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Minimally Invasive vs. Radical Hysterectomy in Cervical Cancer

BY MARY BROPHY MARCUS

The unexpected results of two new studies have "dealt a great blow" to the standard of care for patients who undergo surgery for early cervical cancer, according to an editorial in *The New England Journal of Medicine*.

Both studies were published in the same November 2018 issue and presented at a medical meeting earlier this year.

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Study One Details

The first, a phase III trial involving more than 600 early-stage cervical cancer patients, compared minimally invasive (laparoscopic or robotic) radical hysterectomy to open radical hysterectomy (*N Engl J Med* 2018;379:1895-1904).

Both operations involve taking out the uterus and surrounding structures. Open sur-

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Leukemia Risks Associated With Childhood Exposure to Radiation

BY RICHARD SIMONEAUX

Exposure to moderate or high doses of ionizing radiation (i.e., greater than 500 millisieverts (mSv)), especially in childhood, is a well-documented risk factor for several myeloid-based malignancies, such as acute myeloid leukemia (AML), chronic myeloid leukemia (CML) and, to some degree, acute lymphoblastic leukemia (ALL). However, the risks associated with exposure to low doses of ionizing radiation (i.e., less than 100 mSv), which is relevant for the majority of people, remain largely unstudied.

CME/CNE Article

To address these knowledge gaps, a large international retrospective study was undertaken to assess the risks for leukemia associated with active bone marrow (ABM) exposures to low levels of radiation during childhood (under 21 years of age). One of the participating researchers in this study was Mark P. Little, DPhil, a senior investigator in the Division of Cancer Epidemiology & Genetics of the Radiation Epidemiology Branch within the NCI. The results

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Human Blood Cells Can Directly Reprogram to Neural Stem Cell

Scientists from the German Cancer Research Center (DKFZ) and the stem cell institute HI-STEM in Heidelberg have succeeded for the first time in directly reprogramming human blood cells into a previously unknown type of neural stem cell. These induced stem cells are similar to those that occur during the early embryonic development of the central nervous system. They can be modified and multiplied indefinitely in the culture dish and can represent an important basis for the development of regenerative therapies.

Stem cells are considered to be the all-rounders of our tissues: they can multiply indefinitely and then—if they are pluripotent embryonic stem cells—generate all conceivable cell types. In 2006, the Japanese scientist Shinya Yamanaka, MD, PhD, recognized that such cells could also be produced in the laboratory—from mature body cells. Four genetic factors alone are sufficient to reverse the course of development and produce so-called induced pluripotent stem cells (iPS) that have identical properties to embryonic stem cells. Yamanaka was awarded the Nobel Prize for Medicine in 2012 for this discovery.

"This was a major breakthrough for stem cell research," said Andreas Trumpp, PhD, German Cancer Research Center (DKFZ) and Director of HI-STEM in Heidelberg. "This applies in particular to for research in Germany, where the generation of human embryonic stem cells is not permitted. Stem cells have enormous potential both for basic research and for the development of regenerative therapies that aim to restore diseased tissue in

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from this large study were recently published (*Lancet Haematol* 2018;5:e346–e358).

"The evidence suggests that there is a risk of leukemia associated with low-level exposure to radiation, possibly down to near background levels (20 mSv cumulative), particularly in childhood," Little stated.

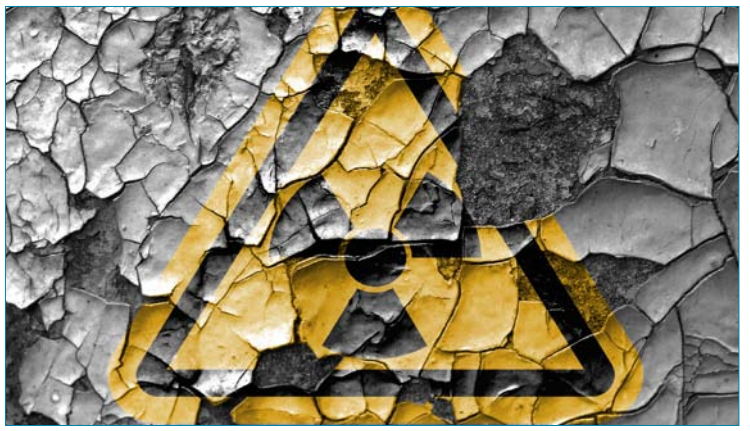
Methodology

For this collection of historical prospective studies, analyses utilized patients who had received mean cumulative ABM radiation exposures of more than 5 mSv, with first dose prior to 21 years of age; individual cohorts consisted of patients from studies with at least five cases of leukemia or other myeloid malignancy.

The malignancies included in this analysis were AML with or without myelodysplastic syndromes (MDS); CML; other myeloid neoplasms (e.g., myeloproliferative neoplasm); ALL; and other unspecified leukemias (other than chronic lymphocytic leukemia (CLL), which is currently considered a non-Hodgkin lymphoma).

Some older endpoint groupings (acute leukemia, leukemia excluding CLL) were also used for comparability with results of older studies. A minimum cutoff of five cases was utilized because cohorts with fewer than that number of malignancies would most likely be uninformative in cohort-stratified specific subtype analyses.

Importantly, lymphomas, including CLL, and multiple myeloma were not included in these analyses, because of evidence that suggests these diseases have low sensitivity to radiation-mediated induction (United Nations Scientific Committee on the Effects of Atomic Radiation, UNSCEAR 2006 Report). In addition, any studies having patients who were being treated for malignant disease were excluded, since chemotherapy had the potential to be a strong confounder, and



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because of the potential for bone marrow ablation. Studies with inadequate dosimetry data were excluded; cumulative ABM dose estimates were required for each participant. Participants were also excluded if radiation exposure was due to internally deposited radionuclides.

Although there were 10 cohorts that met the eligibility criteria, only nine were utilized in the final analysis, as one of these, the Israeli tinea capitis cohort, had no patients with ABM exposures of less than 100 mSv. The nine cohorts of patients included in the final analysis were the following:

- Massachusetts tuberculosis fluoroscopy cohort (those patients first treated with radiation before 21 years of age);
- Canadian tuberculosis fluoroscopy cohort (those patients first treated with radiation before 21 years of age and, if unexposed, those younger than 21 years of age at first admission to a treatment institution);
- French hemangioma cohort;
- Göteborg hemangioma cohort;
- Stockholm hemangioma cohort;
- Japanese atomic bomb survivor Life Span Study (LSS) cohort (those who had radiation exposure before 20 years of age);
- Rochester thymus enlargement cohort;
- US scoliosis cohort (those who had first radiation exposure before 21 years of age); and
- UK-NCI CT cohort (those who had first radiation exposure before 21 years of age).

There were four cohorts which had no specified upper exposure age limit; in these instances, the whole cohort was used. However, these participants generally had first and last radiation exposures before 21 years of age. It is also interesting to note that, eight of the nine cohorts consisted of medically-exposed patients; the lone exception was the LSS cohort, the Japanese atomic bomb survivors. For the purposes of this study, analyses were limited to those cohort members who had received mean cumulative ABM doses of less than 100 mSv.

When asked about the methodologies utilized to determine the patients' radiation exposures, Little replied, "Cumulative doses averaged over the whole-body ABM were calculated for each participant in the cohorts, in accordance with methods described in the appendix to our article.

"Several different methods were used in the component cohorts, but most were based on medical record abstraction of the original treatments (including descriptions of treatments received) and relevant patient data, except the Japanese atomic bomb survivor LSS cohort; for the Massachusetts tuberculosis, Canadian tuberculosis, LSS, US spinal curvature, and UK-NCI CT cohorts, Monte Carlo-simulated dosimetry was used, but for all other cohorts, a method based on physical measurements was used to estimate doses," he added.

Study Results

A total of 262,573 people was included in the nine cohorts utilized in these analyses. Participants had ABM radiation exposures ranging from 0–100 mSv before 21 years of age and had an accumulated 5,154,464 person-years of follow-up.

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Learning Objectives for This Month's CME/CNE Activity:

After participating in this CME/CNE activity, readers should be better able to: 1. Summarize the purpose and methodology of this study on leukemia risks associated with childhood exposure to low-doses of ionizing radiation. 2. Analyze the results of this study and the implications for future research

Disclosure: The author(s), faculty, staff, and planners, including spouses/partners (if any), in any position to control the content of this activity have disclosed that they have no financial relationships with, or financial interests in, any commercial companies relevant to this educational activity.

RADIATION

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Enrollment spanned almost 90 years, from June 4, 1915, to Dec. 31, 2004, with a mean follow-up period of 19.63 years. Among those exposed to radiation, 50.54 percent were male and the mean cumulative ABM dose, when weighted by person-years, was 19.6 mSv, with cohorts having mean values ranging from 10.2 to 52.0 mSv. The mean age at first exposure across all cohorts was 8.85 years, with the cohort means ranging from 0.11-18.16 years.

There was a total of 154 myeloid malignancies and 40 cases of ALL. The myeloid malignancies included the following: AML–79 cases, CML–36 cases; MDS–8 cases, and unspecified myeloid malignancies–31 cases. Grouped categories, which were utilized for comparisons, included 139 cases of acute leukemia and 221 overall cases of leukemia (excluding CLL).

For AML and MDS combined, the fitted relative risk at 100 mSv was 3.09 (95% CI: 1.41–5.92), while for AML alone, this value was 2.56 (95% CI: 1.09–5.06). The fitted relative risk for ALL at 100 mSv was 5.66 (95% CI: 1.35–19.71). However, for CML, there was no clear dose-response; the relative risk at 100 mSv was 0.36 (95% CI: 0.00–2.36). At 100 mSv, the excess absolute risks were in the range of 0.1–0.4 cases or deaths per 10,000 person-years.

Regarding the trends noted between different cohorts, Little stated, "There was little indication of non-linearity in dose response or between-cohort heterogeneity, particularly between the medically exposed groups and the Japanese survivors of the atomic bombs. Collectively, they showed a linear dose response, even at low doses."

Discussion

When asked what lessons were learned in this study, Little replied, "Evidence from this study suggests that there is significant risk of leukemia and other myeloid malignancies even at low doses of radiation. We observed more than two-fold increased risk, and higher, for cumulative exposures less than 100 mSv; excess risk was also apparent for cumulative doses of less than 20 mSv for some endpoints."

He further noted, "These malignancies are rare in the general population, and the excess absolute risk is estimated to be small. However, since low-dose exposure is the most common in the general population, primarily from medical procedures like computed tomography scans, the results of this study suggest that current protocols are appropriately prudent and that every effort should be made to minimize doses, especially for children.

"The strengths of the present study include the large number of cases exposed at low doses, long follow-up periods, the historical cohort designs used throughout, the carefully documented exposure (individual estimates for dose to ABM), and relative homogeneity of risk across cohorts. We considered a number of limitations to our study and what effect they may have had on the results, and in the end, we concluded that these limitations did not significantly alter our risk estimates."

Concerning one of the study limitations, Little observed, "There is heterogeneity in the dose reconstruction methods used in the nine cohorts; heterogeneity is likely to be found in disease-coding within a study or across countries over time. Nevertheless, there was little evidence of heterogeneity in aggregate: the variation in baseline risks between cohorts was modest, even when statistically significant.

"Related to this," he added, "the mixture of mortality and incidence data could complicate interpretation of the findings, particularly the estimates of excess absolute risk. However, since we have considered primarily relative risk models and can reasonably assume that within a given stratum (defined by cohort, age, calendar year, and sex), a fixed proportion of participants with leukemia would die from the disease, regardless of the dose they received (i.e., lethality does not depend on dose), one would not expect the relative risk at 100 mSv to differ appreciably in mortality relative to incidence.

"We also considered the potential effects of selection and survival bias, however, neither the process by which we chose the nine cohorts for study nor the limitation within each cohort to those receiving doses of less than 100 mSv should have introduced bias," Little commented.

In closing, Little stated, "Since most exposures to workers and the public are from low doses of radiation, the present study, among others, suggests that the current system of radiological protection is prudent and not overly protective. The findings of the present study also support efforts already underway to minimize the use of diagnostic radiological imaging, particularly in children, wherever possible." OT

Richard Simoneaux is a contributing writer.

CANCER CARE DISPARITIES

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misconceptions, lack of money, language issues, lack of transportation, fear, and stigma and cultural mistrust, some lingering from historic trials such as the infamous Tuskegee syphilis experiment.

"We need to educate people on clinical trials today," said Shonta Chambers. "We need a new narrative," she added, to combat the lingering stigma surrounding memories of misguided trials such as Tuskegee. Natalie Dickson, MD, Chief Medical Officer for Tennessee Oncology, PLLC, agreed. All cancer patients, including the underserved, need to know that clinical trials represent "an opportunity to get cutting-edge care," she said.

Dana Dornsife, Chairman of the Board and Founder of Lazarex Cancer Foundation, described losing her brother-in-law to pancreatic cancer and forming the Lazarex Foundation with a mission to remove these clinical trial enrollment barriers. In 2006 Dornsife founded the nonprofit to improve the outcome of cancer care for advanced stage cancer patients and the medically underserved by identifying FDA-approved clinical trial options, providing help with ancillary out-of-pocket costs for trial participation and community outreach.

Dornsife said the foundation has supported more than 4,000 patients in need over the past 12 years. She described the foundation's IMPACT (Improving Patient Access to Cancer Clinical Trials) program, which had its beginnings in a partnership with Massachusetts General Hospital called the Lazarex MGH Cancer Care Equity Program.

"We achieved a 29 percent increase in overall participation and doubled minority participation in cancer clinical trials," according to information from the foundation. That effort has been expanded into IMPACT, a 3-year pilot study that will ultimately be rolled out in eight Comprehensive Cancer Centers.

In a related development, the NCI recently revised its clinical trial protocol template to broaden eligibility for cancer clinical trials, a move heralded by ASCO and the Friends of Cancer Research (FOCR). The revisions, which may help to improve trial participation by minorities and the underserved, broaden eligibility in selected trials to patients with brain metastases, HIV/AIDS, chronic hepatitis B, a history of hepatitis C, organ dysfunction, and prior and concurrent malignancies. Both ASCO and the FOCR, working with the FDA, had suggested these revisions through a collaborative effort that began in 2016.

William "Billy" Foster, a jazz musician, elementary school music educator, composer, and radio host who is African-American, described his 6-year participation in a clinical trial and living as a survivor of metastatic kidney cancer for more than 20 years.

He said of clinical trials, "A lot of African-Americans mistrust the system." He noted that his effective cancer care has allowed him to remain actively employed for more than 40 years; his band now performs at cancer events. Foster, who is active with the Kidney Cancer Association and has spoken on panels for the Kidney Cancer Research Program and the City of Hope Cancer Center, said he is dedicated to equitable cancer care for all: "Everyone deserves equal access to good health care. I'm here to bring some understanding to why this isn't currently the case and to help find solutions to these inequities. I believe that with the efforts of all, we can provide the underserved with accessible, quality health care." OT

Peggy Eastman is a contributing writer.