Hansen *et al.*, 2011). However, the difference was relatively small. First, the predictive value of AMH in identifying those women with a diminished ovarian reserve and hence absolute infertility remains to be established. Therefore, ovarian ultrasound to assess the number of small antral follicles remains important.

Growth and osteoporosis

Proper history taking and complete physical examination (including height, sitting height and weight) should be performed in patients treated with radiotherapy which included the spinal areas. Survivors of childhood Hodgkin's lymphoma treated with lower dosages of radiotherapy do n't seem to be prone to develop growth disorders and osteoporosis. If a patient is treated with high dosages of radiotherapy and is at risk for osteoporosis after taking a proper history and complete physical examination, DXA should be performed, which is an easy and reliable way to assess BMD and body composition. If the BMD is decreased with clinical impact, treatment with bisphosphonates could be considered with caution since they remain in the skeleton for decades. Whether the long-term inhibition of bone turnover can be harmful over time remains unresolved (Sambrook and Cooper; 2006). In human, no studies which investigate teratogenicity have been performed, but in animal studies, teratogenicity was suggested (Patlas *et al.*, 1999). Hence, bisphosphonates should not be used during pregnancy. First, it should be investigated that whether the decreased BMD is caused by POF. If this is the case, hormone replacement therapy should be considered first.

Thyroid

Since patients treated with irradiation to the cervical region or total body are at risk for developing thyroid disorders such as hypothyroidism, thyroid nodules and thyroid cancer, these survivors should be in a specific follow-up programme. Thyroid function can easily be followed using TSH and free thyroid hormone in both male and female patients. To detect morphological changes of thyroid tissue, an ultrasound of the thyroid can be useful, especially when radiotherapy to the cervical region was administered (Healy *et al.*, 1996; Solt *et al.*, 2000). However it is important to note that benign changes will be observed that may lead to unnecessary invasive procedures. There is an ongoing debate about implementing this screening because of the high rate of false-positive findings. We advise performing the physical examination (palpation of the thyroid) and measuring TSH and free thyroid hormone levels. If these levels are abnormal, supplementation should be started in order to normalize these hormones.

Prevention

There is no worldwide consensus on the prevention of long-term endocrine side effects. National and international experts are in the process of formulating guidelines. Most important is to adjust treatment to decrease toxicity as much as possible without increasing risk of relapse. Because this is difficult, preservation of gonadal material is an attractive option. Commonly used techniques to preserve gonadal function include sperm, embryo and oocyte cryopreservation and are advised for all applicable patients who are at risk for infertility (Lee *et al.*, 2006). Semen cryopreservation in boys is a feasible method to preserve spermatozoa before gonadotoxic therapy is started and should be offered to all pubertal boys from 12 to 13 years of age despite their young age (van Casteren *et al.*, 2008). Semen is obtained after masturbation in the majority of the boys. When this is impossible, penile vibration or electroejaculation have to be considered (Muller *et al.*, 2000).

No protection was observed when using GnRH-a in young women treated for advanced-stage Hodgkin lymphoma (Behringer *et al.*, 2010). Preventive therapeutic methods such as oocyte vitrification, preservation of entire ovaries and oophoropexy are promising, but remain subject of further research (Donnez *et al.*, 2006; Terenziani *et al.*, 2009).

Conclusions

Childhood cancer survival is increasing. Childhood Hodgkin's lymphoma survival has reached 90% and therefore long-term effects of treatment have gained increasing interest. As shown in this review, the severity of the endocrine toxicity after childhood Hodgkin's lymphoma depends mainly on the type of treatment. Gonadal dysfunction seems to be the most severe endocrine long-term effect. In survivors treated with alkylating agents or pelvic radiotherapy, severe gonadal damage is described and seems to be irreversible in women and partly in men. However, prolonged follow-up is necessary to determine possible recovery. Nowadays, many centres have specific follow-up programmes to detect and, if necessary, treat the long-term side effects of cancer treatment during childhood. The knowledge obtained in these outpatient clinics can help in the search for the

optimal balance between cure and late effects in treatments for childhood and adolescent Hodgkin's lymphoma.

Authors' roles

W.D. manuscript writing, data collection and data analysis; final approval of the version to be published. R.D.B. manuscript writing, data collection and data analysis; final approval of the version to be published. J.S.E.L. manuscript writing, study design; final approval of the version to be published. R.P. manuscript revising, study design; final approval of the version to be published. S.M.P.F.M.K.-S. manuscript writing, study design; final approval of the version to be published. M.M.H.-E. manuscript writing, study design; final approval of the version to be published.

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