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Late Deaths and Second Primary Malignancies Among Long-Term Survivors of Childhood Cancer: An Italian Multicentre Study

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Abstract—*A multicentre registry of children who had been successfully removed from therapy for some common childhood cancers (Hodgkin's disease, non-Hodgkin's lymphoma, neuroblastoma, nephroblastoma, acute lymphatic leukaemia and other leukaemias) was established in Italy in* 1981. *The present study describes mortality and occurrence of second primary malignancies (SPMs) among* 1467 *children who were alive when the registry was established. Follow-up ended on December* 31, 1983 *for mortality and* 1 *year later for the occurrence of SPMs. Sixty-seven deaths were recorded,* 11 *of which wre due to causes other than progression of the original disease. Eleven incident SPMs were identified (i.e.* 3 *acute myeloid leukaemias,* 3 *thyroid carcinomas,* 1 *bilateral breast carcinoma,* 1 *liver malignant mesenchymoma,* 1 *astrocytoma,* 1 *chondrosarcoma and* 1 *osteosarcoma) corresponding to an incidence rate of* 2.1/1000 *patient-years at risk. Anecdotal reports were collected regarding* 2 *further SPMs (a thyroid carcinoma and a myeloid leukaemia) as well as several benign tumours, including* 2 *mammary fibroadenomas.*

INTRODUCTION

LATE deaths and occurrence of second primary malignancies (SPMs) among long-term survivors after a cancer in childhood has been the subject of many case reports and some formal epidemiological studies (for review, see [1]). Risk of second cancers was first estimated by Li *et al.* in a series of 414 long-term survivors at the Children's Cancer Research Foundation in Boston [2]. Subsequently, an international cooperative programme called the Late Effects Study Group (LESG) was launched, the results of which have repeatedly updated [3, 4, 5]. The latest update describes 292 patients with SPMs [5]. Another series of 14 second primary benign or malignant tumours in 330 subjects previously treated with megavoltage radiation for a paediatric tumour has been recently reported [6]. Other studies concentrated on long-term survivors after Wilms' tumour in childhood [7] and on the occurrence of thyroid cancer as SPM [8]. In spite of differences in design and materials in each study, findings have been consistent. In particular, long-term survivors after a childhood cancer are exposed to at least a 10-fold increased risk of developing another incident cancer and the risk is largely attributable to radiotherapy for the first cancer, chemotherapeutic agents having a secondary—albeit detectable—role. In addition, the risk is enhanced by genetic and familial conditions, such as retinoblastoma, neurofibromatosis and xeroderma pigmentosum.

In 1980–1981, a multicentre registry of children successfully completing the first cycle of therapy after a diagnosis of some cancers was created in Italy [9]. The present report describes a prospective follow up of these children, the end points of which were mortality and occurrence of SPMs.

MATERIAL AND METHODS

Early in 1981, Italian institutions known to take care of children with cancer were asked whether

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they would agree to create a multicentre centralized file of children who—independently of subsequent disease evolution—had been able to be removed from treatment for 1 of the following conditions: Hodgkin's lymphoma (HDL), non-Hodgkin's lymphoma (NHD), neuroblastoma (NBL), nephroblastoma (NFB), acute lymphoblastic leukaemia (ALL) and non lymphoblastic leukaemia (nLL). Thirty-six institutions (see list in Appendix 1) agreed to participate, submitting retrospectively a total of 1251 children who had reached the off-therapy (OT) stage since each institution had started to operate. The same procedure was put in operation 1 year later for 268 children removed from treatment in the same institutions in 1981. A more detailed description of the Italian Registry of OT children (ROT) has been reported elsewhere [9]. Further updates and expansions of the ROT taking place in 1984 are not considered in the present report. Of the 36 institutions, 21, 7 and 8 were located respectively in Northern, Central and Southern Italy. Thus, the ROT is neither exhaustive nor representative of all Italian childhood cancers. In addition, no attempts have been made to check the exhaustiveness of submission of cases from each institution.

The 1519 children included 302 HDL, 83 NHD, 144 NBL, 192 NFB, 760 ALL and 38 nLL. Fifty-two of them (respectively 5, 0, 3, 1, 40 and 3) were reported as dying before ROT started to operate. The living status at time of entry in the ROT for the other 1467 children was confirmed through the Registrars of the town of residence of each child at time of diagnosis.

Dying children were identified in the first place through the Registrars. In 1984 they were asked to certify that each child was either alive or dead (for children who had moved to another town the same procedure was applied with the Registrar of the new town of residence). It was so ascertained that 67 children had died between entry to ROT and December 31, 1983 and that 1358 were alive on that date. Of the other 42 children, the relevant institutions were aware that 39 were alive at the end of 1983, whereas they had lost contact with the other 3. All deaths but one had been recorded by the institution taking care of the child.

For 57 of 67 children who died, the Registrars also provided the causes (initial, intermediate and terminal) of death as reported in the death certificate. In addition, for each child who died the relevant institution was asked to report the causes of death according to their records and to state whether the death could be attributed to progression of the original cancer. This procedure allowed for the collection of the causes of death of all 10 children for which the Registrar had not provided it. Causes of death given by the Registrars and by the institutions corresponded in 42 instances. For 4 children who died, cancer was not mentioned in the death certificate whereas it was considered to be the cause of death by the institution; the reverse occurred for 5 children. In 5 other cases, the type of leukaemia or lymphoma indicated in the death certificate was inconsistent with that mentioned in the clinical data. For these 14 children, the information given by the institution was given credit and that derived from the Registrars was disregarded. For the child whose death was unknown to the institution, the information provided by the Registrar was considered as definitive.

Histologically confirmed SPMs diagnosed between entry to ROT and December 31, 1984 were identified early in 1985 through an *ad hoc* enquiry with all the 36 institutions. The latter had lost contacts with a total of 46 children (average year of diagnosis 1973.3 vs 1975.4 in the whole series).

The total number of men-years at risk since entry to ROT to the end of 1983 (mortality study) and to the end of 1984 (SPMs study) was respectively 4020 and 5321. These figures exclude respectively the 3 children whose living status could not be assessed and the 46 who had lost contact with the relevant institution.

Procedures for follow-up allowed also for the identification of a number of children developing a second cancer before entry to ROT as well as some children developing benign tumours, either before or during the period of formal follow-up.

RESULTS

Table 1 reports the distribution of the 1467 ROT children by disease and calendar period of birth, diagnosis and OT.

The 67 children dying between entry to ROT and December 31, 1983, included 5 HDL, 1 NHD, 3 NBL, 5 NFB, 49 ALL and 4 nLL. Their distribution by period elapsed since OT time and death is given in Table 2. Eleven children died of causes other than progression of the original cancer. They included 3 cases of early complications after marrow graft in ALL children (respectively 24, 35 and 85 months after first OT), 3 acute myeloid leukaemias in children whose original diagnosis was respectively ALL (20 months after OT), NHD (31 months) and NFB (83 months), 1 violent death after ALL (44 months), 1 drug-induced myocarditis after ALL (68 months), 1 sepsis after HDL (54 months), 1 leishmaniasis after nLL (9 months) and 1 encephalitis after NFB (31 months). At least 8 further deaths occurred in 1984–1985: 2 were traumatic, one was due to complications of marrow transplant and the cause has not yet been traced for the other 5.

Eleven SPMs were reported to be diagnosed between entry to ROT and December 1984, corre-

Table 1. Period of birth, diagnosis and off-therapy of children who were alive at entry to ROT

	HDL	NHD	NBL	NFB	ALL	nLL	Total
Birth							
1950–54	7	0	0	0	0	0	7
1955–59	19	0	0	0	9	1	29
1960–64	77	17	7	7	69	8	185
1965–69	115	39	13	30	222	11	430
1970–74	76	23	58	79	346	14	596
1975–79	3	4	59	74	74	1	215
1980–81	0	0	4	1	0	0	5
Total	297	83	141	191	720	35	1467
Diagnosis							
1960–64	1	0	1	1	0	0	3
1965–69	18	1	6	16	28	0	69
1970–74	82	16	33	42	231	9	413
1975–79	174	63	84	113	461	22	917
1980–81	22	3	17	19	0	4	65
Total	297	83	141	191	720	35	1467
Off-therapy							
1960–64	0	0	1	1	0	0	2
1965–69	9	1	3	5	1	0	19
1970–74	46	6	18	30	23	0	123
1975–79	187	44	89	101	412	17	850
1980–81	55	32	30	54	284	18	473
Total	297	83	141	191	720	35	1467
Males	204	61	78	93	365	17	818
Females	93	22	63	98	355	18	649

HDL = Hodgkin's lymphoma, NHD = non-Hodgkin's lymphoma, NBL = neuroblastoma, NFB = nephroblastoma, ALL = acute lymphoblastic leukaemia, nLL = non lymphoblastic leukaemia.

Table 2. Children dying after entry to ROT, by period elapsed since first remotion from treatment (in brackets, number of children dying for causes other than progression of disease)

	HDL	NHD	NBL	NFB	ALL	nLL	Total
Period (months)							
< 12	0	0	0	0	1	1 (1)	2 (1)
12–23	1	0	1	0	8 (1)	1	11 (1)
24–35	0	1 (1)	2	1 (1)	16 (2)	0	23 (4)
36–47	0	0	0	0	8 (1)	1	9 (1)
48–71	3 (1)	0	0	0	11 (1)	1	15 (2)
72+	1	0	0	1 (1)	5 (1)	0	7 (2)
Total	5 (1)	1 (1)	3 (0)	5 (2)	49 (6)	4 (1)	67 (11)

sponding to an incidence rate of 2.1/1000/year. They are listed in Table 3. All had received both radiotherapy (with doses ranging between 2400 and 9600 rads) and various combinations of chemotherapeutic agents. Case No. 6 has been previously described [10].

Anecdotal reports on the occurrence of malignant tumours before OT and benign tumours either before or after entry to ROT are listed in Table 4.

DISCUSSION

Criteria for enrolment of children in the present study were such that children dying either before OT or after OT but before entry to ROT were excluded. Therefore, actuarial survival since diagnosis or OT could not be estimated. Nevertheless, it is worth noticing that 22 children who died had been removed from therapy, in the absence of signs of cancer, at least 4 years before death and that for 18 of them the cause of death was a recurrence of the original cancer. This confirms previous observations [11, 12] that late deaths after childhood cancer are a sizable event.

On the other hand, enrolment only of children whose living status at entry was ascertained minimizes selection bias in the estimation of the occurrence of SPMs. In comparison with previous follow-

Table 3. Children developing second primary cancers after entry to ROT

	Sex	Original cancer	Year birth	Year diagn. first cancer	Year diagn. second cancer	Type of second cancer	Dying
1	M	NHD	1967	1977	1981	Acute myeloid leukaemia	1981
2	F	HDL	1968	1974	1981	Thyroid papillary ca.	No
3	F	HDL	1952	1967	1981	Bilateral breast ca.	No
4	F	ALL	1973	1978	1982	Acute myeloid leukaemia	1982
5	M	HDL	1966	1979	1982	Liver malignant mesenchymoma	No
6	F	NFB	1972	1973	1982	Acute myeloid leukaemia	1982
7	M	ALL	1973	1975	1983	Thryoid papillary ca.	No
8	M	ALL	1966	1972	1983	Brain astrocytoma	No
9	M	HDL	1971	1975	1983	Rib chrondrosarcoma	No
10	F	ALL	1969	1973	1984	Thyroid papillary ca.	No
11	M	ALL	1964	1974	1984	Osteosarcoma	No

Table 4. Children developing second primary cancers before entry to ROT and benign tumours either before or after entry to ROT

	Sex	Original cancer	Year birth	Year diagn. first cancer	Year diagn second tumour	Type of second tumour
1	M	HDL	1963	1969	1976	Skin basalioma
2	F	NFB	1967	1969	1977	Lipoma*
3	F	ALL	1964	1969	1978	Glioma†
4	F	HDL	1963	1969	1979	Thyroid papillary carcinoma
5	F	ALL	1972	1978	1981	Chr. myeloid leukaemia‡
6	F	HDL	1969	1978	1981	Mammary fibroadenoma
7	F	HDL	1967	1979	1984	Cutaneous histyocytoma
8	F	NHD	1966	1978	1984	Mammary fibroadenoma

*In the lumbar region, homolateral to the NFB which had been irradiated.
†No histological confirmation.
‡Diagnosed before OT for ALL.

up studies of long-term survivors after a childhood cancer [3, 4, 5, 6, 7], the present series is smaller and limited to some cancer types. It excluded, among others, patients originally diagnosed as having retinoblastoma, which are at high risk of developing SPMs, particularly in the bone and soft tissues [3, 4, 5]. Nevertheless, in the present study, the average incidence rate of SPMs in the period covered by exhaustive follow up was 2.1/1000 patient-years at risk. This figure is comparable to the corresponding rate derived in a recent LESG report [4], i.e. 167 of 50,609 patient-years at risk (3.3/1000 per year). A previous LESG report estimated incidence rates of 0.9 and 1.9/1000 per year respectively during and after the first 5 years after diagnosis [3].

Assuming, for the whole of Italy, an incidence rate of all cancers of 20/100.000/year in ages 0–25 [13, 14], the expected number of incident cancers in the present series was around 1. Also, this approximately 10-fold increase of risk corresponds to that observed in previous studies.

A comparison of risks by original cancer type in the present series with previous studies is impaired by small absolute numbers, as well as by different calendar periods covered by follow-up and different enrolment criteria (the LESG analyses were based on historical rosters of children, whereas in the present study follow-up was prospective). In addition, survival rates of children with cancer are not necessarily the same in Italy and elsewhere [15]. Nevertheless, it is interesting to note that SPMs among long-term survivors of ALL were an exceptional finding in the early LESG reports [3], which was not the case of subsequent LESG analyses [4, 5], other studies [6] and the present series. Since ALL is the most frequent cancer in childhood and its prognosis has markedly improved, in the future more SPMs are likely to be observed among ex-ALL children.

The 13 SPMs in the present study (11 reported in Table 3 plus cases Nos. 4 and 5 in Table 4)

included 4 leukaemias or lymphomas and 4 thyroid cancers. These proportions are similar to those described in the latest LESG report [5], i.e. (limited to the original cancer types considered in the present study) respectively 37 and 19 out of 129.

All SPMs in the present study developed in children who had been treated with both radio- and chemotherapy. The two mammary fibroadenomas (developing respectively after an NHD and an HDL) might simply reflect the frequency of this disease in adolescent girls and no association with treatment can be postulated for the time being.

In conclusion, the occurrence of SPMs in the present study does not seem to be dissimilar to that found in other series. In order to unravel the mechanisms of associations between original cancers, therapy and the occurrence of SPMs there is a need for large series of long-term survivors. The Italian Registry of OT children seems to be a suitable tool in this respect.

APPENDIX

Participating Institutions

Clinica Pediatrica, Bari (A. Ceci, G. Loiacono).
Ospedali Riuniti, Bergamo (R. Lamura).
Clinica Pediatrica III, Bologna (A. Mancini, G. Paolucci).
Ospedale Umberto I, Brescia (G. Calculli).
Clinica Pediatrica I e II, Cagliari (P. Biddau).
Clinica Pediatrica, Catania (A. Russo, G. Schilirò).
Ospedale Civile, Catanzaro (S. Magro).
Ospedale Civile, Chiari (E. Mazzoleni).
Clinica Pediatrica, Firenze (A. Lippi, C. Guazzelli).
Istituto G. Gaslini, Genova (R. Haupt, L. Massimo).
Istituti Ospedalieri, Mantova (S. Miccolis).
Istituto Nazionale Tumori, Milano (F. Fossati-Bellani).
Clinica Pediatrica, Università di Milano-Monza (G. Masera, M.G. Zurlo).
Ente Ospedaliero V. Buzzi, Milano (U. Formica).
Ente Ospedaliero Fatebenefratelli, Milano (M. Massarone).
Ente Ospedaliero Niguarda, Milano (A. Nicolini).
Ente Ospedaliero S. Carlo Borromeo, Milano (S. Razon Veronesi).
Ospedale Pediatrico Regina Elena, Milano (L. Brunelli).
Clinica Pediatrica II, Modena (F. Massolo, A.M. Piccinini).
Ospedale S. Gerardo, Monza (A. Alpini).
Clinica Pediatrica I, Napoli (M. Di Tullio, S. Cutillo).
Ospedale Cardarelli, Napoli (R. Cimino).
Clinica Pediatrica, Padova (M. Carli, L. Zanesco).
Clinica Pediatrica I, Palermo (M. Lo Curto, U. Tripoli).
Ospedali Riuniti, Parma (F. Casa, G. Ghirardini).
Clinica Pediatrica, Pavia (L. Nespoli, R. Burgio).
Clinica Pediatrica, Pisa (P. Macchia, E. Bottone).
Cattedra di Ematologia, Roma (G. Meloni, F. Mandelli).
Clinica Pediatrica I e II, Roma (M. Castello, B. Werner, G. Multari).
Ospedale Bambin Gesù, Roma (C. Miano, D. Rosati).
Clinica Pediatrica Siena (A. Acquaviva A. Fois).
Clinica Pediatrica, Torino (R. Miniero, E. Madon).
Istituto B. Garofolo, Trieste (P. Tamaro, G. Zanazzo).
Ospedale Circolo, Varese (M. Negri).

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