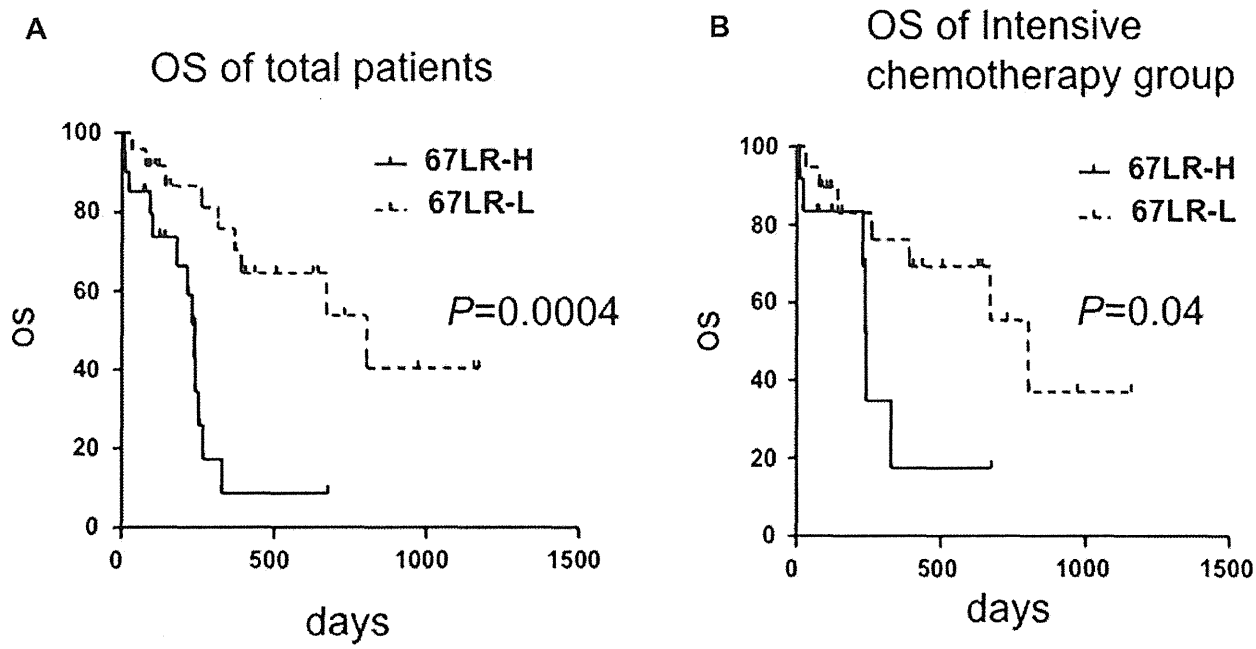
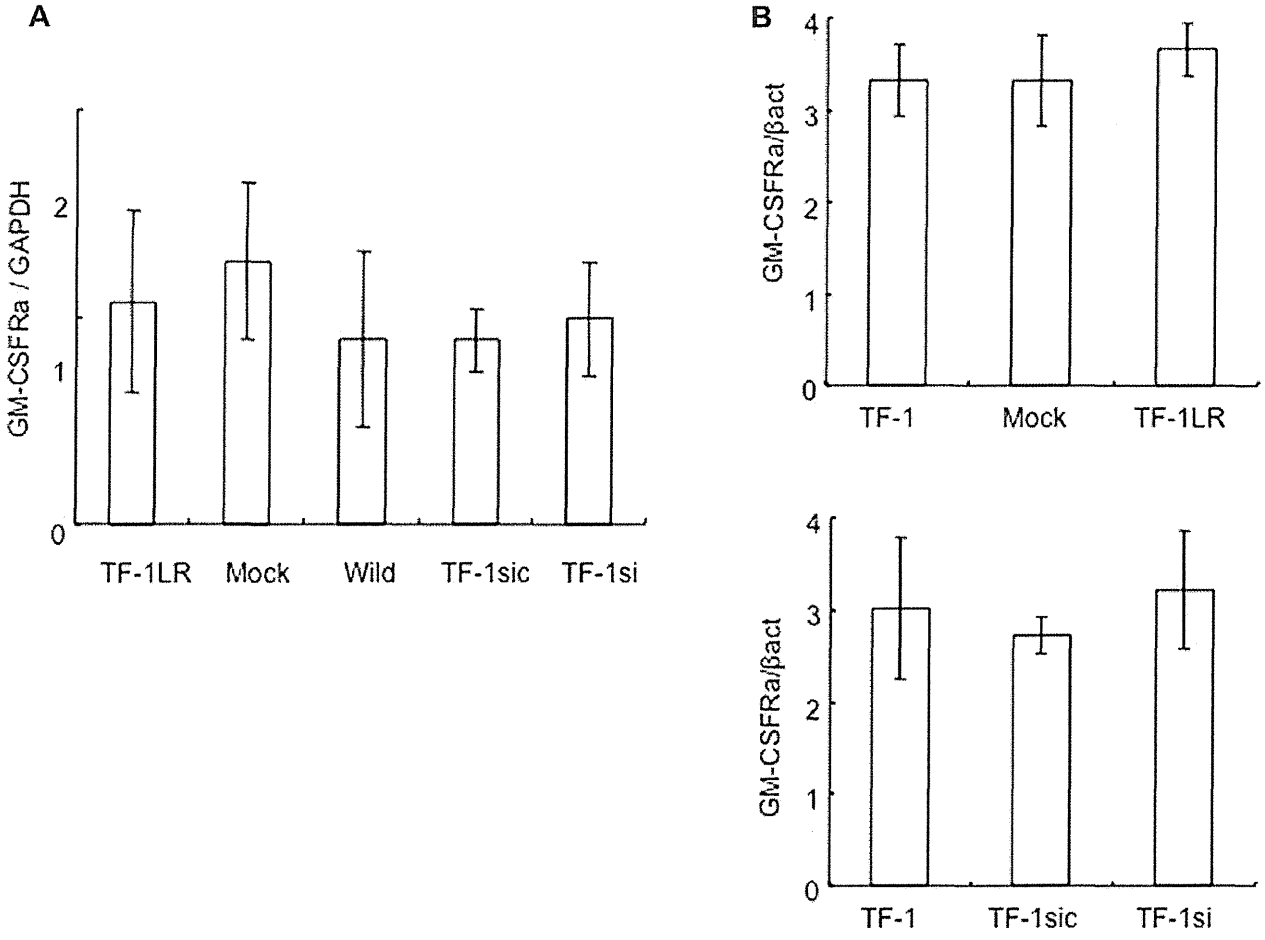
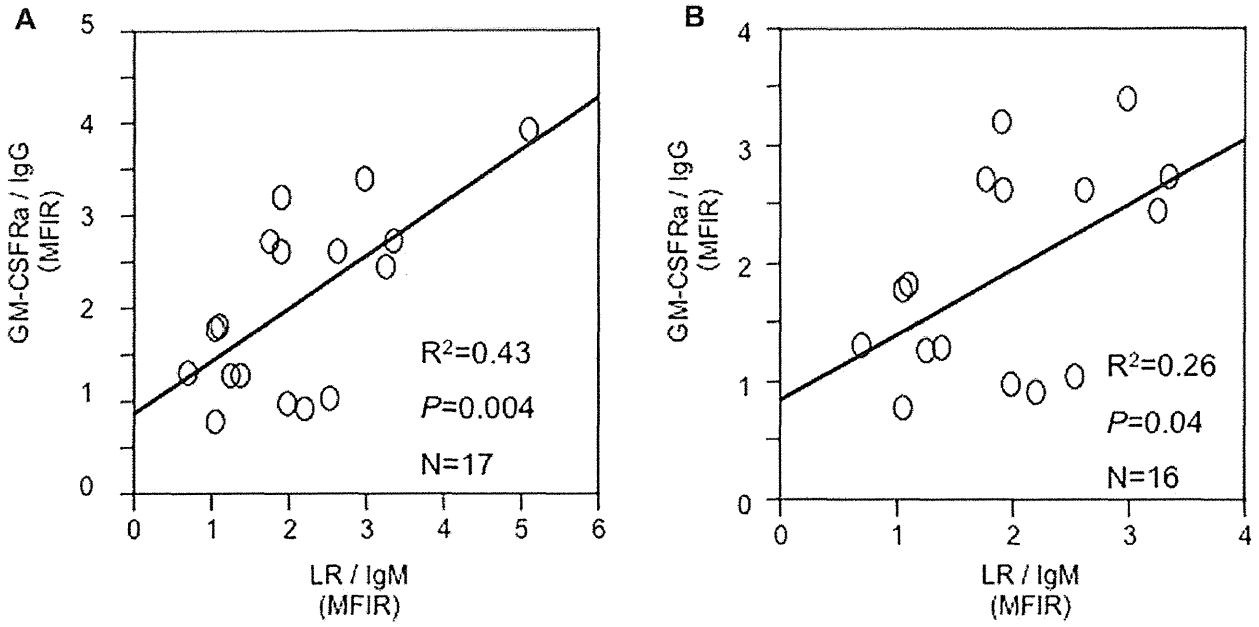


Supplementary Figure E2. Overall survival of patients treated with any chemotherapy (**A**) and intensive chemotherapy (**B**). Overall survival curve of all patients is shown in (**A**), and that of patients treated with intensive chemotherapy regimens is shown in (**B**). Intensive chemotherapy regimens contained standard dose of arabinofuranosyl cytidine and daunorubicin or idarubicin for induction, and high-dose AraC or induction-like regimens for consolidation therapy. These regimens were used in the protocols of Japan Adult Leukemia Study Group (JALSG-AML97 and –AML201 trials) [29].



Supplementary Figure E3. (**A**) Message level of GM-CSFRα in TF-1–related cell lines. The level of GM-CSFRα message was measured using quantitative PCR. The expression of glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as reference. Average of three independent experiments is shown with standard deviation. (**B**) Densitometric measurement of Western blot analysis for GM-CSFα (data from Fig. 4C). Ratios of GM-CSFRα and β-actin from three independent experiments are shown. Mock, control cell line for TF-1LR.



Supplementary Figure E4. Relationship between MFI ratio (MFIR) of LR and GM-CSFRα on AML samples. (**A**) One sample that was plotted at the far right in Figure 4D was removed, then using 17 samples, their relationship was reanalyzed. There was a significant relationship between these factors ($p = 0.004$). (**B**) Reanalysis of MFIR of LR and GM-CSFRα ($n = 16$) deleting two samples located at the far right and uppermost of Figure 4D. Significance still remained in the relationship between MFIR of LR and GM-CSFRα.

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ORIGINAL ARTICLE

A decision analysis of allogeneic hematopoietic stem cell transplantation in adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia in first remission who have an HLA-matched sibling donor

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Clinical studies using genetic randomization cannot accurately answer whether adult patients with Philadelphia chromosome-negative acute lymphoblastic leukemia (ALL) who have a human leukocyte antigen (HLA)-matched sibling should undergo allogeneic hematopoietic stem cell transplantation (HSCT) or chemotherapy in first remission, as, in these studies, patients without a sibling donor undergo alternative donor transplantation or chemotherapy alone after a relapse. Therefore, we performed a decision analysis to identify the optimal strategy in this setting. Transition probabilities and utilities were estimated from prospective studies of the Japan Adult Leukemia Study Group, the database of the Japan Society for Hematopoietic Cell Transplantation and the literature. The primary outcome measure was the 10-year survival probability with or without quality of life (QOL) adjustments. Subgroup analyses were performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior in the whole population (48.3 vs 32.6%) and in all subgroups. With QOL adjustments, a similar tendency was conserved (44.9 vs 31.7% in the whole population). To improve the probability of long-term survival, allogeneic HSCT in first remission is recommended for patients who have an HLA-matched sibling.

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Keywords: decision analysis; acute lymphoblastic leukemia; allogeneic hematopoietic stem cell transplantation; HLA-matched sibling donor; first remission

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Introduction

With modern intensive chemotherapy, 74–93% of adult patients with acute lymphoblastic leukemia (ALL) achieve complete remission. However, the overall survival rate is only 27–48% because of the high rate of relapse.[1] Therefore, the establishment of optimal postremission therapy is important. The efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) for adult patients with ALL in first remission has been demonstrated through clinical studies using genetic randomization, in which patients with a human leukocyte antigen (HLA)-matched sibling donor were allocated to the allogeneic HSCT arm, and those without a donor were placed in the chemotherapy or autologous transplantation arm. First, the LALA-87 trial showed that overall survival in patients with a donor was better than that in patients without a donor in a subgroup analysis of patients with high-risk characteristics.[2] A meta-analysis of seven similar studies confirmed that the donor group was superior to the non-donor group in patients with high-risk ALL in first remission.[3] However, such genetic randomization studies cannot accurately answer the question of whether patients with an HLA-matched sibling should undergo allogeneic HSCT or chemotherapy in first remission. In these studies, patients without a sibling donor had to choose transplantation from an alternative donor or chemotherapy alone once they had a relapse. The outcome of these treatments has been reported to be inferior to that of HSCT from an HLA-matched sibling donor in patients with relapsed ALL; therefore, the expected survival after the decision to continue chemotherapy in first remission in patients without a sibling donor is assumed to be originally poorer than that in patients with a sibling donor. However, it is practically difficult to perform a clinical trial in which patients with an HLA-matched sibling in first remission are randomly assigned to receive allogeneic HSCT or chemotherapy alone. Another important problem has been poor compliance with the assigned treatment in some studies. In addition, previous genetic

randomization studies did not consider the quality of life (QOL), especially that associated with graft-versus-host disease (GVHD). Therefore, we performed a decision analysis incorporating QOL adjustments using a decision tree based on the results of Japan Adult Leukemia Study Group (JALSG) prospective studies (ALL93[4] and ALL97[5]), the database of the Japan Society for Hematopoietic Cell Transplantation (JSHCT)[6] and literature. Patients with Philadelphia chromosome (Ph)-positive ALL were not included in our analysis because the outcome of treatment in these patients has improved dramatically since tyrosine kinase inhibitors became available.[7]

Recently, the Medical Research Council/Eastern Cooperative Oncology Group (MRC/ECOG) trial demonstrated the efficacy of allogeneic HSCT in ALL patients and in standard-risk patients, but not in high-risk patients,[8] which was inconsistent with previous studies. This difference might partly depend on the definition of high-risk patients. In the MRC/ECOG study, an age of higher than 35 years was considered to be a high-risk factor. Therefore, we performed separate subgroup analyses according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years.

Methods

Model structure

We constructed a decision tree (Figure 1) to identify the optimal treatment strategy for adult patients with Ph-negative ALL in first remission who have an HLA-matched sibling.[9,10] The square at the left represents a decision node. We can decide to either proceed to allogeneic HSCT or continue chemotherapy in first remission. We did not include a decision to perform autologous HSCT, as autologous HSCT has not been shown to be superior to chemotherapy alone in a meta-analysis.[3] Circles, called chance nodes, follow each decision, and each chance node has two or three possible outcomes with a specific probability called the transition probability (TP). Every branch finally ends with triangles, called terminal nodes, and each terminal node has an assigned payoff value, called utility, according to different health states. Calculations were performed backward, from right to left in the decision tree. The sum of the products of TPs and utilities of the branches becomes the expected value for each chance node, and eventually the sum of the expected values in all of the chance nodes following the decision nodes becomes the expected value of each decision. The following analyses were performed using TreeAge Pro 2009 software (Williamstown, MA, USA). This study was approved by the Committee for Nationwide Survey Data Management of JSHCT, and the Institutional Review Board of Jichi Medical University.

Data sources

Outcomes after continuing chemotherapy in first remission were estimated from JASLG studies (ALL93 and ALL97). Patients with Ph-negative ALL, aged 15–54 years, were included, and those who never achieved remission with chemotherapy were excluded. Data from 122 patients in ALL93 and 119 patients from ALL97 were analyzed separately, and then combined by weighting the number of patients. Outcomes after allogeneic HSCT in various disease statuses were estimated from the database of the JSHCT. Patients with Ph-negative ALL, aged 16–54 years, who underwent a first myeloablative allogeneic HSCT from a serologically HLA-A, -B, -DR loci-matched sibling between 1993 and 2007 were included. Of them, 408, 61, 14 and 94 patients were in first remission, second remission, third or later remission and non-remission, respectively, at allogeneic HSCT.

The characteristics of the patients included in this study are summarized in Table 1. There was no significant difference in their baseline characteristics. To determine the following TPs,

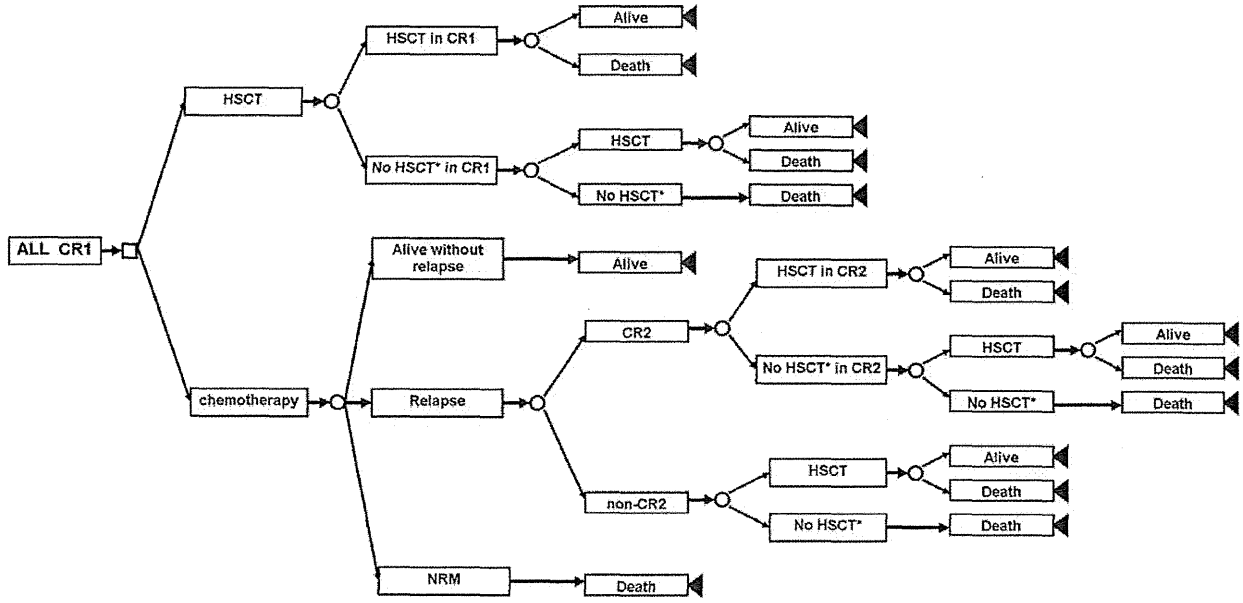

Figure 1 Decision tree used in this study. Decision analysis was performed on the basis of a decision tree. A square indicates a decision node and open circles indicate chance nodes. In analyses with a QOL adjustment, 'Alive' after transplantation was followed by two branches with or without active chronic GVHD. *HSCT was not performed because of early relapse, death and so on. ALL, acute lymphoblastic leukemia; CR, complete remission; NRM, non-relapse mortality.

Table 1 Patient characteristics in the three data sources

	Chemotherapy in CR1		*HSCT in CR1*	P[a]
	JALSG ALL93	*JALSG ALL97*	*JSHCT*	
No. of patients	122	119	408	
Median age (range)	26 (15–54)	26 (15–54)	29 (16–54)	0.72
No. of males/females	72/50	54/65	230/178	0.06
Median WBC count at diagnosis (range) ($\times 10^9$/l)	9.5 (0.6–468.0)	10.2 (0.3–398.0)	10.4 (0.4–801.0)	0.91
Karyotype standard:high[b], ratio	20:1	30:1	15.4:1	0.55

Abbreviations: CR, complete remission; HSCT, hematopoietic stem cell transplantation; JALSG, Japan Adult Leukemia Study Group; JSHCT, Japan Society for Hematopoietic Cell Transplantation; WBC, white blood cell.
[a]Statistical analyses were performed using the Kruskal–Wallis test for continuous variables and the χ^2-test for categorical variables.
[b]t(4;11) and t(1;19) were classified as high-risk karyotypes, and other karyotypes were classified as standard risk.

overall survival and leukemia-free survival (LFS) with a 95% confidence interval (CI) were calculated using the Kaplan–Meier method, whereas the cumulative incidences of non-relapse mortality and relapse with 95% CI were calculated using Gray's method,[11] considering each other as a competing risk. Probabilities that we could not estimate from these data were estimated from the literature.

Transition probabilities (TPs) and utilities

TPs of the whole population were determined as summarized in Table 2. Each TP has a baseline value and a plausible range. Baseline decision analyses were performed on the basis of baseline values.

Patients may have been precluded from undergoing allogeneic HSCT because of early relapse or comorbidities even if they decided to undergo allogeneic HSCT, and therefore the TP of actually undergoing allogeneic HSCT in first remission after the decision branch to undergo allogeneic HSCT was determined as follows: first, the median duration between the achievement of first remission and HSCT without relapse was calculated as 152 days on the basis of JSHCT data. Next, LFS rates at 152 days after achieving first remission were calculated using the data of all patients who achieved remission in the JALSG studies, and the combined LFS was 0.80 (95% CI: 0.76–0.85). We considered this to be the TP for actually receiving HSCT in first remission, and assigned a baseline value of 0.80 and 95% CI to the plausible range. Similarly, patients may be precluded from undergoing allogeneic HSCT even though they have achieved second remission after they had a relapse of leukemia following a decision to continue chemotherapy. This TP of undergoing allogeneic HSCT in second remission could not be calculated from our data. We assigned a plausible range of 0.5–0.80; the former value was the only available rate in a large study[12] and the latter was the TP calculated above. The median of this range was taken as the baseline value. Probabilities regarding the actual rate of receiving HSCT in other disease statuses could not be obtained, even in the literature. Therefore, a baseline value of 0.5 was assigned with a wide plausible range of 0.3–0.7, although these values may not be closely related to the final expected value, as the probability of survival after receiving HSCT in these situations was extremely low. The TPs of 'Alive at 10 years' following HSCT in various disease statuses were determined on the basis of the JSHCT database. We assigned 95% CI to the plausible ranges.

The TPs of 'Alive without relapse at 10 years' and non-relapse mortality following chemotherapy in first remission were determined on the basis of JALSG studies, and the TP of relapse following chemotherapy was determined by subtracting the sum of these TPs from 1. The TP of achieving second remission after relapse in patients who decided not to undergo allogeneic HSCT in first remission was estimated to have a baseline value of 0.4, with a plausible range of 0.3–0.5 based on the literature.[12–14]

The primary outcome measure was the 10-year survival probability as described in the Discussion. The survival curve nearly reaches a plateau after 5 years and therefore 'Alive at 10 years' reflects 'Cure of leukemia', which is the primary goal of allogeneic HSCT. First, we considered only two kinds of health states, 'Alive at 10 years' and 'Dead', and assigned utility values of 100 to the former and 0 to the latter without considering QOL. Next, we performed a decision analysis while adjusting for QOL. 'Alive after chemotherapy without relapse at 10 years', 'Alive with active GVHD at 10 years' and 'Alive without active GVHD at 10 years' were considered as different health states. The proportion of patients with active GVHD among those who

Table 2 *Transition probabilities of the whole population*

	Baseline value (plausible range)
HSCT in CR1	0.80 (0.76–0.85)
Alive at 10 years following HSCT in CR1	0.57 (0.52–0.63)
HSCT after failure of HSCT in CR1	0.5 (0.3–0.7)
Alive at 10 years following HSCT after failure of HSCT in CR1[a]	0.27 (0.16–0.38)
Alive at 10 years without relapse following CTx	0.21 (0.15–0.28)
NRM at 10 years following CTx	0.07 (0.04–0.10)
Achievement of CR2 after relapse following CTx	0.4 (0.3–0.5)
HSCT in CR2	0.66 (0.5–0.80)
Alive at 10 years following HSCT in CR2	0.38 (0.27–0.53)
HSCT after failure of HSCT in CR2	0.5 (0.3–0.7)
Alive at 10 years following HSCT after failure of HSCT in CR2[b]	0.18 (0.16–0.2)
HSCT in non-CR after relapse following CTx	0.5 (0.3–0.7)
Alive at 10 years following HSCT in non-CR after relapse	0.16 (0.1–0.27)
Rate of active GVHD at 10 years[c]	0.18 (0.1–0.25)

Abbreviations: CR, complete remission; CTx, chemotherapy; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
[a]This rate was estimated from the survival rate following HSCT in CR2 and HSCT in non-CR.
[b]This rate was estimated from the survival rate following HSCT in CR3 or more and HSCT in non-CR.
[c]The same baseline value and plausible range were used as the rate of active GVHD at 10 years following HSCT in various disease statuses, but one-way sensitivity analyses were performed separately in each status.

Table 3 Transition probabilities of subgroups

	Baseline value (plausible range)			
	Standard-risk	*High-risk*	*Lower age*	*Higher age*
HSCT in CR1	0.86 (0.81–0.92)	0.65 (0.54–0.77)	0.81 (0.76–0.86)	0.80 (0.72–0.87)
Alive at 10 years following HSCT in CR1	0.6 (0.53–0.68)	0.51 (0.4–0.66)	0.62 (0.55–0.69)	0.48 (0.39–0.58)
Alive at 10 years following HSCT after failure of HSCT in CR1	0.31 (0.24–0.38)	0.28 (0.13–0.43)	0.3 (0.21–0.39)	0.23 (0.11–0.35)
Alive at 10 years without relapse following CTx	0.27 (0.18–0.37)	0.13 (0.03–0.22)	0.19 (0.11–0.27)	0.25 (0.16–0.35)
NRM at 10 years following CTx	0.06 (0.02–0.11)	0.07 (0–0.14)	0.04 (0.01–0.08)	0.11 (0.05–0.18)
HSCT in CR2	0.68 (0.5–0.86)	0.58 (0.5–0.65)	0.66 (0.5–0.81)	0.65 (0.5–0.80)
Alive at 10 years following HSCT in CR2	0.38 (0.23–0.61)	0.43 (0.22–0.84)	0.39 (0.26–0.58)	0.35 (0.19–0.64)
Alive at 10 years following HSCT after failure of HSCT in CR2[a]	0.24 (0.12–0.45)	0.13 (0.05–0.35)	0.21 (0.12–0.36)	0.11 (0.04–0.3)
Alive at 10 years following HSCT in non-CR after relapse	0.24 (0.12–0.45)	0.13 (0.05–0.35)	0.21 (0.12–0.36)	0.11 (0.04–0.3)

Abbreviations: CR, complete remission; CTx, chemotherapy; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality.
Transition probabilities that are not in Table 3 are the same as those mentioned in the whole population.
[a]As the number of patients who underwent HSCT in CR3 or more was not enough, the same rate of survival following HSCT in non-CR was used.

were alive at 10 years was determined on the basis of the literature.[15–17] We assigned a value of 100 to the utility for being alive without relapse at 10 years after chemotherapy alone, and a value of 0 to the utility for being dead in all situations. We assigned a fixed value of 98 to the utility for being alive without active GVHD at 10 years following HSCT, and assigned a value of 70 with a wide plausible range of 0–98 to the utility for being alive with active GVHD at 10 years. These utilities were determined on the basis of opinions of 10 doctors who were familiar with HSCT and the literature.[9,18]

Subgroup analyses were also performed according to risk stratification on the basis of white blood cell count and cytogenetics, and according to age stratification with a cutoff of 35 years. Patients with a high white blood cell count (more than 30×10^9/l for B lineage and more than 100×10^9/l for T lineage) and/or with t(4;11) or t(1;19) were classified as a high-risk group, and all other patients were classified as standard-risk group. All TPs, based on the JALSG studies and the JSHCT data, were recalculated using the data of patients in each subgroup (Table 3). Other TPs and utilities were the same as those for the overall patient analyses.

Sensitivity analyses

To evaluate the robustness of the decision model, we performed one-way sensitivity analyses for all TPs, in which the decision tree was recalculated by varying each TP value in its plausible range, and confirmed whether the decision of the baseline analyses changed. In the analyses that included adjustments for QOL, the utility for being alive with active GVHD at 10 years was also subjected to a one-way sensitivity analysis.

We also performed a probabilistic sensitivity analysis using Monte Carlo simulation in which the uncertainties of all TPs were considered simultaneously.[19] The distribution of the random variables for each TP was determined to follow a normal distribution, with 95% of the random variables included in the plausible range. Following 1000 simulations based on the decision tree, the mean and s.d. of the expected value for each decision were calculated.

Results

Baseline analysis

The baseline analysis in the whole population without adjusting for QOL revealed an expected 10-year survival of 48.3% for the decision to perform allogeneic HSCT in first remission, which was better than that of 32.6% for the decision to continue chemotherapy. The decision to perform allogeneic HSCT continued to be superior even after adjusting for QOL (44.9% for HSCT vs 31.7% for chemotherapy, Table 4).

Table 4 Expected 10-year survival probabilities with and without adjusting for QOL

	Expected survival probability without a QOL adjustment		*Expected survival probability with a QOL adjustment*	
	HSCT (%)	*Chemotherapy (%)*	*HSCT (%)*	*Chemotherapy (%)*
All patients	48.3	32.6	44.9	31.7
Standard-risk patients	53.8	39.8	50.0	38.9
High-risk patients	38.0	25.0	35.4	24.1
Lower-aged patients[a]	53.1	32.9	49.3	31.9
Higher-aged patients[a]	40.7	33.4	37.8	32.8

Abbreviation: HSCT, hematopoietic stem cell transplantation; QOL, quality of life
[a]Lower-aged patients include those aged 35 years or younger. Higher-aged patients include those aged older than 35 years.

Sensitivity analysis

First, we performed one-way sensitivity analyses for all TPs in the decision model without adjusting for QOL. A better expected survival for the decision to perform HSCT was consistently demonstrated in all TPs within the plausible ranges. In the probabilistic sensitivity analysis, the mean value and s.d. of the expected survival probability for HSCT were 48.3 and 2.6%, and those for chemotherapy were 32.7 and 3.4%, respectively.

Next, we performed one-way sensitivity analyses for all TPs and for the utility for being alive with active GVHD at 10 years in the decision model adjusted for QOL. Even in these analyses, the result of the baseline analysis did not reverse in all TPs. In addition, a higher expected survival probability for HSCT was retained, assuming that the utility for being alive with active GVHD ranged between 0 and 98 (Figure 2a). In the probabilistic sensitivity analysis, the mean value and s.d. of the expected survival probability for HSCT were 44.8 and 2.6%, and those for chemotherapy were 31.8 and 3.4%, respectively.

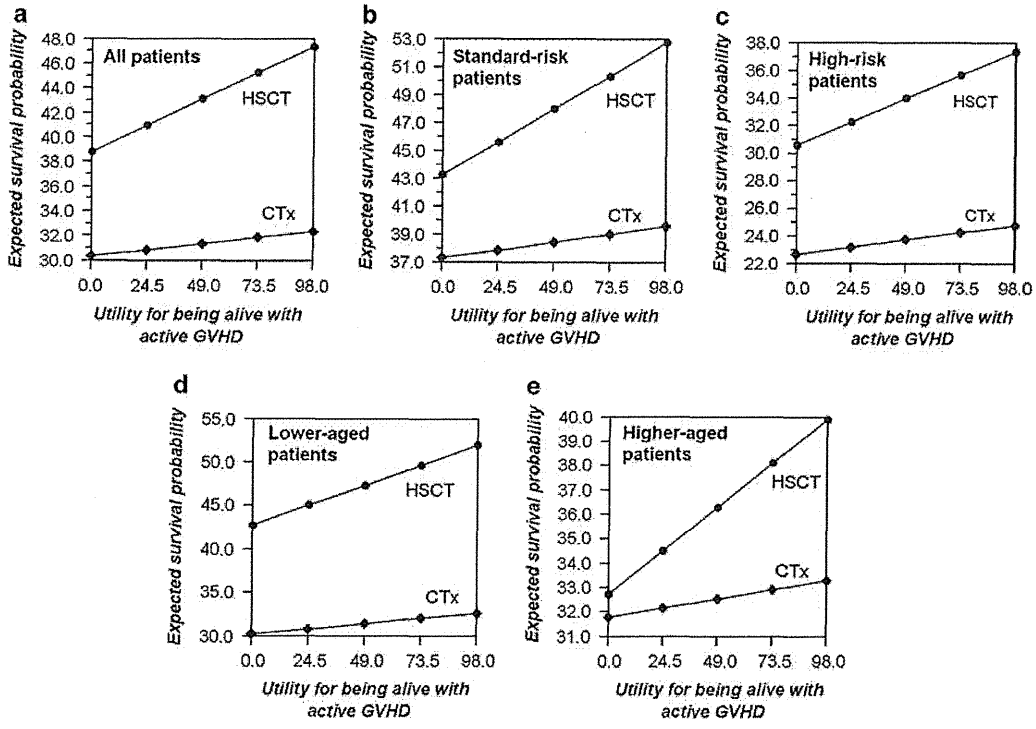

Figure 2 One-way sensitivity analysis for the utility for being alive with active GVHD. We performed one-way sensitivity analyses for the utility for being alive with active GVHD in the model, with adjustment for QOL. The superiority of allogeneic HSCT compared with chemotherapy (CTx) was consistently observed even with a wide plausible range of the utility in the whole population (**a**) and all subgroups (**b**–**e**).

Subgroup analyses

In subgroup analyses, both with and without adjustment for QOL, a better expected survival probability for HSCT was consistently observed in all subgroups (Table 4).

We also performed one-way sensitivity analyses in all subgroups. In the decision model without adjusting for QOL, varying each TP value in its plausible range did not affect the results of baseline analyses in all subgroups, except for higher-aged patients. In higher-aged patients, the result of the baseline analysis reversed only if the probability of LFS at 10 years following chemotherapy in first remission was more than 0.334. Even in the decision model with adjustment for QOL, varying each TP value did not affect the result of the baseline analyses in all subgroups, except for higher-aged patients. In higher-aged patients, the result reversed in favor of chemotherapy if the probability of LFS at 10 years without relapse following chemotherapy was more than 0.307 (Figure 3a) or the probability of overall survival at 10 years following HSCT in first remission was less than 0.413 (Figure 3b). On the other hand, non-relapse mortality at 10 years following chemotherapy did not affect the result. We also performed one-way sensitivity analyses for the utility of being alive with active GVHD ranging between 0 and 98. A higher expected survival probability for HSCT was retained in all subgroups (Figures 2b–e).

Discussion

Decision analysis is a statistical technique that aids the clinical decision-making process under uncertainty. This approach has also been used in situations in which a well-designed clinical trial is practically difficult to perform. In the present case, a prospective trial to randomly assign patients with ALL in first remission who have an HLA-matched sibling to undergo allogeneic HSCT or chemotherapy alone is practically difficult. Therefore, we tried to determine the optimal strategy in this clinical situation by using a decision analysis. We chose the 10-year survival probability as the primary outcome measure rather than life expectancy, as the cure rate, rather than how long they can survive, is important for young patients with acute leukemia to make a decision whether they should undergo allogeneic HSCT in first remission. When we performed the decision analysis using the 5-year survival probability as the primary outcome measure, however, the findings in this study did not change, as the survival curve nearly reaches a plateau after 5 years. Further, we adjusted for QOL by considering the presence or absence of persisting symptoms associated with chronic GVHD rather than by calculating quality-adjusted life years, as most patients who choose allogeneic HSCT may tolerate transiently impaired QOL and attach much importance to long-term QOL. Under these conditions, we decided to use a simple decision analysis model rather than a Markov model that allows probabilities and utilities to change with time, as the benefit of using a Markov model is limited in this situation. In addition, a large number of patients are required for the Markov model to define appropriate TPs that change with time. In this study, the number of patients was limited because we used data from the JALSG prospective studies to avoid biases of using retrospective data. We used the database of the JSHCT to calculate TPs in patients who underwent HSCT, because the number of patients who underwent HSCT was further limited in the JALSG prospective studies. However, outcomes after allogeneic HSCT in first remission were not significantly

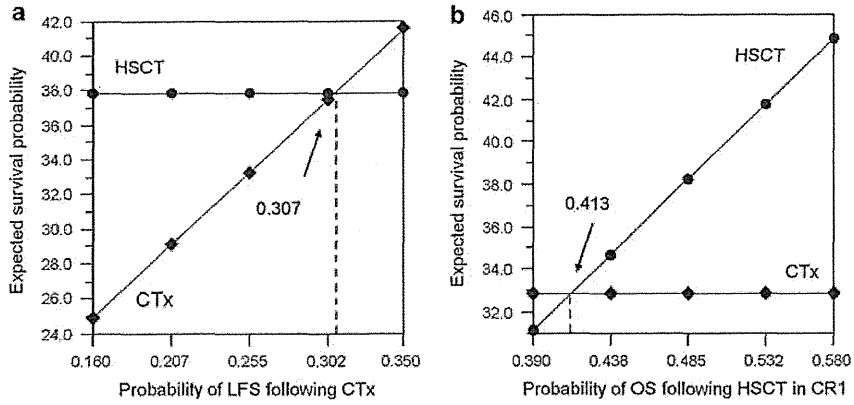

Figure 3 *One-way sensitivity analysis in higher-aged patients. We performed one-way sensitivity analyses for all TPs in the decision model both with and without adjustment for QOL. In higher-aged patients, the result reversed if the probability of LFS at 10 years without relapse following chemotherapy (CTx) was more than 0.307* (**a**), *or the probability of overall survival at 10 years following allogeneic HSCT in first complete remission (CR1) was less than 0.413* (**b**).

different among the JALSG prospective studies and the JSHCT database (data not shown).

In our baseline analysis both with and without adjustment for QOL, the superiority of HSCT in first remission was demonstrated in the whole population and also in all subgroups. In the whole population, probabilistic sensitivity analysis using a Monte Carlo simulation also supported this result. However, in one-way sensitivity analyses, we should note that the decision model was sensitive to the probability of LFS following chemotherapy in first remission in higher-aged patients (Figure 3a). The adaptation of intensified chemotherapy according to pediatric regimens has led to improved outcomes in adolescents and young adults,[20] and even in older patients in recent trials,[21] and therefore this decision might change in the future.

The risk stratification we used in subgroup analyses was different from that used in the MRC/ECOG study.[8] Therefore, we added subgroup analyses according to the risk stratification used in the MRC/ECOG study. In analyses without QOL adjustments, allogeneic HSCT in first remission was superior both in standard-risk (56.6 vs 36.2%) and high-risk (42.4 vs 33.3%) patients. With QOL adjustments, the similar tendency was observed in both standard-risk (52.6 vs 35.1%) and high-risk (39.4 vs 32.6%) patients. These findings were consistent with those based on our original risk stratification. In addition, we further subdivided patients into four different age categories: 15–25, 26–35, 36–45 and 46–54 years. The superiority of the decision to perform allogeneic HSCT in first remission was conserved in all age categories (data not shown).

A possible concern in this study was the long median duration of 152 days from achieving complete remission to allogeneic HSCT. In the current decision model, this long duration precluded allogeneic HSCT in first remission in about 20% of patients in the allogeneic HSCT branch (mainly because of early relapse), and thereby impaired the expected probability of survival for the decision to undergo allogeneic HSCT. In reality, a meta-regression analysis by Yanada *et al.*[3] revealed that compliance with allogeneic HSCT was significantly and positively correlated with survival.[3] Another fact to be noted is the low incidence of severe GVHD in Japanese patients, which might have favorably affected the decision to perform HSCT.[22] Therefore, the current conclusion should be cautiously applied to Western patients.

The QOL after HSCT is most strongly affected by the status of chronic GVHD, but it is difficult to determine the appropriate utility for each status of GVHD. Therefore, we performed a one-way sensitivity analysis with a wide plausible range of the utility for being alive with active GVHD. In our decision model, the superiority of HSCT was consistently observed regardless of the utility for being alive with active GVHD both in the whole population and in all subgroups (Figure 2).

In conclusion, to improve the long-term probability of survival, allogeneic HSCT in first remission is recommended for all adult patients with Ph-negative ALL who have an HLA-matched sibling. Even when we considered QOL, the superiority of HSCT was confirmed in the whole population and in all subgroups. However, this result might change by the adaptation of intensified chemotherapy, especially in higher-aged patients.

Conflict of interest

The authors declare no conflict of interest.

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JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Risk of Myelodysplastic Syndromes in People Exposed to Ionizing Radiation: A Retrospective Cohort Study of Nagasaki Atomic Bomb Survivors

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ABSTRACT

Purpose
The risk of myelodysplastic syndromes (MDS) has not been fully investigated among people exposed to ionizing radiation. We investigate MDS risk and radiation dose-response in Japanese atomic bomb survivors.

Patients and Methods
We conducted a retrospective cohort study by using two databases of Nagasaki atomic bomb survivors: 64,026 people with known exposure distance in the database of Nagasaki University Atomic-Bomb Disease Institute (ABDI) and 22,245 people with estimated radiation dose in the Radiation Effects Research Foundation Life Span Study (LSS). Patients with MDS diagnosed from 1985 to 2004 were identified by record linkage between the cohorts and the Nagasaki Prefecture Cancer Registry. Cox and Poisson regression models were used to estimate relationships between exposure distance or dose and MDS risk.

Results
There were 151 patients with MDS in the ABDI cohort and 47 patients with MDS in the LSS cohort. MDS rate increased inversely with exposure distance, with an excess relative risk (ERR) decay per km of 1.2 (95% CI, 0.4 to 3.0; $P < .001$) for ABDI. MDS risk also showed a significant linear response to exposure dose level ($P < .001$) with an ERR per Gy of 4.3 (95% CI, 1.6 to 9.5; $P < .001$). After adjustment for sex, attained age, and birth year, the MDS risk was significantly greater in those exposed when young.

Conclusion
A significant linear radiation dose-response for MDS exists in atomic bomb survivors 40 to 60 years after radiation exposure. Clinicians should perform careful long-term follow-up of irradiated people to detect MDS as early as possible.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of disorders characterized by clonal and ineffective hematopoiesis, morphologic dysplasia, and an increased risk of developing acute myeloid leukemia (AML).[1] MDS can arise de novo or secondary after chemo- and/or radiotherapy (therapy-related MDS).

The pathogenesis and established causative factors remain elusive for most patients with MDS. A widely accepted multistep pathogenesis model involves initial damage to hematopoietic stem cells caused by genotoxic or environmental agents followed by additional genetic or cytogenetic changes, resulting in the expansion of the MDS clone and the subsequent leukemic transformation.[2,3] Ionizing radiation is a well-known environmental carcinogen that induces chromosomal and genetic abnormalities. When an individual's bone marrow is exposed to ionizing radiation, hematopoietic stem cells may be damaged randomly, and some of these changes could induce MDS.

In contrast to the well-documented radiation-induced leukemia,[4-6] there has been no conclusive evidence that radiation exposure plays a significant role in the development of MDS. So far, radiation exposure remains a probable causative factor for MDS.[2] Most review articles have described radiation exposure as a definite causative factor for MDS on the basis of clinical studies of therapy-related MDS/AML. However, the original sources seldom

evaluated the radiation dose-response relationship for MDS alone. Epidemiologic studies of people exposed to a variety of radiations reported only a small number of cases.[7-10] In a previous study of atomic bomb survivors,[11] a possible radiation dose-response relationship for MDS was suggested, but the analysis included only 12 patients. MDS research among the atomic bomb survivors has been hampered by the fact that case ascertainment was incomplete before publication of the 1982 French-American-British (FAB) classification[1] and that no regional cancer registry officially registered MDS until 2000.

A radiation dose-response relationship for MDS might be predictable from that for AML because of the clinical similarity between the two diseases. However, much data have been accumulated to support that MDS has features that are distinct from AML with regard to latency of onset, genetic and cytogenetic abnormalities, apoptotic activity, and so on.[12,13] These biologic differences between MDS and AML suggest that radiation-induced MDS and AML may have distinct features as a consequence of different damage caused by radiation exposure. Therefore, it is important to evaluate the radiation dose relationship for MDS risk in people exposed to radiation.

In response to the increasing concern about MDS risk in atomic bomb survivors,[14] we initiated a multi-institutional epidemiologic research project. The aim of this study was to assess MDS risk and the radiation dose-response relationship 40 to 60 years after exposure.

PATIENTS AND METHODS

Study Project

This project, begun in April 2004, was a collaboration between the Atomic Bomb Disease Institute (ABDI) of the Nagasaki University Graduate School of Biomedical Sciences, the Nagasaki Prefecture Cancer Registry (NPCR),[15] the hematology departments in five hospitals in Nagasaki City (see Acknowledgment), and the Radiation Effects Research Foundation (RERF). The Institutional Review Boards of Nagasaki University (Research Protocol 16031797) and RERF (Research Protocols 18-66 and 1-75) approved this study.

Patients

We collected clinical information on MDS patients diagnosed in the five hospitals from 1982 to 2004, without regard for exposure status. Skilled hematologists in the hospitals and two authors (M.I. and M.To.) re-evaluated the clinical information, including bone marrow specimens, by using FAB criteria[1] to classify patients as refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-t), or chronic myelomonocytic leukemia (CMML). We also classified the diagnostic certainty for each patient as either definite, possible, undetermined, or non-MDS by using the criteria listed in Table 1. All reviewed patients were reported to the NPCR to be checked for multiple enrollments, the earliest date of MDS diagnosis, and the presence of malignancies before the MDS diagnosis. MDS patients who received chemotherapy and/or radiation therapy for their earlier malignancy were treated as therapy-related MDS, but those who had only surgery for their earlier malignancy were treated as primary MDS. International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3) codes[16] for MDS were assigned to all patients. We also added information on date of death, date of progression to overt leukemia, if present, and the last recorded follow-up date.

Population

We used two different cohorts of Nagasaki atomic bomb survivors: a cohort defined by the ABDI Data Center and RERF's Life Span Study (LSS) cohort. Although there is some overlap between the cohorts, they were established independently and each has its own strengths and limitations. The ABDI cohort is larger than the LSS cohort but lacks information on individual dose, whereas the LSS cohort has detailed individual dose estimates but fewer Nagasaki survivors. The main reason for using two cohorts in our study was to give more credibility to the LSS dose-response findings by confirming similar distance-response patterns in the two cohorts.

The ABDI database was established in 1977 and consists of data on approximately 120,000 Nagasaki atomic bomb survivors. Available data include information on exposure status, death and migration dates, and the results of medical checkups and cancer screenings conducted at the Nagasaki Atomic Bomb Casualty Council Health Management Center. Details about the ABDI database were given previously.[17]

The LSS database was established in 1950, consisting of approximately 94,000 Hiroshima and Nagasaki atomic bomb survivors and 26,000 nonexposed city residents. Available data include information on exposure status, death and cancer diagnosis dates, and individual organ dose estimates computed by using the Dosimetry System 2002 (DS02).[18] The LSS database includes approximately 32,000 Nagasaki survivors. Details about the LSS database were given previously.[19]

Identification of MDS in Atomic Bomb Survivors

Of the 796 patients with MDS registered in the NPCR, 44 were excluded because of misdiagnosis and 147 were excluded because of residence outside the catchment area. The remaining 605 eligible patients with MDS were linked to the ADBI and LSS databases to identify atomic bomb survivors with MDS (ABDI-MDS and LSS-MDS, respectively). Follow-up for this study began in January 1985 when the FAB classification of MDS had been widely used in Japan. Figure 1 summarizes the patient selection process and provides information on the final cohorts used for analyses.

Statistical Analysis

We performed risk analyses only for those with known exposure distances or dose. Patients were limited to those with a definite or possible level of diagnostic certainty for MDS. Patients of therapy-related MDS (ICD-O-3 code 9987/3) or with an undetermined level of certainty were censored at the date of diagnosis. Follow-up began on January 1, 1985, and continued to the earliest of the date of the primary MDS diagnosis, death, or December 31, 2004. The

Table 1. *Criteria for the Level of Diagnostic Certainty for MDS in Case Review*

Level	Objective Evidence
Definite	Reaffirmation of dysmegakaryopoiesis and/or dysgranulopoiesis on the bone marrow aspirate smear.
	Bone marrow aspirate smear was not available, but there was a clear description of dysmegakaryopoiesis and/or dysgranulopoiesis on the medical record.
	Bone marrow aspirate smear was not available and there was no clear description of dysmegakaryopoiesis and/or dysgranulopoiesis, but there was a description of the presence of dysplasia in blood cells, myeloblast < 30%, and chromosome aberration on the medical record.
Possible	Morphologic evaluation was not available, but there was a clear clinical course from FAB-refractory anemia or refractory anemia with excess blasts to leukemia on the medical record.
Undetermined	Only the name of MDS was available on the medical record and the death certificate.

Abbreviations: MDS, myelodysplastic syndromes; FAB, French-American-British classification.

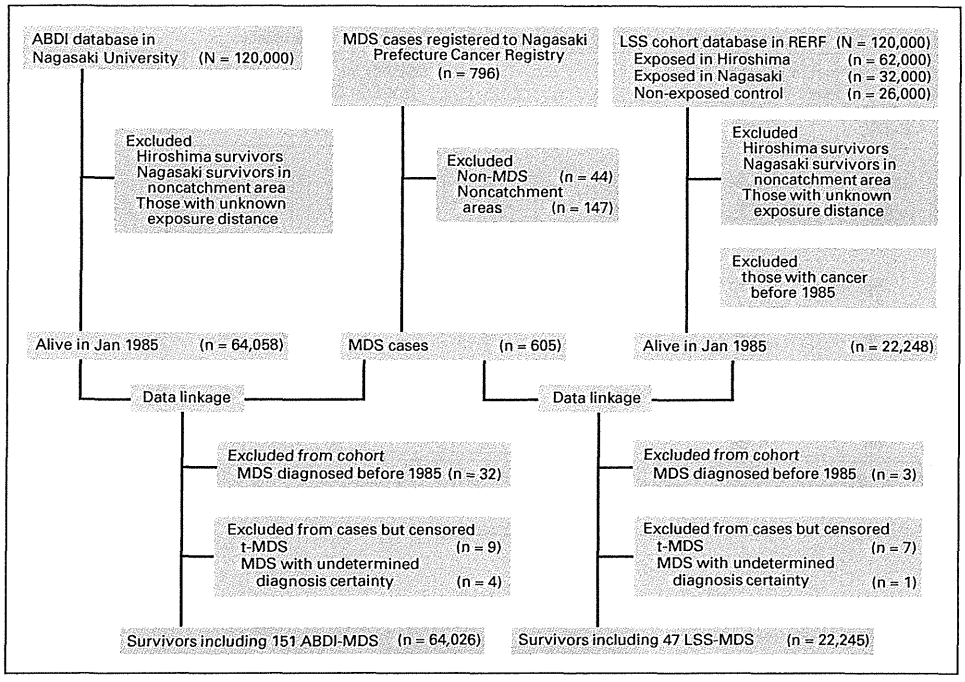

Fig 1. Study profile. ABDI, Atomic Bomb Disease Institute; MDS, myelodysplastic syndromes; LSS, Life Span Study; RERF, *Radiation Effects Research Foundation*; t-MDS, therapy-related MDS.

person-year calculations took into account date of migration in the ABDI data set, and a migration adjustment was made in the LSS data set. For the LSS data set, we also excluded those with cancer before 1985, and the follow-up was censored at the date of treatment with chemo- or radiotherapy for any cancer, if present, because all LSS cohort members are routinely linked to the NPCR. We treated patients with MDS either together, by FAB category, or by a dichotomized category of low-risk (RA and RARS) and high-risk (RAEB and RAEB-t).[20] We did not include CMML or "not otherwise specified" in the dichotomized category.

We used Cox regression models to estimate the effects of sex, age at exposure, exposure distance, and dose on MDS incidence rates. Relative risk (RR) estimates were computed by using SAS software (version 9.1; SAS Institute, Cary, NC). We used the asymptotic SEs as the basis for hypothesis tests and 95% CIs. Interactions between factors were also tested. We treated age at exposure as two (0 to19 and $\geq$ 20 years) or three groups (0 to 9, 10 to 19, and $\geq$ 20 years) or as continuous, as necessary, and exposure distance in km as three groups ($<$ 1.5, 1.5 to 2.99, and 3.0 to 10.0 km) or more detailed categories, and the weighted DS02 bone marrow dose in Gy as three groups ($<$ 0.005, 0.005 to 0.999, and $\geq$ 1 Gy) or as continuous. The cutoff values for exposure distance or dose were chosen on the basis of data from previous reports.[17,19,21] For categoric data, tests for independence or trend were carried out by using χ^2 or Fisher's exact tests, as appropriate. A two-tailed P value of $<$ 0.05 was judged significant.

We examined linear, linear-quadratic, and other dose-response functions for the LSS data adjusting for sex, age at exposure, and attained age or time since exposure, in a manner similar to earlier leukemia dose-response analyses,[6] and estimated the excess relative risk (ERR) per Gy by using weighted DS02 bone marrow dose. The basic ERR dose-response model can be written as BR $[1+ \alpha d]$, where BR is the baseline rate described as a parametric function of sex and attained age. We also examined ERR distance-response functions in the ABDI and the LSS cohorts with exposure distance treated as a continuous variable truncated at 3km (r[inf]3k) or with exposure distance categories of $<$ 1.25, 1.25 to1.49, 1.5 to1.74, 1.75 to1.99, 2.0 to 2.49, 2.5 to 2.99, and $\geq$ 3.0 km. The continuous exposure-distance model can be written as BR $[1 + \gamma \exp(-\beta r$[inf]3k)] where the BRs are modeled as for the dose-response model, β is a distance-decay parameter, and γ is a scaling parameter. The distance-decay parameter value (x) is transformed to the percentage decrease in the ERR per km, which is calculated from the formula, $[1-\exp(-x)] \times 100\%$. ERR models were fit and likelihood-based P values and CIs were computed by using EPICURE software (Hirosoft International, Seattle, WA).[22]

RESULTS

The ABDI data set consisted of 64,026 Nagasaki atomic bomb survivors with information on exposure distance, including 151 ABDI patients with MDS who were diagnosed from 1985 to 2004. Of those, 147 (97%) were definite MDS patients and 4 (3%) were possible patients. The LSS data set consisted of 22,245 Nagasaki atomic bomb survivors for whom dose estimates were available. The 47 LSS patients with MDS included 45 (96%) definite and two (4%) possible patients. Table 2 presents the frequencies of FAB subtypes in both data sets. The distribution of subtypes in the ABDI and LSS cohorts did not differ (P = .54). The distribution characteristics, particularly the high frequency of RA relative to RARS and CMML, were typical for Japanese patients with MDS.[23] Cytogenetics data were available for 107 (71%) of 151 ABDI-MDS patients (Appendix Table A1, online only). The median age at exposure and the median age at diagnosis were 18.5 years (range, 0.3 to 43.4 years) and 71.0 years (range, 42.0 to 96.6 years) for ABDI-MDS, respectively, and 16.5 years (range, 2.5 to 48.8 years) and 72.4 years (range, 48.5 to 94.3 years) for LSS-MDS, respectively. The median time to development of MDS from 1985 was 12.0 years (range, 0.3 to 19.9 years) for ABDI-MDS and 14.5 years (range, 0.9 to 19.5 years) for LSS-MDS.

The total numbers of person-years in the ABDI and LSS cohorts were 947,215 and 270,619, respectively. The crude MDS incidence rates in the ABDI and LSS cohorts were 15.9 and 17.4 patients per 100,000 person-years, respectively. Table 3 summarizes the crude incidence rate and crude RR estimates by exposure status. MDS rates were higher for men than for women and increased with age at exposure. MDS rates also increased with decreasing distance from the hypocenter and with increasing estimated dose.

Table 2. Distribution of MDS by Exposure Distance or Dose in Two Cohorts of Atomic Bomb Survivors

Variable	Exposure Distance (km) for Nagasaki Atomic Bomb Disease Institute Cohort				DS02 Bone Marrow Weighted Dose (Gy) for Life Span Study-Nagasaki Cohort			
	< 1.5	1.5-2.99	≥ 3.0	Total	≥ 1	0.005-0.999	< 0.005	Total
Sex								
Male	1,693	6,485	16,092	24,270	273	2,665	5,904	8,842
Female	2,258	10,663	26,835	39,756	351	4,201	8,851	13,403
Total	3,951	17,148	42,927	64,026	624	6,866	14,755	22,245
MDS FAB subtypes								
RA	15	28	57	100	5	9	20	34
RARS	0	1	3	4	0	1	0	1
RAEB	7	8	14	29	2	3	2	7
RAEB-t	2	2	2	6	1	2	0	3
CMML	1	3	4	8	0	0	0	0
Unclassified	0	2	2	4	0	0	2	2
Total	25	44	82	151	8	15	24	47

Abbreviations: MDS, myelodysplastic syndromes; DS02, Dosimetry System 2002; FAB, French-American-British classification; RA, refractory anemia; RARS, RA with ringed sideroblasts; RAEB, RA with excess blasts; RABEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia.

In Cox analyses for the ABDI cohort with adjustment for sex and age at exposure, the MDS incidence rate was significantly and inversely related to the exposure distance. The RR estimates for those exposed at < 1.5 and 1.5 to 2.99 km from the hypocenter were 2.8 (95% CI, 1.8 to 4.5; $P < .001$) and 1.3 (95% CI, 0.9 to 1.9; $P = .13$), respectively. Analyses of the LSS cohort also revealed that dose was a strong risk factor for MDS. Effects of exposure distance and dose on MDS were observed in both high-risk and low-risk MDS in both cohorts (Figs 2A and 2B). In a joint analysis of the dose and distance effects on MDS rates, there was a suggestion ($P = .08$) of larger radiation effects in high-risk MDS than in low-risk MDS. A significant linear dose association was observed in each risk group ($P < .001$). Effects of exposure distance and dose on MDS were also observed for those exposed before and after age 20 in both cohorts (Figs 2C and 2D). When we adjusted for attained age in 1985 in the ABDI cohort, age-specific MDS risks increased with increasing year of birth, with risks for those born after 1925 being about 1.75 (95% CI, 1.05 to 2.90) times the risks for those born in earlier years. The adjusted MDS risk using exposure dose in the LSS data showed similar results (RR, 1.71; 95% CI, 0.95 to 3.10). After allowing for birth cohort effects on the MDS risk, there was no evidence of a statistically significant interaction between distance or dose and age at exposure in either cohort (ABDI $P = .06$; LSS $P = .36$).

MDS rates decreased significantly with increasing distance for both cohorts ($P < .001$ for both). The fitted ERR curves were similar for the two cohorts. The decay parameters for ABDI and LSS cohorts were 1.2 per km (95% CI, 0.4 to 3.0) and 2.1 per km (95% CI, 0.6 to 4.6), respectively. In other words, the ERR is estimated to decrease by 70% per km (95% CI, 33% to 95%) in the ABDI and 88% per km (95% CI, 43% to 99%) in the LSS cohort. Figure 2E shows the fitted distance-response curves and point estimates of the distance category–specific ERRs with 95% CIs. There was a statistically significant ($P < .001$) linear dose-response for MDS in the LSS cohort with an ERR per Gy estimate of 4.3 (95% CI, 1.6 to 9.5; Fig 2F). A linear-quadratic model that fit the AML[6] did not improve the fit ($P = .46$).

DISCUSSION

To the best of our knowledge, this is the largest study to date evaluating the association between MDS risk and radiation exposure, and the first to provide quantitative estimates of the effect of radiation on MDS risk. We observed a significant ($P < .001$) linear relation between radiation dose and MDS risk among atomic bomb survivors with an ERR per Gy of 4.3. We also observed that the effect of radiation on MDS risk was greater in advanced subtypes of MDS and in those exposed at younger ages.

Our finding of a significant linear dose-response pattern for MDS is in contrast to the significant linear-quadratic dose-response pattern for AML.[6] The fact that the radiation-associated increases of MDS risk still exist 40 or more years after exposure is also in contrast to the risk of radiation-induced leukemia in which the largest dose-related increases were seen in the first 10 to 15 years after the bombings and then decreased slowly with time.[5,6] The linear dose-response pattern and the appearance with a long latency for MDS in atomic bomb survivors seems similar to those seen for radiation-associated solid cancers.[19]

Differences in the dose-response patterns for MDS and AML suggest that the nature of the radiation-induced genetic damages in hematopoietic stem cells may differ for the two diseases. Mutations in the *AML1/RUNX1* gene[24,25] may be one of the genetic damages associated with MDS that occurred in hematopoietic stem cells of atomic bomb survivors because of radiation exposure. Accumulating data on the different characteristics of the molecular and clinical spectrum, including chromosome aberrations between MDS and AML,[12,13,26-29] could shed some light on differences in the role of radiation exposure on these diseases.

Why is radiation-induced MDS seen in atomic bomb survivors more than 40 years after exposure? A primary reason for the long latency of MDS risk could be that atomic bomb survivors, even those exposed early in life, are reaching ages at which MDS rates are increased. In fact, in recent years, hematologists in Nagasaki City have identified an increasing number of MDS occurrences among atomic bomb survivors. Moreover, on the basis of the multistep pathogenesis

Table 3. Crude Incidence and Crude Relative Risk of Myelodysplastic Syndromes by Exposure Status in Nagasaki Atomic Bomb Survivors

Variable	Nagasaki Atomic Bomb Disease Institute Cohort						Life Span Study-Nagasaki Cohort					
	Exposure Distance (km)				Crude		Weighted Bone Marrow Dose (Gy)				Crude	
	< 1.5	1.5-2.99	≥ 3.0	Total	RR	95% CI*	≥ 1	0.005-0.999	< 0.005	Total	RR	95% CI*
Sex												
Male												
Population at risk	1,693	6,485	16,092	24,270			273	2,665	5,904	8,842		
No. of patients	12	21	34	67			3	8	10	21		
Person-years	23,071	91,880	233,191	348,144			2,959	29,789	66,102	98,850		
Crude rate†	52.0	22.9	14.6	19.2	1.3	1.0 to 1.9	101.4	26.9	15.1	21.2	1.4	0.8 to 2.5
Female												
Population at risk	2,258	10,663	26,835	39,756			351	4,201	8,851	13,403		
No. of patients	13	23	48	84			5	7	14	26		
Person-years	34,946	158,144	405,980	599,071			4,480	52,926	114,363	171,769		
Crude rate†	37.2	14.5	11.8	14.0	Ref		111.6	13.2	12.2	15.1	Ref	
Age at exposure, years												
0-9												
Population at risk	615	4,770	13,730	19,115			161	2,464	5,064	7,689		
No. of patients	6	9	13	28			3	6	3	12		
Person-years	9,756	77,132	225,071	311,960			1,750	29,274	60,572	91,596		
Crude rate†	61.5	11.7	5.8	9.0	Ref		171.4	20.5	5.0	13.1	Ref	
10-19												
Population at risk	1,950	5,620	13,611	21,181			280	2,256	4,841	7,377		
No. of patients	13	16	29	58			2	5	8	15		
Person-years	31,325	91,011	225,009	347,346			3,532	29,182	63,714	96,428		
Crude rate†	41.5	17.6	12.9	16.7	1.9	1.2 to 3.0	56.6	17.1	12.6	15.6	1.2	0.6 to 2.5
≥ 20												
Population at risk	1,386	6,758	15,586	23,730			183	2,146	4,850	7,179		
No. of patients	6	19	40	65			1	11	8	20		
Person-years	16,937	81,882	189,091	287,909			2,157	24,259	56,179	82,595		
Crude rate†	35.4	23.2	21.2	22.6	2.9	1.9 to 4.5	46.4	45.3	10.7	21.8	1.8	0.9 to 3.8
Total												
Population at risk, n	3,951	17,148	42,927	64,026			624	6,866	14,755	22,245		
No. of patients	25	44	82	151			6	22	19	47		
Person-years	58,018	250,025	639,171	947,215			7,439	82,715	180,465	270,619		
Crude rate†	43.1	17.6	12.8	15.9			80.7	26.6	10.5	17.4		
Crude RR	3.2	1.4	Ref				8.1	1.4	Ref			
95% CI*	2.0 to 5.0	1.0 to 2.0					3.1 to 18.0	0.7 to 2.6				

Abbreviations: RR, relative risk; Ref, reference.
*Analyses were performed using the Cox regression.
†The crude incidence was calculated as the total number of patients divided by person-years accumulated in each row and is presented per 100,000 person-years.

model,[3] we may speculate that hematopoietic stem cells of people exposed to higher radiation doses had more genetic damage than those of people exposed to lower dose or than those of the elderly population in general. However, we feel that the multistep pathogenesis model does not fully explain the recent increased risk of MDS. Chromosomal and genetic instabilities as consequences of targeted and/or nontargeted effects of radiation exposure[30] may play a role in the late development of MDS as well as solid cancers in atomic bomb survivors. In fact, we observed higher frequencies of complex karyotypic abnormalities, including random aneuploidies, among proximally exposed MDS patients in this study (Appendix Table A1). Another possible paradigm is the cancer stem-cell theory, including leukemic stem cells.[31,32] Trosko[33] suggests the role of organ-specific adult stem cells as the target cells for radiation-induced carcinogenesis, and the age-related changes in quality of the injured stem cells could affect cancer risks later in life. This concept may explain the long latency of MDS risk in atomic bomb survivors, although little is known about MDS stem cells.

This study has several limitations. Follow-up is limited and there is no information on MDS risks until 40 years after exposure. It was not possible to determine whether or not the incidence rate of MDS were elevated in the decades immediately after the bombings, since MDS was not recognized as a distinct entity until the mid-1980s. The dose-response analyses were performed for a small number of patients. The distance analyses did not account for variations in shielding among survivors, which would modify their actual doses. Information on dates of prior cancers and other prior chemotherapy or radiotherapy was not available for the ABDI data set.

As of 2007, we confirmed that 42 patients among the 151 ABDI-MDS patients progressed to overt leukemia (data not shown). Further studies are needed to clarify the effect of radiation on leukemic transformation as well as the nature of the radiation-induced MDS and the dose-response pattern. Efforts to expand the study to include MDS occurring among Hiroshima survivors are underway.

In conclusion, this study showed that acute radiation exposure is associated with increased risk of developing MDS later in life. This

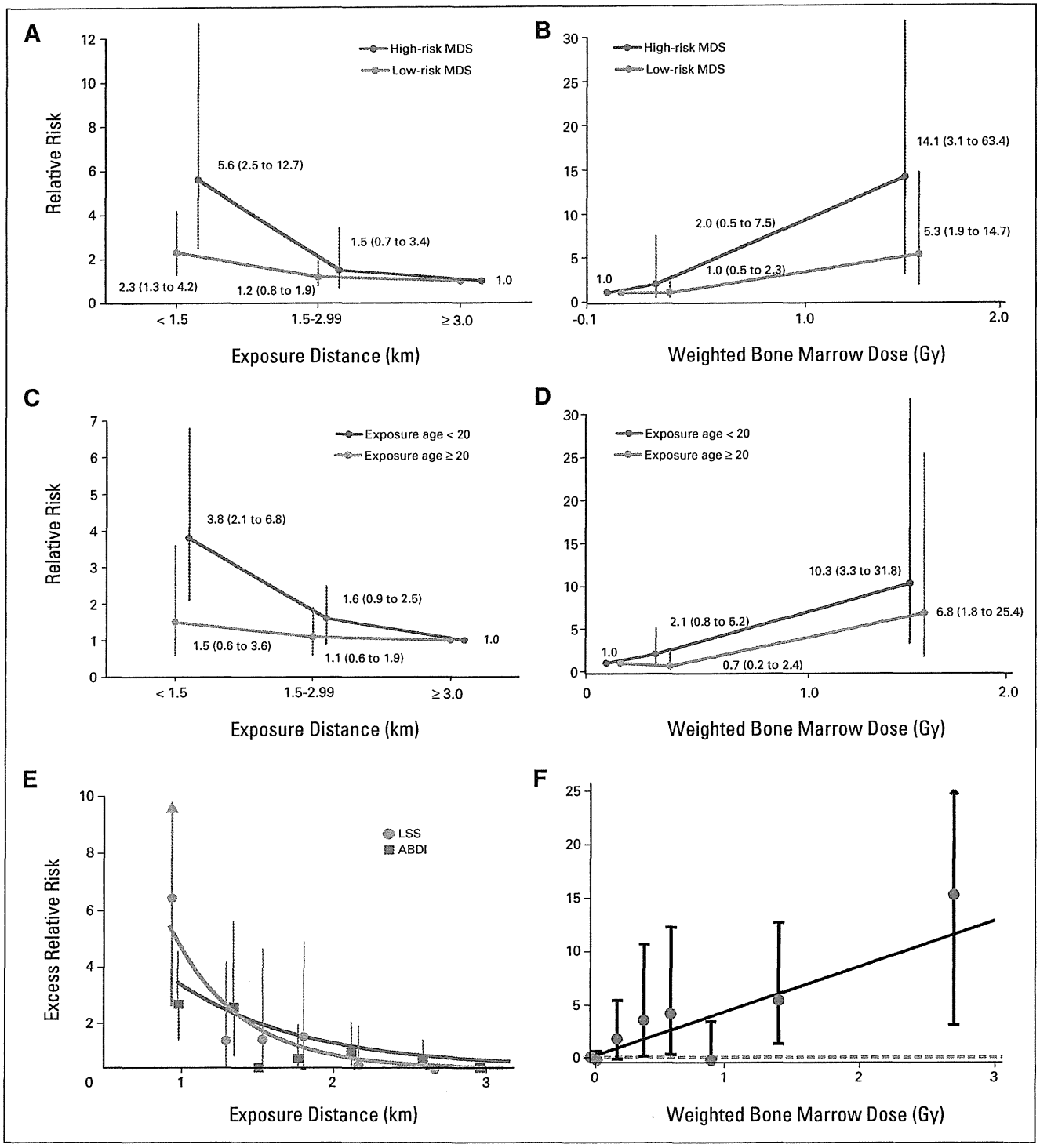

Fig 2. Risk of myelodysplastic syndromes (MDS) by exposure distance and dose. (A) Relative risks of MDS by French-American-British classification subtype in Atomic Bomb Disease Institute cohort, and (B) in Life Span Study-Nagasaki cohort. The high-risk MDS indicates French-American-British classification subtypes of refractive anemia with excess blasts and refractive anemia with excess blasts in transformation, and the low-risk MDS indicates the subtypes of refractive anemia and refractive anemia with ringed sideroblasts. (C) Relative risks of MDS by age at exposure in Atomic Bomb Disease Institute cohort, and (D) in Life Span Study-Nagasaki cohort. (E) Sex- and age-adjusted distance-response for MDS. The lines display the best-fitted excess relative risk curves based on distance category–specific relative risk. (F) Sex- and age-adjusted radiation dose-response for MDS. The line displays the best-fitted linear excess relative risk dose-response without risk modification based on dose category–specific relative risk. The dashed horizontal line represents excess relative risk = 0. Whiskers show the 95% CIs.

suggests that radiation-induced MDS might involve a different pathogenesis than radiation-induced leukemia. Clinicians should perform careful long-term follow-up of people who have been exposed to radiation to detect MDS as early as possible and reduce the risk of leukemic transformation by using new drugs such as DNA hypomethylating agents.[34]

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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Appendix

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Table A1. Cytogenetic Features of Patients With MDS Among Nagasaki Atomic Bomb Survivors

Exposure Distance (km)	Age at Exposure (years)	Age at Diagnosis (years)	FAB Subtype	Abnormal Karyotype
< 1.5*				
0.7	20	76	RA	46,XX, del(1)(p13p22), del(9)(q13), del(11)(q13) [14/20]
0.7	17	63	RAEB	46,XX,t(1;11)(p32;q23), del(1)(p32), inv(3)(p21q27), del(5)(q15), -6, [-9, mar1, +mar2
0.8	39	79	RA	46,XY,del(9)(q?) [18/20]
				46,XY,t(20;22)(p11;p13) [1/20]
0.9	2	61	RA	46,XY, del (1)(p?),add (2) (p23), del(5)(q?),add(6)(p21), -7,add(8)(q24), add(11)(q13),marl [5/20]
				46, idem,-del(1),;der(1)del(1)add(1)(q42),+ 8,-add (8) [10/20]
1.0	31	89	RA	47,XY, -1, +der(?)t(?;1)(?;q21)x2 [4/20]
				45,XY, t(1;9)(q12;q21),-2 [1/20]
1.0	14	68	RA	46,XX,t(1;3)(p36;q21) [2/20]
1.0	9	65	RA	46,XX,t(13;14)(q14;q24) [4/16]
1.0	16	75	RA	47,XY,+8 [3/20]
1.0	28	78	RAEB	45, XX, -7 [1/15]
				42, idem, -x, add(3)(q1?), -5, -9, add(10)(p11), add(11)(p1?), der(11)del(11)(p1?)(q?), add(12)(p11), -13, add(13)(p1) , -17, +2mar [3/15]
				43, idem, -X, add3(q1?), -5, -9, add(10)(p11), add(11)(p1?), -13, add(13)(p1), -17, +2mar, +mar1 [1/15]
1.0	20	70	RAEB	62,XX, -X, -4, -5, -7, add(11)(q23), -14, -16, -17, -19, -21, +22, +mar [3/18]
				63, idem, +mar [3/18]
				68, idem, +x, -3, +7, +8, -11, +14, +16, +19, +21, +22 [9/18]
1.0	14	63	RAEB	45,XY, -7, -20, +mar
1.0	4	59	RAEB-t	46,XX,t(5;22)(p15;q11) [4/20]
				46,XX,add(14)(q32),del(20)(q1?) [1/20]
1.1	17	75	RA	46,XY, del (20)(q1?) [5/19]
				46,idem,del(3)(p?),add(7)(p11),t(13;15)(q32;q13), add(17)(p11) [6/19]
				46,XY,del(7)(q?),t(12;17)(p10;p10),del (13)(q?),der(13)t(13;15)(q32;q13),add(14)(q22),add(15)(q11)add(17)(p11) [5/19]
				46,XY, t(1;13)(q21;q14),t(8;12)(q24;q13),del(9)(q?)del(q?) [1/19]
1.1	16	69	RAEB	45,XX,5q -, -12[7/20]
				45,idem,+r[3/20]
				45,XX, ,3p-, 4p+q-, -12, 12q+, 15q-[1/20]
				Tetraploid [8/20]
1.2	16	75	RA	46,XY, del(20)(q11;q13.3)[16/20]
				46,XY, inv(6)(q23;q21) [2/20]
1.2	21	73	RA	46,XX, -20, +mar1 [10/20]
1.2	3	54	RAEB	45,XY, -5, add(7)(q11), t(14,15)(q32;q15), der(15;17)(q10;q10), -19, del(20)(q11), +21, +mar [11/20]
				45,XY, -5, add(7)(q11), t(14,15)(q32;q15), der(15;17)(q10;q10), del(20)(q11), +21 [5/20]
				45, XY, -5, add(7)(q11), t(14,15)(q32;q15), del(17)(p11), -19 [4/20]
1.4	18	75	RA	46,XY, t(3;7)(q27;p12) [1/19]
1.4	32	80	RAEB	49,XY,add(1)(3?4), add(3)(q27), del(5)(q?), +8, -12, -18, +2r. +mar1x2 [1/17]
				49,idem, +Y, -13, -16, -r, +mar2, +mar3 [2/17]
				50,idem, +Y, -13, -16, -r, +mar2, +mar3, +mar [5/17]
				51, idem, +2mar [3/17], 46,XY [6/17]
1.5-2.99†				
1.5	15	63	RA	46,XY, 20q- [17/20]
1.5	15	73	RA	45,X, -Y [3/20]
1.8	7	64	RA	47,XX, +8 [3/20]
1.8	19	74	RA	46, X, idic(x)(q13)[9/20]
2.0	17	71	RA	46,XY,add(3)(p11),del(5)(q?),add(6)(p11),+8,dr(15;17)(q10;q10) [14/20]
				46,idem,der(10)t(1;10)(p13;p13) [5/20]
2.0	27	75	RAEB	46,XX,inv(16)(p13q22) [4/20]
				46, idem, add(17)(q25) [4/20]
2.4	6	60	RA	46,XY, del(13)(q12q24) [20/20]
2.4	4	48	RAEB	47,XX,+8 [20/20]
2.5	18	70	RA	46,XY, i(17)(q10) [7/20]
				47,idem,+17 [1/20]
2.5	13	63	RA	46,XX, add(3)(p21) [6/20]
2.5	3	57	RA	46,XY, del(20)(q11) [9/20]
				45,XY, del(20)(q11),-7 [3/20]

(continued on following page)

Table A1. Cytogenetic Features of Patients With MDS Among Nagasaki Atomic Bomb Survivors (continued)

Exposure Distance (km)	Age at Exposure (years)	Age at Diagnosis (years)	FAB Subtype	Abnormal Karyotype
2.5	15	74	RAEB	45,X, -Y [3/20]
2.6	34	90	RA	46,XY, t(1;1)(q25;q32) [1/20]
2.6	14	54	RA	47,XX,+8 [19/20]
				49,XX, 1p+, +8,+10, +21[1/20]
2.8	4	51	RA	46,XY,+der(1;7)(q10;p10), -7 [11/20]
				46,idem, 6q-[1/20]
2.9	17	68	RAEB-t	45,XX,add(4)(p1?)del5(q?), -7, +8, -12, add15(p1?)
≥ 3.0‡				
3.0	15	63	RA	46,XX, +1, der(1;7)(q10;p10)
3.0	12	62	RA	75,XY, very complex
3.0	23	71	RAEB	46,XY,+der(1;7)(q10;p10),-7 [1/20]
3.0	29	71	RAEB	47,XY,-7,+8,+mar
3.0	33	77	RAEB-t	47,XY, +8
3.1	15	71	RA	46,XY,del(5)(q13q31), i(17)(q10)
3.2	19	73	RA	55,XX, +1, +3, +6, +7, +1-, +11, +12, +19, +20 [1/20]
3.2	26	79	RA	45,X,-Y [2/20]
3.3	16	70	RA	46,XY, del(11)(p?)[2/20]
3.6	13	69	RAEB	46,XX,del(12)(p?) [15/20]
				46,idem,i(17)(q10) [3/20]
				47,idem,+8 [2/20]
4.0	28	78	RA	45,X, -Y, 11q-
4.1	10	69	RA	46,XX, 5q-[1/20]
4.5	12	68	RA	46,XY, add(2)(p23) [20/20]
5.3	27	81	CMML	45,X, -Y [20/20]
5.4	23	82	RA	47,XX,+8 [3/20]
5.4	0.3	42	RAEB	45,XY, -7, -17, t(5;12)(q22;p13), t(9;17)(q22q12), del(20)q
5.8	11	69	RAEB	46,XY, del(20)(q11)[3/20]
6.0	9	49	CMML	48, XY, +6, +8, +8
6.0	8	55	RARS	46,XY,20q -
8.5	7	65	RAEB	46,XX,del(5)(q?) [8/20]

NOTE. Patients with abnormal karyotype are listed with their karyotype. Data in square brackets indicate the number of the karyotype in a total number of metaphase cells.

Abbreviations: MDS, myelodysplastic syndromes; FAB, French-American-British classification; RA, refractory anemia; RAEB, RA with excess blasts; RAEB-t, RAEB in transformation; CMML, chronic myelomonocytic leukemia; RARS, RA with ringed sideroblasts.

*Normal karyotype (n = 4), abnormal karyotype (n = 19), unkown karyotype (n = 2).

†Normal karyotype (n = 13), abnormal karyotype (n = 16), dry tap (n = 2), unknown karyotype (n = 13).

‡Normal karyotype (n = 32), abnormal karyotype (n = 20), dry tap (n = 1), unknown karyotype (n = 29).

