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Trends in cancer mortality in Japanese adolescents and young adults aged 15–29 years, 1970–2006

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Objective: The primary objective of this study is to describe cancer mortality rates and trends among Japanese adolescents and young adults aged 15–29 years for the period 1970–2006.

Materials and methods: Age-standardized mortality rates were calculated by the direct method using age-specific mortality rates at 5-year age intervals and weights based on the age distribution of the standard world population. The joinpoint regression model was used to describe changes in trends.

Results: For all cancers combined, the mortality rate at age 15–29 years during 2000–2006 was 4.41 (per 100 000 population) for males and 3.81 (per 100 000) for females. Trends of mortality from cancer in Japan were similar to that in other developed countries. A notable exception was cervical cancer, for which Japanese young women showed a significant increase, on average 4.0% per year throughout the period.

Conclusion: This report presents updated figures and trends in cancer mortality among adolescents and young adults aged 15–29 years in Japan and other developed countries. We hope this study will raise public awareness on cancer in this age group and provide the impetus for further research to improve the survival and quality of life of the young people in Japan.

Key words: adolescent, cancer, epidemiology, mortality, time trends, young adult

introduction

Cancer is the leading cause of disease-related deaths in adolescents and young adults (AYAs) in Japan. Nearly 7000 adolescents and young adults aged 15–29 died from cancer in Japan in the 7-year period of 2000–2006. Overall cancer patterns reflect cancers that are most prevalent in middle and old age, especially breast, prostate, lung and colorectal. However, the spectrum of malignant diseases among younger ages (childhood, adolescence and young adulthood) differs from patterns at older ages and even among themselves. A prior monograph from the Surveillance, Epidemiology and End Result (SEER) program indicated that malignant disease in persons aged 15–29 years is unique in the distribution of types that occur, with Hodgkin's lymphoma, melanoma, testis cancer, female genital tract malignancies, thyroid cancer, soft tissue sarcomas, and nongonadal germ-cell tumors accounting for 95% of the cancers in this age group. The vast majority of cancers diagnosed before age 30 appears to be spontaneous and unrelated to either carcinogens in the environment or inherited factors [1].

Compared with younger and older age groups, adolescents and young adults have experienced little or no improvement in cancer survival rates in more than two decades. The SEER reports have addressed concerns about the deficit in survival improvement in this population and attributed it to a lack of awareness of the cancer problem in this age group, lack of health-care insurance coverage and access to health care [1–4]. During recent years, more attention has been drawn to the need for further development of treatment services available to adolescents and young adults with cancer. Some developed countries have also reported descriptive epidemiologic results based on population data for AYAs with cancer [5–14]. However, little attention and few resources have been devoted to studying the incidence, risk factors, survival and mortality in this age group in Japan.

To provide a comprehensive picture of the cancer mortality and trend analysis in individuals aged 15–29 years in Japan, we analyzed the occurrence of death from cancer among AYAs at the population level over the period of 1970–2006, using official death certificates, which record 100% of deaths in Japan.

materials and methods

The number of deaths by cause, stratified for sex and by 5-year age group for cancer for the period 1970–2006, was derived from vital statistics compiled by the Ministry of Health, Labor and Welfare of Japan.

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Population figures were obtained from census data and intercensus estimates, by calendar year, age and gender. Population censuses of Japan are conducted every 5 years by the Statistics Bureau, Ministry of Internal Affair and Communications.

For comparison, we also calculated the cancer mortality rate in other developed countries, including Canada (2000–2004), the United States (2000–2005) and UK, England and Wales (2000–2005). Deaths at age 15–19, 20–24 and 25–29 years were derived from the World Health Organization (WHO) mortality database. Estimates of the residential population, based on official censuses, were obtained from the same WHO database.

During 1970–2006, three different revisions of the International Classification of Disease (ICD) were used. In Japan, this included ICD-8 from 1970 to 1978, ICD-9 from 1979 to 1994 and ICD-10 from 1995 onward. Since the differences were minor in various revisions, we recorded cancer sites, including all cancer combined (ICD-10: C00–97), lip, oral and cavity and pharynx (ICD10: C00–14), digestive organs (ICD-10: C15–26), colorectal (ICD-10:C18–21), respiratory and intrathoracic organs (ICD-10: C30–C39), bone and articular cartilage (ICD-10: C40–C41), melanoma of skin (ICD-10: C43–C44), mesothelial and soft tissue (ICD10:C45–C49), genitourinary organs (ICD-10:C51–C68), testis (ICD-10:C62), cervix (ICD-10: C53), ovary (ICD-10:C56), central nervous system (CNS) tumors (ICD-10: C70–C72), thyroid and other endocrine glands (ICD-10:C73–C75), leukemia (ICD10: C91–C95), lymphoid leukemia (ICD-10: C91), myeloid leukemia (ICD-10: C92), lymphomas (ICD-10: C81–85), Hodgkin's disease (ICD-10: C81) and non-Hodgkin's lymphoma (ICD-10: C82–85). Age-standardized mortality rates at age 15–29 years were calculated by the direct method using age-specific mortality rates for 5-year age intervals and weights based on the age distribution of the standard world population.

Joinpoint software 3.3.1 from the Surveillance Research Program of the US National Cancer Institute was used for trend analysis [15, 16]. We allowed up to four joinpoints for each model. Mortality rates and their standard errors were calculated using SAS 9.0. Time trends were assessed by site and sex. Mortality trends for Canada (1970–2004), the United States (1970–2005) and UK, England and Wales (1970–2005) were included for comparison.

The standardized mortality ratio (SMR) by sex was calculated for 47 prefectures in Japan by taking the ratio of the observed to expected deaths. The z value was computed for each SMR, based on the assumption that observed deaths follow a Poisson distribution. The maps were developed using SMR by gender.

results

Table 1 gives age-adjusted 15–29 years mortality rates from all malignant tumors and the main types of cancer in Japan and other developed countries. Age-adjusted mortality rates in Japan for six successive 5-year calendar periods, i.e. 1970–1974, 1975–1979, 1980–1984, 1985–1989, 1990–1994 and 1995–1999, and also for the 7-year period of 2000–2006 were calculated. For all cancers combined, the mortality rate at age 15–29 years during 2000–2006 was 4.41 (per 100 000 population) for males and 3.81 (per 100 000) for females. Trends of age-standardized mortality from cancer are shown in Figures 1 and 2 and Table 2. The mortality for all cancers combined has declined since 1970s for both sexes. The average annual percent change (AAPC) in the last 10 years was -3.1% ($P < 0.05$) for males and -1.6% ($P < 0.05$) for females.

malignant neoplasm of lip, oral cavity and pharynx

Mortality rates from lip, oral cavity and pharynx cancer remained stable at a low level for both genders throughout the period. Death rate was 0.13 (per 100 000) for males and 0.08 (per 100 000) for females during 2000–2006.

colorectal cancer

Since 1970, colorectal cancer mortality has declined among AYA population aged 15–29 years. The reduction during the past 10 years averaged 2.6% per year in males and 3.0% per year in females.

malignant neoplasm of respiratory and intrathoracic organs

Mortality rates from respiratory organs cancer in adolescents and young men increased in the 1970s and fell significantly from 0.20 per 100 000 in 1979 to 0.09 per 100 000 in 2006. For females, the death rates declined throughout the period. The AAPC in the last 10 years was -2.7% for males and -2.1% for females.

malignant neoplasm of bone, connective tissue, skin and breast

Mortality for malignant bone tumors during 2000–2006 was 0.38 (per 100 000) for males and 0.22 (per 100 000) for females. Reduction was observed throughout the period for both sexes (1.4% per year in males and 2.1% per year in females). Figures 1 and 2 show increases in mortality for mesothelial and soft tissue tumors of 3.2% per year in males and 3.0% per year in females in the period 1970–2006. Mortality for melanoma of skin remained low and stable in females from 1970 to 2006. For males, a decline trend has been observed in the last 6 years with an average of 23.8% per year. The rate for both sexes was ~0.05 (per 100 000) during 2000–2006. Female breast cancer mortality rates peaked in 1980 and then fell significantly from 0.35 (per 100 000) to 0.24 (per 100 000) with 1.9% per year during 1980–2006.

genitourinary organ cancer

Mortality rates from testicular cancer increased by 7.1% per year from 1970 to 1977 and fell significantly from 0.54 (per 100 000) in 1977 to 0.16 (per 100 000) in 2006. Relative to cervical cancer, mortality significant increased by an average of 4.0% per year throughout the period. For ovary cancer, the rates have remained stable for the past decade.

CNS tumors

CNS tumors mortality among AYA population was 0.30 (per 100 000) for females and 0.42 (per 100 000) for males from 2000 to 2006. Mortality for males increased significantly by 7.1% per year until 1981 at which point there was a slight and nonsignificant rise. For females, mortality increased by 1.4% per year in the whole period.

malignant neoplasm of thyroid and other endocrine glands

Mortality rates were stable throughout the period for both sexes, with the rate ~0.07 (per 100 000) for males and 0.04 (per 100 000) for females from 2000 to 2006.

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Table 1. Age-adjusted mortality rate (per 100 000) by sex and diagnostic group at age 15–29 years in Japan and other developed countries

Tumor	Japan							Canada	United States	England and Wales
	1970–1974	1975–1979	1980–1984	1985–1989	1990–1994	1995–1999	2000–2006	2000–2004	2000–2005	2000–2005
Males										
Total malignant tumors	8.76	8.39	7.36	6.61	5.92	5.46	4.41	4.91	5.53	5.77
Lip, oral cavity and pharynx	0.12	0.14	0.12	0.09	0.15	0.15	0.13	0.08	0.09	0.13
Digestive organs	2.98	2.39	1.83	1.40	1.12	0.97	0.73	0.43	0.55	0.52
Colorectal	0.78	0.51	0.41	0.37	0.31	0.27	0.24	0.20	0.25	0.20
Respiratory and intrathoracic organs	0.42	0.45	0.41	0.38	0.31	0.27	0.24	0.11	0.17	0.11
Bone and articular cartilage	0.64	0.53	0.46	0.50	0.45	0.44	0.38	0.56	0.51	0.64
Meothelial and soft tissue	0.11	0.15	0.18	0.25	0.22	0.34	0.31	0.29	0.42	0.39
Melanoma of skin	0.06	0.06	0.03	0.04	0.04	0.05	0.05	0.21	0.22	0.28
Genitourinary organs	0.47	0.61	0.51	0.46	0.42	0.28	0.23	0.35	0.35	0.32
Testis	0.38	0.50	0.42	0.35	0.31	0.21	0.16	0.24	0.26	0.21
Central nervous system	0.22	0.29	0.43	0.38	0.39	0.43	0.42	0.72	0.72	0.94
Thyroid and other endocrine glands	0.05	0.10	0.06	0.06	0.06	0.08	0.07	0.06	0.07	0.09
Leukemia	2.56	2.54	2.25	2.12	1.86	1.70	1.23	1.04	1.31	1.18
Lymphoid leukemia	0.25	0.38	0.62	0.74	0.74	0.72	0.53	0.49	0.56	0.59
Myeloid leukemia	1.59	1.46	1.12	1.00	0.84	0.80	0.59	0.36	0.50	0.52
Lymphoma	0.89	0.95	0.85	0.78	0.76	0.58	0.49	0.76	0.76	0.82
Hodgkin's lymphoma	0.13	0.10	0.07	0.06	0.05	0.03	0.04	0.24	0.23	0.26
Non-Hodgkin's lymphoma	0.76	0.85	0.78	0.72	0.71	0.55	0.45	0.51	0.53	0.55
Females										
Total malignant tumors	8.46	7.59	6.74	5.63	4.62	4.32	3.81	4.19	4.45	5.08
Lip, oral cavity and pharynx	0.06	0.07	0.07	0.06	0.06	0.08	0.08	0.08	0.06	0.05
Digestive organs	3.26	2.68	2.10	1.61	1.10	0.90	0.71	0.38	0.42	0.41
Colorectal	0.57	0.39	0.34	0.31	0.25	0.23	0.22	0.10	0.19	0.17
Respiratory and intrathoracic organs	0.28	0.24	0.21	0.20	0.17	0.16	0.14	0.13	0.10	0.10
Bone and articular cartilage	0.33	0.28	0.27	0.24	0.22	0.25	0.22	0.28	0.30	0.46
Meothelial and soft tissue	0.10	0.13	0.20	0.19	0.20	0.29	0.28	0.31	0.32	0.27
Melanoma of skin	0.05	0.06	0.04	0.04	0.03	0.04	0.05	0.12	0.16	0.25
Breast	0.21	0.25	0.31	0.27	0.20	0.21	0.20	0.22	0.28	0.42
Genitourinary organs	1.29	1.02	0.87	0.69	0.59	0.56	0.55	0.54	0.55	0.67
Cervix	0.06	0.05	0.06	0.09	0.13	0.15	0.16	0.26	0.24	0.35
Ovary	0.79	0.71	0.62	0.43	0.31	0.30	0.26	0.19	0.20	0.23
Central nervous system	0.18	0.24	0.22	0.22	0.23	0.30	0.30	0.50	0.51	0.72
Thyroid and other endocrine glands	0.05	0.07	0.07	0.05	0.06	0.04	0.04	0.07	0.07	0.06
Leukemia	2.00	1.90	1.68	1.50	1.28	1.07	0.86	0.78	0.88	0.85
Lymphoid leukemia	0.17	0.24	0.45	0.45	0.48	0.42	0.34	0.18	0.29	0.34
Myeloid leukemia	1.20	1.16	0.84	0.73	0.60	0.53	0.44	0.36	0.43	0.47
Lymphoma	0.40	0.46	0.49	0.41	0.38	0.30	0.27	0.58	0.54	0.59
Hodgkin's lymphoma	0.05	0.06	0.06	0.03	0.02	0.03	0.03	0.25	0.22	0.24
Non-Hodgkin's lymphoma	0.35	0.39	0.44	0.39	0.35	0.27	0.23	0.33	0.32	0.35

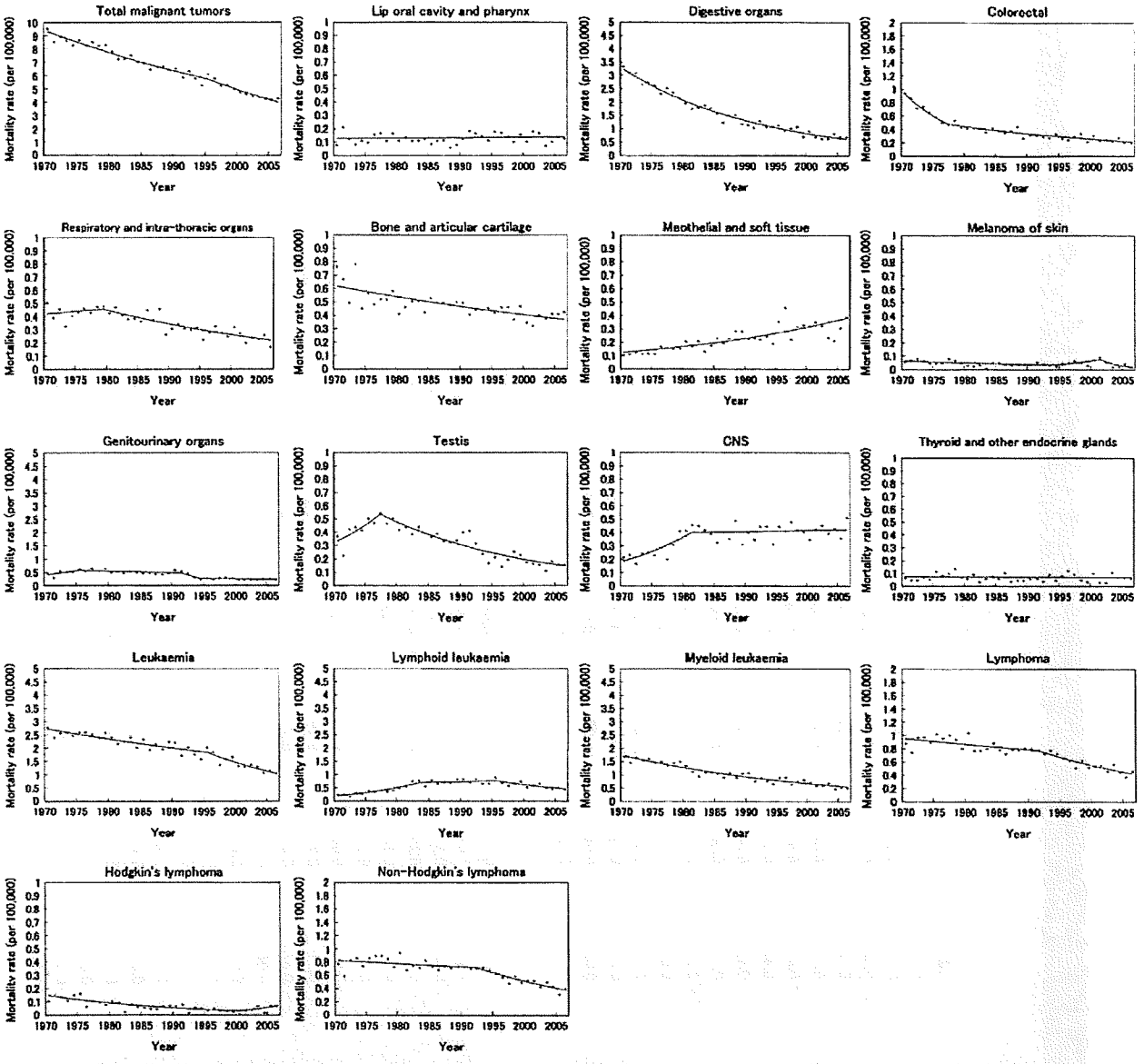

Figure 1. Trends on age-adjusted mortality for cancer among adolescents and young adults aged 15–29 years, Males, Japan, 1970–2006.

malignant neoplasm of lymphoid, hematopoietic and related tissue

Death rate from leukemia during 2000–2006 was 1.23 (per 100 000) for males and 0.86 (per 100 000) for females. Mortality showed continued improvement over time for both sexes. For lymphoma, rate among young people aged 15–29 years was 0.49 (per 100 000) in males and 0.27 (per 100 000) in females during 2000–2006. Significant decline was observed in both sexes (by 3.9% per year in males and 2.8% per year in females in recent decade).

Mortality rates varied among prefectures in Japan. A map of SMR by gender is shown in Figure 3. The SMR was significantly highest among AYAs aged 15–29 years in Hokkaido, Iwate, Akita, Fukushima, Niigata and Miyazaki prefectures for males and Akita, Fukushima, Tochigi, Kochi and Miyazaki prefectures for females.

discussion

This study has presented detailed analysis on the trends of cancer mortality in AYAs aged 15–29 years in Japan. There were 60 959 adolescents and young adults who died from cancer during 1970–2006. Approximately 900 deaths were attributed to cancer in AYAs aged 15–29 years in 2006, which is two times more common than mortality during the first 15 years of life.

Mortality rates decreased during the study period in both sexes. It is unlikely that the observed time trends in the mortality rate are due to variations in the completeness and accuracy of the population data, because the data we used were provided by official sources, which were founded on the population census. The AAPC was also reported in this study. The AAPC can be used to characterize a short segment based on a joinpoint model fit over a much longer series. This is

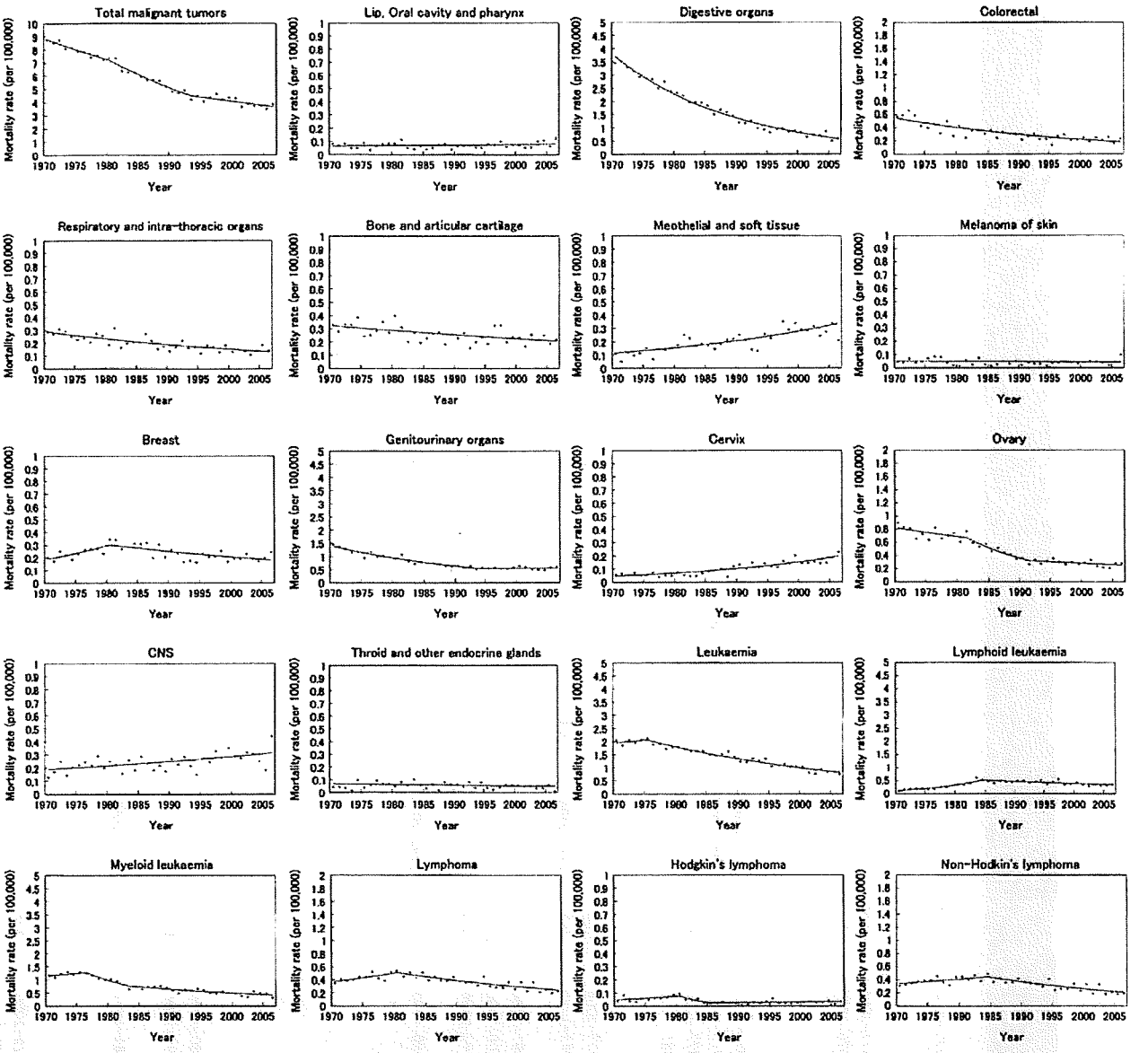

Figure 2. Trends on age-adjusted mortality for cancer among adolescents and young adults aged 15–29 years, Females, Japan, 1970–2006.

especially advantageous when data are sparse (e.g. a rare cancer or data from a small geographic area) [17]. According to trend analysis, marked mortality reductions occurred for cancer of digestive and respiratory organs, testicular cancer, leukemia and lymphoma. Similar decline trends were also observed in the United States, Canada and England and Wales in recent decade. These declines have been attributable to improving treatment for leukemia, lymphoma and testicular cancer.

Compared with the childhood cancers we reported previously [18], the reduction in the cancer mortality rate among AYAs aged 15–29 years has lagged behind the reduction in children. The AAPC in the last 10 years for pediatric cancer were −3.8% per year for boys and −1.9% per year for girls, while comparable declines for AYA population were −3.1% per year for males and −1.6% per years for females in the same period. Similar patterns have also been reported in the United States. A recent monograph published by SEER revealed that cancer mortality rates among this population have mysteriously flattened, while those of children and older adults have steadily improved [19]. The different distribution of cancer type between children and young people might partly explain this lowered reduction in mortality rate among AYA population. Furthermore, survival studies focused on AYAs have also found that some cancers common in adolescents, such as acute myeloid leukemia, acute lymphoblastic leukemia, rhabdomyosarcomam, osteogenic sarcoma and Ewing's sarcoma, are associated with lower 5-year disease-free survival rates in adolescents and young people [12], likely contributing to this deficit in mortality reduction between young adults and children. A report from the United States also attributes this discrepancy in part to the widespread gap in clinical trial participants and health-care insurance coverage between

Table 2. Joinpoint analysis for all cancer combined and selected diagnostic group of cancers, at ages 15–29 years in Japan, 1970–2006

Tumor	Japan								AAPC*			
	Trend 1		Trend 2		Trend 3		Trend 4		Japan	Canada	United States	England and Wales
	Years	APC	Years	APC	Years	APC	Years	APC	1997–2006	1995–2004	1996–2005	1996–2005
Male												
Total malignant tumors	1970–1995	−1.9*	1995–2006	−3.1*					−3.1*	−2.2*	−1.7*	−2.2*
Lip, oral cavity and pharynx	1970–2006	0.2							0.2	−1.0	−1.0*	0.4
Digestive organs	1970–2006	−4.5*							−4.5*	−2.9*	−0.9*	−2.0*
Colorectal	1970–1977	−9.2*	1977–2006	−2.6*					−2.6*	7.5	−0.4	−0.7
Respiratory and intrathoracic organs	1970–1979	0.9	1979–2006	−2.7*					−2.7*	−1.9*	−2.5*	−5.5*
Bone and articular cartilage	1970–2006	−1.4*							−1.4*	−1.6*	1.0*	−0.7*
Meothelial and soft tissue	1970–2006	3.2*							3.2*	−1.7	0.1	1.0*
Melanoma of skin	1970–1994	−2.5*	1994–2001	11.9	2001–2006	−23.8*			−9.6	−1.5*	−3.2*	−0.1
Genitourinary organs	1970–1975	7.0	1975–1991	−1.2	1991–1994	−17.2	1994–2006	−1.4	−1.4	−3.9*	−2.3*	−5.5*
Testis	1970–1977	7.1*	1977–2006	−4.3*					−4.3*	−4.7*	−2.3*	−6.5*
Central nervous system	1970–1981	7.1*	1981–2006	0.2					0.2	−1.3*	−0.9*	−1.4*
Thyroid and other endocrine glands	1970–2006	−0.1							−0.1	0.7	−1.9*	0.4
Leukemia	1970–1995	−1.5*	1995–2006	−5.0*					−5.0*	−2.7*	−1.6*	−3.3*
Lymphoid leukemia	1970–1983	9.8*	1983–1995	0.8	1995–2006	−4.6*			−4.6*	−1.7*	−0.7*	−3.7*
Myeloid leukemia	1970–2006	−3.1*							−3.1*	−2.6*	−3.5*	−2.6*
Lymphoma	1970–1991	−1.0*	1991–2006	−3.9*					−3.9*	−2.8*	−4.8*	−3.3*
Hodgkin's lymphoma	1970–2000	−5.0*	2000–2006	14.0					7.3	−4.2*	−4.5*	−5.2*
Non-Hodgkin's lymphoma	1970–1992	−0.6	1992–2006	−4.4*					−4.4*	−1.1*	−4.7*	−1.5*
Female												
Total malignant tumors	1970–1980	−2.0*	1980–1993	−3.5*	1993–2006	−1.6*			−1.6*	−1.7*	−2.1*	−1.6*
Lip, oral cavity and pharynx	1970–2006	0.5							0.5	−0.1	−0.4	−1.3
Digestive organs	1970–2006	−5.0*							−5.0*	−1.6*	−0.6*	−1.6*
Colorectal	1970–2006	−3.0*							−3.0*	−3.2*	−1.3*	−1.2*
Respiratory and intrathoracic organs	1970–2006	−2.1*							−2.1*	−2.1*	−2.4*	1.6
Bone and articular cartilage	1970–2006	−1.2*							−1.2*	−0.7	0.8	−0.6
Meothelial and soft tissue	1970–2006	3.0*							3.0*	1.3	−0.1	−2.6
Melanoma of skin	1970–2006	−0.6							−0.6	−2.7*	−2.9*	−1.4*
Breast	1970–1980	4.7*	1980–2006	−1.9*					−1.9*	−2.4*	−4.6*	−1.6*
Genitourinary organs	1970–1993	−3.9*	1993–2006	0.1					0.1	−2.2*	−1.6*	−3.8*
Cervix	1970–2006	4.0*							4.0*	−1.1*	−1.2*	−4.5*
Ovary	1970–1981	−1.8*	1981–1991	−7.0*	1991–2006	−1.6			−1.6	−2.7*	0.7	−3.0*
Central nervous system	1970–2006	1.4*							1.4*	−1.6*	−1.1*	−1.5*
Thyroid and other endocrine glands	1970–2006	−0.9							−0.9	0.6	−1.3*	−0.1
Leukemia	1970–1975	1.0	1975–2006	−2.9*					−2.9*	−2.3*	−1.7*	−1.9*
Lymphoid leukemia	1970–1984	10.7*	1984–2006	−1.9*					−1.9*	−6.2*	−0.8*	−0.3

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Table 2. (*Continued*)

Tumor	Japan						AAPC*					
	Trend 1		Trend 2		Trend 3		Japan	Canada	United States	England and Wales
	Years	APC	Years	APC	Years	APC	1997–2006	1995–2004	1996–2005	1996–2005
Myeloid leukemia	1970–1976	1.7	1976–1983	−7.0*	1983–2006	−2.6*	−2.6*	−2.1*	−2.3*	−2.4*
Lymphoma	1970–1980	3.2*	1980–2006	−2.8*			−2.8*	−1.6*	−1.3*	−2.4*
Hodgkin's lymphoma	1970–1980	5.2	1980–1985	−19.9	1985–2006	1.3	1.3	−1.7*	−3.2*	−3.6*
Non-Hodgkin's lymphoma	1970–1984	1.9*	1984–2006	−3.3*			−3.3*	−0.1	−5.0*	−1.0*

[a]Last 10 observations.

*$P < 0.05$.

APC, annual percent change; AAPC, average annual percent change.

pediatric and young adults [20]. The proportion of Japanese teenagers with cancer who are included in national and international clinical trials and studies is still unknown. Further studies focused on health-care services and survival outcome among adolescents and young adults in Japan need to be conducted.

There was no decline in mortality from CNS tumors among AYAs in Japan. This implied an unfavorable trend in the incidence of CNS tumors in these populations, although improved diagnosis and certification could not be completely ruled out as contributing factors. The etiology of CNS tumors is complicated and remains largely unknown. Environmental factors are suggested to have a relationship with brain tumors. Increased incidences among children based on local population-based cancer registry data in Japan have been reported previously [21]. Investigations of the incidence of CNS tumors among adolescents and young people are necessary.

The increase in mortality from cervical cancer in AYAs suggests an increased incidence in these populations. This hypothesis can be proved by data from 11 regional population-based cancer registries in Japan [22]. The incidence rate increased from 0.7 (per 100 000) in 1975–1979 to 2.1 (per 100 000) in 2000–2002 among the AYA population aged 15–29 years. The reason for this increase trend among young women is complicated. Some research has attributed it to changes in sexual habits, oral contraceptive use, tobacco smoking, sexually transmitted diseases (papillomavirus) and the extension and distribution of screening among adolescents and young women. The cervical cancer-screening program in Japan was only offered to women aged >30 until 2004, and the coverage rate fell behind that of other developed countries. According to the Organization for Economic Co-operation and Development health data 2008, the coverage of cervical cancer screening was 23% among Japanese women aged 20–69 years, compared with 83.5% in the United States, and 72.4% in Germany [23].

Although Levi et al. [24] reported mortality trends in AYAs aged 15–24 years in Europe, including Japan for comparison previously, they primarily mentioned about seven diagnostic groups (bone sarcoma, soft tissue sarcoma, vary, testis, non-Hodgkin's lymphomas, Hodgkin's disease and leukemia) and only presented data up to 1998. Our report provides updated mortality rates and reliable time trend analysis for AYAs aged 15–29 years in Japan. Trends of mortality from cancer in Japan were generally comparable with other developed countries, but different patterns among countries have been found in this study. For example, the mortality rate from CNS tumors has decreased in the United States, Canada and UK in recent decades; however, no evidence of decline was found in Japan. Unfavorable mortality trends from cervical cancer in young Japanese women throughout the period were not observed in the United States, Canada and UK. Differences in the distribution of the histology pattern among different countries might play a role. Meanwhile, as mentioned above, the lag time in intervention in Japan might contribute to unfavorable trends in cancer mortality.

There are some limitations of this study. The low number of deaths from rare cancers may have biased the result. Some

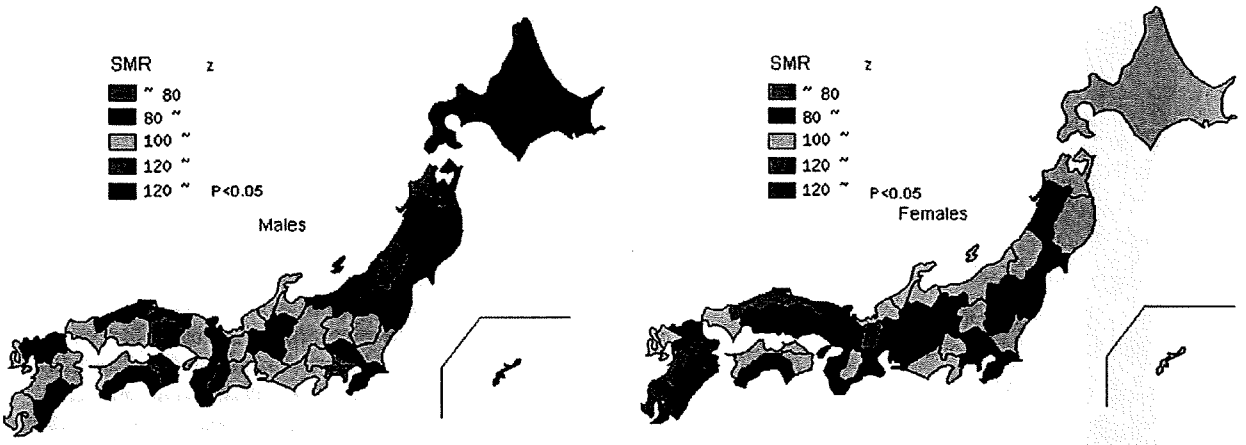

Figure 3. Standardized mortality ratios for cancer among adolescents and young adults aged 15–29 years in Japan, 2000–2006 by prefecture.

stable trends in the present study, such as mortality in thyroid cancer and Hodgkin's lymphoma, are more difficult to explain because of the small absolute number and substantial random variation. On the other hand, mortality rates are not a good substitute for incidence, because treatment for cancers has improved rapidly over time, and survival varies between age groups and populations. Furthermore, deaths occurring in adolescents and young adults relate to cancer diagnosed several years earlier, at younger ages.

Despite these limitations, this report is the first national large-scale study on mortality trends among individuals aged 15–29 years in Japan, which covered 100% AYA deaths from cancer. Moreover, there is no national-level cancer registry system in Japan. Against this background, the analysis of mortality trends over several decades remains an important method to provide additional insight into the cancer burden among AYA population. We believe that these analyses and observations will help to estimate care needs, to plan cancer prevention strategies and to provide reasonable health services for this group of patients.

conclusions

This report presents updated figures and trends in cancer mortality among adolescents and young adults aged 15–29 years in Japan and other developed countries. Mortality has improved for AYAs over the 37-year study period; however, the improvement lags behind that for children. The increased cervical cancer mortality presented here implies an increase in incidence among young Japanese women and draws attention to the need to strengthen 'cervical cancer screening in Japan'. We hope that this study will raise public awareness about cancer in this age group and provide the impetus for further research to improve the survival and quality of life of the young people in Japan.

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LY designed and carried out analyses and drafted the paper; DQ prepared data and created the figure and JF and N.S. edited the paper and commented on the interpretation of the results. All authors read and approved the final draft of the paper.

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EDUCATIONAL REPORT

Long-term results of Tokyo Children's Cancer Study Group trials for childhood acute lymphoblastic leukemia, 1984–1999

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We report the long-term results of Tokyo Children's Cancer Study Group's studies L84-11, L89-12, L92-13, and L95-14 for 1846 children with acute lymphoblastic leukemia, which were conducted between 1984 and 1999. The value of event-free survival (EFS) ± s.e. was 67.2 ± 2.2% at 10 years in L84-11, which was not improved in the following two studies, and eventually improved to 75.0 ± 1.8% at 10 years in L95-14 study. The lower EFS of the L89-12 reflected a high rate of induction failure because of infection and delayed remission in very high-risk patients. The L92-13 study was characterized by short maintenance therapy; it resulted in poor EFS, particularly in the standard-risk (SR) group and boys. Females did significantly better than males in EFS in the early three studies. The gender difference was not significant in overall survival, partly because >60% of the males survived after the testicular relapse. Randomized studies in the former three protocols revealed that intermediate- or high-dose methotrexate therapy significantly reduced the testicular relapse rate. In the L95-14 study, gender difference disappeared in EFS. Contrary to the results of larger-scale studies, the randomized control study in the L95-14 reconfirmed with updated data that dexamethasone 8 mg/m^2 had no advantage over prednisolone 60 mg/m^2 in the SR and intermediate-risk groups. Prophylactic cranial irradiation was assigned to 100, 80, 44, and 44% of the patients in the studies, respectively. Isolated central nervous system relapse rates decreased to <2% in the last two trials. Secondary brain tumors developed in 12 patients at 8–22 years after cranial irradiation. Improvement of the remission induction rates and the complete omission of irradiation are currently main objectives in our studies.
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Introduction

We present here the long-term results of four studies for childhood acute lymphoblastic leukemia (ALL) of Tokyo Children's Cancer Study Group (TCCSG) conducted between 1984 and 1999.

Treatment protocol for SR and IR of the L84-11 study[1,2] was based on the early St Jude's total therapy.[3] ALL-BFM 81[4] protocol was modified and introduced to extremely high-risk group regimen for the first time. The protocols of the following three studies L89-12,[1,5] L92-13,[1,6] and L95-14,[7] were designed on the basis of the ALL-BFM framework. All the four protocols contained trials to reduce the number of patients who received irradiation, as had been reported in other studies.[8,9] The second point of analysis was on a gender difference[10–12] with respect to long-term event-free survival (EFS) and overall survival (OS). Randomized studies were mostly designed to test whether or not intermediate-dose methotrexate (ID-MTX) and high-dose methotrexate (HD-MTX) could replace the cranial irradiation. It is needed to describe the further long-term outcome of the patients who were treated in L92-13 study, which was characterized by very short maintenance therapy. We published the discordant results on the randomized comparison between dexamethasone and prednisolone in 2005, which was updated in this analysis.[7]

Materials and methods

Total of 1846 newly diagnosed patients with ALL aged 1–15 years entered into the four studies—that is L84-11 (n=484),

Table 1 Event-free survival, overall survival, and CNS relapse of TCCSG studies L84-11, L89-12, L92-13, and L95-14

Study	*Year*	*Number of patients*	*Complete remission rate (corrected)*[a]	*Event-free survival ± s.e.%*			*Overall survival ± s.e.%*			*Isolated and any CNS relapse rate ± s.e.% 10 year*
				5 years	*10 years*	*15 years*	*5 years*	*10 years*	*15 year*	
L84-11	1984–1989	484	97.3 (98.6)%	71.2 ± 2.1	67.2 ± 2.2	66.3 ± 2.2	80.7 ± 1.8	74.3 ± 2.0	73.5 ± 2.1	4.1 ± 1.0 5.5 ± 1.1
L89-12	1989–1992	418	92.8 (95.7)%	67.2 ± 2.4	64.4 ± 2.4	62.3 ± 2.6	77.7 (2.1)	73.5 ± 2.2	71.9 ± 2.2	3.7 ± 1.1 5.4 ± 1.3
L92-13	1992–1995	347	96.5 (97.7)%	63.7 ± 2.7	60.1 ± 2.7	57.7 ± 2.9	80.4 (2.1)	77.9 ± 2.2	77.4 ± 2.4	1.0 ± 0.6 2.6 ± 1.0
L95-14	1995–1999	597	95.0 (97.4)%	76.8 ± 1.8	75.0 ± 1.8	—	84.9 (1.5)	82.0 ± 1.6	—	1.7 ± 0.6 2.8 ± 0.7

Abbreviations: CNS, central nervous system; s.e., standard error; TCCSG, Tokyo Children's Cancer Study Group.
[a]Corrected remission (rate %): patients who achieved delayed remission were included in remission, and censored patients during the induction phase were excluded from the total.

L89-12 ($n=418$), L92-13 ($n=347$), and L95-14 ($N=597$)—as shown in Table 1. Diagnoses were made based on morphology, immunophenotype, and cytogenetics in each institution; the ALL committee evaluated these results for eligibility. Patients aged 1–6 years presented with a leukocyte count $<20\times10^9$/l and B-precursor phenotype were classified into the standard-risk (SR) group in all the studies. Definitions of the intermediate-risk (IR) and high-risk (HR) or extremely high-risk groups varied across the four studies. Nonetheless, HR patients were mostly defined as having one of the following: initial leukocyte count $\geqslant100\times10^9$/l, age of $\geqslant10$ years, leukocyte count $\geqslant50\times10^9$/l; Philadelphia chromosome (Ph) or BCR–ABL fusion gene product positive, 11q23 chromosome translocation or MLL gene rearrangements, and T-ALL with otherwise IR-risk factors. The reminder of the SR and HR patients was assigned to the IR group. Analysis of the outcome was based on the risk classification of the NCI/Rome criteria.[13]

Leukemic-cell karyotype was obtained from 20 to 30% of the patients in the first three studies. The DNA index was measured by flow cytometry.

Infants were excluded from these studies, and their treatment results were already published elsewhere.[14–16]

Treatment

The precise regimens of L84-11,[2] L89-12,[5] L92-13,[6] and L95-14[7] studies were available in earlier publications. Table 2 provides a summary of regimens in each study.

L84-11 study (1984–1989). Both the SR and HR groups were randomized at early intensification into two arms—that is S1 and S2, and H1 and H2, respectively. In the S2 and H2 arms, the patients received three courses of ID-MTX (500 mg/m^2) with a single dose of leucovorin rescue (12 mg/m^2) at 48 h, in conjunction with double-drug intrathecal injections (DIT) before cranial irradiation. In the S1and H1 arms, 18 Gy of cranial irradiation with five doses of triple-drug intrathecal injections (TIT) were administered without ID-MTX.

The DIT consisted of methotrexate (MTX) 15 mg/m^2 $\leqslant$15 mg and hydrocortisone 30 mg/m^2 $\leqslant$30 mg, respectively. The TIT consisted of DIT and cytosine arabinoside (CA) 30 mg/m^2 $\leqslant$30 mg.

L89-12 study (1989–1992). The regimen was based on the BFM backbone in all three risk groups. There was a week of prophase treatment with prednisolone alone to evaluate initial steroid response, as BFM group described.[17] The main objective was to determine whether cranial irradiation was essential to the treatment of SR patients or not. To do so, the SR patients were randomly assigned to the SR0 and SR18 arms, and patients in the SR0 arm were given three courses of HD-MTX (3 g/m^2) with three DIT without cranial irradiation. The doses of intrathecal injection were reduced from those of the earlier study, changing to age-adjusted calculation. The patients assigned to the SR18 arm received 18 Gy of cranial irradiation and three doses of TIT. The randomization ratio in SR arms changed from 1:1 to 2:1 in the last half period, so that there were 83 patients enrolled in SR0 arm and 64 in SR18 arm. The HR group was treated with a single arm of BFM-style therapy for 2 years, modified with an insertion of HD-MTX (3 g/m^2, two courses) between the induction (Ia) and early intensification and cranial irradiation (Ib). Four courses of multiple-drug intensifications were given during the first year followed by 1-year maintenance therapy.

L92-13 study (1992–1994). A major objective was to evaluate 1-year therapy in all risk groups. The length of the maintenance therapy was kept to a minimum of 6 months in the SR group and 3 months in each of the IR and HR groups. All three risk regimens had BFM-type structures. This protocol was characterized by the use of intermediate-dose cytosine arabinoside (ID-CA, 500 mg/m^2/day for 4 days) and high-dose cytosine arabinoside (HD-CA, 1 or 2 g/m^2/day for 4 days) in the early intensification and in the re-intensification phases.

The SR regimen had two courses of HD-MTX (3 g/m^2) and two DITs. The early intensification phases were complete before week 28; 24 weeks were left for the continuous therapy. IR group was randomized either to IR18 arm with 18-Gy cranial irradiation, or to IR0 arm with two courses of HD-MTX (3 g/m^2/day) without cranial irradiation. All patients of the HR group were given 2 weekly courses of HD-CA (2 g/m^2, six doses for 3 days) and mitoxantrone (2 days) after remission induction.

L95-14 study (1994–1999). SR and IR groups were randomized into prednisolone arm (PSL) and dexamethasone arm (DEX) not only in the induction, but also in re-induction phase and three courses of late intensification for SR and two courses for IR. During remission induction, prednisolone (60 mg/m^2) or dexamethasone (8 mg/m^2) was given for 4 weeks and tapered. In the re-induction and intensification courses, prednisolone (40 mg/m^2) or dexamethasone (6 mg/m^2) were given for 2 weeks in each arm. For patients presenting with leukocyte count $\geqslant150\times10^9$/l and aged 7 years or older (assigned to allo-stem-cell transplantation (SCT) group), allogeneic bone marrow transplantation from HLA-matched family donor, if any, and autologous blood or marrow SCT or chemotherapy could be elected. For patients presented with

Table 2 Treatment protocols of the four studies

Studies	*TCCSG risk*	*Number*	*Therapy period (years)*	*Cranial irradiation***		*Remission induction*	*Early intensification*	*CNS prophylaxis*	*Reindution*	*Intensification*	*Continuation*
L84-11	SR	194	3.5	100%	100%	P V5 Asp	**Randomized S1:CRX18/ itMHC(5) vs S2:IDMTX(3)/ itMH(3)**	**S1:none vs S2:CRX18/itMHC(5)**	Dex V2/itMH..q16m(7) Dex V2 IDMTX/itMH..q12w(4)—2.5–3.5 years		MTX+6mp (throughout)
	HR	244	3.5		100%	P V5 Asp Cy	**Randomized H1:CRX24/ itMHC(5) vs H2:IDMTX(3)/ itMH(3)**	**H1:none vs H2:CRX24/itMHC(5)**	Dex V2 D2, Dex V2 Cy, Dex B Acr, Dex V2 Asp, Dex V2 MTX(iv)—first, second year Cy(4), HDCA(4), IDMTX/itMHC(4)—third year		MTX+6mp (throughout)
	HEX	48	2.5		100%	P V4 Asp D3 Cy1 itMHC(3)	Cy1 CA(4x4) 6mp	CRX24/itMHC(5)	Dex V4 Ad4 Asp, Cy B(8) itMH(2)	itMHC(8), PV2(4)	MTX+6mp
L89-12	SR	142	2	80%	44%	P V4 Asp T2 itMHC(1)	Vp CA(4x3) 6mp itMHC(3)	**Randomized HDMTX/ itMH(3) vs CRX18/itMHC(3)**	Dex V3 Asp T(3)	Vp4 B4 6mp/itMH(2)	MTX+6mp (1.5 years)
	IR	100	2		100%	P V4 Asp T3 itMHC(1)	CRX18 itMH(3)	Cy1 CA(4x4) 6mp itMHC(3)	Dex V3 Asp T4	P Vp4 B4 Acr(2), P Vp4 Cy4 Aap(2)	MTX+6mp (1 year)
	HR	146	2		100%	P V4 Asp T3 itMHC(1-2)	HDMTX(2)/itMH(2)	CRX18 /itMHC(3) Cy2 CA(4x4) 6mp	Dex V3 Asp T4	mP HDCA Asp Mit(2), P Vp4 B4 Acr(2), P Vp4 Cy4 Asp(2)	MTX+6mp (1 year)
L92-13	SR	124	1	44%	0%	P V4 Asp T2 itMH(1)	Mit CA(4x4) 6mp	HDMTX/itMH(2)	P V3 Asp T2	IDCA0.5gx4/Mit(2)	MTX+6mp (6 months)
	IR	122	1		47%	P V4 Asp T3 itMH(1)	Cy1 CA(4x4) 6mp itMHC(3)	**Randomized HDMTX(2)/ itMH(2) vs CRX18/itMH (3)**	P V3 Asp T2	HDCA1gx4/Mit(2) it(MH), Vp B Asp(2)	MTX+6mp (3–4 months)
	HR	101	1		100%	P V4 Asp T3 itMHC(2-3)	HDCA2gx6/Mit (2) itMH(2)	CRX18/itMHC(3) Cy1 CA(4x4) 6mp	P V3 Asp T(2)	HDCA2gx4/Mit/ it(MH)(2), Vp B Asp(2)	MTX(iv)q4W+ 6mp (3–4 months)
L95-14	SR	231	2	44%	0%	**Randomized* P vs Dex** and V5 Asp T2 itMH(2)	Cy1 CA(5x3) 6mp itMHC(3)	HDMTX/itMH(3)	**P vs Dex*** V3 Asp T3	Cy1 CA(2x5) 6mp(1), **P vs Dex*** V3 Asp(3) IDMTX(no CF)/itMH(3)	MTX(iv)+6mp, MTX+6mp (1 year+)
	IR	129	2		18%	**Randomized* P vs Dex** and V5 Asp T2 Cy1 itMH(2)	Cy1 CA(5x3) 6mp itMHC(3)	**Randomized HDMTX/itMH(3) vs CRX18/itMH(3)** Asp MTX+6mp	**P vs Dex*** V3 Asp T3	Cy1CA(2x5) 6mp(1), **P vs Dex*** V3 Asp T3(2) HDCA/Asp(1), IDMTX(no CF)(2), Cy1 CA(2x5) 6mp(1)	MTX(iv)q2W+ 6mp, MTX+6mp (1 year+)
	HR	237	2		100%	P V5 Asp D4 Cy2/ itMH(2-3)	HDCA2gx4/Asp(2)/itMH(2)	CRX18/itMHC(3) Cy1 CA(5x3) 6mp(1)	Dex V4 Ad4 Asp(1), P V3 Asp Ad2(2)	HDCA2gx8/itMH(2) IDMTX(no CF)(2), Cy1 CA(2x5) 6mp(1)	MTX+6mp (1 year)

Abbreviations: CNS, central nervous system; HEX, extremely high risk; HR, high risk; IR, intermediate risk; SR, standard risk; TCCSG, Tokyo Children's Cancer Study Group.
Acr, aclarubicin; Ad, doxorubicin; Asp, L-asparaginase; B, behenoyl cytosine arabinoside; CA, cytosine arabinoside; CRX18, cranial irradiation 18 Gy; Cy, cytoxan; D, daunorubicin; Dex, dexamethasone (8 mg/m^2 in induction 6 mg/m^2 consolidation of dex arm); HDCA, high-dose cytosine arabinoside (1–2 g/m^2); HDMTX, high-dose methotrexate (3 g/m^2); IDCA, intermediate-dose cytosine arabinoside (500 mg/m^2); itMH, double intrathecal injection of methotrexate and hydrocortisone; itMHC, triple intrathecal injection of methotrexate, cytosine arabinoside, and hydrocortisone; IDMTX, intermediate-dose methotrexate (500 mg/m^2); Mit, mitoxantrone; mP, methy-prednisolone; MTX, oral methotrexate; MTX(iv), intravenous MTX (75 mg/m^2); (noCF), no leucovorine rescue; P, prednisolone (*60 mg/m^2 in induction 40 mg/m^2 consolidation of P arm); T, THP-adriamycin (pirarubicin); V, vincristine; Vp, etoposide; 6mp, oral 6 mercapropurine.
Number after drug-dose, (Numer), repeat. Randomizations were written with bold letters. Randomized*, initially randomized for whole course. **Proportion of the patients who were initially assigned to cranial irradiation arm; actual proportion was lower than the assigned.

leukocyte count $\geqslant 100 \times 10^9$/l, or 10 years old or older with leukocyte count $\geqslant 50 \times 10^9$/l (assigned to auto-SCT group), autologous blood or marrow SCT or chemotherapy could be elected. Each institute declared the choice in advance of the study initiation.

Statistical analysis

The duration of EFS was defined as the time from the initiation of therapy to the date of failure (that is any relapse, death, or diagnosis of secondary malignancy) or to the date when patients were confirmed to be in remission and alive. Patients who did not achieve complete remission at the end of the initial induction phase or who died before the confirmation of remission were considered to have failed at day 0, even if they entered remission later with a second course or through additional treatment. The probability of EFS and s.e. was estimated by the Kaplan–Meier method (Greenwood), and differences were tested by the log-rank test. Analysis was performed with the intent to treat. 'Any central nervous system (CNS) relapse' include both 'isolated CNS relapse' and CNS relapse combined with other sites. Probability of cumulative CNS relapse was estimated by inversed Kaplan–Meier method, which involves subtraction of Kaplan–Meier products from 100%. Only patients who had CNS relapse were failure, and all the others were censored. Cumulative probability of any secondary malignancy was calculated using the same method. Patients who received modified treatment were censored at that point in time. The patients who did not enter complete remission or had died during induction were treated as at the date of the beginning of treatment. Patients who were confirmed as remaining in first remission and alive, or who were lost of follow-up, were censored for EFS analysis; all those who were alive with or without disease were censored in OS analysis at the date of last contact.

Follow-up was updated in 2008. The proportions of patients whose data of the last 5 years were available were 144 of 357 (40.3%) in L84-11 study, 197 of 306 (64.3%) in L89-12, 220 of 266 (82.7%) in L92-13, and 449 of 489 (91.8%) in L95-14.

Results

Probability of EFS, OS, and cumulative CNS relapse rate of each study are shown in Tables 1 and 3. There was no improvement in EFS during the first three studies. The OS of L92-13 improved,

Table 3 Summary of the study results

Studies	*L84-11*	*L89-12*	*L92-13*	*L95-14*
Number of eligible patients (B+T)	484	418	347	597
Number of B/T	420/32	375/43	315/32	539/58
Average age (B/T) year	5.7/8.8	5.9/8.2	5.8/7.7	5.9/7.7
Average WBC (B/T)	20.1/108.0	31.6/137.5	38.4/146.1	30.6/167.0
Number of censored early	0	1 (0.2%)	2 (0.6%)	9 (1.5%)[a]
Death during induction	3 (0.6%)	12 (2.9%)[b]	5 (1.4%)	10 (1.7%)[c]
Failure of initial remission	11 (2.3%)[d]	17 (4.1%)[e]	5 (1.4%)	11 (1.8%)[f]
Complete remission (rate)	470 (97.1%)	388 (92.8%)	335 (96.0%)	567 (95.0%)
Corrected remission (rate)[g]	477 (98.6%)	399 (95.7%)	337 (97.7%)	573 (97.4%)
Death in first remission	19 (3.9%)	7 (1.7%)	6 (1.7%)	22 (3.7%)[h]
Number of censored in first remission	13 (2.7%)	13 (3.1%)[i]	31 (8.9%)[j]	21 (3.5%)[k]
Number of patients at event free	308 (63.6%)	256 (61.2%)	180 (55.3%)	428 (71.7%)
Number of relapse after remission	123 (26.1%)	104 (26.9%)	112 (33.4%)	92 (16.7%)
Site of relapse: total	123 (100%)	104 (100%)	112 (100%)	92 (100%)
Isolated bone marrow (BM)	72 (58.5%)	70 (67.3%)	87 (78.4%)	68 (73.9%)
Isolated CNS	17 (13.8%)	13 (12.5%)	3 (2.7%)	10 (10.9%)
Isolated testis	19 (15.4%)	6 (5.8%)	9 (78.4%)	7 (7.6%)
BM+CNS	6 (4.9%)	4 (3.8%)	3 (7.2%)	5 (5.4%)
BM+testis	7 (5.7%)	7 (6.7%)	6 (3.6%	1 (1.1%)
CNS+testis	1 (0.8%)	1 (0.9%)	0	0 (0%)
Other sites	1 (0.8%)	3 (2.9%)	3 (2.7%)	1 (1.1%)
Secondary AML/MDS	0/1	3/1	0/0	2/1
Brain tumor/Other	5/1[l]	4	2	1
Any BM	85 (69.1%)	81 (77.9%)	97 (87.4%)	74 (80.4%)
Any CNS	24 (19.5%)	18 (17.3%)	6 (5.4%)	15 (16.3%)
Any testis	27 (22.0%)	14 (13.5%)	15 (13.3%)	8 (8.7%)
Any testis/males	27 (10.3%)	14 (5.8%)	15 (8.5%)	8 (2.4%)

Abbreviations: AML, acute myeloid leukemia; CNS, central nervous system; MDS, myelodysplastic syndrome; SCT, stem-cell transplantation; WBC, white blood cells.
[a]Four patients assigned in dexamethasone arm dropped off, one in prednisolone arm, and four in HR risk group dropped off.
[b]Marrow suppression and infection.
[c]Five deaths in dexamethasone arm, two deaths in prednisolone arm, three deaths in HR risk.
[d]7/11 entered into remission in the following phase.
[e]11/17 patients entered remission in the following phase.
[f]All 11 failures in HR risk group; 3 Ph+ALL, 4 chromosomal translocations, 6/11 entered into remission in the following phase.
[g]Corrected remission (rate %): patients who achieved delayed remission were included in remission, and censored patients during the induction phase were excluded from the total.
[h]18/22 deaths in HR risk group, 5 related with transplants.
[i]7/13 patients underwent SCT in CR1.
[j]26/31 patients underwent SCT in CR1.
[k]9/21 patients underwent SCT in CR1.
[l]Olfactory neuroblastoma.

compared with these of the earlier two studies. The L95-14 study achieved internationally acceptable level of EFS and OS (log-rank $P<0.0001$). The cumulative 'any CNS relapse' rate decreased from 5.5% (any CNS) in the L84-11 study to 2.8% in the L95-14 study.

Twelve treatment-related brain tumors developed in patients who had received cranial irradiation in the four studies—that is 5, 4, 2, and 1 patient, respectively. They developed in six males and six females. No brain tumor occurred in the non-irradiated patients. The tumors developed between 8 and 22 years after cranial irradiation, seven in the 18-Gy irradiated group and five in the 24-Gy irradiated group. The probability of cumulative incidence (±s.e.) of brain tumors was 1.9±0.6% at 15 years and 2.8±0.9% at 20 years among the 1234 irradiated patients. Secondary acute myeloid leukemia (AML)/myelodysplastic syndrome (MDS) developed in eight patients—that is 0/1, 3/1, 0, and 2/1 in each study. Two of them (L89-12) were confirmed to have 11q23 chromosome abnormality. Seven of the eight patients were female, whereas brain tumors developed evenly in terms of gender. AML/MDS occurred only in the irradiated patients without exception. The probability of cumulative incidence±s.e. of AML/MDS among irradiated patients was 0.57±0.25% at 3 years and 1.1±0.4% at 10 years.

Cerebrovasucular lesions such as Moyamoya disease developed after radiation in the TCCSG studies and published elsewhere.[18] Neurocognitive evaluation study was not carried out as a group.

Protocol-specific treatment result

L84-11 study. For 484 patients enrolled, EFS±s.e. and OS±s.e. were 66.3±2.2 and 73.5±2.1% at 15 years, respectively. There were 357 long-term survivors, and their median follow-up period was 16.6 years. Among survivors, seven had serious neurological sequelae, such as paraparesis or leukoencephalopathy, which developed most probably because of cranial irradiation and concentrated use of five TITs at body-surface-adjusted dose setting. Probability of cumulative incidence of brain tumors in L84-11 was 1.2±0.7% at 15 years (Tables 3 and 4; Figure 1).

Males fared significantly worse than females in terms of EFS (Table 4; $P=0.006$), but not in terms of OS ($P=0.205$). Isolated or combined testicular relapses developed in 27 out of 261 males (10.3%) and they comprised 22% of all relapses.

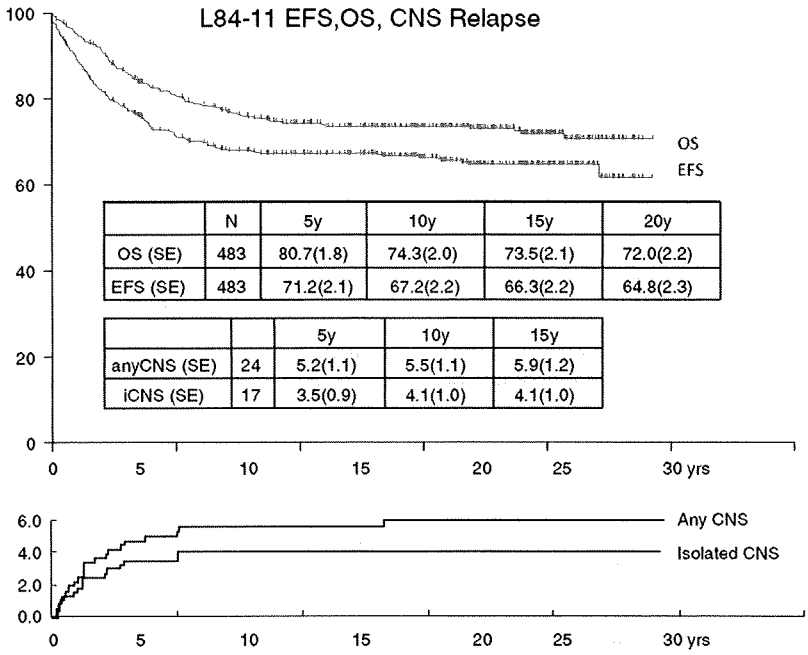
As a result of the randomized comparison in SR, the EFS±s.e. rates of the S1 and S2 arms were 68.5±4.8 and 81.0±4.1%, respectively, at 15 years (log-rank test, $P=0.071$). The probabilities of cumulative incidence ±s.e. of any testicular relapse were 24.3±6.7% in S1 arm and 4.7±3.3% in S2 arm (log-rank $P=0.015$).

L89-12 study. For the 418 patients enrolled, the EFS±s.e. and OS rate were 62.3±2.6 and 71.9±2.2% at 1 year, respectively. Probability of cumulative isolated CNS and any

Table 4 Treatment results according to presenting features in non-infant patients treated in study L84-11

Factors	*Number of patients*	*Event-free survival±s.e.%*				*Overall survival±s.e.%*			
		5 years	*10 years*	*15 years*	*log-rank P-value*	*5 years*	*10 years*	*15 years*	*log-rank P-value*
Non-T lineage									
NCI standard	314	72.8±2.5	69.4±2.6	68.5±2.7	0.074	83.4±2.1	77.6±2.4	77.2±2.4	0.012
NCI high	106	67.6±4.7	61.0±4.9	59.0±5.1		73.6±4.4	66.1±4.8	64.8±5.0	
T-lineage									
NCI standard	9	55.6±16.6	44.4±16.6	44.4±16.6	0.636	66.7±15.7	55.6±16.6	41.7±17.3	0.487
NCI high	23	60.9±10.1	60.9±10.1	60.9±10.1		65.2±9.9	65.2±9.9	65.2±9.9	
Sex									
Male	261	66.4±3.0	61.3±3.2	60.8±3.1	0.006	80.1±2.5	72.1±2.8	71.1±2.9	0.205
Female	222	78.1±3.0	74.5±3.0	73.1±3.1		81.5±2.6	76.9±2.9	76.4±2.9	
Age at diagnosis (years)									
1–9	392	72.6±2.3	69.2±2.4	68.5±2.4	0.068	82.7±1.9	76.5±2.2	75.9±2.2	0.007
⩾10	91	65.0±5.2	58.7±5.3	56.8±5.5		72.0±4.8	64.7±5.1	63.2±5.2	
WBC x 10^9/l									
<10k	265	76.5±2.6	73.1±2.8	71.9±2.9	0.0131	86.4±2.1	80.9±2.5	80.4±2.5	0.002
10–49k	159	64.6±3.9	59.7±4.0	5.9±4.0		75.8±3.4	67.5±3.8	66.0±3.9	
50–99k	31	63.5±8.8	56.0±9.2	56.0±9.2		70.0±8.3	58.4±9.3	58.4±9.3	
⩾100k	28	67.9±8.8	67.9±8.8	67.9±8.8		67.3±9.0	67.3±9.0	67.3±9.0	
Cell lineage									
Non-T	420	71.5±2.2	67.3±2.3	66.3±2.4	0.121	81.0±1.9	74.7±2.2	74.1±2.2	0.038
T	32	59.4±8.7	55.9±8.8	55.9±8.8		65.6±8.4	62.2±8.6	58.5±8.1	
TCCSG risk arms									
S1	102	74.4±4.4	69.9±4.7	68.5±4.8	0.071	91.0±2.9	83.1±3.8	79.6±5.1	0.227
S2	93	85.7±3.7	81.0±4.1	79.1±4.5		94.5±2.5	87.3±3.6	87.3±3.6	
H1	129	69.8±4.1	67.2±4.2	66.0±4.3	0.131	77.7±3.7	73.4±4.0	71.4±4.1	0.046
H2	113	62.7±4.6	57.5±4.8	57.5±4.8		70.9±4.3	61.9±4.7	61.9±4.7	
S1 testis	49	21.8±6.4	24.3±6.7	24.3±6.7	0.009				
S2 testis	50	2.3±2.3	4.7±3.3	4.7±3.3					

Abbreviations: NCI, National Cancer Institute risk group; s.e., standard error; TCCSG, Tokyo Children's Cancer Study Group, WBC, white blood cells. Testis: probability of cumulative any testicular relapse rate in males.



	N	5y	10y	15y	20y
OS (SE)	483	80.7(1.8)	74.3(2.0)	73.5(2.1)	72.0(2.2)
EFS (SE)	483	71.2(2.1)	67.2(2.2)	66.3(2.2)	64.8(2.3)

		5y	10y	15y
anyCNS (SE)	24	5.2(1.1)	5.5(1.1)	5.9(1.2)
iCNS (SE)	17	3.5(0.9)	4.1(1.0)	4.1(1.0)

Figure 1 EFS, OS, and cumulative incidence of isolated or any CNS relapses in L84-11 study.

CNS relapse rates were 3.7 ± 1.1 and 5.4 ± 1.3% at 15 years, respectively. Of the 306 surviving patients, the median survival period was 14.6 years. Secondary neoplasms consisted of four brain tumors, three AML, and one MDS. Remission induction rate was 92.8%, which was the lowest of the four studies (Table 3). Twelve patients (2.9%) died during or after the remission induction course, between days 10 and 82. The major cause of death was prolonged marrow suppression and infection. Of 17 patients (4.1%) failed to enter remission at the end of induction, six patients (1.4%) died within 4–24 months; one Ph positive ALL, and four with leukocyte count $>145 \times 10^9$/l. The other 11 patients entered remission in the following phase; five patients with leukocyte counts $>100 \times 10^9$/l, seven Ph positive ALL. The corrected remission rate was 95.7% when the patients who entered into delayed remission were included in remission and those who were dropped off during induction were excluded from the total number. Pirarubicin used for induction at a dosage of 30 mg/m^2 (two or three doses) was amended to 20 mg/m^2 in October 1990. Nine out of 12 deaths occurred before the amendment. Testicular relapse was significantly fewer in incidence in SR0 (HD-MTX) arm than the SR18 arm ($P=0.018$; Tables 3, 5; Figure 2).

L92-13 study. EFS ± s.e. and OS ± s.e. for 347 eligible patients enrolled were 60.1 ± 2.7 and 77.9 ± 2.2% at 10 years, respectively. Cumulative rate of isolated CNS relapse was 1.0 ± 1.0 at 10 years, which might be underestimated by high bone marrow relapse rate. The median follow-up period was 13.0 years for the 271 (78.1%) patients remaining alive, including 64 patients who experienced relapse. Twenty-one HR patients underwent hematopoietic SCT at first remission (treated as censored), and 18 were alive in CR (Tables 3, 6; Figure 3).

Brain tumors occurred in two patients. No myeloid leukemia or MDS developed. The rate of remission induction was 96.0%.

Seven of 26 relapses among 62 males in SR group relapsed very late at 5–13 years of the initial therapy, whereas females stopped recurring at 5 years. Overall, the EFS in males was 47.5 ± 4.3% at 15 years, which was significantly lower than that in females (68.0 ± 3.8%, $P=0.0003$). Males were, however, more efficiently salvaged. The OS of males was 75.8 ± 3.3% and that of females 80.3 ± 3.1% ($P=0.731$; Table 6). Ten of 14 patients with isolated or combined testicular survived. After relapse, 51 patients survived out of 84 who had undergone hematopoietic SCT (actual survival 60.7%). Of 25 who had been treated with chemotherapy, 15 survived after relapse (60%). The OS rate of 77.4 ± 2.4% eventually exceeded the preceding two studies.

L95-14 study. L95-14 study achieved 5-year EFS ± s.e 75.0 ± 1.8% and the OS ± s.e. 82.0 ± 1.6%, at 10 years' follow-up. For the 489 patients who remained alive, the median follow-up period was 10.0 years. The remission induction rate after the initial course was 95.0%. The corrected remission induction rate was 97.5% when nine patients who were off during induction were excluded and six patients who entered into remission in the following phase were included. The cumulative isolated CNS relapse rate was 1.7 ± 0.6% and 'any CNS relapse' rates was 2.8 ± 0.7% for all patients, and the latter level was 4.3 ± 1.4% in the HR. One brain tumor occurred at 8.3 years, two AML, and one MDS all were diagnosed between 1.5 and 5.2 years of therapy (Tables 3, 7; Figures 4).

The results of randomized control study was updated and showed again no advantage of DEX arm over PSL arm in SR and IR groups[7] (Tables 2, 7). Three extramedullary relapses occurred in the DEX arm, whereas eight developed in the PSL arm.

Hematopoietic SCTs, either allogeneic or autologous blood and marrow source, were elected by institutional intention to

Table 5 Treatment results according to presenting features in non-infant patients treated in study L89-12

Factors	*Number of patients*	*Event-free survival ± s.e.%*				*Overall survival ± s.e.%*			
		5 years	*10 years*	*15 years*	*log-rank P-value*	*5 years*	*10 years*	*15 years*	*log-rank P-value*
Non-T lineage									
NCI standard	314	72.8 ± 2.5	69.4 ± 2.6	68.5 ± 2.7	0.074	83.4 ± 2.1	77.6 ± 2.4	77.2 ± 2.4	0.012
NCI high	106	67.6 ± 4.7	61.0 ± 4.9	59.0 ± 5.1		73.6 ± 4.4	66.1 ± 4.8	64.8 ± 5.0	
T-lineage									
NCI standard	11	70.1 ± 14.7	70.1 ± 14.7	70.1 ± 14.7	0.169	70.1 ± 14.7	70.1 ± 14.7	70.1 ± 14.7	0.369
NCI high	32	51.9 ± 9.0	51.9 ± 9.0	43.3 ± 10.9		55.3 ± 8.9	55.3 ± 8.9	55.3 ± 8.9	
Sex									
Male	240	62.1 ± 3.2	59.8 ± 3.3	57.8 ± 3.4	0.044	76.3 ± 2.8	72.2 ± 3.5	71.1 ± 3.0	0.564
Female	178	74.1 ± 3.4	70.8 ± 3.5	68.3 ± 3.7		79.6 ± 3.1	75.2 ± 3.3	73.0 ± 3.5	
Age at diagnosis (years)									
1–9	320	70.8 ± 2.6	68.0 ± 2.7	66.6 ± 2.7	0.0002	81.8 ± 2.2	78.3 ± 2.4	77.5 ± 2.4	<0.0001
⩾10	97	54.3 ± 5.3	51.6 ± 5.4	46.2 ± 5.7		64.2 ± 4.9	57.5 ± 5.1	53.0 ± 5.4	
WBC × 10^9/l									
<10k	203	75.5 ± 3.1	70.7 ± 3.4	67.8 ± 3.5	<0.0001	88.1 ± 2.3	83.5 ± 2.7	81.5 ± 3.0	<0.0001
10–49k	133	67.7 ± 4.1	66.0 ± 4.2	66.0 ± 4.2		77.5 ± 3.7	73.5 ± 3.9	72.7 ± 3.9	
50–99k	31	47.1 ± 9.1	43.5 ± 9.1	43.5 ± 9.1		61.2 ± 8.7	54.8 ± 8.9	51.4 ± 9.0	
⩾100k	50	44.4 ± 7.2	44.4 ± 7.2	40.0 ± 7.7		46.7 ± 7.2	44.6 ± 7.2	44.6 ± 7.2	
Cell lineage									
Non-T	374	68.3 ± 2.5	65.2 ± 2.6	63.3 ± 2.6	0.053	79.8 ± 2.1	75.0 ± 2.3	73.3 ± 2.4	0.009
T	43	57.1 ± 7.7	50.7 ± 9.1	50.7 ± 9.1		59.1 ± 7.7	59.1 ± 7.7	59.1 ± 7.7	
CNS status									
CNS blast +	12	42.9 ± 15.7	42.9 ± 15.7	42.9 ± 15.7	0.132	56.3 ± 14.8	46.9 ± 15.0	46.9 ± 15.0	0.033
CNS blast −	406	68.1 ± 2.4	65.0 ± 2.4	62.8 ± 2.5		78.3 ± 2.1	74.2 ± 2.2	72.6 ± 2.3	
TCCSG SR arms									
SR0	83	75.4 ± 4.9	72.7 ± 5.1	72.7 ± 5.1	0.399	90.6 ± 3.4	89.2 ± 3.6	87.7 ± 3.9	0.148
SR18	64	71.5 ± 5.7	66.5 ± 6.0	66.5 ± 6.0		85.8 ± 4.4	80.9 ± 5.0	78.1 ± 5.5	
SR0 CNS	83	5.4 ± 2.6	—	—	0.999				
SR18 CNS	64	5.2 ± 2.9	—	—					
SR0 testis	83	3.3 ± 3.3	—	—	0.018				
SR18 testis	64	19.4 ± 7.1	22.9 ± 7.6	—					

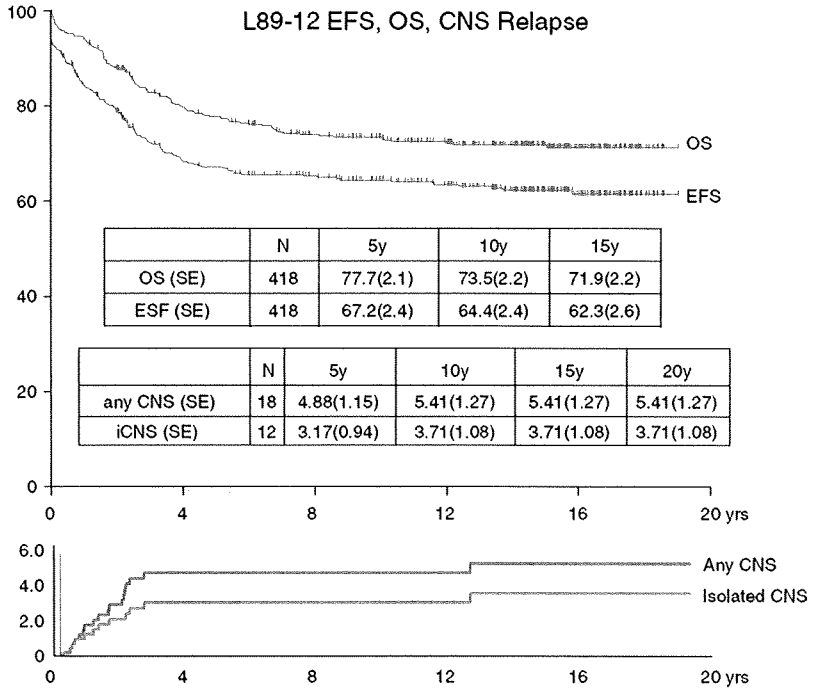
Abbreviations: CNS, central nervous system; NCI, National Cancer Institute risk group; s.e., standard error; SR, standard risk; TCCSG, Tokyo Children's Cancer Study Group; WBC, white blood cells.
CNS: probability of cumulative any CNS relapse rate.
Testis: probability of cumulative any testicular relapse rate.

treat decision in advance and executed for 61 (37 allo-SCT and 24 auto-SCT) of 126 patients who assigned to SCT (59 allo-SCT and 67 auto-SCT), among which 44 (actual rate72.1%) were alive without relapse. Of the 65 patients who assigned to SCT group, but elected chemotherapy, 30 (46, 2%) patients were alive; 29 were in first remission.

Treatment results according to presenting features

Well-documented prognostic factors were analyzed in each of the four studies (Tables 4–7). Infants were not included in these studies. Patients with B-precursor ALL and T-ALL were analyzed separately in each of the four studies, according to the NCI / Rome criteria. Age and leukocyte count at diagnosis were still independently strong prognostic factors.

Patients with T-ALL had poor prognosis. This was more evident in terms of OS (Tables 2–5). Clearly, patients with T-ALL could not be easily salvaged after relapse. Females fared significantly better than males in terms of EFS at 10 years by 13.2 points (L84-11, $P=0.006$), 11.0 points (L89-12, $P=0.044$), 15.6 points (L92-13, $P=0.003$), and –2.8 points (L95-14, males fared better, $P=0.519$), respectively (Table 3). 'Any testicular relapse' rate was 10.3, 5.8, 8.5, and 2.4% of all the males in the four studies, respectively (Table 3). The cumulative incidence of testicular relapse was significantly lower in ID-MTX or HD-MTX arms in randomized trials of the L84-11 SR, L89-12 IR, and L92-13 IR, as has been described.[19] The gender difference in EFS correlated well with the incidence of testicular relapse. Approximately 60% of the patients with any testicular relapse survived and contributed to the recovery of male OS to the same level as females. CNS involvement at presentation had negative prognostic impact on EFS (Tables 4 and 5). In L95-14 study (Table 7), patients who presented with DNA index of 1.16–1.60 showed EFS 84.2 ± 3.5%, which was significantly higher than the EFS rate of 72.3 ± 2.2% among those with DNA index < 1.16 ($P=0.005$).[20] DNA index 1.16–1.60 group of patients also fared better than those with DNA index over 1.6 (EFS of 50.0 ± 17.7%, $P=0.003$).The outcome of the patients with Ph chromosome was dismal. Hematopoietic SCT was only curative treatment strategy so far.[21]



	N	5y	10y	15y
OS (SE)	418	77.7(2.1)	73.5(2.2)	71.9(2.2)
ESF (SE)	418	67.2(2.4)	64.4(2.4)	62.3(2.6)

	N	5y	10y	15y	20y
any CNS (SE)	18	4.88(1.15)	5.41(1.27)	5.41(1.27)	5.41(1.27)
iCNS (SE)	12	3.17(0.94)	3.71(1.08)	3.71(1.08)	3.71(1.08)

Figure 2 EFS, OS, and cumulative incidence of isolated or any CNS relapses in L89-12 study.

Discussion

Nine years passed since the earlier issue was published in '*Leukemia* 2000.'[1] The 1423 survivors in the four studies are now 22.5 years old on an average, ranging from 11.6 to 39.8 years of age. Of 1233 patients who received cranial irradiation, 873 were surviving. Twelve secondary brain tumors developed very late, that is at 8–22 years after initial therapy including cranial irradiation in the four studies presented here. The development of the brain tumors seemed not to depend on the studies. Hijiya *et al.*[22] reported from the St Jude that the cumulative incidence of brain tumor except for meningioma was $3.00 \pm 0.59\%$ at 30 years. It was $2.8 \pm 0.9\%$ at 20 years in the four studies.

As for the secondary AML/MDS, the incidence was variable depending on the study. They developed only in the irradiated patients without exception. Regimens of L89-12 and L92-13 studies included etoposide, which is a topo-II inhibitor and was highly associated with the development of secondary MAL/MDS with 11q23 chromosome translocations.[23,24] Two cases were confirmed to be associated with chromosome 11q23 translocations in L89-12 study. It was noteworthy that seven out of eight secondary AML/MDS patients were female, whereas the brain tumors developed equally across genders. It was described that girls were more sensitive to anthracycline cardiac toxicity than boys.[25] In addition, cognitive impairment, short stature, and excessive weight were all more prevalent among females than males.[26] Females responded more to the chemotherapy and remained in higher EFS than that of males. All these facts may suggest that girls are more sensitive to anti-leukemic drugs, resulting in better outcome of ALL and developed more therapy-related secondary AML/MDS.

Schmiegelow recently reported from NOPHO studies that children with low thiopurine methyltransferase activity were at lower risk of relapse of ALL[27] and were at higher risk of developing secondary malignancy.[28] In the latter article, of 20 secondary malignancies, 16 AML/MDS occurred in 6 males and 10 females, although the author did not mention the gender difference.

We had not performed neurocognitive assessment as a group, but many studies showed the negative influence of the cranial irradiation on the neurocognitive function particularly for the young patients,[26] and other study described that normal neurological function was preserved when irradiation was omitted.[29]

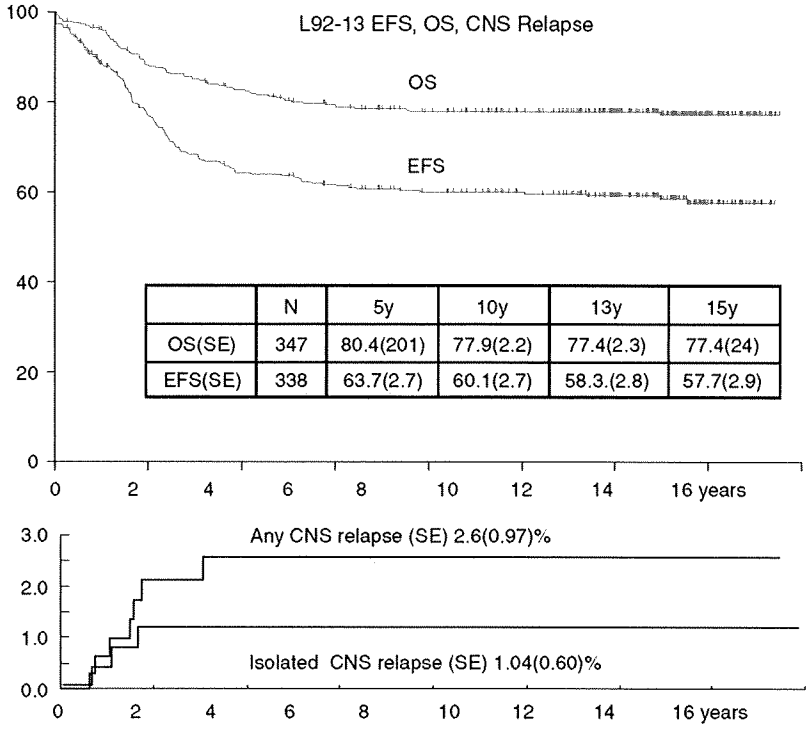
In the next study of TCCSG ALL L99-15, irradiated patients were limited to <10%. In the currently active study, T-ALL and prednisolone poor responders were irradiated. The outcomes have already been reported on the protocols with no cranial irradiation from St Jude Children's Research Hospital,[30] EORTC,[31] Nordic countries,[32] and Netherlands.[33] To eliminate the cranial irradiation, the function of intrathecal injections would be expected. The 9–11 times intrathecal injections ended before 40 weeks in TCCSG protocols even when no cranial irradiation was administered. The proper number and timing of the extended intrathecal injections for patients at risk of CNS relapse such as hyper-leukocytosis and T-ALL remained to be determined in our future studies.

Gajjar *et al.*[34] express strong caution to traumatic lumber punctures as a risk factor of CNS relapse. The L89-12 and L92-13 studies had 1-week prophase of single therapy with oral prednisolone, and the initial intrathecal injection and cerebrospinal fluid examination was given on day 8.[5,35] The prednisolone prophase without spinal puncture might well have alleviated cerebrospinal fluid infiltration before the assessment. Consequently, initial ratio of patients with CNS-2 or CNS-3 was

Table 6 Treatment results according to presenting features in non-infant patients treated in study L92-13

Factors	*Number of patients*	*Event-free survival ± s.e.%*				*Overall survival ± s.e.%*			
		5 years	*10 years*	*15 years*	*log-rank P-value*	*5 years*	*10 years*	*15 years*	*log-rank P-value*
Non-T lineage									
NCI standard	206	68.1 ± 3.3	64.0 ± 3.4	62.8 ± 3.4	0.01	88.7 ± 2.2	86.1 ± 2.4	86.1 ± 2.4	<0.0001
NCI high	108	56.5 ± 5.1	52.9 ± 5.1	52.9 ± 5.1		68.1 ± 4.5	64.9 ± 4.7	64.9 ± 4.7	
T-lineage									
NCI standard	7	83.3 ± 15.2	83.3 ± 15.2	83.3 ± 15.2	0.132	100	100	100	0.062
NCI high	25	50.8 ± 11.4	50.8 ± 11.4	50.8 ± 11.4		60.0 ± 9.8	60.0 ± 9.8	60.0 ± 9.8	
Sex									
Male	177	56.2 ± 3.9	52.4 ± 3.9	47.5 ± 4.9	0.003	80.5 ± 3.0	77.0 ± 3.0	75.8 ± 3.3	0.731
Female	170	71.3 ± 3.6	68.0 ± 3.7	68.0 ± 3.8		80.3 ± 3.0	80.3 ± 3.1	80.3 ± 3.2	
Age at diagnosis (years)									
1–9	264	66.4 ± 3.0	62.7 ± 3.1	59.7 ± 3.3	0.025	86.7 ± 2.1	84.7 ± 2.3	84.0 ± 2.4	<0.0001
⩾10	83	55.0 ± 5.8	51.7 ± 5.9	51.7 ± 5.10		67.7 ± 5.2	55.2 ± 5.3	55.2 ± 5.4	
WBC × 10^9/l									
<10k	164	65.9 ± 3.4	60.6 ± 3.9	59.9 ± 11.1	0.302	85.2 ± 2.8	82.7 ± 3.0	82.7 ± 3.1	0.008
10–49k	109	79.1 ± 4.0	64.5 ± 4.7	58.1 ± 5.4		81.5 ± 3.7	78.6 ± 4.0	77.1 ± 4.2	
50–99k	21	65.3 ± 10.6	59.9 ± 11.0	59.9 ± 11.1		76.2 ± 9.3	78.6 ± 4.0	77.1 ± 4.2	
⩾100k	50	53.9 ± 7.8	53.9 ± 7.8	53.9 ± 7.9		63.7 ± 6.8	63.7 ± 6.8	63.7 ± 6.8	
Cell lineage									
Non-T	315	64.1 ± 2.8%	60.3 ± 2.9%	57.6 ± 3.1%	0.779	81.6 ± 2.2%	78.9 ± 2.3%	78.2 ± 2.4%	0.177
T	32	58.5 ± 9.8%	58.5 ± 9.9%	58.5 ± 9.10%		68.7 ± 8.2%	68.7 ± 8.3%	68.7 ± 8.4%	
CNS status									
CNS-1	323	65.5 ± 2.8	61.7 ± 2.9	60.8 ± 2.9	0.525	80.9 ± 2.2	79.2 ± 2.4	78.5 ± 2.1	0.128
CNS-2	12	55.0 ± 15.0	55.0 ± 15.0	55.0 ± 15.0	0.076*	66.7 ± 13.6	58.3 ± 14.2	58.3 ± 14.2	
CNS-3	9	37.5 ± 17.1	37.5 ± 17.1	37.5 ± 17.1		88.9 ± 10.5	88.9 ± 10.5	88.9 ± 10.5	
DNA index or chromosome number (50–60 or others, others include cases not tested)									
1.16–1.60	25	68.0 ± 9.3	52.0 ± 10.0	52.0 ± 10.0	0.775	92.0 ± 5.4)	92.0 ± 5.4)	92.0 ± 5.4)	
Others	322	63.0 ± 2.8	60.5 ± 2.8	59.0 ± 2.9		78.5 ± 2.3)	76.9 ± 2.4)	76.3 ± 2.4)	
t(9;22) or BCR/ABL chimera message									
Present	12	16.7 ± 10.8	-	-	<0.0001	33.3 ± 13.6	33.3 ± 13.6	33.3 ± 13.6	<0.0001
Absent	335	64.6 ± 3.0	61.0 ± 2.8)	60.2 ± 2.8		82.1 ± 2.1	79.6 ± 2.2	79.0 ± 2.3	
TCCSG arms									
SR	123	65.9 ± 4.3	59.9 ± 4.5	56.3 ± 4.6		88.3 ± 2.9	84.9 ± 3.3	83.5 ± 3.5	
IR0	71	61.0 ± 5.9	58.0 ± 6.0	58.0 ± 6.0	0.942	87.1 ± 4.0	87.1 ± 4.0	87.1 ± 4.0	0.021
IR18	50	64.0 ± 6.8	60.0 ± 6.9	60.0 ± 6.9		74.0 ± 6.2	69.9 ± 6.5	69.9 ± 6.5	
IR0 testis	37	7.8 ± 5.5	7.8 ± 5.6	7.8 ± 5.7	0.053				
IR18 testis	22	26.4 ± 10.2	26.4 ± 10.3	26.4 ± 10.4					

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; NCI, National Cancer Institute risk group; s.e., standard error; SR, standard risk; TCCSG, Tokyo Children's Cancer Study Group; WBC, white blood cells.
IR0: the arm without cranial irradiation.
IR18: the arm with cranial irradiation.
Testis: probability of cumulative any testicular rate in males.
*CSF-1 vs CSF2 + 3.



	N	5y	10y	13y	15y
OS(SE)	347	80.4(201)	77.9(2.2)	77.4(2.3)	77.4(24)
EFS(SE)	338	63.7(2.7)	60.1(2.7)	58.3.(2.8)	57.7(2.9)

Figure 3 EFS, OS, and cumulative incidence of isolated or any CNS relapses in L92-13 study.

lower on day 8 in our studies than that on day 1 of other studies. It has been shown that the day 8 puncture did not increase CNS relapse.[5] The initial day 8 lumbar puncture is a safe method to avoid inadvertent introduction of leukemic blasts into the cerebrospinal fluid.

The duration of the maintenance therapy had been shortened step by step from 4 years in L81-10 study, 3 years for SR in L84-11 study, and 1.5 years for SR and 1 year for HR in L89-12 study without increasing relapses. The ID-MTX in S2 arm of L84-11 study efficiently reduced relapse after off therapy, whereas the control arm showed clusters of relapse starting at the point of off therapy. These results developed a hypothesis that an addition of a new intensified treatment on early phase might make it possible to shorten the duration of therapy further without sacrificing overall outcome. Randomized study could not be realized because a control arm was difficult to set. For the intensification of early therapy, ID-CA and HD-CA and mitoxantrone were administered in all risk groups. As a result, the relapse increased in both SR and HR groups. The short maintenance therapy affected more negatively on the lower-risk patients and males than on the higher risk and females (Table 6). EFS of HR patients was almost equivalent to that of SR. The early intensification might be more effective in HR than SR as CCG reported.[36] Randomized comparison of length in maintenance therapy for 18 months vs 24 months came to conclusion in ALL-BFM 81[4] and 83[37] studies, and ALL-BFM 86[38] study was amended to extend all the maintenance from 18 to 24 months. The appropriate length of maintenance therapy must be essential, particularly for the lower-risk patients and males. The duration between 18 months and 24 months were needed in the protocols of BFM-type structure. The boys had a higher risk of late relapse without sufficient maintenance therapy.

In 95-14, the randomized study in SR and IR compared between prednisolone (60 mg/m^2 at induction and 40 mg/m^2 at intensifications) and dexamethasone (8 mg/m^2 at induction and 6 mg/m^2 at intensifications) resulted in no significant difference in EFS rate.[7] Analysis with updated data on this comparison resulted in the same conclusion. Our results did not fully accord with those of other larger-scale studies. The results of CCG-1922 study[39] showed significantly better outcome in SR patients treated with dexamethasone at 6 mg/m^2 than prednisolone 40 mg/m^2. In UK Medical Research Council ALL97 trial,[40] dexamethasone given at 6.5 mg/m^2 and prednisolone given at 40 mg/m^2 were compared, and the dexamethasone arm showed better outcome. A conclusive result is anticipated in the trials with higher dose of dexamethasone at 10 mg/m^2 along with the evaluation of side effects.

In conclusion, analysis of long-term follow-up results brought us invaluable suggestions to consider for our future studies. Girls may generally be more drug sensitive than boys and they could be cured with shorter maintenance therapy than boys; at the same time, they may be at higher risk of secondary AML/MDS. The testicular relapse and lower EFS in boys were almost resolved in L95-14. TCCSG currently limited the indication of cranial irradiation to <10% of the patients. To avoid the secondary malignancy and neurological sequelae, it is of primary importance to omit the cranial irradiation and the etoposide completely as a primary therapy. Safe and effective induction and immediately given intensification, as well as appropriate length of maintenance therapy, are still major subjects to study. We seriously realized that an establishment of firm long-term follow-up system is mandatory to evaluate the ultimate result of the protocols.

Table 7 Treatment results according to presenting features in non-infant patients treated in study L95-14

Factors	*Number of patients*	*Event-free survival ± s.e.%*				*Overall survival ± s.e.%*			
		5 years	*10 years*	*13 years*	*log-rank value*	*5 years*	*10 years*	*13 years*	*log-rank P value*
Non-T lineage									
NCI standard	373	82.7 ± 2.0	81.3 ± 2.1	80.5. ± 2.2	<0.0001	92.5 ± 1.3	90.6 ± 1.5	88.9 ± 2.0	<0.0001
NCI high	183	67.4 ± 3.6	64.4 ± 3.7	64.4 ± 3.7		72.8 ± 3.3	68.5 ± 3.6	67.3 ± 3.7	
T-lineage									
NCI standard	8	87.5(11.7)	87.5(11.7)	87.5(11.7)	0.2676	100	100	100	0.095
NCI high	50	66.9 ± 6.8	66.9 ± 6.8	66.9 ± 6.8		70.0 ± 6.5	68.0 ± 6.6	68.0 ± 6.6	
Sex									
Male	340	78.5 ± 2.6	76.5 ± 2.7	76.5 ± 2.7	0.519	86.1 ± 2.1	84.4 ± 2.3	82.9 ± 2.7	0.211
Female	257	75.4 ± 2.4	73.7 ± 2.5	72.9 ± 2.6		84.0 ± 2.0	80.1 ± 2.2	78.7 ± 2.4	
Age at diagnosis (years)									
1–9	460	79.1 ± 1.9	77.6 ± 2.0	77.0 ± 2.1	0.002	88.6 ± 1.5	85.7 ± 1.7	83.8 ± 2.0	<0.0001
⩾10	134	68.6 ± 4.1	65.6 ± 4.3	65.6 ± 4.3		72.4 ± 3.9	69.2 ± 4.1	69.2 ± 4.1	
WBC × 10^9/l									
<10k	306	79.1 ± 2.3	77.2 ± 2.4	75.7 ± 2.6	<0.0001	91.1 ± 1.6	88.0 ± 1.9	86.52 ± 2.4	<0.0001
10–49k	160	74.8 ± 3.4	74.1 ± 3.4	74.1 ± 3.4		86.7 ± 2.7	85.3 ± 2.8	85.3 ± 2.8	
50–99k	58	56.9 ± 6.5	56.9 ± 6.5	56.9 ± 6.5		70.7 ± 6.0	65.8 ± 6.6	62.3 ± 7.1	
⩾100k	70	57.7 ± 6.0	55.6 ± 6.1	55.6 ± 6.1		65.4 ± 5.7	65.4 ± 5.7	65.4 ± 5.7	
Cell lineage									
Non-T	539	77.5 ± 1.8	75.5 ± 1.9	75.3 ± 2.0	0.159	86.1 ± 1.5	83.4 ± 1.7	81.4 ± 1.9	0.021
T	58	69.7 ± 6.2	69.7 ± 6.2	69.7 ± 6.2		73.9 ± 5.8	72.1 ± 5.9	72.1 ± 5.9	
CNS status									
0	378	85.6 ± 1.8	82.3 ± 2.0	81.8 ± 2.1	0.962	77.9 ± 2.0	77.9 ± 2.0	77.9 ± 2.0	0.514
1–4	183	85.1 ± 2.6	83.9 ± 2.7	80.2 ± 3		77.5 ± 3.0	74.7 ± 3.0	74.7 ± 3.0	
5–	20	90.0 ± 6.7	77.9 ± 9.9	77.9 ± 9.9		65.8 ± 11.0	65.8 ± 11.0	65.8 ± 11.0	
DNA index									
<1.16	464	74.3 ± 2.1	72.9 ± 2.1	72.3 ± 2.2	0.005*	82.5 ± 1.8	79.2 ± 2.9	78.2 ± 2.0	0.001*
1.16–1.60	124	87.5 ± 3.0	84.2 ± 3.5	84.2 ± 3.5	0.003**	94.3 ± 2.1	92.7 ± 2.4	92.7 ± 2.4	0.005**
>1.60	9	50.0 ± 17.7	50.0 ± 17.7	50.0 ± 17.7		77.8 ± 13.9	77.8 ± 13.9	77.8 ± 13.9	
t(9;22) or BCR/ABL chimera message									
Present	24	26.4 ± 9.7	26.4 ± 9.7	26.4 ± 9.7	<0.0001	41.7 ± 10.1	31.3 ± 9.9	25,9 ± 9.7	<0.0001
Absent	573	78.7 ± 1.7	76.9 ± 1.8	76.4 ± 1.9		86.8 ± 1.4	84.1 ± 15.7	83.9 ± 1.8	
t(1;19) or E2A/PBX1 chimera message									
Present	26	70.2 ± 9.5	70.2 ± 9.5	70.2 ± 9.5	0.449	73.0 ± 8.7	73.0 ± 8.7	73.0 ± 8.7	0.182
Absent	568	77.1 ± 1.8	75.1 ± 1.9	74,7 ± 1.9		85.5 ± 1.5	82.4 ± 1.6	80.8 ± 1.9	
11q23 or MLL rearrangement									
Present	5	75.0 ± 21.5	75.0 ± 21.5	75.0 ± 21.5	0.962	80.0 ± 17.9	80.0 ± 17.9	80.0 ± 17.9	0.879
Absent	589	76.8 ± 1.8	74.9 ± 1.8	74.5 ± 1.9		85.0 ± 1.5	82.0 ± 1.6	80.5 ± 1.8	
TCCSG SR+HR arm									
Dexamethasone	179	82.15 ± 2.9	80.5 ± 3.1	80.5 ± 3.1	0.5178	91.5 ± 2.1	89.1 ± 2.4	88.1 ± 2.6	0.190
Prednisolone	180	85.6 ± 2.7	83.5 ± 2.9	81.9 ± 3.2		95.0 ± 1.6	93.2 ± 1.9	90.2 ± 3.5	

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid; NCI, National Cancer Institute risk group; s.e., standard error; SR, standard risk; TCCSG, Tokyo Children's Cancer Study Group; WBC, white blood cells.
*<1.16 vs 1.16-1.60, **1.16-1.60 vs>1.60.