Can Cancer Be Treated with Low Doses of Radiation?

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ABSTRACT

Strong sources of radiation became available in the 1950s. Since then, intense ionizing beams have been employed against cancer to destroy or shrink tumors. Today, nearly all radiation treatments for cancer apply high doses to local regions of the body.

It is generally believed that radiation in any amount will only damage cells and that the mutated cells could become cancers. However, a large amount of research over the past century on the effects of low doses of ionizing radiation on biological organisms has shown beneficial health effects, called hormesis. Moreover, there is considerable evidence that total or half-body low-dose irradiation may cure cancer or significantly delay its progression, leading to a reduction in cancer mortality without symptomatic side effects.

This paper reviews reports of successful applications of low-dose irradiation (LDI) for cancer therapy and urges physicians to carry out controlled clinical studies.

Historical Background

Beneficial health effects following low doses of ionizing radiation have been observed for more than a century.[1] The first therapeutic application reported the disappearance of inflammatory symptoms following treatment. Hazards of skin damage, bone marrow damage, and malignancy following high doses were also noted early on.

The Standard Chemical Company began producing radium at the end of 1912, and in 1913 the journal *Radium* was established in which physicians could record the results of the treatments of many diseases through internal or external applications.[2] The American Medical Association endorsed radium as a medication in 1915, and physicians treated hundreds of patients orally and intravenously with radium until the early 1930s.

More than 400,000 bottles of radium water were sold over the counter and by mail to the public during the 1920s, as an elixir. This practice was stopped in 1932 following a well-publicized case of a large overdose. A recent historical review by Berk and Hodes shows clearly that Roentgen therapy was used extensively and successfully for the treatment of many types of infections before the advent of antibiotics.[3]

Kelly and Dowell reviewed the low-dose radiation treatment of 364 cases of gas gangrene infection from 1928 to 1940. Several doses of X-rays (50 or 75 rad), applied locally, reduced mortality from approximately 50 percent with amputation to 5 percent without amputation.[4] Nevertheless, such applications fell into disrepute following the incorrect association of these treatments with homeopathy.[1]

Fear of radiation was generated by use of the atomic bomb in World War II and the subsequent development, testing, and stockpiling of very large numbers of nuclear weapons. Scientists who wanted to stop further weapons testing promoted fear of low-dose radiation. The linear no-threshold model of radiation carcinogenesis–the LNT model–that had been debated in the 1950s was adopted by regulators to protect people from avoidable exposures to radiation.

In the 1950s, strong sources of cobalt-60 gamma radiation became available and were used in cancer treatment. Physicians can destroy or shrink a deep-seated tumor by exposing it to an intense beam of ionizing radiation from an external source. The tumor is exposed from different directions to deliver a high dose to tumor cells while minimizing the dose to the surrounding healthy tissue. Normal tissue is able to recover from this injury because of less sensitivity to radiation than rapidly dividing cells and natural cell repair and replacement mechanisms.

In the 1970s, particle accelerators became available. These are used in a similar way to deliver high doses of radiation to tumor cells. Many sources and methods of radiation therapy are now used in cancer treatment, and nearly all employ localized high doses.

Because of unfortunate historical developments, personality conflicts, and scientific criticism in the 1930s and 1940s, the low-dose treatments with radiation hormesis fell out of favor.[5] As a result, most physicians are not aware of the large amount of research that has been carried out over the past century on the effects of low doses of ionizing radiation on biological organisms, especially the beneficial hormetic effects observed following exposures to such doses. Not having been taught otherwise, nor having researched the issue for themselves, they believe that radiation in any amount will only damage cells, and that the resulting mutated cells could become cancers. However, there is considerable evidence that total or half-body LDI (TBI or HBI) shrinks cancers or significantly delays cancer progression, leading to a reduction in cancer mortality without symptomatic side effects.

Though current cancer treatments have good results in many cases, major international efforts are underway to improve our understanding of cancer and to develop better treatments. It is therefore important to examine the evidence of the effects of LDI and its potential effectiveness for various types of cancer. LDI therapy might, for example, be particularly advantageous for the treatment of prostate cancer as well as breast cancer.

Low-Dose Irradiation Therapy

Intensive, wide-ranging research has been carried out on the effects of radiation on living organisms, including humans.[6-9] Generally, cellular stimulatory effects are observed following low doses–short-term exposures in the range 0.01-0.50 Gy (1 - 50 rad)–while damaging or lethal cellular effects are observed following high doses. This biphasic radiation dose response is known as radiation hormesis, an adaptive response of biological organisms to low levels of stress or damage–a modest overcompensation to a disruption–resulting in improved fitness.[10, 11]

"The hormetic model is not an exception to the rule–it is the rule."[12]

Recent discoveries indicate that oxidative DNA damage occurs naturally to living cells at an enormous rate. Survival to old age depends on the performance of a very capable damage-control biosystem, which prevents, repairs, or removes almost all the DNA alterations.[13, 14]

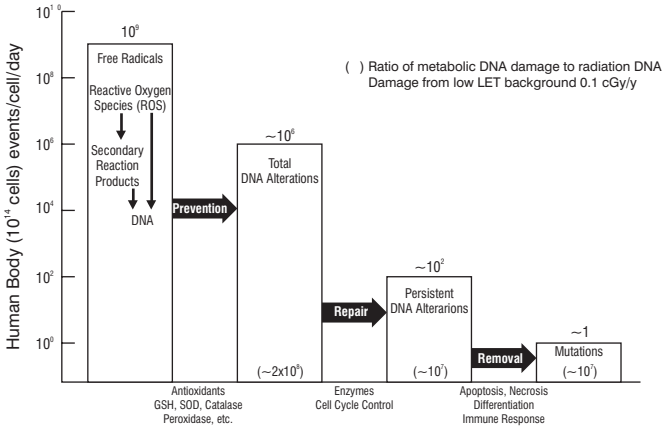

Figure 1. Antimutagenic DNA Damage-Control Biosystem[15]

Figure 1 illustrates the very powerful antimutagenic performance of this biosystem.[15] Those DNA alterations not eliminated by this protective system are residual mutations, a very small fraction of which eventually develops into cancer. As indicated in Figure 1, the rate of DNA mutations caused directly by background radiation compared to the rate produced by endogenous oxygen metabolism is extremely small; nevertheless, radiation has a very important effect on the damage-control biosystem.

While high doses decrease biosystem activity, causing increased cancer mortality, low doses stimulate biosystem activity causing lower-than-normal cancer mortality. Stimulation of the immune system increases the attack and killing of cancer cells globally. These stimulatory effects reduce or delay significantly the incidence of cancers due to oxidative DNA damage or other causes.

The dose-response relationship of the changes in different cell types of the immune system after whole-body irradiation has been analyzed on the basis of measured systemic data and recent reports in the literature.[16] For T lymphocytes, J or inverted J-shaped curves are usually observed after irradiation. For macrophages, dose-response curves of chiefly stimulation with irregular patterns are often observed. The intercellular reactions between the antigen presenting cells and T lymphocytes in the immunological synapse, via expression of surface molecules and secretion of cytokines by the two cell types after different doses of radiation, have been studied. The different pathways of signal transduction thus facilitated in the T lymphocytes by different doses of radiation have been analyzed to explain the mechanism of the phenomenon of low-dose stimulation and high-dose suppression of immunity. LDI has been shown to retard tumor growth, reduce metastases, increase the efficacy of conventional radiotherapy and chemotherapy, and alleviate the suppression of immunity caused by tumor burden.[16]

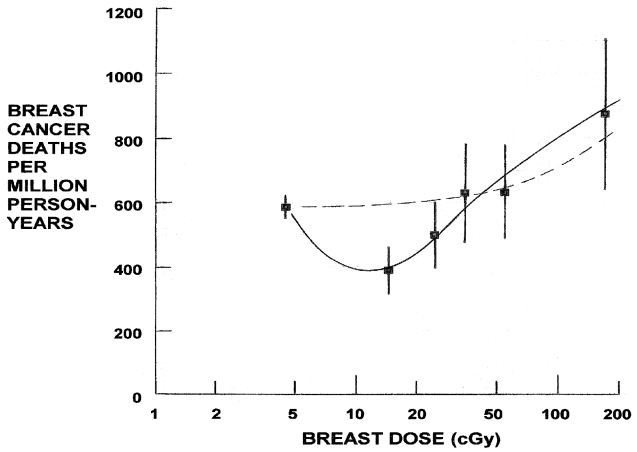

Figure 2. Reduced Breast Cancer Mortality for Tuberculosis Patients Who Received LDI During Fluoroscopy. Data from Miller et al.[18]

There is considerable evidence of hormetic effects of radiation exposure on cancer.[17] Figure 2 is a semi-log graph of data from of a study of a cohort of 31,710 women who had been treated for tuberculosis between 1930 and 1952.[18] The authors correlated the accumulated dose to the breast in multiple fluoroscopy examinations with the incidence of breast cancer mortality. Patients who received a total dose in the range from 5 to 30 cGy had a breast cancer incidence up to one-third less than the background incidence. A hormetic model (solid line) fits the data better than the linear model that was fitted by the authors of the study (dashed line).

There is evidence of the effectiveness of low-dose radiation treatment of patients with cancer. TBI or HBI, shown in Figure 3, has been tested and used successfully by several medical groups for the treatment of several hundred non-Hodgkin's lymphoma (NHL) patients.[19-22] This LDI protocol delivers 10 or 15 fractionated X-ray

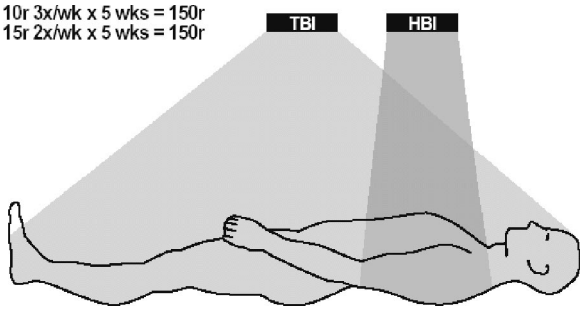

Figure 3. Treatment Configuration for LDI Therapy

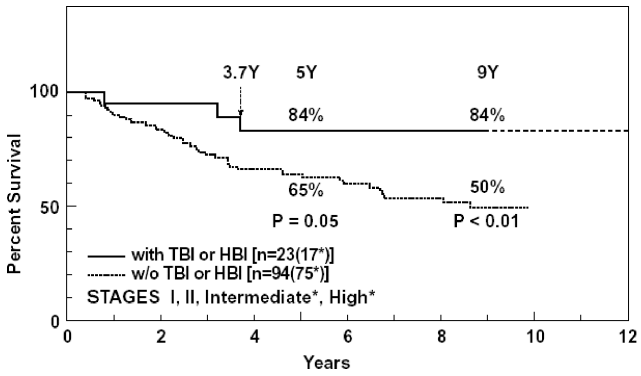

Figure 4. Non-Hodgkin's Lymphoma Survival Increased by Using LDI Therapy Instead of Chemotherapy. Data from Sakamoto et al.[21] and Sakamoto K, personal communication, 2000.

exposures of 15 or 10 rad (cGy), each lasting 3 or 2 minutes–30 rad per week for five weeks–a total dose of 150 rad. Figure 4 shows the highly significant, markedly increased survival following LDI therapy compared to the survival following chemotherapy. This therapy was employed successfully to treat other cancer types, such as ovarian cancer, colon cancer, and hematologic cancer, with no symptomatic side effects.[21,23]

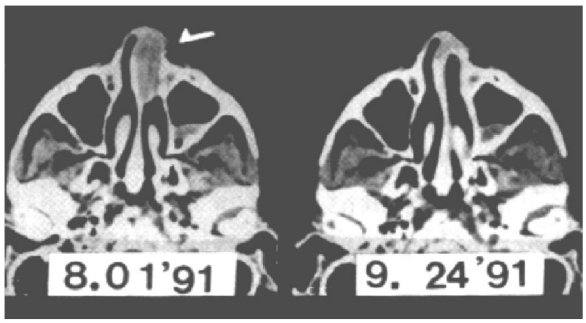

Figure 5. CT Scans of Upper Nasal Cavity Before and After HBI Therapy: Though entirely outside HBI field, nasal tumor completely disappeared. Originally published by Takai et al,[24] reprinted with permission.

In Figure 5, HBI therapy to an NHL patient appeared to cure a nasal tumor that was located outside the radiation field.[24] Tumors do disappear spontaneously, but rarely. In this case, LDI treatment was specifically delivered to stimulate the patient's immune system to attack and kill cancer cells globally. The CT image on the left was taken Aug. 1, 1991, before the twice-weekly 15 cGy/fraction therapy began. The image on the right was taken Sept. 24, 1991, after a total dose of 150 cGy over five weeks. Primary tumors in the tonsils and/or neck lymph nodes also responded to HBI in other NHL patients.

Figure 6 shows the reduction in the concentration of abnormal IgM achieved with a five-week course of asymptomatic LDI therapy, which is comparable to the reduction achieved with six months of chemotherapy during the previous year.[23] While it is true that some cancers spontaneously disappear, in this case there is a very good correlation in time between the application of LDI therapy, from Sept. 10 to Oct. 11, 1999, and the start of progressive changes in the values of the many variables measured.

LDI caused small amounts of damage overall, and the natural defenses, including the immune system, appear to have increased their level of activity to repair this damage and restore homeostasis.

Date	IgM mg/dL	PVIS Plasma viscosity	PLTS platelet count x 1000/mL	HgB Hemo-globin g/dL	T Help cells/mm³	TH/TS Ratio of helper to suppresser	CD4 cells/mm³	NK Natural killer cells per mm³	WBC White blood cells per mm3	RBC Red blood cells x 10^6 per ,mm³	PCV Packed cell volume	Spleen volume cm³
Normal	50-330	1.3-1.8	150-400	14-17	variable	changes in life		changes in life	4k to 11k			
Chemo												
1998 Jan	4080	3.3	300	9.9								
1998 Jun	1605	1.8	100	12.4								
TBI												
1999 Aug 31	4170		335	11.1	43.1	1.32	637 43.0		7680	3.75	34.1	
1999 Sep 07	3870	2.9										100.4
1999 Sep 16			301	10.8	48.3	1.43	659 48.3	16	7050	3.63	32.6	
1999 Sep 23	4040	3.1	301	11.2	54.5	1.67	808 54.5	14	5280	3.74	33.7	
1999 Sep 30			199	10.8	52.6	1.62	745 52.6		5450	3.59	32.8	
1999 Oct 07			95	10.8	54.1	1.71	589 ----		3600	3.61		
1999 Oct 11	2530	2.2	74	10.8	55.9	1.65	654 55.9	9	3930	3.53	32.5	72.4
1999 Oct 19	1770	1.9	73	11.1					2200	3.47		
1999 Oct 27			69	10.9					2200	3.41		
1999 Nov 03	1630	1.8	134	11.9					2500	3.57		
1999 Nov 10			174	10.6					2600	3.11		
1999 Nov 17			171	10.9					3600	3.33		
1999 Nov 18			178	11.4					3600	3.38		
1999 Dec 01	1794		266	12.1					5400	3.61		
1999 Dec 31	2420		211	12.9					4800	3.88		
2000 Jan 28	2540	1.7	228	12.4					5400	3.81		
2000 Mar 06	2760	1.9										

Figure 6. Treatment of Waldenstrom's Macroglobulinemia with LDI Therapy Reprinted with permission from the *Bulletin of the Canadian Nuclear Society.*

At the same time, the level of the cancer (Waldenstrom's macroglobulinemia) appears to have been reduced, as observed by the dramatic reduction in the concentration of the IgM, leading to lower plasma viscosity and the restoration of the spleen to normal size. The patient felt invigorated during and after LDI, in contrast to the adverse side effects he experienced during the course of the chemotherapy that he took from January to June 1998.

What about individuals who, because of their genetic makeup, are radiation sensitive and cancer prone? Very recent research has been carried out on genetically modified (Trp53+/-) mice that model radiation-sensitive, cancer-prone people. It demonstrated that a low dose of cobalt-60 radiation affected cancer latency, reducing the rate at which spontaneously initiated cells progressed to malignancy. The effect of this adaptive response persisted for the life span of all the animals that developed tumors. Figure 7 illustrates the extensions in lifespan of the mice that died from lymphoma.[25]

Based on the evidence of efficacy and negligible risk, it is certainly reasonable to suggest LDI as an option for cancer patients. Stimulation of the patient's defenses will not be an adequate treatment for every case. It may be necessary to employ one or more conventional treatments to supplement the LDI therapy. Most radiation oncology centers have the capability of providing this therapy. For routine LDI therapy, the irradiation equipment could be much simpler and less costly than the elaborate cancer therapy machines currently in service for delivering

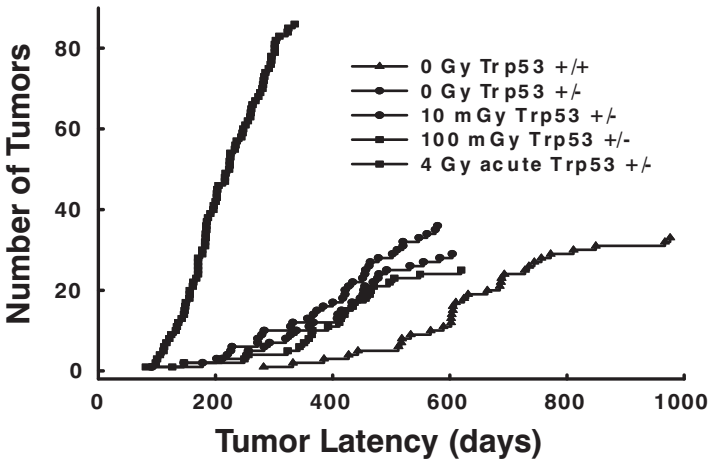

Figure 7. Latency of Lymphomas in Normal Mice and *Trp53* Heterozygous Mice. Reprinted with permission of Atomic Energy Canada Ltd.

localized exposures of high-dose radiation, typically 200 rad, for a total of 4,000-5,000 rad.

Controlled Pilot Study Needed

Controlled studies of LDI therapy should be initiated for patients who could receive a significant benefit with very low risk. Such cases would provide an early indication of the treatment's effectiveness. Promising groups are patients diagnosed with breast or prostate cancer. These patients could be offered LDI therapy as an alternative to conventional treatments. LDI would avoid the immediate side effects and the risk of long-term side effects, with their quality-of-life issues.

LDI therapy would be expected to slow tumor growth and suppress metastases.[16, 21, 26, 27] Patients receiving this therapy would have measurements of specific tumor markers in the blood, such as PSA, and CT imaging procedures performed before and after the five-week course of LDI. A good therapeutic response would be followed by patient monitoring and further LDI therapy as needed. On the other hand, if the initial response to LDI were poor, the patient would be advised to consider a conventional therapy. LDI therapy would also be indicated to treat known or undetected metastases or prevent their occurrence after removal of a primary cancer site by surgery or high-dose localized irradiation.

The expected benefit of LDI therapy would be important and immediate; the risk of new potential cancers from the low doses of radiation would be comparatively insignificant and deferred by at least 10 years.

Conclusions

LDI has been used successfully to treat a variety of cancers without causing significant symptoms or incurring significant risk. Evidence suggests that LDI therapy can slow or reverse tumor growth and prevent metastases.

Given the high prevalence of breast and prostate cancer, and evidence of LDI efficacy in other cancers, controlled studies of LDI in breast or prostate cancer are suggested. Monitoring of specific tumor markers in the blood, such as PSA, and CT images, would provide an early indication of regression or lack thereof.

LDI therapy appears to be a promising complement or option in treatment of cancer, based upon the hormesis effect. The information about the relative risks and benefits of this therapy should be publicized widely, so patients and their physicians can make informed choices about optimal treatment options.

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