Original article

Annals of Oncology 13: 1786–1791, 2002
DOI: 10.1093/annonc/mdf289

Long-term risk of second malignancy after treatment of Hodgkin's disease: the influence of treatment, age and follow-up time

A. Foss Abrahamsen[1]*, A. Andersen[2], O. Nome[1], A. B. Jacobsen[1], H. Holte[1], J. Foss Abrahamsen[1] & S. Kvaløy[1]

[1]*Department of Medical Oncology and Radiotherapy, The Norwegian Radium Hospital, Oslo;* [2]*The Cancer Registry of Norway, Oslo, Norway*

Received 15 January 2002; revised 2 May 2002; accepted 22 May 2002

Background: To quantify the long-term risk of second cancers (SCs) up to 30 years after primary treatment for Hodgkin's disease (HD)

Material and methods: In the period 1968 to 1985, an unselected population of 1024 patients started treatment for HD at the Norwegian Radium Hospital (NRH) and were followed for SC from 1969 through 1998 by The Norwegian Cancer Registry. The median age at diagnosis of HD was 40 years, and the median time at follow-up was 14 years.

Results: Of 197 SCs, 14 were acute non-lymphocytic leukemia (ANLL), 31 non-Hodgkin's lymphoma (NHL) and 152 solid cancers. The standardized incidence ratio (SIR) was significantly increased for SCs as a group, and for the subgroups ANLL, NHL, lung cancer, breast cancer, stomach cancer and melanoma. ANLL was related to heavy treatment with chemotherapy (CT) and combined CT and radiotherapy (RT), NHL was not treatment related, and solid tumors were related to radiotherapy only or combined RT and CT. The SIR of ANLL and NHL reached a peak between 5 and 10 years after treatment. Solid and non-solid tumors increased with young age at diagnosis of HD and solid tumors increased with follow-up time up to 28 years

Conclusion: In a long-term follow-up study of HD patients of all ages, the SIR of solid tumors was high in patients treated at young age and decreased with increasing age. Most solid tumors had started within or at the edge of the irradiated field, and SIR of solid tumors increased even 20–30 years after diagnosis.

Key words: Hodgkin's disease, second malignancies

Introduction

Combination chemotherapy (CT) and extensive radiotherapy (RT) introduced in the late 1960s greatly improved survival rates in Hodgkin's disease (HD), but increased risk of second cancer (SC) was reported from the early 1970s [1, 2]. Later, numerous studies have reported on this issue [3–19]. An increased incidence of ANLL in patients treated with CT alone or combined RT and CT, and solid tumors in those treated with RT or combined RT and CT, have consistently been reported. The development of secondary non-Hodgkin's lymphoma (NHL) has been reported following both RT and CT, which it has been claimed is not treatment related, but part of the natural history of HD [3–5]. Increased risk of ANLL and NHL has been found up to 10 years after treatment. In contrast, SCs increase steadily with time up to 20 years after treatment. It is not clear whether the increased risk of SCs observed in the 10–20 years follow-up interval will continue to increase further with more prolonged follow-up, or level off or decrease at some point of time after >20 years follow-up. In a recent study, HD patients treated during adolescence or young adulthood still had an increased risk of SC even >20 years after first treatment [7, 9]. In this study we present a follow-up study of an adult patient population up to 30 years after initial treatment.

Patients and methods

Data collection procedures

The Tumor Registry of the Norwegian Radium Hospital (NRH) keeps information on date of diagnosis and start of treatment, histology, stage, first relapse and treatment, and death for all HD patients admitted to the hospital. Through this registry we identified 1203 patients who started their first treatment for HD in the period 1968 through 1985. We excluded

**Correspondence to:* Dr A. F. Abrahamsen, The Norwegian Radium Hospital, Montebello, N-0310 Oslo, Norway. Tel: +47-22-93-40-00; Fax: +47-22-93-58-08; E-mail: harald.holte@klinmed.uio.no

176 patients who survived <1 year after HD diagnosis and three patients with missing information. Thus, 1024 HD patients were eligable for the study. The Norwegian Cancer Registry keeps information of all cancers diagnosed in Norway since 1953. From this national registry we identified 197 SCs in 174 patients treated at NRH diagnosed >1 year after HD diagnosis. Twenty-two patients had two SCs and one patient three SCs. Patients with non-melanoma skin cancer were excluded.

Material

Some characteristics of the study population are listed in Table 1. The median age was 40 years, and 58% were first treated at the age of 40 years or younger. Only 3% were <15 years old, and 17% were >60 years old. Forty-five percent had advanced disease (stage III and IV). Fifty-two percent of the population were in continous complete remission, 15% had one relapse, 4% had two or more relapses, and 29% had not obtained complete remission. Forty-four per cent had received RT only, 36% had received combined RT and CT, and 20% had received CT only.The median follow-up time for the whole study population was 14 years.

Table 1. Characteristics of 1024 Hodgkin's disease (HD) patients included in the present study

	No.	%
Sex		
Male	624	61
Female	400	39
Age at diagnosis (years)		
0–15	27	3
15–40	560	55
41–50	133	13
51–60	131	13
60+	173	17
Histology		
Lymphocyte predominance	161	15.7
Nodular sclerosis	391	38.2
Mixed cellularity	236	32.8
Lymphocyte depletion	61	6
Unclassified	75	7.3
Stage		
I and II	567	55.4
III and IV	457	44.6
Total treatment		
RT only	447	43.7
CT only	202	19.7
RT + CT	363	35.5
Observed untreated	12	1.1
Follow-up time (years)		
1–4	245	23.9
5–9	131	12.8
10–14	159	15.5
15–19	221	21.6
20+	268	26.2

Treatment

The Ann Arbor staging classification was used, and treatment was provided according to the stage of disease and histology. In the periods 1968 through 1970 and 1980 through 1997, clinical staging was performed. From 1970 to 1979 clinical stage I and II patients had pathological staging by exploratory laparotomy with splenectomy. The treatment of HD in Norway was changed in 1980. Before that time, stage I and II patients received only RT as mantle or inverted Y field, stage III patients received total nodal irradiation and stage IV patients received six to eight courses of combination CT. After 1980, stage I and II patients with high risk of relapse (B symptoms, a large mediastinal mass, subdiaphragmatic disease, more than three involved sites or lymphocytic-depleted histology) received four courses of combination CT before RT. Stage III and IV patients received combination chemotherapy. RT was administered using a 7 MeV linear accelerator in the majority of cases. The midplane dose was 38–40 Gy, administered at 2 Gy/fraction, five fractions weekly. Since 1984 fractions of 1.8 Gy were given 5 days a week to a total of 41.4 Gy. A selection of standard blocks were adapted to optimize lung shielding. Since 1987 the lung shields have been made individually. Subcarinal blocks were adapted after 30.6 Gy if the patient showed no evidence of subcarinal disease. CT consisted of a combination of nitrogen mustard (mechlorethamine) or chlorambucil, vinblastine, procarbazine and prednisolone (MVPP, LVPP), doxorubicin, bleomycin, vincristine and dacarbazine (ABOD), or alternating LVPP/ABOD.

Total treatment includes first-line and relapse treatment.

Statistical analysis

The follow-up evaluation of SCs started 1 year after the date of diagnosis of HD. All patients were monitored until the end of 1998 or to the middle of the year of death or emigration, whichever came first. The study was based on comparison of the observed and expected numbers of cancers in the cohort. The 5-year, age-specific national incidence rates for each sex and for each year 1969 through 1998 were used to estimate the expected number of cancer cases. The standardized incidence ratio (SIR) was calculated for total cases of cancer and for selected cancer sites. Ninety-five percent confidence intervals (95% CIs) were determined by assuming a Poisson distribution of the observed number of cancer cases. A result was considered to be statistically significant if the 95% CI did not include 1.00.

Absolute excess risk, which estimates the excess number of SCs per 10000 patients per year, is the most appropriate risk measure to judge which SC contributes most to the excess risk.

Results

Risk of SCs

The observed and expected numbers of SC according to site are listed in Table 2. There were statistically elevated risks of all SCs combined, ANLL, NHL, lung cancer, breast cancer, stomach cancer and melanoma

Risk of SC by type of treatment and treatment results

ANLL was related to CT alone or to combined CT and RT (Table 3). All patients were heavily treated, four patients

Table 2. Observed and expected numbers of second cancers (SCs) according to site

Site	Observed cases	SIR	95% CI
All SCs	194	3.5	3.1–4.1
ANLL	14	13	7.1–21.8
NHL	31	24.2	16.4–34.3
Solid tumors			
Lung	26	5.1	3.3–7.5
Breast	23	3.8	2.4–5.8
Melanoma	8	2.8	1.2–5.5
Stomach	12	4.4	2.3–7.7
Colon	9	1.9	0.9–3.7
Rectum	7	2.7	1–5.5
Prostate	10	1.7	0.8–3
Cervix	2	1.5	0.2–5.4
Pancreas	2	1.3	0.2–4.7
Others	53	2.7	2–3.6

SIR, standardized incidence ratio.

received total nodal irradiation and six or more cycles of CT, five patients had received mantle or inverted Y field plus CT, and five patients had received eight to 16 cycles of CT. The chemotherapy included in all patients procarbazine and an alkylating agent.

For NHL, the risk seemed to be equally increased for all treatment categories.

The excess risk of developing solid tumors like lung cancer, breast cancer and stomach cancer was statistically increased after RT alone or after combined RT and CT, but was not as related to CT alone. Melanoma was observed only after RT.

The relation between the localization of solid cancers and the irradiated field is shown in Table 4. Most of the solid cancers were found within or at the edge of the irradiated field.

The SIR of ANLL was increased in patients with one relapse (SIR 25) and in patients with two or more relapses (SIR 45) as compared with not relapsed patients (SIR 14). In solid tumors the SIR of SC was not different in relapsed and not relapsed patients

Risk of SC by age at diagnosis of HD

The effect of age at diagnosis on the risk of developing SCs is shown in Table 5. The observed numbers and SIR of all SCs combined, and of ANLLs, NHLs and solid tumors were highest for young patients up to 40 years old, except breast cancer, which dominated in patients <25 years old. Significantly increased SIR was not observed in stomach cancer and melanoma after age 40 years, in breast cancer after age 50 years, and in ANLL and lung cancer after age 60 years at HD diagnosis.

Risk of SC by follow-up time

As shown in Table 6, SIR for developing a SC increased with follow-up time for all second malignancies, even >20 years after diagnosis. For ANLL and NHL the excess risk was highest during the first 5–10 years of follow-up. ANLL was not observed after 20 years of follow-up. Lung, breast and stomach cancer increased with increasing follow-up time. In contrast to other solid tumors, the SIR of melanoma was statistically increased only during the first 5 years of follow-up.

The actuarial risks of all SCs, solid tumors combined, ANLL and NHL are shown in Figure 1. The risks of all SCs and of all solid tumors increased steadily up to 28 years after HD diagnosis. The mean cumulative risks after 28 years were: for all SCs 18.8%, all solid tumors 14.4%, NHL 3% and ANLL 1.5%

Discussion

This long-term follow-up study in survivors of HD showed that the risk of second malignancies continued to increase significantly >20 years after diagnosis. In 20-year survivors,

Table 3. Observed number and relative risk of second cancers (SCs) according to type of treatment

Type SC	RT only			CT only			RT + CT		
	Obs	SIR	95% CI	Obs	SIR	95% CI	Obs	SIR	95% CI
All	103	4.1	3.4–5	32	2.6	1.8–3.6	61	3.8	2.9–4.9
ANLL	2	4	0.5–14.5	4	15.4	4.2–39.3	8	26.9	11.6–53
NHL	15	26.1	14.6–42.9	6	24.9	9.1–54.1	10	22.9	11–42.1
Lung	14	6.6	3.6–11	3	2.5	0.5–7.2	9	5.6	2.5–10.6
Breast	16	5	2.8–8	1	1	0–5.4	6	3.5	1.3–7.7
Stomach	6	4.9	1.8–10.7	2	2.7	0.3–9.7	4	5.8	1.6–14.8
Melanoma	7	5.1	2–10.5	0	0		1	1	0–5.8

Obs, observed.

Table 4. Relation between development of solid cancers and radiotherapy (RT) field

Solid cancer	No.	Within RT field	Outside RT field	CT only
Lung	26	22	1	3
Breast	23	19	3	1
Stomach	12	9	1	2
Melanoma	8	6	2	0

Table 5. Relative and absolute excess risks of second cancers (SCs) according to age at Hodgkin's disease (HD) diagnosis

Age at diagnosis of HD	Observed number	SIR	95% CI	AER
All malignancies				
0–40	91	6.2	5–7.6	10
41–50	34	3.7	2.6–5.2	209
51–60	35	2.5	1.7–3.5	265
60+	37	2.1	1.5–2.9	372
ANLL				
0–40	7	24.9	10–51.2	8
51–50	3	20.1	4.2–58.8	18
51–60	2	8.3	1–29.9	16
60+	2	5	0.6–17.8	20
NHL				
0–40	18	33.2	19.7–52.4	20
41–50	3	13.2	2.7–38.7	18
51–60	4	14.5	4–37.2	16
60+	6	25.2	9.3–55	60
Lung				
0–40	9	9.8	4.5–18.6	20
41–50	7	6.6	2.7–13.6	43
51–60	7	4.7	1.9–9.7	56
60+	3	1.8	0.4–5.3	30
Breast				
0–15	2	201.3	24.4–727.2	29
16–20	5	30.2	9.8–70.5	34
21–25	6	14.2	5.2–31	29
26–40	5	2.2	0.7–5.1	10
41–50	5	4.4	1.4–10.3	30
51–60	0			
60+	0			
Stomach				
0–40	6	17.7	6.5–38.5	7
41–50	1	2.7	0.1–15.3	6
51–60	3	4.4	0.9–12.9	24
60+	2	1.5	0,2-5.4	20
Melanoma				
0–40	6	3.7	1.4–8	7
41–50	1	2	0.1–11.1	6
51–60	1	2.4	0.1–13.3	8
60+	0			

AER, absolute excess risk per 10 000 patients per year.

the excess number of cancer cases was 277 per 10 000 patients per year. Solid cancers contributed the most to this excess risk (87%). The SIR of ANLL, NHL, lung cancer, breast cancer, stomach cancer and melanoma were significantly increased as compared with general population expectations. The increased risk of ANLL and NHL leveled off at 10 years after first treatment. The solid tumors continued to increase >20 years after first treatment. The SIR of SCs greatly increased with younger age at first treatment. Breast cancer dominated in women <25 years old. Heavy treatment with CT alone or combined CT and RT predisposed subjects to ANLL. RT alone or combined with CT predisposed subjects to solid tumors. NHL seemed not to be related to treatment type.

Only a few studies have compared long-term SC risk between age groups other than in childhood, adolescence and adults <40 years old. Recent long-term follow-up studies from two Dutch cancer centers [9] and one from a US center [7] have shown increased risks of SCs at ages <40 years at HD diagnosis, and also a British total population-based study like ours [8]. Our data have confirmed these authors' observations as to the high risks in young patients. In addition, our study has shown decreased SIR of SCs after the age of 40 years, and not significantly increased SIR in older patients.

The SIR of ANLL reached a peak during 5–10 years after treatment, as stated in other studies [8–11]. All these patients had received combination chemotherapy including an alkylating agent and procarbazine. The extensive treatment received by these patients and the increased SIR in relapsed patients point to the importance of intense treatment for developing ANLL.

The increased risk of developing NHL reached a peak during the first 10 years of follow-up, as shown in two previous studies [8, 19]. In general, however, a consistent pattern has not been reported [10, 11]. The SIR of NHL was not related to age or treatment modality. It is suggested that these patients have a propensity for lymphoproliferative disorders, possibly associated with some immune deficiency [3].

Most studies have generally attributed the excess risk of solid cancers to RT [8–11, 17]. In our study, the SIR of lung cancer increased with follow-up time. Eighty-eight percent of patients with lung cancer had received RT, most of them mantle field. Twenty-two of 23 irradiated patients (96%) had a tumor within or at the edge of the radiation field. These data support RT to be the dominant risk factor for lung cancer after HD.

An unresolved issue in the literature is whether CT for HD can also induce solid cancers and, if so, at which sites [9]. A few recent studies have raised concern about a possible long-

Table 6. Relative and absolute excess risk of second cancers (SCs), according to follow-up time

Follow-up time (years)	Observed cases	SIR	95% CI	AER
All malignancies				
1–4	28	2.2	1.5–3.2	80
5–9	47	3.5	2.6–4.7	133
10–19	89	4.1	3.3–5	184
20+	33	4.5	3.1–6.4	277
ANLL				
1–4	3	9.9	2–29	9
5–9	6	21.1	7.8–46	17
10–19	5	13.2	4.3–30.8	10
20+	0	0	0	0
NHL				
1–4	4	24.4	7.6–62.5	11
5–9	11	41.1	20.5–73.6	31
10–19	13	20.9	11.1–35.7	27
20+	3	13	2.7–38.3	35
Lung				
1–4	2	1.7	0.2–6.3	6
5–9	6	4.8	1.8–10.5	17
10–19	13	6.4	3.4–11	27
20+	5	7.3	2.4–17.1	42
Breast				
1–4	2	1.9	0.2–7	6
5–9	1	0.8	0–4.5	3
10–19	13	5	2.7–8.5	27
20+	7	6.2	2.5–12.8	59
Stomach				
1–4	1	1.2	0–6.4	3
5–9	1	1.3	0–7.5	3
10–19	7	8	3.2–16.4	14
20+	3	13	2.7–38.1	25
Melanoma				
1–4	3	6	1.2–17.6	9
5–9	1	1.5	0–8.3	3
10–19	3	2.3	0.5–6.9	6
20+	1	2.4	0.1–13.5	8

AER, absolute excess risk per 10 000 persons per year.

term effect of CT on lung cancer risk [9, 15, 20–22]. We could not show increased risk of solid tumors after CT alone, but the expected percentage in our study was only 3%.

Breast cancer dominated in women aged <25 years, and was not observed in women >50 years old, at HD diagnosis. The SIR of breast cancer was not increased during the first 10 years

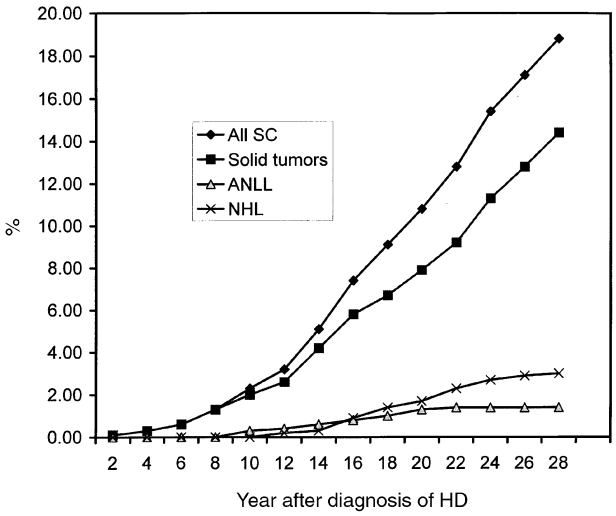

Figure 1. Actuarial risk of second cancer (SC) in 1024 patients treated for Hodgkin's disease.

after diagnosis, but increased with long-term follow-up. Most of the patients had received RT alone or combined RT and CT, and only one of 23 patients had received CT only. Most of the patients had received mantle field irradiation, and 19 of 23 patients (83%) had the tumor localized within or at the edge of the radiation field. The increased risk of breast cancer in long-term follow-up of young HD patients is in agreement with the findings of previous studies [8, 9, 11, 17].

We observed a significantly increased SIR of stomach cancer and a borderline risk of rectum cancer. Stomach cancer was not significantly increased during the first 10 years after diagnosis, but the SIR increased with long-term follow-up. Increased risk of stomach cancer was only observed in patients <40 years old at HD diagnosis. The increasing risk of gastrointestinal cancers with longer follow-up of HD has been observed previously [8, 9, 11]. There are, however, limited data available on treatment-related risks of gastrointestinal cancer after HD. In our study, the SIR of stomach cancer was related to previous RT and combined RT and CT, but not to CT alone. A British study [8] observed a borderline significant risk after RT, but a larger and highly significant risk after combined RT and CT. The risk after CT alone was not significantly increased, which is in agreement with our results. Nine of 12 patients with stomach cancer (75%) had the tumor localized within or at the edge of the irradiated field.

We observed an increased SIR of melanoma in patients <40 years old at treatment, and only during the first 5 years of follow-up. In contrast to other solid tumors, the risk of melanoma was not increased in long-term survivors. Seven of eight patients had received RT only, and none had received CT only. The increased risk of melanoma in this cohort is in accordance with previous findings [8, 10, 11]. The timing of this risk in the first years after treatment accords with two previous studies [8, 23]. There was previously limited evidence of an association of risk of melanoma with RT. The previous

dominant treatment in our melanoma patients was RT alone (91%), and in another study [8] all melanoma patients had received RT alone. In general the development of melanoma has not been associated with RT. It has been suggested that the early risk of melanoma after RT might reflect immunological dysfunction from HD and immunosuppressive effects of the treatment [24].

In conclusion, treatment-related SCs remain a major problem in long-term survivors of HD. The risk is greatly increased in childhood, adolescent or young adult patients at first treatment. The increased risk of ANLL and NHL levelled off at 10 years after treatment. Solid cancers increased with follow-up time up to 28 years after first treatment. ANLL was related to CT with procarbazine and an alkylating agent, and may be substantially decreased after introduction of ABOD-based regimens [9, 11]. NHL seemed not to be related to treatment modality. The solid cancers were related to RT or combined RT and CT, and most of them occurred within or at the edge of the irradiated field. Reduced radiation doses and fields may reduce the development of some solid cancers [24].

References

1. Arsenau JC, Sponzo RW, Levin DL et al. Nonlymphomatous malignant tumors complicating Hodgkin's disease. Possible association with intensive chemotherapy. N Engl J Med 1972; 287: 1119–1122.
2. Canellos GP, DeVita VT, Arsenau JC et al. Second malignancies complicating Hodgkin's disease in remission. Lancet 1975; i: 947–949.
3. Bennett MH, MacLennan KA, Vaughan Hudson G et al. Non-Hodgkin's lymphoma arising in patients treated for Hodgkin's disease in the BNLI: A 20-year experience. Ann Oncol 1991; 2: 83–92.
4. Harris NL. The relationship between Hodgkin's disease and non-Hodgkin's lymphoma. Semin Diagn Pathol 1992; 9: 304–310.
5. Jaffe ES, Zarate-Osorno A, Kingma DW et al. The interrelationship between Hodgkin's disease and non-Hodgkin's lymphomas. Ann Oncol 1994; 5 (Suppl 1): 7–11.
6. Van Leeuwen FE, Swerdlow AJ, Valagussa P, Tucker MA. Second cancers after treatment of Hodgkin's disease. In Mauch PM, Armitage JO, Diehl V et al. (eds): Hodgkin's Disease. Philadelphia, PA: Lippincott Williams & Wilkins 1999; 607–632.
7. Green DM, Hyland A, Barcos MP et al. Second malignant neoplasms after treatment for Hodgkin's disease in childhood and adolescence. J Clin Oncol 2000; 18: 1492–1499.
8. Swerdlow AJ, Barber JA, Vaughan Hudson G et al. Risk of second malignancy after Hodgkin's disease in a collaborative British cohort: the relation to age at treatment. J Clin Oncol 2000; 18: 498–509.
9. Van Leeuwen FE, Klokman WJ, van't Veer MB et al. Long-term risk of second malignancy in survivors of Hodgkin's disease treated during adolescence or young adulthood. J Clin Oncol 2000; 18: 487–497.
10. Abrahamsen JF, Andersen A, Hannisdal E et al. Second malignancies after treatment of Hodgkin's disease. The influence of treatment, follow-up time and age. J Clin Oncol 1993; 11: 255–261.
11. Van Leeuwen FE, Klokman WJ, Hagenbeck A et al. Second cancer risk following Hodgkin's disease; a 20-year follow-up study. J Clin Oncol 1994; 12: 312–325.
12. Boivin JF, Hutchison GW, Zauber AG et al. Incidence of second cancers in patients treated for Hodgkin's disease. J Natl Cancer Inst 1995; 87: 732–741.
13. Sankila R, Garwicz, Olsen JH et al. Risk of subsequent malignant neoplams among 1,641 Hodgkin's disease patients diagnosed in childhood and adolescence. A population-based cohort study in five Nordic countries. J Clin Oncol 1996; 14: 1442–1446.
14. Donaldson SS, Hancock SL. Second cancer after Hodgkin's disease in childhood (editorial). N Engl J Med 1996; 334: 792–794.
15. Biti G, Cellai E, Magrini SM et al. Second solid tumors and leukemia after treatment for Hodgkin's disease. An analysis of 1121 patients from a single institution. Int J Radiat Oncol Biol Phys 1994; 29: 25–31.
16. Swerdlow AJ, Douglas AJ, Vaughan Hudson G et al. Risk of second primary cancer after Hodgkin's disease in patients in the British National Lymphoma Investigation: relationships to host factors, histology and stage of Hodgkin's disease, and splenectomy. Br J Cancer 1993; 68: 1006–1011.
17. Hancock SL, Tucker A, Hoppe RT et al. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993; 85: 25–31.
18. Goss PE, Sierra S. Current perspectives on radiation-induced breast cancer. J Clin Oncol 1998; 16: 338–347.
19. Mauch PM, Kalish LA, Marcus KC et al. Second malignancies after treatment for laparotomy-staged IA–IIIB stage Hodgkin's disease. Long-time analysis of risk factors and outcome. Blood 1996; 87: 3625–3632.
20. Swerdlow AJ, Douglas AJ, Vaughan Hudson G et al. Risk of second primary cancers after Hodgkin's disease by type of treatment. Analysis of 2846 patients in the British National Lymphoma Investigation. Br Med J 1992; 304: 1137–1143.
21. Kaldor JM, Day NE, Bell J et al. Lung cancer following Hodgkin's disease: a case–control study. Int J Cancer 1992; 52: 677–812.
22. Aisenberg AC, Finkelstein DM, Doppke KP et al. High risk of breast carcinoma after irradiation of young women with Hodgkin's disease. Cancer 1997; 79: 1203–1210.
23. Tucker MA, Misfeldt D, Coleman CN et al. Cutaneous malignant melanoma after Hodgkin's disease. Ann Intern Med 1985; 102: 37–41.
24. Wolf J, Schellong G, Diehl V. Breast cancer following treatment of Hodgkin's disease—more reasons for less radiotherapy (editorial)? Eur J Cancer 1997; 33: 2293–2294.