original paper
Haematologica 1997; 82:57-63

ANALYSIS OF THE RISK OF SOLID TUMOR FOLLOWING HODGKIN'S DISEASE

RICCARDO MAURIZI ENRICI,* ANNA PAOLA ANSELMO,# MATTIA FALCHETTO OSTI,° MARIAQUILA SANTORO,° VINCENZO TOMBOLINI,° FRANCO MANDELLI,# CARISSIMO BIAGINI°

**Chair of Radiation Oncology, Hospital "S. Maria di Collemaggio", University of L'Aquila; °Department of Radiation Oncology, Institute of Radiology, Policlinico Umberto I, University "La Sapienza", Rome; #Department of Human Biopathology, Hematology Section, University "La Sapienza", Rome, Italy*

ABSTRACT

Background and Objective. This study examines the occurrence of solid tumor (ST) in relation to the different types of therapy (radiotherapy, chemotherapy and radiochemotherapy; splenectomy or splenic irradiation vs no splenectomy - no splenic irradiation) received by patients treated for Hodgkin's disease (HD).

Methods. The study included 1,045 HD patients treated at the Department of Radiation Oncology, the Institute of Radiology and the Department of Human Biopathology, Hematology Section, University of Rome, "La Sapienza", from 1972 to 1992. For 23% of the patients the follow-up period was longer than 10 years. The average follow-up period was 72 months. For a more accurate calculation of the risk of ST occurrence, the patients were first divided into 3 subgroups according to initial treatment and then according to the total treatment they had received. Moreover, to establish a probable connection between solid tumor and splenic treatment the patients were also divided into 3 subgroups (splenectomy, splenic irradiation and no splenectomy/no splenic irradiation).

Results. We recorded twenty-four cases of ST after initial treatment. Secondary solid tumor showed a cumulative risk of 0.2% and 13.4% at 5 and 20 years, respectively. After initial treatment with radiotherapy (RT) alone, the cumulative risk was 1.7% and 5.2% at 10 and 20 years, respectively; in the chemotherapy (CT) group, it was 2.4% and 18.1%; in the CT+RT group, it was 1.7% and 9%. No statistically significant differences were observed among the different types of treatment (splenectomy, splenic irradiation or no splenectomy/no splenic irradiation) as regards the occurrence of ST. According to multivariate analysis, the most important factor in the risk of ST was age (>40). Relative risk was 5.2, p = 0.0001.

Interpretation and Conclusions. We conclude that an age of over 40 at diagnosis and treatment with CT alone greatly increase the risk of solid tumor occurrence.

Key words: Hodgkin's disease, solid tumors, risk factors, radiotherapy, chemotherapy

At present, patients with Hodgkin's disease (HD) have a high probability of cure; however, treatment-related sequelae have enormous clinical importance. An increase in second primary cancers (SPC) has been observed among long-term survivors of HD, in particular acute nonlymphoid leukemia (ANLL), non-Hodgkin's lymphoma (NHL) and secondary solid tumors (ST).[1-10] The increase in the risk of ANLL has been associated with host-related factors and with the type of treatment patients have been given.[11] Several authors have demonstrated that secondary ANLL is likely linked with chemotherapy. The risk is higher in patients treated with combined radiotherapy (RT) and chemotherapy (CT) that includes mechlorethamine and procarbazine.[3,12-16]

NHL has been related to radiochemotherapy treatment;[12,17] the risk is concentrated in the first year following the start of treatment and declines over the next 5 years.[10] Recently, several studies have focused attention on the incidence of ST. The risk increases with the length of follow-up and is related to treatment with RT alone or in combination with CT.[5,7] The risk of ST after radiation therapy is well known from studies of cancer patients treated with radiotherapy and from investigations of other groups exposed to radiation.[18,19] The risk of cancer after chemotherapy is less clear, however, because the use of chemotherapy is more recent and many different therapeutic agents have been used. The most frequent solid tumors are lung cancer, breast cancer, skin melanoma, gastrointestinal cancer and sarcoma of the bone.

For this study, we analyzed a cohort of 1045 patients with HD. The aim was to assess the risk associated with radiotherapy, chemotherapy and other factors in the development of solid tumors.

Materials and Methods

Patient population

Between 1972 and 1992, a total group of 1,045 consecutive HD patients received primary treatment at the Department of Radiation Oncology, the Institute of Radiology and the Hema-

Correspondence: Prof. Riccardo Maurizi Enrici, Chair of Radiation Oncology, Hospital "S. Maria di Collemaggio", University of L'Aquila, 67100 L'Aquila, Italy. Tel. international +39.862.778843 or 26164, Fax. international +39.862.410997.
Received July 29, 1996; accepted December 18, 1996.

tology Section of the Department of Human Biopathology of the University of Rome "La Sapienza". Diagnosis of HD was formulated according to the Rye classification and patients were staged according to the Ann Arbor classification. For 608 patients (58.2%), medical status was collected up to December 1, 1992. Eighty-two (0.8%) patients were lost to follow-up; of these, 29 were observed for less than 12 months and 19 for 12-24 months. The remaining patients were observed for over 24 months (range 24-60 months).

Table 1 shows the clinical characteristics of the 1,045 patients. Diagnosis of ST was histologically confirmed in all cases. Radiotherapy records were re-examined to establish whether secondary cancers occurred within or outside previously irradiated fields. Cancer developing in a previously irradiated field was seen as occurring within or at the margins of the zone.

Treatment

Before 1976 patients had not been included in standardized treatment protocols. Cases were discussed every week with hematologists, as still happens for the most interesting cases and relapses. Between 1976 and 1992, patients were included in two consecutive clinical protocols (ROMA HD 76 and ROMA HD 83). For a more accurate calculation of the risk of ST and its connection with the types of treatment received, patients were first divided into 3 groups according to their initial treatment:

1. three hundred and seventy (35.4%) patients were treated with RT alone (98 patients received RT + one adriamycin, bleomycin, vinblastine and dacarbazine, or ABVD course): 166 (44.9%) received sub-total nodal irradiation (STNI), 55 (14.9%) total nodal irradiation (TNI), 123 (33.2%) mantle field, and 26 (7%) inverted Y;
2. two hundred and six (19.7%) patients received CT alone; of these, 102 (49.5%) were given 6 mechlorethamine, vincristine, procarbazine and prednisone (MOPP) courses; 60 (29.1%) were given 6 ABVD courses; 37 (18%) received alternating MOPP/ABVD (8 courses); 7 (3.4%) were given 8 vincristine, procarbazine and prednisone (OPP)/ABVD courses;
3. combined CT plus RT induction treatment was administered to 469 patients (44.9%). In this group, RT (35 Gy, total nodal irradiation) + MOPP (6 courses) was used in 128 (27.3%) cases; RT (35 Gy, total nodal irradiation) + ABVD (6 courses) in 72 (15.3%) cases; RT (20 Gy involved field irradiation) + MOPP/ABVD (8 courses) in 119 (25.4%) cases; RT (20 Gy involved field irradiation) + OPP/ABVD (8 courses) in 76 (16.2%) cases; RT (30 Gy subtotal nodal irradiation) + cyclophosphamide, vincristine, procarbazine and prednisone (COPP)/ABVD (2 courses) in 35 (7.5%) cases and RT (30 Gy, subtotal nodal irradiation) + COPP/adriamycin, bleomycin, and vinblastine (ABV)/ifosfamide, methotrexate, etoposide and prednisone (IMEP) (2 courses) in 39 (8.3%) cases.

The patients were then divided again according to treatment, taking December 1, 1992 as the date of reference:

1. radiotherapy only, total: 289 patients (282 at presentation and 7 at relapse);
2. chemotherapy only, total: 197 patients (126 at presentation and 71 at relapse);
3. radiotherapy and chemotherapy, total: 559 patients (355 CT+RT at presentation only; 51 at presentation and at relapse; 67 patients received radiotherapy at presentation and chemotherapy at relapse; 51 CT+RT at presentation and RT at relapse; 14 RT at presentation and CT+RT at relapse; 12 CT+RT at presentation and CT at relapse; 3 CT at presentation and RT at relapse; 6 CT at presentation and CT+RT at relapse).

To establish the cancer risk after splenic treatment (splenic irradiation or splenectomy), the patients were divided into 3 subgroups:

1. six hundred and seventeen (59%) underwent splenectomy;
2. ninety-nine (9.5%) received radiation to the spleen;
3. three hundred and twenty-nine (31.5%) patients underwent neither splenectomy nor splenic irradiation.

Table 1. Clinical characteristics of patients with Hodgkin's disease.

Characteristics	*No. patients*	*%*
All patients	1045	100
Male	540	52
Female	505	48
Stage		
I	156	14.9
II	489	46.8
III	273	26.1
IV	127	12.2
Age		
< 25	336	32.1
25-40	403	38.6
> 40	306	29.3
Histology		
MC	459	44
NS	397	38
LP	83	7.9
LD	83	7.9
Unclassified	23	2.2
Initial treatment		
RT alone *	370	35.4
CT alone	206	19.7
Combined therapy (CT+RT)	469	44.9
Splenic treatment		
Spl.tomy	617	59
Splenic irrad.	99	9.5
No Spl.tomy/No Splenic irrad.	329	31.5
Average follow-up (in months)	72	

Abbreviations. MC: mixed cellularity; NS: nodular sclerosis; LP: lymphocytic predominance; LD: lymphocytic depletion; RT: radiotherapy; CT: chemotherapy; Spl.tomy: splenectomy; Splenic irrad.: splenic irradiation.
**98 patients received one adriamycin, bleomycin, vinblastine and dacarbazine (ABVD) course.*

Data analysis

To establish a probable connection between solid tumors and treatment received, two different methods of analysis were used: (a) the cumulative risk (confidence interval, CI) was evaluated in relation to treatment (initial and at the time of salvage), and (b) the Cox model was applied to identify the variables which play a role in the occurrence of secondary solid cancer.

The cumulative risk (CI) of developing ST was evaluated with the Kaplan and Meier method.[20] The Mantel-Cox and Breslow tests were used to compare the importance of clinical characteristics and types of treatment in the development of ST. The period of risk for ST was calculated as beginning on the date of HD diagnosis and ending on the date of ST diagnosis or the date of last known vital status or the date of death, or the date of progression/relapse, or December 1, 1992, whichever came first.

Relapsing or progressing patients were assessed on the date of relapse and were considered second primary cancer free on that date. For patients with progression and/or relapse, the period of risk of ST was redefined as beginning at treatment for progression and/or relapse and ending on the date of ST diagnosis or the date of last known vital status or the date of death, or December 1, 1992, whichever came first.

The risk of ST occurrence was analyzed (a) in relation to

treatment given at presentation in all patients considered disease-free (relapsed patients, assessed at relapse, were considered disease-free until the onset of relapse), and (b) in all patients in relation to the different treatment given to each patient at presentation (for patients who did not relapse) and, for relapsing or progressing patients, in relation to the sum of the different types of treatment given to each patient at presentation and, after relapse and/or progression, at salvage. Finally, the two risks obtained were compared. A multiple variable analysis was performed using the Cox Proportional Hazard Model. Time-dependent covariate analysis was applied for progressing and/or relapsing patients.

Data were analyzed using the 1L and 2L programs in the BMDP[21] packages.

Results

Among the 1,045 patients with an average follow-up of 72 months (maximum follow-up time 22.9 years), we observed 24 cases of ST which developed between 18 and 194 months (average 96 months) after the initial treatment. Table 2 shows the clinical characteristics of ST patients. Of these 24 patients, twelve were males and twelve females, with age ranging between 11 and 66 years (average 35 years). Among the patients who developed ST, 17 cases were patients who did not relapse and 7 occurred after a relapse. In our observations the most frequent forms of cancer were lung cancer (5 cases), salivary gland cancer (3 cases), skin cancer (3 cases), gastroenteric tract cancer (3 cases) and breast cancer (2 cases).

Synchronous ST and skin melanoma cancer were not recorded in our study. Among the 24 ST cases, 4 developed within a previously irradiated field and 2 at the margins. Of 4 in-field ST, 2 were breast cancers, which developed in women treated with mantle-field irradiation: one patient, treated at the age of 16 years, developed primary breast cancer after 169 months; the other, treated at the age of 29 years, developed breast cancer after 124 months. Of the 24 cases of ST, 9 of from secondary neoplasm (range 3-80 months); in 3 cases diagnosis of ST was made at necroscopy and was negative for HD.

Nineteen cases of ST were observed in splenectomized patients, one case in a patient whose spleen was irradiated and four in patients who did not undergo splenic treatment.

Table 2. Characteristics of patients with solid tumor.

No Cases	Age°	Sex	Histology of HD	Stage	Splenic treatment	Total treatment	Time elapsed from first therapy (in months)	Relapse	Cancer sites	Status
1	59	M	MC	II A	Splenectomy	RT	58	No	Rectum	Dead
2	48	M	NS	II A	Splenectomy	MOPP/ABVD+RT	21	Yes	Lung	Dead
3	41	M	MC	I A	Splenectomy	MOPP+RT	194	Yes	Salivary gland	Alive
4	11	F	MC	III A	Splenectomy	MOPP+RT	164	No	Surrenal gland	Alive
5	16	F	NS	II A	Splenectomy	MOPP+RT	169	Yes	Breast	Dead
6	20	F	NS	II A	Splenectomy	RT	161	No	Thyroid	Alive
7	59	M	NS	II B	Spleen irrad.	ABVD+RT	34	No	Colon	Alive
8	20	F	NS	IV A	Splenectomy	ABVD+RT	76	No	Sarcoma	Alive
9	29	F	NS	III A	Splenectomy	MOPP/ABVD+RT	124	No	Breast	Alive
10	66	M	MC	II B	No splenic treatment	MOPP+RT	24	No	Skin	Alive
11	46	M	LP	III A	Splenectomy	ABVD+RT	121	Yes	Lung	Dead
12	12	M	MC	III A	Splenectomy	MOPP+RT	131	No	Leiomyo sarcoma	Alive
13	33	M	MC	III A	Splenectomy	ABVD+RT	83	No	Liver	Dead
14	42	M	MC	II A	Splenectomy	MOPP+RT	83	Yes	Salivary gland	Alive
15	51	M	MC	IV A	No splenic treatment	ABVD	115	No	Lung	Dead
16	53	F	MC	III B	Splenectomy	ABVD	119	No	Lung	Dead
17	47	M	MC	III B	Splenectomy	MOPP	32	Yes	Skin	Dead
18	44	F	SN	IV A	No splenic treatment	ABVD	144	Yes	Kidney	Alive
19	55	F	MC	III A	Splenectomy	MOPP	69	No	Lung	Dead
20	19	F	MC	III A	Splenectomy	RT	66	No	Skin	Dead
21	27	F	LD	II A	Splenectomy	MOPP+RT	123	No	Nervous system	Dead
22	33	M	MC	III B	Splenectomy	MOPP	170	No	Rectum	Dead
23	22	F	MC	II A	Splenectomy	RT	70	No	Pleura	Alive
24	27	F	SN	IV B	No splenic treatment	MOPP/ABVD	18	Yes	Salivary gland	Dead

Abbreviations. HD: Hodgkin's disease; RT: radiotherapy; MOPP/ABVD: mechlorethamine, vincristine, procarbazine and prednisone/adriamycin, bleomycin, vinblastine, and dacarbazine; ABVD: adriamycin, bleomycin, vinblastine, and dacarbazine; MOPP: mechlorethamine, vincristine, procarbazine and prednisone; Spleen irrad.: spleen irradiation; MC: mixed cellularity; NS: nodular sclerosis; LP: lymphocytic predominance; LD: lymphocytic depletion.

°Age at diagnosis of Hodgkin's disease.

Risk of ST: cumulative risk overall and in relation to splenic treatment

Cumulative risk rates, irrespective of treatment, calculated for ST at 10 and 20 years were 2% (0.9-3) and 13.4% (5.9-20.9).

In regard to splenic treatment, the cumulative risk was 2.4 (0.7-3.9) at 10 years and 16.0 (6.1-25.8) at 20 years for splenectomized patients, and 1.1 (0-3.3) at 10 and 20 years for patients whose spleens were irradiated. For patients whose spleen was not irradiated and not removed, the cumulative risk was 0.9 (0-2.1) and 6.1 (0-13.8) at 10 and 20 years, respectively. No statistically significant differences were observed among the different types of treatment (splenectomy, splenic irradiation or no splenectomy/no splenic irradiation) as regards ST occurrence (p= 0.7247 in the Mantel-Cox and p= 0.9890 in the Breslow test, Table 3).

Risk of ST development: cumulative risk in relation to initial and total treatment

First: the relationship of initial therapy (i.e. RT alone, CT alone and combined methods without treatment for recurrence) to the occurrence of ST was evaluated. The risk of all solid tumors increased with the length of the follow-up period. At 10 and 20 years the cumulative risk was, respectively, 1.7% (0-3.6) and 5.2% (0-12.3) in the RT group; in the CT group it was 2.4% (0.7-5.6) and 18.1% (0-40.2), in the CT+RT group it was 1.7% (0-3.7) and 9% (0-18.1). The highest risk of ST was found in the CT group (Table 4).

Second: the cumulative probability of developing ST can be related to the sum of the different types of treatment given to each patient at presentation and, in case of relapse, at salvage.

The highest risk of developing ST was found in patients treated with CT alone. At 20 years, the cumulative risk was 18.8% (0-40.7) in the CT group, 5.4% (0-12.8) in the RT group and 12.2% (3.1-21.3) in the CT+RT group (p = 0.27 in the Mantel-Cox and p = 0.28 in the Breslow test).

An increased risk of ST (at 20 years) was observed in patients who received CT+RT as treatment for HD relapse: cumulative risk 12.2%, compared to patients given CT+RT as primary treatment, for whom the cumulative risk was 8.9%.

Risk factor for ST occurrence: multivariate analysis

Table 5 shows the results of multivariate analysis of the effects of the different types of treatment and of the various clinical characteristics on the risk of ST. The most important factor in the risk of ST was age (>40). Relative risk (RR) was 5.2, p = 0.0001. In the multivariate analysis (using a time-dependent covariate), the factors associated with an increased risk of ST (in non-relapsing patients) were treatment with RT alone (RR = 0.25, p = 0.0286) and CT+RT (RR = 0.30, p = 0.0388).

Discussion

This study demonstrates that one of the most serious treatment-related sequelae in long-term survivors of HD is the onset of solid tumors,[1,4-8,11,13,22-25] which have been observed even following treatments performed during childhood and adolescence.[26]

An increased risk of ST was observed after CT alone, either as primary treatment or at the time of salvage. On the occurrence of solid tumors in patients treated with CT alone, the results of Rodriguez *et al*.[9] and the BNLI[27] agree with these conclusions: further study is required for a better examination of the increase in risk of ST after treatment with CT. Moreover, our results indicate that additional therapy for relapsing patients (CT+RT after initial therapy with RT alone) does not increase the risk of ST, while in a recent study[28] the addition of combined therapy for recurrent disease in patients previously treated with radiotherapy showed a significant increase in the relative risk of ST. In the authors' opinion, it is possible that either the cumulative dose of radiation received after secondary treatment with CT was responsible for a

Table 3. Cumulative risk (confidence interval) x 100 and frequency of solid tumor in relation to splenic treatment.

			Cumulative Risk (CI) x 100			
		No ST/ No pts.	5 Years	10 Years	15 Years	20 Years
ST (24/1045)	Splenectomy	19/617	0.2 (0-0.5)	2.4 (0.7-3.9)	4.7 (1.9-7.5)	16 (6.1-25.8)
	Splenic irradiation	1/99	0	1.1 (0-3.3)	1.1 (0-3.3)	1.1 (0-3.3)
	No splenectomy No splenic irradiation	4/329	0.4 (0-2.1)	0.9 (0-3.1)	6.1 (0-2.1)	6.1 (0-13.8)

p value=0.8373 (Mantel-Cox); p value=0.7156 (Breslow). Abbreviations. ST: solid tumor; Spl.tomy: splenectomy; Splenic irrad.: splenic irradiation.

Table 4. Cumulative risk (confidence interval) x 100 and frequency of solid tumor in relation to treatment.

Years	Initial treatment (N. ST/N. Patients)			Total treatment (N. ST/N. Patients)		
	RT (4/370)	CT (6/206)	RT+CT (6/469)	RT (4/289)	CT (7/197)	RT+CT (13/559)
5	0	1 (0-2.3)	0	0	0.6 (0-1.7)	0.4 (0-1.1)
10	1.7 (0-3.6)	2.4 (0.7-5.6)	1.7 (0-3.7)	1.8 (0-3.7)	4 (0-8.1)	2.3 (0.5-4.1)
15	1.7 (0-3.6)	7.6 (0.3-15.4)	4.5 (0.1-8.9)	1.8 (0-3.7)	5.8 (0.4-11.3)	7 (2-12)
20	5.2 (0-12.3)	18.1 (0-40.2)	9 (0-18.7)	5.4 (0-12.8)	18.8 (0-40.7)	12.2 (3.1-21.3)
	p=0.23 (Mantel-Cox) p=0.07 (Breslow)			p=0.27 (Mantel-Cox) p=0.28 (Breslow)		

Abbreviations. ST: solid tumor; RT: radiotherapy; CT: chemotherapy

high occurrence of ST, or that the increase in ST occurrence was due to the initial radiation.

Other reports have focused attention on the role of the spleen in SPC occurrence.[29-33] With regard to splenic irradiation, Daley *et al*.[29] described most radiation-induced changes: the spleen was smaller with respect to that of non-irradiated patients: there was an increase in fibrosis of the red pulp, thickening of the capsule, and myointimal proliferation of arteries. Although none of these pathological features is specific, their combined appearance indicates radiation damage. Moreover, splenic atrophy after radiation treatment, estimated at approximately 30-40%, predisposes patients to fulminant pneumococcal sepsis and the Waterhouse-Friderichsen syndrome.[30] Coleman *et al*.[31] showed that patients treated for HD or NHL who have had approximately 4000 rads of splenic irradiation developed functional hyposplenia. Dietrich *et al*.[32] suggest that splenectomy and splenic irradiation lead to an increased risk of second cancers, and postulate that splenic treatment increases the damage to tumoral immunosurveillance capabilities. In Mellemkjoer *et al*.'s experience[33] on 6,315 people splenectomized for trauma and for other conditions (malignant and non malignant disease), an increased risk of secondary cancers was reported among the ones who underwent splenectomy for non-traumatic reasons, since splenectomy may increase the immunological dysfunction due to the

Table 5. Cox proportional hazard model of risk factors in development of solid tumor.

Variables	Coefficient	Standard error	Relative risk	p value
Age (>40/<40)	1.65	0.42	5.2	0.0001
Gender (M/F)	-0.27	0.42	0.76	0.52
Stage (III-IV/I-II)	0.19	0.42	1.2	0.64
Initial treatment				
CT vs RT	0.33	0.33	1.4	0.33
CT +RT vs RT	0.07	0.34	1.07	0.83
Total treatment*				
RT alone (no relapse)	-1.38	0.64	0.25	0.0286
CT alone (no relapse)	-0.92	0.66	0.40	0.16
CT+RT (no relapse)	-1.22	0.59	0.30	0.0388
CT+RT (at presentation) and RT (at relapse)	0.69	0.84	2.0	0.44
RT (at presentation) and CT (at relapse)	0.59	1.11	1.8	0.62
Splenic treatment				
Splenectomy vs no splenectomy/no splenic irradiation	-0.3	0.42	0.74	0.45
Splenic irradiation vs no splenic irradiation/no splenectomy	-0.05	0.73	0.95	0.95

*Abbreviations - CT: chemotherapy; RT: radiotherapy; Spl.tomy: splenectomy; Splenic irrad.: splenic irradiation. *Time-dependent covariate. Mutually exclusive.*

disease itself. On the other hand, after traumatic rupture the splenic cells spill on the peritoneal surfaces and determine a partial return of splenic function.[34] The mechanism by which spleen hypofunctioning or the absence of the spleen may lead to the occurrence of secondary cancer has not been established.

In our experience, age was the variable with statistical significance (p= 0.0001).[7-9,13,23,24,35] Age is the major risk factor for solid tumors in the HD population in the same way that age is a major risk factor for almost all solid cancers in the general population. It is uncertain whether this biological phenomenon is related to age or to the HD status of patients, or whether it is an undifferentiated effect of treatment (RT or CT or CT+RT).

With respect to the location of ST, no definite relationship could be found between the treatment received (radiotherapy alone or radiotherapy with chemotherapy) and the tumor tissue. For example, lung cancer was observed more often in patients who had received RT,[3,7] but it was also seen in patients treated with CT alone. In their detailed analysis of various solid tumors, Kaldor *et al*.[36] pointed out that the occurrence of lung cancer is higher in long-term HD survivors than in the general population. They conclude that this higher risk is due to the cancer-inducing effects of both CT and RT, compared with those produced by other risk factors, e.g. smoking for lung cancer. Van Leeuwen *et al*.[37] studied a cohort of 1,939 patients treated for HD who developed 30 lung cancers, and examined the relationship between the carcinogenic effect of smoking and radiation. They concluded that the appearance of lung cancer is related both to the radiation dose received by the lung and to smoking after radiation exposure.

Regarding the occurrence of breast cancer, less recent studies have demonstrated an increased risk after exposure of the breast to low doses of radiation;[38-40] in fact, breast cancer has been found after therapeutic irradiation for *post-partum* mastitis,[41] in atomic bomb survivors[42] and in patients with tuberculosis subjected to repeated fluoroscopic examinations.[43] Van Leeuwen *et al*.[10] and Yahalom *et al*.[44] reported an increased risk of breast cancer in women who have received radiation therapy for HD at a younger age; our data agree with this. Moreover, Yahalom *et al*.[44] showed that breast cancer following treatment for HD was bilateral and frequently involved the medial half of the breast,while the prognosis of the disease is similar to that of patients with primary cancer. In Hancock's experience,[45] the risk after 15 years is equal in women treated with RT alone and in women receiving RT combined with MOPP. On the other hand, the increased risk of breast cancer after treatment for ovarian cancer with chemotherapy alone may indicate that cytotoxic drugs play a role in the occurrence of second cancer.[46,47]

For other types of cancer such as cancer of the gastroenteric tract, of the soft tissue and of the nervous system, which have been observed in irradiation, there could be a relation with the cancer-inducing effects of radiation after a relatively short time.

In conclusion, a multifactorial etiology can be established. The appearance of ST in HD patients could be explained by an immune deficiency caused by HD itself or by the treatment received to cure it. Genetic factors could also play a role, leading to the appearance of a neoplasm in a small percentage of patients exposed to environmental factors. These is also a higher risk for patients who have had one tumor of developing another.

The increased risk of ST was connected with treatment received and with host-related and environmental factors. Proper treatment strategies should reduce this risk and other late side effects.[48,49] However, since treatment-associated cancer continues beyond 15 years, the survivors of HD should be monitored in order to establish treatment-related carcinogenic effects.

References

1. Maurizi Enrici R, Anselmo AP, Osti MF, Sbarbati S, Tombolini V, Biagini C. Methods of assessment of delayed damage in patients treated for Hodgkin's disease. Minutes of the XX AIRB Congress, 29-30 Sept, 1993:152-70.
2. Young RC, Bookman MA, Longo DL. Late complications of Hodgkin's disease management. Natl Cancer Inst Monogr 1990; 10:55-60.
3. Boivin JF, Hutchinson GB, Lyden M, Godbold J, Chorosh J, Schottenfeld D. Second primary cancer following treatment for Hodgkin's disease. J Natl Cancer Inst 1984; 72:233-41.
4. Coleman CN, Kaplan HS, Cox R, Varghese A, Butterfield P, Rosenberg SA. Leukemias, non-Hodgkin's lymphomas and solid tumors in patients treated for Hodgkin's disease. Cancer Survey 1982; 1:733-44.
5. 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; 11:255-61.
6. Cimino G, Papa G, Tura S, et al. Second primary cancer following Hodgkin's disease: updated results of an Italian multicentric study. J Clin Oncol 1991; 9:432-7.
7. Tucker MA. Solid second cancers following Hodgkin's disease. Hematol Oncol Clin North Am 1993; 7:389-400.
8. Sont JK, Van Stiphout WAH, Noordijk EM, et al. Increased risk of second cancers in managing Hodgkin's disease: the 20-year Leiden experience. Ann Haematol 1992; 65:213-8.
9. Rodriguez MA, Fuller LM, Zimmermann SO, et al. Hodgkin's disease: study of treatment intensities and incidences of second malignancies. Ann Oncol 1993; 4:125-31.
10. 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; 12:312-25.
11. Urba WJ, Longo DL. Hodgkin's disease. N Engl J Med 1992; 326:678-87.
12. Van Leeuwen FE, Somers R, Taal BG, et al. Increased risk of lung cancer, non-Hodgkin's lymphoma and leukemia following Hodgkin's disease. J Clin Oncol 1989; 7:1046-58.
13. Valagussa P, Santoro A, Fossati-Bellani F, Banfi A, Bonadonna G. Second acute leukemia and other malignancies following treatment for Hodgkin's disease. J Clin Oncol 1986; 4:830-7.
14. Papa G, Mauro FR, Anselmo AP, et al. Acute leukemia in patients treated for Hodgkin's disease. Br J Haematol 1984; 58:43-52.
15. Blayney DW, Longo DL, Young RC, et al. Decreasing risk of leukemia with prolonged follow-up after chemotherapy and radiotherapy for Hodgkin's disease. N Engl J Med 1987; 19:710-7.
16. Devereux S, Selassie G, Vaughan-Hudson G, Vaughan-Hudson B, Linch DC. Leukemia complicating treatment for Hodgkin's disease: the experience of the BNLI. Br Med J 1990; 301:1077-80.
17. Krikorian JB, Burke JS, Rosenberg SA, Kaplan HS. Occurrence of non-Hodgkin's lymphoma after therapy for Hodgkin's disease. N

Engl J Med 1979; 300:452-8.
18. National Research Council. Committee on the biological effects of ionizing radiation. The effects on populations of exposure to low levels of ionizing radiation. Washington DC: National Academy Press, 1980.
19. Kohn HI, Fry MRJ. Radiation carcinogenesis. N Engl J Med 1984; 23:504-11.
20. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. J Am Stat Ass 1958; 53:457-81.
21. Benedetti J, Yenu K, Young L. Life tables and survival functions. In: Dixon WJ, eds. BMDP statistical software, Berkeley: University of California Press, 1983. p. 557-75.
22. Valagussa P. Second neoplasm following treatment of Hodgkin's disease. Curr Opin Oncol 1993; 5:805-11.
23. Economopoulos T, Stathakis N, Alexopoulos C, et al. Second malignancies following treatment for Hodgkin's disease: a Greek experience. Haematologica 1994; 79:273-6.
24. Henry-Amar M. Second cancer after the treatment for Hodgkin's disease: a report from the International Database on Hodgkin's disease. Ann Oncol 1992; 3 (suppl. 4):117-28.
25. Boivin JF, O'Brien K. Solid cancer risk after treatment of Hodgkin's disease. Cancer 1988; 61:2541-6.
26. Maurizi Enrici R, Anselmo AP, Osti MF, et al. Long-term results of treatment of childhood and adolescent Hodgkin's disease in 73 patients:the experience of the Departments of Radiology and Hematology of the University of Rome "La Sapienza". Haematologica 1996; 81:245-52.
27. Swerdlow AJ, Douglas AJ, Vaughan Hudson G, Vaughan Hudson B, Bennett MH, MacLennan KA. 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; 304:1137-43.
28. Doria R, Holford T, Farber L, Prosnitz LR, Cooper DL. Second solid malignancies after combined modality therapy for Hodgkin's disease. J Clin Oncol 1995; 13:2016-22.
29. Daley MO, Coleman CN, Fajardo LF. Splenic injury caused by therapeutic irradiation. Am J Surg Pathol 1981; 5:325-31.
30. Daley MO, Coleman CN, Kaplan HS. Radiation-induced splenic atrophy in patients with Hodgkin's disease and non-Hodgkin's lymphomas. N Engl J Med 1980; 302:215-7.
31. Coleman CN, McDougall IR, Daley MO, Ager P, Bush S, Kaplan HS. Functional hyposplenia after splenic irradiation for Hodgkin's disease. Ann Int Med 1982; 96:44-7.
32. Dietrich PY, Henry-Amar M, Cosset JM, Bodis S, Bosq J, Hayat M. Second primary cancer in patients continuously disease-free from Hodgkin's disease: a protective role for the spleen? Blood 1994; 84:1209-15.
33. Mellemkjoer L, Olsen JH, Linet MS, Linet AMS, Gridley G, McLaughlin JK. Cancer risk after splenectomy. Cancer 1995; 75:577-83.
34. Pearson HA, Johnston D, Smith KA, Touloukian RJ. The born-again spleen. Return of splenic function after splenectomy for trauma. N Engl J Med 1978; 298:1389-92.
35. Biti GP, Cellai E, Magrini SM, Papi MG, Ponticelli P, Boddi V. Second solid tumors and leukemia after treatment for Hodgkin's disease:an analysis of 1121 patients from a single institution. Int J Rad Oncol Biol Phys 1994; 29:25-31.
36. Kaldor JM, Day NE, Bell J, et al. Lung cancer following Hodgkin's disease: a case-control study. Int J Cancer 1992; 52:677-81.
37. Van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. J Natl Cancer Inst 1995; 87:1530-7.
38. Land CE, Boice JD Jr, Shore RE, Norman JE, Tokunaga M. Breast cancer risk from low-dose exposures to ionizing radiation: results of parallel analysis of three exposed populations of women. J Natl Cancer Inst 1980; 65:353-76.
39. Modan B, Chetrit A, Alfandary E, Katz L. Increased risk of breast cancer after low-dose irradiation [letter]. Lancet 1989; 1:629.
40. Hildreth NG, Shore RE, Dvoretsky PM. The risk of breast cancer after irradiation on the thymus in infancy. N Engl J Med 1989; 321:1281-4.
41. Shore RE, Hildreth N, Woodard E, Dvoretsky P, Hempelmann L, Pasternack B. Breast cancer among women given X-ray therapy for acute post-partum mastitis. J Natl Cancer Inst 1986; 77:689-96.
42. Tokunaga M, Land CE, Yamamoto T, et al. Incidence of female breast cancer among atomic bomb survivors, Hiroshima and Nagasaki, 1950-1980. Radiat Res 1987; 112:243-72.
43. Miller AB, Howe GR, Sherman GJ, et al. Mortality from breast cancer after irradiation during fluoroscopic examinations in patients being treated for tuberculosis. N Engl J Med 1989; 321:1285-9.
44. Yahalom J, Petrek JA, Biddinger PW, et al. Breast cancer in patients irradiated for Hodgkin's disease: a clinical and pathologic analysis of 45 events in 37 patients. J Clin Oncol 1992; 10:1674-81.
45. Hancock SL, Tucker MA, Hoppe RT. Breast cancer after treatment of Hodgkin's disease. J Natl Cancer Inst 1993; 85:25-31.
46. Kaldor JM, Day NE, Band P, et al. Second malignancies following testicular cancer, ovarian cancer and Hodgkin's disease: an international colloborative study among cancer registries. Int J Cancer 1987; 39:571-85.
47. IARC. Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Some anticancer and immunosoppressive drugs. Lyon, 1981; 2.
48. Zinzani PL, Gherlinzoni F, Piovaccari G, et al. Cardiac injury as late toxicity of mediastinal radiation therapy for Hodgkin's disease patients. Haematologica1996; 81:132-7
49. Frezza G, Barbieri E, Zinzani PL, Babini L, Tura S. Supradiaphragmatic early stage Hodgkin's disease: does mantle radiation therapy still have a role? Haematologica 1996; 81:138-42.