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<th>Clinical features and prognosis of patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki</th>
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<td>Author(s)</td>
<td>Matsuo, Masatoshi; Iwanaga, Masako; Kondo, Hisayoshi; Soda, Midori; Jo, Tatsuro; Horio, Kensuke; Takasaki, Yumi; Kawaguchi, Yasuhisa; Tsushima, Hideki; Imaizumi, Yoshitaka; Imanishi, Daisuke; Taguchi, Jun; Sawaya, Yasushi; Hata, Tomoko; Miyazaki, Yasushi</td>
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Clinical features and prognosis of patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki

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Key words
Atomic bomb survivors, myelodysplastic syndromes, prognosis, radiation exposure, therapy-related myeloid neoplasms

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Myelodysplastic syndromes comprise a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, morphological dysplasia, and leukemic transformation. Most MDS arise primarily or de novo without known causative agents, but approximately 15–20% of MDS develop following cytotoxic chemotherapy and/or radiotherapy for a primary malignancy, which are classified as t-MDS or/and t-MDS/t-AML or, recently, included into therapy-related myeloid neoplasms. It is known that approximately 30% of patients with primary MDS will progress to AML. In order to assess the risk of leukemic transformation and poor survival of primary MDS, several risk-scoring systems have been proposed, such as the IPSS, the IPSS-R and the WHO Classification-based Prognostic Scoring System.

The pathogenesis of primary MDS remains elusive. A multi-step pathogenesis model has been widely accepted from initial damage to hematopoietic stem cells caused by genotoxic or environmental agents followed by additional genetic or cytogenetic changes. However, the established causative factors for primary MDS also remain elusive. Aging, male sex, and environmental exposure to smoking, benzene, and ionizing radiation have been suggested as risk factors for developing primary MDS in the general population. Of the suggested...
risk factors, ionizing radiation is a well-known carcinogen that induces chromosomal and genetic abnormalities. The association between non-therapeutic ionizing radiation and the incidence of primary MDS were reported in a UK case-control study,\(^{(9)}\) a case report of six aircrews exposed to cosmic radiation mostly in the range of 2–4 mSv per year,\(^{(10)}\) and a retrospective cohort study of children with brain tumor who were examined with CT scan.\(^{(11)}\) However, none evaluated the effect of ionizing radiation on the prognosis of MDS.

We previously reported a significant radiation dose-dependent increase in the incidence of primary MDS in Nagasaki A-bomb survivors,\(^{(12)}\) who were typically exposed to environmental radiation with low to high doses.\(^{(13)}\) In the previous study, we found that more primary MDS patients occurred in those exposed to the higher radiation dose, and that they had the complex chromosomal abnormality similar to that seen in t-MDS.\(^{(12)}\) Also recently, Jo et al.\(^{(14)}\) reported that Nagasaki A-bomb survivors with MDS who were treated with azacitidine, in particular those exposed at an age of 10 years, showed poorer survival than patients with de novo MDS who were treated with azacitidine. However, whether MDS among A-bomb survivors had a higher risk of leukemic transformation than de novo MDS, and whether A-bomb radiation is an independent prognostic factor even after taking into account the existing prognostic scoring systems for MDS, has not been previously reported.

Therefore, in the present study, we aimed to elucidate the clinical features of patients with MDS that occurred in A-bomb survivors by exposure status in detail, and to evaluate whether exposure to A-bomb radiation is significantly associated with progression to overt leukemia and survival, being independent of the effect of existing prognostic scoring systems for MDS.

Methods

Study design. This is a retrospective observational study on the basis of data collected in our previous study\(^{(12)}\) and the extension work undertaken by a collaborative team consisting of the ABDI of Nagasaki University, the NPCR,\(^{(15)}\) and five hospitals in Nagasaki City (all Nagasaki, Japan). The institutional review boards of ABDI (approval numbers 16031797 and 13042607) and NPCR (approved numbers 24-1520 and 25-1445) approved this study. The respective institutional review boards of five collaborative hospitals also approved to join this study and to provide clinical data of patients.

Patients. A total of 226 patients with primary MDS were enrolled in this study. Of them, 151 patients had been already identified in 1985–2004 among Nagasaki A-bomb survivors who were directly exposed to A-bomb radiation and for whom information on exposure distance (in km) was included in our previous work of the ABDI dataset.\(^{(12)}\) An additional 75 patients with primary MDS were included who were diagnosed in 2005–2011 in our extension work in the same manner as our previous study. Briefly, any MDS cases diagnosed at the five collaborative hospitals were re-examined. The diagnosis certainty was based on detailed clinical information by hematologists and then registered into NPCR. International Classification of Diseases for Oncology, 3rd Edition codes were assigned to all cases in NPCR,\(^{(16)}\) followed by linkage to the ABDI database, and then extracted for analysis. In this process, we carefully eliminated MDS patients with pre-existing malignancies before the diagnosis of MDS and those with International Classification of Diseases for Oncology, 3rd Edition code 99873; t-MDS.

Clinical data. We retrospectively reviewed clinical data of each case at diagnosis, including peripheral blood cell counts, blast counts in bone marrow, cytogenetic examination, the FAB classification,\(^{(1)}\) and the 2000 WHO classification.\(^{(4)}\) We also accumulated information on outcome data including date of death, date of progression to overt leukemia, and the last recorded follow-up date until March 2014. After classified into subtypes according to the FAB and WHO classifications, we combined the subtypes into RA, RARS, RAEB/RAEB-t, WHO-RCMD, and WHO-RAEB-1/RAEB-2, because of the small number of cases in this study. Cytogenetic information was obtained as a karyotype report during the routine diagnostic procedure at the respective hospitals, which were described in accordance with the International System for Human Cytogenetic Nomenclature version at the time of diagnosis. Risk category by cytogenetics was then classified into good, intermediate, and poor according to the IPSS,\(^{(5)}\) or into very good, good, intermediate, poor, and very poor according to the IPSS-R.\(^{(6)}\) Clinical risk was stratified using IPSS (low, INT-1, NT-2, and high). We did not evaluate the IPSS-R prognostic risk categories and the WHO Classification-based Prognostic Scoring System score because data on bone marrow blast percentage and transfusion-dependency were not fully available.

Radiation exposure status. Available data regarding radiation exposure status include sex, age in years at the time of the A-bomb, exposure distance in km from the hypocenter, and death and migration dates. Exposure dose estimate was not available. Age at exposure was treated as a continuous value, categorized into 5-year groups, or dichotomized (<19 and ≥20 years). Exposure distance in km was categorized into three groups (<1.5, 1.5–2.99, and 3.0–10.0 km). The cut-off values for exposure distance were chosen on the basis of our previous report.\(^{(12)}\) Roughly speaking, the cut-off point of exposure distance 1.5 km corresponds to approximate exposure radiation dose of 1 Gy and 3.0 km corresponds to 0.005 Gy, if exposed outside without shielding.

Statistical analysis. Frequencies of categorical variables were compared using the χ²-test or Fisher’s exact test. Continuous variables are presented as the median with ranges and compared with the use of Wilcoxon’s rank-sum test or the Kruskal–Wallis test, or were categorized into several groups as necessary. Cumulative probabilities and the 95% CI of OS and EFS were estimated by the Kaplan–Meier method, and compared between groups using the log-rank test. Overall survival was censored at the time of death or last follow-up. Event-free survival was censored at the time of death, progression to overt leukemia, or last follow-up, whichever occurred first. Effects of factors on OS and EFS were evaluated by using univariate and multivariate Cox regression hazard models. In multivariate analyses, interactions between factors were also tested. Cumulative incidence rate of leukemic transformation was estimated by taking into account the competing risk of non-leukemic death, and compared between groups using Gray’s test. Statistical analyses were carried out using SAS version 9.3 (SAS Institute, Cary, NC, USA), R version 2.12.1 (R Foundation, Vienna, Austria), and EZR version 1.27 (Saitama Medical Center, Jichi Medical University, Saitama, Japan). P-values <0.05 were defined as significant.

Results

Patient characteristics. Among 226 patients, 86 were not evaluable for IPSS or IPSS-R due to the lack of information.
Therefore, a total of 140 patients who were evaluable for IPSS-R cytogenetics, 51 (44%) were classified into the INT/poor/very poor group.

Impacts of exposure distance and clinical factors on outcomes. By the end of March 2014, 47 (34%) patients had progressed to overt leukemia and 106 (75.7%) had died. Causes of deaths, time from diagnosis to outcomes, and the probability of OS, EFS, and CIR-L were summarized in Table 3. In all patients, the median follow-up for survival was 3.2 years (range, 0.1–21.0 years); the estimated 10-year OS, EFS, and the CIR of progression to overt leukemia were 24.8% (95% CI, 17.1–33.2%), 23.4% (95% CI, 16.1–31.7%), and 35.4% (95% CI, 27.0–43.9%), respectively.

There were no statistically significant differences among exposure distance groups in the OS (Fig. 1a) and EFS (Fig. 1b), although patients exposed at <1.5 km tended toward worse OS and EFS than those exposed at 3.0–10.0 km, in particular at the time of the 10-year follow-up. There was also no statistically significant difference among exposure distance groups in the CIR of progression to overt leukemia (Fig. 2a), although patients exposed at <1.5 km and 1.5–2.99 km tended to have a higher progression to overt leukemia and deaths without leukemic transformation as a competing event by exposure distance, patients who were exposed at <1.5 km and 1.5–2.99 km tended to progress to

### Table 1. Demographic characteristics of patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, grouped by radiation exposure status

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%) or median (range)</th>
<th>&lt;1.5 km</th>
<th>1.5–2.99 km</th>
<th>≥3.0 km</th>
<th>P for difference among three groups</th>
<th>P for difference between &lt;1.5 km and ≥3.0 km</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>140</td>
<td>31</td>
<td>35</td>
<td>74</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>73 (52)</td>
<td>16 (52)</td>
<td>21 (60)</td>
<td>36 (49)</td>
<td>0.54</td>
<td>0.78</td>
</tr>
<tr>
<td>Female</td>
<td>67 (48)</td>
<td>15 (48)</td>
<td>14 (40)</td>
<td>38 (51)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at exposure †</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), years</td>
<td>15.5 (0.3–40.6)</td>
<td>16.5 (2.5–39.4)</td>
<td>15.0 (3.2–40.6)</td>
<td>14.8 (0.3–33.5)</td>
<td>0.87</td>
<td>0.81</td>
</tr>
<tr>
<td>≥20</td>
<td>106 (76)</td>
<td>25 (81)</td>
<td>28 (80)</td>
<td>53 (72)</td>
<td>0.48</td>
<td>0.34</td>
</tr>
<tr>
<td>≥20</td>
<td>34 (24)</td>
<td>6 (19)</td>
<td>7 (20)</td>
<td>21 (28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis §</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (range), years</td>
<td>72.0 (42.0–94.6)</td>
<td>74.4 (54.8–89.3)</td>
<td>72.4 (485.8–90.7)</td>
<td>71.3 (42.0–94.6)</td>
<td>0.92</td>
<td>0.76</td>
</tr>
<tr>
<td>&lt;72</td>
<td>70 (50)</td>
<td>14 (45)</td>
<td>17 (49)</td>
<td>39 (53)</td>
<td>0.77</td>
<td>0.78</td>
</tr>
<tr>
<td>≥72</td>
<td>70 (50)</td>
<td>17 (55)</td>
<td>18 (51)</td>
<td>35 (47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1985–1994</td>
<td>24 (17)</td>
<td>5 (16)</td>
<td>6 (17)</td>
<td>13 (18)</td>
<td>0.94</td>
<td>0.70</td>
</tr>
<tr>
<td>1995–2004</td>
<td>78 (56)</td>
<td>19 (61)</td>
<td>20 (54)</td>
<td>39 (53)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2005–2013</td>
<td>38 (27)</td>
<td>7 (23)</td>
<td>9 (25)</td>
<td>22 (30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from exposure, years</td>
<td>55.6 (39.7–67.8)</td>
<td>55.6 (39.7–67.5)</td>
<td>55.4 (40.2–89.9)</td>
<td>56.2 (40.0–67.8)</td>
<td>0.88</td>
<td>0.62</td>
</tr>
</tbody>
</table>

†The cut-off values of 1.5 and 3.0 km were chosen according to previous studies. ‡The cut-off point of exposure distance 1.5 km corresponds to an approximate exposure radiation dose of 1 Gy, and 3.0 km corresponds to 0.005 Gy, if exposed outside. §Cut-off value of 20 years was chosen according to previous studies. 2 The cut-off value of 72 years was chosen according to median.
leukemia earlier, within 10 years after the diagnosis of MDS (Fig. 2b,c), although there was no statistical significance. In fact, patients exposed at <1.5 km tended toward a shorter interval from MDS diagnosis to overt leukemia (median, 0.9 years) (Table 3). In contrast, in patients who were exposed at 3.0–10.0 km, the CIR of non-leukemia death was greater than that of progression to overt leukemia (Fig. 2d).

Multivariate Cox regression models revealed that cytogenetic abnormalities, IPSS intermediate/poor karyotype, IPSS INT-2/high category, and IPSS-R cytogenetics INT/poor/very poor risk group were significantly poor prognostic factors on both OS and EFS, but exposure distance was not associated with any outcomes (Tables S1,S2).

**Discussion**

This is the first study evaluating the impact of A-bomb exposure status in terms of clinical characteristics, progression to overt leukemia, and survival of primary MDS that occurred in Nagasaki A-bomb survivors. The major findings in the present study were that “the more proximally exposed to A-bomb (probably exposed to the higher radiation dose)” was associated with developing MDS having a higher risk of cytogenetic abnormalities such as IPSS INT/poor cytogenetic and IPSS-R INT/poor/very poor cytogenetic categories. In particular, abnormal karyotype was observed in 77% of patients exposed at <1.5 km, the rate of which is similar to those of t-MDS exposed to cytotoxic agents. It is well known that the cytogenetic risk categories of currently available prognostic scoring systems for de novo MDS (IPSS and IPSS-R) are highly significant factors for the prognosis of MDS. However, exposure distance was not a statistically significant independent risk factor for the progression of overt leukemia, nor OS, although patients exposed at the more proximal distance tended toward a shorter interval from MDS diagnosis to overt leukemia. It is possible that the number of cases in this study was not large enough to properly reflect the prognostic power of “the distance from the hypocenter”, or the prognostic impact of karyotype might be different between MDS related to A-bomb radiation and general MDS such as de novo and therapy-related.

Although there was no statistically significant difference among exposure distance groups, the present study revealed that OS (Fig. 1a) and EFS (Fig. 1b) were lower in patients...
exposed at <1.5 km than those exposed >1.5 km, in particular at the time of approximately 10 years follow-up. This may reflect in part the difference in the interval from MDS diagnosis to overt leukemia among exposure distance groups (Table 2, Fig. 2), which may be due to the higher frequency of abnormal karyotype and the poorer cytogenetic abnormalities in those exposed at <1.5 km than those in other categories (Table 2).

Few studies have investigated the clinical characteristics of primary MDS after accidental radiation exposure. Recently, Gluzman et al. reported data on MDS among clean-up workers who were exposed to radiation at the Chernobyl nuclear power plant accident during 1986–1987 (exposure dose range, 0.075–0.25 Gy). They diagnosed 23 MDS and five CMML cases based on the WHO classification during 1996–2012, but did not assess the effect of exposure dose on the clinical course. Instead, they reported that 15.2% of AML cases were accompanied with myelodysplasia, contrary to 1.5% in those among the non-exposed population, suggesting that overt AML developed more frequently following preceding MDS among the Chernobyl clean-up workers. This is an important point of view because researchers of the University of Chicago (Chicago, IL, USA) reported approximately 70% patients with t-AML had characteristics of myelodysplasia, regardless of the treatment content. In the present study, we found that 34% of MDS transformed into AML. The rate was greater in those exposed at <3.0 km (40%) than those exposed ≥3.0 km (28%), and the overall CIR-L of MDS was higher in those exposed proximally than those exposed distally (Table 3, Fig. 1c), although the differences were not statistically significant.

Many studies investigated t-MDS after radiotherapy alone. However, its prognostic impact on t-MDS has been controversial. Smith et al. reported 306 patients with t-MDS/t-AML in Chicago, including 28 with t-MDS who underwent radiotherapy alone. They reported that 86% of t-MDS/t-AML patients who underwent radiotherapy alone had

Table 3. Summary of outcomes in patients with myelodysplastic syndromes (MDS) who were exposed to atomic bomb radiation in Nagasaki, grouped by radiation exposure status

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total (n = 140)</th>
<th>Exposure distance</th>
<th>P for difference &lt;1.5 km vs ≥3.0 km</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progression to overt leukemia, n (% of total)</td>
<td>47 (34)</td>
<td>&lt;1.5 km (n = 31)</td>
<td>12 (39)</td>
</tr>
<tr>
<td>Deaths, n (% of total)</td>
<td>106 (76)</td>
<td>1.5–2.99 km (n = 35)</td>
<td>24 (77)</td>
</tr>
<tr>
<td>Cause of death, n (% of deaths)</td>
<td>44 (31)</td>
<td>≥3.0 km (n = 74)</td>
<td>12 (50)</td>
</tr>
<tr>
<td>Leukemia or leukemia-related comorbidities</td>
<td>29 (21)</td>
<td></td>
<td>7 (29)</td>
</tr>
<tr>
<td>MDS or MDS-related comorbidities</td>
<td>33 (24)</td>
<td></td>
<td>5 (21)</td>
</tr>
<tr>
<td>Other diseases</td>
<td></td>
<td></td>
<td>8 (31)</td>
</tr>
<tr>
<td>Time from diagnosis to outcome, years</td>
<td></td>
<td></td>
<td>15 (27)</td>
</tr>
<tr>
<td>To last follow-up, median (range)</td>
<td>3.2 (0.1–21.0)</td>
<td></td>
<td>3.7 (0.2–24.1)</td>
</tr>
<tr>
<td>To overt leukemia, median (range)</td>
<td>1.2 (0.1–11.7)</td>
<td></td>
<td>1.0 (0.1–11.7)</td>
</tr>
<tr>
<td>Probability of outcomes, %</td>
<td></td>
<td></td>
<td>0.7 (0.0–0.8)</td>
</tr>
<tr>
<td>10-year OS† (95% CI)</td>
<td>24.8 (17.1–33.2)</td>
<td></td>
<td>16.1 (4.5–34.1)</td>
</tr>
<tr>
<td>Final OS† (95% CI)</td>
<td>5.0 (1.5–12.1)</td>
<td></td>
<td>0.0 (0.0–0.0)</td>
</tr>
<tr>
<td>10-year EFS§ (95% CI)</td>
<td>23.4 (16.1–31.7)</td>
<td></td>
<td>11.4 (2.2–29.1)</td>
</tr>
<tr>
<td>Final EFS§ (95% CI)</td>
<td>5.2 (1.5–12.3)</td>
<td></td>
<td>0.0 (0.0–0.0)</td>
</tr>
<tr>
<td>5-year CIR-L (95% CI)</td>
<td>29.5 (21.9–37.5)</td>
<td></td>
<td>34.1 (17.5–51.6)</td>
</tr>
<tr>
<td>10-year CIR-L (95% CI)</td>
<td>35.4 (27.0–43.9)</td>
<td></td>
<td>44.4 (23.6–63.4)</td>
</tr>
<tr>
<td>Final CIR-L (95% CI)</td>
<td>37.8 (29.1–46.6)</td>
<td></td>
<td>44.4 (23.6–63.4)</td>
</tr>
</tbody>
</table>

†Overall survival (OS) was censored at the time of death or last follow-up. Event-free survival (EFS) was censored at the time of death, progression to overt leukemia, or last follow-up, whichever occurred first. §Cumulative incidence rate (CIR) was censored at the time of progression to overt leukemia or last follow-up, whichever occurred first, considering death without progression to overt leukemia as a competing event. CI, confidence interval; CIR-L, cumulative incidence rate of leukemia.

Fig. 1. Kaplan–Meier curves for overall survival (OS) (a) and event-free survival (EFS) (b) in three groups of patients with myelodysplastic syndromes who were directly exposed to the Nagasaki atomic bomb, grouped according exposure distance.
chromosome abnormalities and 39% of t-MDS who underwent radiotherapy alone progressed to t-AML. However, they found no significant difference in the clinical course between t-MDS patients who underwent radiotherapy alone and those with de novo MDS. A recent German study reported that, among patients with t-MDS following treatment with radioiodine alone for thyroid diseases, 80% had an abnormal karyotype, 48% were in the higher risk IPSS category (INT-2/high), and 33% of cases had transformed into AML. However, their OS was not different to de novo MDS. A US study also reported that 51% of patients with t-MDS after radiotherapy alone had chromosomal abnormality and the OS rate was poor (38%), but the OS rate was, again, not different from de novo MDS. Taken together, these previous studies suggest that radiation exposure is undoubtedly associated with the development of MDS having unfavorable karyotype, and that the cytogenetic risk, not morphological subclassification nor previous therapy, would determine the clinical course of t-MDS.

The importance of cytogenetic abnormalities on outcome of MDS may lead to the importance of genetic abnormalities themselves in determining the biological and clinical characteristics of either de novo or t-MDS. Somatic mutations of RUNX1, TP53, EZH2, ETV6, ASXL1, and other many genes are identified as being potentially related to pathogenesis of MDS and leukemic transformation. Among those, RUNX1 mutation was already reported to be frequently observed (46%) in MDS patients among A-bomb survivors. The TP53 mutation may be another candidate mutation for radiation-induced MDS, because several studies reported the association with complex chromosomal abnormalities, leukemic transformation, and a worse prognosis. Nevertheless, one by one mutation cannot explain MDS among A-bomb survivors, because more than 70% of those proximally exposed to the A-bomb had extremely complex karyotype (see appendix in our previous report). Ionizing radiation is a known carcinogen and the great sensitivity of the hematopoietic tissue has been reported since the beginning of this century.

Fig. 2. Cumulative incidence rate curves for leukemic transformation (CIR-L) in three groups of patients with myelodysplastic syndromes who were directly exposed to the Nagasaki atomic bomb, grouped according exposure distance (a). CIR-L and cumulative incidence of non-leukemia death in those exposed at <1.5 km (b), 1.5–2.99 km (c), and ≥3.0 km (d).
Chromosomal instabilities due to A-bomb radiation may cause a variety of random genetic and/or epigenetic alterations including driver mutations for MDS, age-related changes on hematopoietic stem cells, and in the bone marrow microenvironment. Ethnic differences between Asian and non-Asian patients were reported in the clinical characteristics of de novo MDS; RA among Asian patients tended to occur at a younger age, and more likely to have severe cytopenia and less cytogenetic aberrations but had better prognosis than non-Asian patients. However, it was difficult to discuss the effect of ethnic differences on the results in our study, because the patients were special in that they were exposed to A-bomb radiation, and age at diagnosis was older than that of the Japanese patients in the previous study. Also, the period of diagnosis in this study (only including those diagnosed after 1985) was different from the previous reports that included those diagnosed since the 1970s. In this regard, further work is needed to extend our results to those in other ethnic groups.

The limitations of this study were that the sample size was too small and clinical data available were insufficient to evaluate the prognostic power of “the distance from the hypocenter”, IPSS, and IPSS-R because of the retrospective study design. Treatment information was not available, either, which may influence the outcomes. Although data of leukemic transformation and deaths were obtained based on databases of cancer registries and ABDI, follow-up information were also insufficient. To overcome these limitations, long-term, prospective observation of the prognosis of MDS, in particular the transformation to AML, are warranted. This is because the most recent incidence analysis of leukemia among A-bomb survivors found that a significant excess incidence rate due to radiation was observed only for AML. Whether the proportion of AML transformed from MDS among A-bomb survivors is increasing or not is our next concern.

In conclusion, this study showed that the greater dose of A-bomb radiation was not directly associated with poor prognosis of MDS, but was associated with developing poor cytogenetic abnormalities in MDS, which might consequently lead to transformation to overt leukemia and the poor prognosis of MDS among survivors. Atomic bomb survivors are unique in terms of developing primary MDS over 40 years after exposure to a wide range of radiation doses, from low to high 4 Gy or greater on the whole body, at one time, directly, and externally. Results of the clinical courses would provide a better understanding for those with t-MDS after radiation therapy alone in clinical practice.

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Disclosure Statement
The authors have no conflict of interest.

Abbreviations
ABDI Atomic Bomb Disease Institute
A-bomb atomic bomb
CI confidence interval
CIR cumulative incidence rate
CIR-L CIR of leukemic transformation
EFS event-free survival
FAB French–American–British
INT intermediate
IPSS International Prognostic Scoring System
IPSS-R revised IPSS
MDS myelodysplastic syndrome
NPCR Nagasaki Prefecture Cancer Registry
OS overall survival
RA refractory anemia
RAEB RA with excess blasts
RAEB-t RAEB in transformation
RARS RA with ringed sideroblasts
RCMD refractory cytopenia with multilineage dysplasia
t-AML therapy-related acute myeloid leukemia
t-MDS therapy-related MDS

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Supporting Information

Additional Supporting Information may be found online in the supporting information tab for this article:

Table S1. Effects of factors on overall survival (OS) as hazard ratios (HRs) in patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, calculated with Cox proportional hazards models. (A) All patients based on the French–American–British (FAB) classification. (B) All patients based on the WHO classification. (C) Patients exposed <1.5 or >3.0 km only.

Table S2. Effects of factors on event-free survival (EFS) as hazard ratios (HRs) in patients with myelodysplastic syndromes who were exposed to atomic bomb radiation in Nagasaki, calculated with Cox proportional hazards models. (A) All patients based on the French–American–British (FAB) classification. (B) All patients based on the WHO classification. (C) Patients exposed <1.5 or >3.0 km only.