Cancer Incidence in C3H Mice Protected from Lethal Total-Body Radiation after Amifostine


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Cancer Incidence in C3H Mice Protected from Lethal Total-Body Radiation after Amifostine

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Amifostine is a potent antioxidant that protects against ionizing radiation effects. In this study, we evaluated the effect of Amifostine administered before total-body irradiation (TBI), at a drug dose that protects against TBI lethality, for potential protection against radiation-induced late effects such as a shortened lifespan and cancer. Three groups of mice were studied: 0 Gy control; 10.8 Gy TBI with Amifostine pretreatment; and 5.4 Gy TBI alone. Animals were monitored for their entire lifespan. The median survival times for mice receiving 0, 5.4 or 10.8 Gy TBI were 706, 460 and 491 days, respectively. Median survival of both irradiated groups was significantly shorter compared to nonirradiated mice (P < 0.0001). Cancer incidence (hematopoietic and solid tumors) was similar between the irradiated groups and was significantly greater than for the 0 Gy controls. The ratio of hematopoietic-to-solid tumors differed among the groups, with the 5.4 Gy group having a higher incidence of hematopoietic neoplasms compared to the 10.8 Gy/Amifostine group (1.8-fold). Solid tumor incidence was greater in the 10.8 Gy/Amifostine group (1.6-fold). There are few mouse lifespan studies for agents that protect against radiation-induced lethality. Mice treated with 10.8 Gy/Amifostine yielded a lower incidence of hematopoietic neoplasms and higher incidence of solid neoplasms. In conclusion, mice protected from lethal TBI have a shortened lifespan, due in large part to cancer incidence after exposure compared to nonexposed controls. Amifostine treatment did protect against radiation-induced hematopoietic tumors, while protection against solid neoplasms was significant but incomplete.

INTRODUCTION

There is currently a significant research effort directed toward identifying means of protecting and/or mitigating the acute effects of ionizing radiation. The existence of nuclear weapons, as well as nuclear reactors used to generate electrical power, have led to concerns about intentional and accidental exposures of large populations to radiation. Developing ways to protect and/or mitigate the early acute effects of radiation is clearly an important objective. Depending on dose and the extent of body coverage, acute radiation effects can range from hematological compromise, skin damage, organ damage to lethality. With respect to radiation-induced lethality, countermeasures presently available require that the agent be administered prior to exposure to provide maximal protection. Such is the case for the only FDA-approved radioprotective drug, Amifostine. When administered prior to TBI in mice, Amifostine is a most effective radioprotector against acute lethality-yielding radiation dose protection factors (radiation dose with protector divided by control radiation dose at 50% survival level) in excess of 2.0 (10, 15, 17, 30). Amifostine (or to be more specific, the active component WR-1065) may provide chemical protection to DNA by either repairing radiation-induced DNA radical formation, directly interacting with hydroxyl radicals prior to damaging DNA, or thiol oxidation leading to tissue hypoxia (20). There are many published studies showing that WR-1065 can reduce both radiation-induced mutations as well as in vitro carcinogenesis (6). While Amifostine is a potent antioxidant and radioprotector, it has toxic side effects when administered to humans, which include nausea and hypotension (8, 19).

In addition to acute radiation sickness, longer term consequences from sublethal doses can result in serious health problems. One such late effect of TBI (or partial-body irradiation) that emerges from nonlethal doses in animals and humans is carcinogenesis (16, 23–25). This prompts the question as to whether an agent that protects against acute effects of radiation, such as lethality, would also protect against radiation-induced late effects, such as carcinogenesis. While this is an important issue, there has been limited research done using Amifostine as a carcinogenic protector. The purpose of the current study was to evaluate Amifostine, a potent antioxidant and...
radioprotector, administered before TBI at a drug dose that protects against TBI lethality, for potential protection against the late effect of carcinogenesis.

MATERIALS AND METHODS

Animals

Female C3H/Hentac-MTV (Taconic Farms, Germantown, NY) mice were used. A special breeding program for mice was initiated to provide mice at 5 weeks of age. The animals were housed in a specific pathogen-free facility and maintained a 12 h light/dark schedule with standard laboratory chow and water *ad libitum*. The study started when the animals were 8–10 weeks of age. Groups of animals received either 5.4 Gy (n = 129) or 10.8 Gy (n = 164) TBI using a Cesium-137 irradiator at a dose rate of 0.90 Gy/min. Animals exposed to 10.8 Gy TBI were pretreated with an i.p. injection of Amifostine (400 mg/kg) (Division of Veterinary Resources Pharmacy, NIH, Bethesda, MD) 30 min prior to exposure. To conserve animals, the 0 Gy control group data was shared between the current study and a previously published study (14). Both studies were conducted at the same time using mice from the same source. At two weeks after TBI, both groups were switched to bacon-flavored chow (Bio-Serv®, Frenchtown, NJ) to maintain continuity of chow used among lifespan studies. Periodic weight assessments were performed approximately monthly after TBI. Animals were carefully monitored a minimum of three times per week for their entire lifespan. The end point for the study was tumor formation (not to exceed 2 cm diameter) or until the animal reached a humane end point (rapid weight loss, debilitating diarrhea, rough hair coat, hunched posture, labored breathing, lethargy, persistent recumbence, jaundice, significantly abnormal neurological signs, bleeding from any orifice, proptosis or abnormal appearance of eyes, impaired mobility or inability to obtain food or water), at which time the animal was euthanized and evaluated for the presence of tumor and cause of death. A comprehensive necropsy examination was performed on each mouse with descriptions of gross lesions, collection of all major organs, tissues and lesions and fixation of pathology materials in 10% buffered neutral formalin. Tissues were processed and stained with H&E. A board-certified veterinary pathologist performed pathological evaluation. Special stains and immunohistochemistry were performed on a subset of animals to clarify the major form of hematopoietic neoplasms. All experiments were conducted under the aegis of a protocol approved by the National Cancer Institute Animal Care and Use Committee and complied with the National Research Council Guide for the Care and Use of Laboratory Animal (2008).

Statistical Analysis

Data were analyzed using WinSTAT® (Microsoft Excel). Overall survival probabilities by age were estimated using the Kaplan-Meier method. The log-rank test (Cox-Mantel) was used to test for significant differences for survival among groups. Cumulative incidence curves by age were calculated for deaths by hematopoietic neoplasm, deaths after nonhematopoietic neoplasm and non-cancer deaths. For mice with both hematopoietic and nonhematopoietic neoplasms, the former was counted as the first event. Differences in cancer subtypes between the two irradiated groups was cancer (Table 1). While there were important differences in cancer subtypes between the two irradiated groups, the overall cancer-related deaths were essentially the same (Table 1). Figure 2 shows a Kaplan-Meier survival curve for both groups of irradiated mice compared to untreated control mice. Both the 5.4 Gy and 10.8 Gy/Amifostine groups exhibited a shortened lifespan compared to nonirradiated controls. Furthermore, median survival times of 460 and 491 days for 5.4 Gy and 10.8 Gy/Amifostine, respectively, were essentially the same.

While the survival curves for both irradiated groups were similar, the latency periods for different cancer types and incidence were different between the two dose groups. Table 1 and Fig. 3A show that Amifostine significantly protected against the emergence and incidence of hematopoietic neoplasms, the former was counted as the first event. Differences in cancer subtypes between the two irradiated groups was cancer (Table 1). While there were important differences in cancer subtypes between the two irradiated groups, the overall cancer-related deaths were essentially the same (Table 1). Figure 2 shows a Kaplan-Meier survival curve for both groups of irradiated mice compared to untreated control mice. Both the 5.4 Gy and 10.8 Gy/Amifostine groups exhibited a shortened lifespan compared to nonirradiated controls. Furthermore, median survival times of 460 and 491 days for 5.4 Gy and 10.8 Gy/Amifostine, respectively, were essentially the same.

RESULTS

Since Amifostine is a very effective agent for protection against radiation-induced lethality after TBI, a pilot study was done to examine the dosing and timing of Amifostine administration in our C3H mouse strain exposed to a range of TBI doses. Figure 1 shows the dose-response survival curve for these mice with and without Amifostine. Amifostine provided complete protection with exposure up to 12 Gy, while there was no survival for ~8.5 Gy exposed animals that did not receive Amifostine. The protection factor at 50% survival was 2.1, which was consistent with values reported elsewhere (30).

Previously published studies from our laboratory used a 3 Gy TBI dose to study lifespan survival/carcinogenesis (14). With Amifostine affording a protection factor of 2.1, a TBI dose of ~6 Gy would not be lethal. To evaluate a lethal dose of radiation with Amifostine treatment, we chose to compare 5.4 Gy to 10.8 Gy with Amifostine treatment (see Fig. 1). Animals that received either 5.4 Gy (n = 129) or 10.8 Gy irradiated with Amifostine (n = 164) tolerated treatment without toxicity or lethality. After irradiation, the animals were monitored for their entire lifespan. The predominant cause of death for animals in both exposure groups was cancer (Table 1). While there were important differences in cancer subtypes between the two irradiated groups, the overall cancer-related deaths were essentially the same (Table 1). Figure 2 shows a Kaplan-Meier survival curve for both groups of irradiated mice compared to untreated control mice. Both the 5.4 Gy and 10.8 Gy/Amifostine groups exhibited a shortened lifespan compared to nonirradiated controls. Furthermore, median survival times of 460 and 491 days for 5.4 Gy and 10.8 Gy/Amifostine, respectively, were essentially the same.

While the survival curves for both irradiated groups were similar, the latency periods for different cancer types and incidence were different between the two dose groups. Table 1 and Fig. 3A show that Amifostine significantly protected against the emergence and incidence of hemato-
poietic neoplasms (predominantly lymphoblastic lymphomas) in the 10.8 Gy/Amifostine group compared to mice the 5.4 Gy group. As shown in Table 2, Amifostine treatment delayed time to 10% hematopoietic neoplasm incidence (252 days for 5.4 Gy vs. 297 days for 10.8 Gy/Amifostine). Furthermore, the incidence of hematopoietic neoplasms at 80 weeks postirradiation was reduced from 47% to 24% for 5.4 Gy and 10.8 Gy/Amifostine, respectively (P < 0.0002). In contrast to the hematopoietic neoplasm results, 10.8 Gy/Amifostine decreased the latency period of tumor development and increased incidence of solid neoplasms compared to 5.4 Gy only (Fig. 3B). The time to 10% solid neoplasm incidence was 356 days for 10.8 Gy/Amifostine and 426 days for 5.4 Gy (Table 2). The incidence of nonhematopoietic neoplasms at 100 weeks postirradiation was increased from 38% to 59% for 5.4 Gy and 10.8/Gy Amifostine, respectively (P < 0.002). There was no significant difference in non-cancer deaths between the 5.4 Gy and 10.8 Gy/Amifostine groups (Fig. 3C).

With respect to tumor types, Table 3 shows a comparison of the 5.4 Gy and 10.8 Gy/Amifostine groups based on cause of death. Forty-five hematopoietic neoplasms were observed in the 5.4 Gy group and 28 in the 10.8 Gy/Amifostine group (corrected for the number of animals in each group). For solid neoplasms, the numbers were approximately reversed; there were 55 solid neoplasms in the 5.4 Gy group and 102 in the 10.8 Gy/Amifostine group. The number of deaths due to non-cancer-related causes was essentially the same between the two groups. The distribution of neoplasms was different between the two groups. In particular, specific types of hematopoietic neoplasms were significantly altered by Amifostine administration. The incidence of lymphoblastic lymphomas, which were dominant in the 5.4 Gy group (26% incidence), was markedly reduced in the 10.8 Gy/Amifostine group (0.62% incidence) (P < 0.0001). In contrast, diffuse large cell lymphomas were slightly elevated in the 10.8 Gy/Amifostine group compared to the 5.4 Gy group (8.7% vs. 2.5%, respectively) (P < 0.03). For deaths due to solid neoplasms, a difference was observed for Harderian gland adenocarcinomas, with 3.9% in the 5.4 Gy group and 10.8% in the 10.8 Gy/Amifostine group (P < 0.04). While overall deaths from the other solid tumors were not significantly different between the 5.4 Gy and 10.8 Gy/Amifostine groups, the total number of solid tumor deaths was significantly different between the two groups (Table 1).

**DISCUSSION**

When Amifostine (WR-2721) is administered to animals, it undergoes dephosphorylation to yield WR-1065, the active aminothiol that provides protection against radiation (26, 27). *In vitro* WR-1065 has been shown to protect against radiation-induced HGPRT mutation (5), neoplastic transformation (6) and genomic instability (3), providing evidence that WR-1065 might be effective against radiation-induced cancer in *vivo*. This possibility was in fact supported by studies where Amifostine was administered 30 min prior to high-dose irradiation (34–57 Gy) to the leg of mice (13). Eighty-seven percent of mice developed solid tumors (predominantly sarcomas) in the leg after irradiation alone versus 26% in the irradiated/Amifostine-treated mice.

![FIG. 2. Kaplan-Meier survival plot of 5.4 Gy alone or 10.8 Gy/Amifostine pretreatment animals was shortened compared to nonirradiated controls. Survival of 5.4 Gy and 10.8 Gy animals were not significantly different.](image-url)

**TABLE 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of animals</th>
<th>Median survival in days (range)</th>
<th>No. of neoplasm (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of solid (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of HN&lt;sup&gt;a&lt;/sup&gt;</th>
<th>No. of benign&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control&lt;sup&gt;b&lt;/sup&gt;</td>
<td>93</td>
<td>706 (680–63)</td>
<td>74 (80)</td>
<td>39 (7.2)</td>
<td>11</td>
<td>46</td>
</tr>
<tr>
<td>5.4 Gy&lt;sup&gt;c&lt;/sup&gt;</td>
<td>129</td>
<td>460 (425–507)</td>
<td>124 (96)</td>
<td>45 (14)</td>
<td>44</td>
<td>52</td>
</tr>
<tr>
<td>10.8 Gy/Amifostine&lt;sup&gt;d&lt;/sup&gt;</td>
<td>164</td>
<td>491 (430–512)</td>
<td>160 (98)</td>
<td>58 (20.9)</td>
<td>22</td>
<td>65</td>
</tr>
</tbody>
</table>

*Notes. Solid neoplasms: (1) vs. (2), nonsignificant; (1) vs. (3) and (2) vs. (3), P < 0.005; hematopoietic neoplasm (HN): (1) vs. (2) vs. (3), P < 0.001; (2) vs. (3), P < 0.01; benign: (1) vs. (2) nonsignificant; (1) vs. (3), P < 0.001; (2) vs. (3), P < 0.02. Note: Data from Mitchell et al. (14).<sup>a</sup> Percentage of animals with cancers. <sup>b</sup> Number of tumors corrected for the number of animals in each group. <sup>d</sup> Percentage of animals with metastasis.
This group conducted a second study where the leg of tumor-bearing mice was exposed to doses ranging from 20–70 Gy with and without Amifostine pretreatment. In this study, Amifostine provided a protection factor of 1.75 with respect to induced sarcomas. The studies described above used local exposure, which does have a different cancer induction profile than that of TBI (no hematopoietic tumors).

In regards to TBI, Grdina et al. evaluated the lifespan of male and female B6CF1 mice irradiated with and without Amifostine treatment. The X-ray dose was 206 cGy and the neutron dose was 10 cGy (the RBE for neutrons is 20, thus the equivalent dose in X rays would be 200 cGy). For X-ray dose at the 50% survival level, Amifostine did not provide significant protection for male mice, but ~10% protection for female mice. For neutron exposure at the 50% survival level, Amifostine did not afford significant protection for either male or female mice. In this study, it was reported that the majority of deaths in all the groups was due to carcinogenesis; however, no pathological data were presented. This finding is in relative agreement with the study of Maisin et al., who found that radioprotective agents offered little survival advantage for radiation doses <3.5 Gy.

In an extensive series of studies, Maisin et al. evaluated a mixture of radioprotectors [glutathione; 2-beta-aminoethylisothiouronium-Br-HBr; serotonin-creatine sulfate; cysteine; mercaptopoethylamine (henceforth known as: GASCM)] using a wide range of radiation doses with respect to lifespan survival of two different mouse strains coupled with extensive pathology to identify the causes of death, in particular, different types of cancer. GASCM provided protection factors for acute radiation effects comparable to Amifostine in mice, although there was appreciable toxicity of the mixture. Findings from the study included; 1. The effectiveness of GASCM radioprotection was dependent on the strain of mice, and radiation dose level; 2. Life shortening of mice after <3.5 Gy TBI was not significantly modified by GASCM treatment; and 3. For >5 Gy TBI, GASCM provided significant protection against life shortening. After exposure to doses of 4–7 Gy, the primary cause of death was cancer, with thymic lymphomas (female) and leukemia (males) representing the dominant cancers. GASCM combined with radiation primarily reduced the incidence of lymphomas and leukemias as opposed to solid tumors.

In the current study, a lethal 10.8 Gy dose was used (with Amifostine) and thus, there was no control for this radiation dose. With the combined treatments of Amifostine and 10.8 Gy, all animals treated (164 total) survived and had similar survival to that of the animals that received 5.4 Gy alone. However, temporal cancer incidence and pathology differed between the two groups. While there was no difference in the emergence of hematopoietic neoplasms in either group, the incidence of hematopoietic neoplasms was significantly reduced in the 10.8 Gy/Amifostine group compared to the 5.4 Gy group (24% vs. 48%, at ~80 weeks post-TBI). For solid neoplasms, the 10.8 Gy/Amifostine group exhibited a significantly higher
incidence (21%) compared to the 5.4 Gy alone group. Further, solid neoplasms in the 10.8 Gy/Amifostine group emerged faster than was seen for mice receiving 5.4 Gy. For the hematopoietic neoplasms, the results of the current study agree with Maisin et al., as discussed above, despite the use of different radioprotectors and use of different mouse strains. However, there was a sharp difference for solid neoplasms, since Maisin et al. showed little protective effect on solid neoplasm induction by GASCM. While the reduction in hematopoietic neoplasms seen with the 10.8 Gy/Amifostine group should have translated into a survival advantage, this increased survival was not found (Fig. 1). Figure 3 shows that there was a compensatory increase in solid tumors (mainly carcinomas; Table 4) and thus, no decrease in life shortening compared to the 5.4 Gy alone group. It is interesting that a sub-analysis of the types of solid tumors found after 10.8 Gy/Amifostine indicated that sarcoma induction was strongly reduced with Amifostine administration (Table 4). Since Suit et al. demonstrated that increasing radiation dose leads to increasing solid tumor induction, we assumed a twofold increase in radiation dose would induce a twofold increase in solid tumors (21). Given that there were as many sarcomas in the 10.8/Amifostine group as in the 5.4 Gy group, this would suggest a protection factor of 2. Hunter et al. showed a protection factor of 1.75 with Amifostine for high radiation dose to local tumor induction in the leg, in which the predominate tumors induced were sarcomas (7). The protection factor for carcinomas was observed to be less (though still very good), as there were more carcinomas found in the 10.8 Gy/Amifostine group compared to the 5.4 Gy group (Table 4). A possible reason for this discrepancy, apart from the use of different radioprotectors and mice, could reside in pharmacological and physiological differences between Amifostine and the GASCM mixture.

Yuhas et al. studied the pharmacology of Amifostine in a variety of tissues (28). Amifostine levels rapidly
TABLE 4

Analysis of Amifostine on Solid Tumor Carcinogenesis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tissue/tumor^a</th>
<th>Total</th>
<th>Observed</th>
<th>Expected</th>
<th>P value^b</th>
<th>Protection factor^c</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.4 Gy</td>
<td>Sarcoma, total</td>
<td>129</td>
<td>49</td>
<td>53</td>
<td>0.36</td>
<td>1.94</td>
</tr>
<tr>
<td>10.8 Gy/Amifostine</td>
<td></td>
<td>164</td>
<td>71</td>
<td>67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4 Gy</td>
<td>Sarcoma, deaths</td>
<td>129</td>
<td>18</td>
<td>19</td>
<td>0.76</td>
<td>1.96</td>
</tr>
<tr>
<td>10.8 Gy/Amifostine</td>
<td></td>
<td>164</td>
<td>25</td>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4 Gy</td>
<td>Carcinoma, total</td>
<td>129</td>
<td>45</td>
<td>63</td>
<td>1.5E–5</td>
<td>1.78</td>
</tr>
<tr>
<td>10.8 Gy/Amifostine</td>
<td></td>
<td>164</td>
<td>99</td>
<td>81</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4 Gy</td>
<td>Carcinoma, deaths</td>
<td>129</td>
<td>16</td>
<td>25</td>
<td>0.0068</td>
<td>1.72</td>
</tr>
<tr>
<td>10.8 Gy/Amifostine</td>
<td></td>
<td>164</td>
<td>41</td>
<td>32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.4 Gy</td>
<td>Liver, adenomas, total</td>
<td>127</td>
<td>25</td>
<td>43</td>
<td>8.8E–6</td>
<td>1.68</td>
</tr>
<tr>
<td>10.8 Gy/Amifostine</td>
<td></td>
<td>164</td>
<td>73</td>
<td>55</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a Total tumors included all tumors of a specific type identified by pathological analysis. Tumors determined to be the cause of death of the animal were used for the deaths analyses.

^b Data analyzed using Chi-square statistics.

^c Protection factor = [2 minus (observed minus expected/expected)]. A protection factor of 2 was assumed based on the acute protection with Amifostine.

increased in most normal tissues compared to tumor after injection, and the levels plateaued in approximately 10–15 min (28). Bone marrow was not evaluated for Amifostine uptake in these studies, but other studies did examine radiolabeled Amifostine pharmacology in bone marrow and skin, where the distribution of the drug was found to be heterogeneous (29). Interestingly, the bone marrow, skin, thymus and liver are normal tissues that reside in lower oxygen tensions than most other normal tissues (2). Aminothiols such as Amifostine are known to induce hypoxia when administered to animals (1, 22), thus, the protective effect of Amifostine on hematopoietic neoplasms could have resulted in part from bone marrow hypoxia. Recently reported studies suggest that lymphoma formation after TBI may be suppressed by hematopoietic stem/progenitor cells (HPSC), which originate from the bone marrow and can populate the thymus (9). After TBI, the HPSC cells are reduced in both the thymus and bone marrow and thus, B- and T-cells in the thymus, which are initiated to become tumorigenic, are potentially the source of radiation-induced lymphomas observed in our study, as well as other studies (9). The ability of Amifostine to protect the bone marrow and the HPSC cells (by whatever mechanism) may allow for the movement of the lymphoma-suppressing HPSC cells into the thymus, thus preventing or reducing lymphoma formation. The 10.8 Gy/Amifostine group had higher levels of solid neoplasms, possibly because high levels of Amifostine in tissues did not necessarily translate to significant protection in specific tissues (18). Thus, these tissues could have received a radiation dose that was higher than 5.4 Gy, increasing the probability for enhanced solid tumor induction and shorter latency period. This is only speculative and warrants further study.

In summary, the results of the current study show that Amifostine protected 10.8 Gy irradiated mice from lethality; however, these animals experienced radiation-induced life shortening and cancer induction similar to 5.4 Gy irradiated mice. The distribution of hematopoietic and solid neoplasms differed between the two groups. This is an important finding in consideration of first responders who must enter high-radiation zones, and who should be informed about protections that may be available to avoid lethality, while understanding there would still be an elevated risk for cancer induction. This means that close medical surveillance should be exercised to detect neoplasms early on, when there are several effective treatment options available. This study underscores the importance that during the development of new radioprotective countermeasures, late effects including carcinogenesis should be considered, as well as acute effects.

INNOVATION

Countermeasures for accidental or intentional radiation exposure are necessary because of the widespread use of nuclear power and weapons. Antioxidants such as Amifostine protect against TBI-induced lethality, but few studies have addressed long-term survival. Compared to nonirradiated controls, animals spared radiation-induced lethality by Amifostine nevertheless had a shortened lifespan and increased carcinogenesis, suggesting the necessity of enhanced cancer surveillance after radiation exposure to detect cancers earlier when treatment options are more effective.

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