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Adjuvant Therapy for Resected Exocrine Pancreatic Cancer by Half-Body Low-Dose Irradiation

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Abstract

After surgery, pancreatic cancer has an extremely high rate of systemic recurrence and a very high rate of local recurrence, more than 80 percent and 20 percent, respectively. Conventional adjuvant therapy prolongs median survival, 28 versus 15 months, by eliminating many of the metastases before they grow into new tumours. In an effort to improve outcomes, the authors recommend evaluating half-body low-dose irradiation (HB LDI) therapy because limited clinical studies have shown HB LDI to be successful as an adjuvant treatment for different types of cancer. Each dose fraction in LDI therapy is 15 cGy, about 13 times below the 200 cGy dose fraction employed in each normal (high-dose) radiation treatment to destroy cancer cells. The LDI mechanism is stress-related repeated stimulation of the patient's very powerful adaptive protection systems by repeated exposure of the patient's upper body to a low dose of radiation. Five weeks of applying this repetitive stress to the patient appears to prolong the enhanced cancer-cell-killing and tissue repair for many months. A booster of this treatment after six months would extend the stimulation for years. This therapy can be started immediately after surgery because it also promotes tissue healing and has no adverse symptomatic side effects. Since adjuvant chemotherapy would normally start within four to six weeks after resection, there is little risk of a delay in providing HB LDI therapy and evaluating its benefit. In most cases the serum marker CA 19-9 can be monitored. If the effectiveness of this therapy is judged to be inadequate, then conventional adjuvant therapies would be provided.

Keywords: Exocrine pancreatic cancer; Adjuvant therapy; Metastases; Low-dose irradiation; LDI; Booster treatment

Introduction to Pancreatic Cancer

Cancer of the exocrine pancreas is highly lethal. It is the fourth leading cause of cancer-related death in the United States, approximately 49,000 people each year, second to colorectal cancer as a cause of digestive cancer-related death. Surgical resection is the only potentially curative treatment, but only 15 to 20 percent of patients are candidates for surgery because of the late presentation. Furthermore, prognosis is poor, even after a complete resection. Five-year survival is about 25 to 30 percent for node-negative and 10 percent for node-positive disease [1].

The most common presenting symptoms in patients are pain, jaundice, steatorrhea, weight loss and diarrhea. Steatorrhea results from loss of the pancreas' ability to secrete fat-digesting enzymes or due to blockage of the main pancreatic duct, (Figure 1). Jaundice is mostly caused by obstruction of the common bile duct, and may be accompanied by pruritus, darkening of the urine and pale stools. Signs of metastatic disease may be present, affecting the liver, peritoneum, lungs, and less frequently, bone. The diagnostic evaluation of a patient includes evaluation of serum and other bodily fluids and abdominal imaging, followed by additional testing based upon the findings, patient's symptoms and risk factors. A determination is made on the nature of the disease (location, aggressiveness, size, and spread) and whether or not the disease is operable. Pancreatic cancers are categorized on a continuum from resectable to unresectable according to the involvement of adjacent structures and the presence of distant metastases [1].

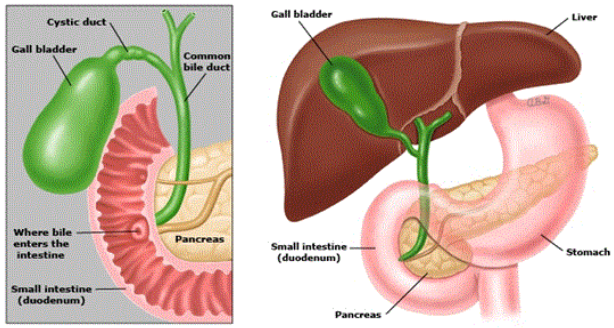

Figure 1: Anatomy of gall bladder and pancreas [1].

The most useful of the serum markers for pancreatic cancer is carbohydrate antigen 19-9, or CA 19-9, only if it is elevated prior to

surgery. Its sensitivity and specificity rates range from 70 to 92, and 68 to 92 percent, respectively; however, sensitivity is closely related to tumour size. Furthermore, CA 19-9 requires the Lewis blood group antigen to be expressed, which is most common. Levels of CA 19-9 are prognostic markers and an indicator of disease activity only in patients with initially elevated levels. CA 19-9 level monitoring is employed to follow patients after surgery and those receiving chemotherapy for advanced disease [1-3].

Early stage pancreatic cancer can often be treated and even cured with surgery. However, surgery is frequently not possible because the cancer is advanced when it is diagnosed. In this case, radiation, chemotherapy or both are often used to shrink the cancer, reduce symptoms and prolong life. Even after the tumour has been completely removed, very often cancer cells remain in the body and continue to grow, causing relapse after surgery. Pancreatic cancer has an extremely high rate of systemic recurrence and a high rate of local recurrence, >80 percent and >20 percent, respectively. Adjuvant therapy prolongs median survival 28 versus 15 months by eliminating many of the remaining cancer cells before they grow into new tumours. This therapy usually starts as soon as possible after surgery, typically within four to six weeks, and is administered for a total of six months. Adjuvant therapy is sometimes delayed to allow full recovery from surgery. Options (for stage II or III pancreatic cancer) are chemotherapy alone or a combination of chemotherapy and radiation therapy. The time to start chemotherapy (within eight weeks of surgery versus later) was an important survival factor only for the subgroup of patients who did not complete all six months of therapy (and in this group, survival inexplicably favoured later initiation of therapy). There seemed to be no difference in outcomes when chemotherapy was delayed for up to 12 weeks. There are several confounding reasons that might explain this observation [1,4]. The effectiveness of therapy also depends on the stage of the disease, advanced stages being less responsive than early stages.

Clinical Trial of Low-Dose Irradiations as an Adjuvant Therapy

Low-dose irradiation (LDI) therapy is a potential adjuvant treatment following pancreatic cancer resection. This therapy could improve outcomes significantly, especially in patients who are not very old [5]. It has been employed successfully as an adjuvant treatment for other types of cancer, including metastatic colon cancer, as discussed below. The mechanism is extended up-regulation of the patient's adaptive protection systems by multiple low-dose exposures.

Normal radiation therapy delivers fractionated, high-radiation doses, usually 200 centigray (cGy)† each, to a small tumour volume. To provide a LDI, the beam is widened to expose the total body (TB) or half body (HB), as shown in (Figure 2). The beam energy, which is in the megavolt range, is sufficient to deliver a uniform dose through the body, and its intensity is lowered to deposit an absorbed low dose of 10 to 15 cGy (± 10%). The duration of the dose fraction is typically under a minute, depending on the distance from the therapy machine and the inherent dose-rate. The choice of the 15 cGy dose fraction is discussed below.

†The gray (Gy) is the System International unit for absorbed ionizing radiation dose, energy in joules per kilogram of mass. A dose of 1 Gy = 1 J/kg. 1 cGy = 1 rad.

‡An average cell weighs about 10^{-9} grams. Therefore, a person weighing 70 kg has about 70 trillion cells.

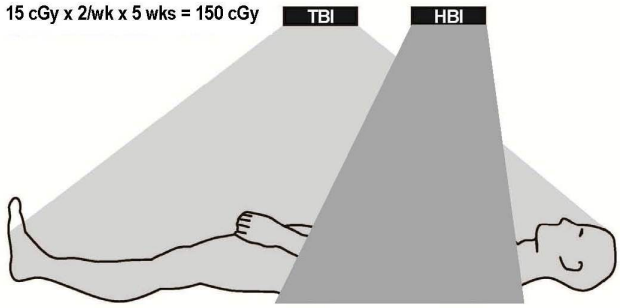

Figure 2: Beam coverage for total body (TB) irradiation or half body (HB) irradiation

How much harm does a low radiation dose cause? The spontaneous rate of DNA damage is enormous [6]. The average number of endogenous DNA alterations, per average cell‡, per day is about 10^6. About 10^{-1} are double-strand breaks (DSBs). The main cause of this damage is metabolic reactive oxygen species. Surprisingly, the rate of DNA damage caused by a low level of ionizing radiation is relatively negligible. A background radiation level of 1 milligray (mGy) per year induces about 10^{-2} DNA alterations per cell, per day. About 10^{-4} DNA alterations per cell, per day are DSBs. The endogenous DNA damage rate is about 100 million times the rate from background radiation. The DSB rate is about 1000 times the DSB rate from 1 mGy per year [7]. The risk of radiation-induced cancer is discussed below.

The protection systems prevent, repair and remove cell and tissue damage, regardless of the causes - endogenous metabolic processes or toxic damage by all of the exogenous causes, including radiation. These systems, which include the immune system, act to restore and maintain all biological functions necessary for survival in good health. All organisms adapt to their environment, so when a small increase in ambient radiation level occurs, the protection systems adjust to this additional stress by becoming up-regulated, i.e., by increasing their levels of activity.

The observed results are net beneficial health effects, including increased life span [8-11], as shown in Figures 3a and 3b. On the other hand, a very high, acute exposure causes tissue damage by cell killing, as in radiation therapy of tumors. A high dose-rate over a long period of time is harmful because it inhibits the protection systems and may damage them. Figure 4 illustrates the dose-response behaviour of this phenomenon.

There is a threshold dose or dose-rate level, above which a beneficial health effect is observed [12]. This observed health effect transitions from beneficial to harmful above the no observed adverse effects level (NOAEL). The dose-locations of the threshold and NOAEL and the amount of benefit or harm for a particular radiation-induced health effect at a given dose depend on the patient's genetic characteristics, age and medical condition. This applies not only to ionizing radiations but to any physical or chemical stressor.

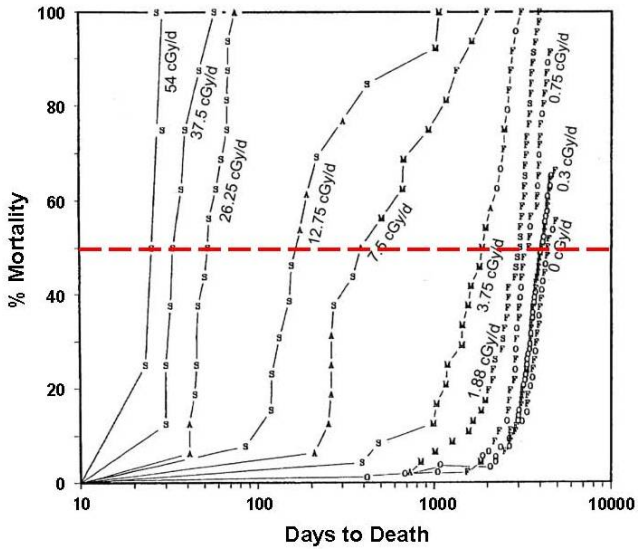

Figure 3a: Mortality curves for groups of dogs in different Co^{60} radiation levels [13]. Note that the intersection of the red dashed line (at 50% mortality) with each mortality curve defines the median lifespan of the group of dogs in the indicated radiation level.

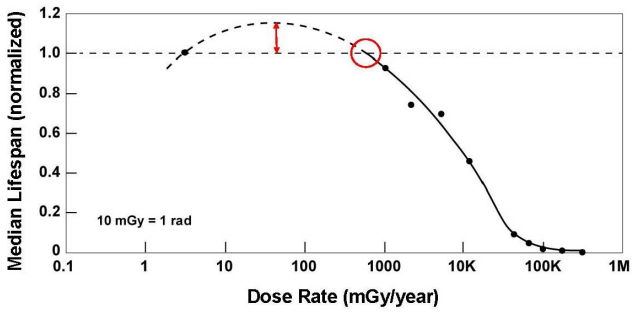

Figure 3b: Median lifespan vs. radiation level [14]. Note that the NOAEL for gamma radiation-induced lifespan reduction of dogs is about 700 mGy/year (70 cGy/year).

A patient's static defences act when stresses exceed threshold levels. The metabolic or dynamic defences include: 1) fast-acting ones that start immediately after an injury occurs and 2) delayed ones (involving more than 150 genes) that can adapt to a chronic stress or be up-regulated for a long duration by repeated short-term stresses.

The adaptive protections are highly stimulated by a 150 mGy acute radiation dose. Up-regulated adaptive systems persist and may last for more than a year, protecting against renewed toxic impacts from both radiation sources and non-radiation sources [15,16]. Induced damage removal, for instance by immune responses against cancer cells, brings a life-long benefit.

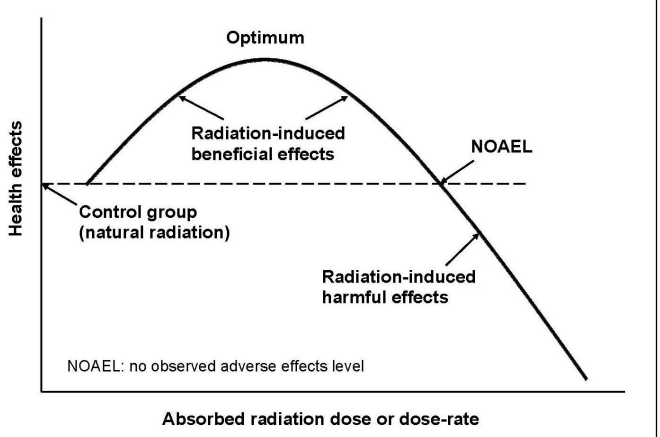

Figure 4: Dose-response model for ionizing radiation

Benefits and Risks of HB LDI vs. Conventional Adjuvant Therapies

Chemotherapy kills cancer cells. The patient is given optimal doses of a chemical poison that preferentially kills cancer cells throughout the body. Its symptomatic side-effects are generally very harsh because many healthy cells are harmed as well. The standard radiation treatment is designed to preferentially kill cancer cells by delivering a series of high-dose ionizing radiation exposures to the local tumour area. Each dose fraction is about 200 cGy (vs. 15 cGy for LDI). Its side-effects are harsh, due to killing and scarring of adjacent healthy tissue. The patient's recovery is slow. As mentioned above, conventional adjuvant therapy prolongs median survival by only a year, 28 versus 15 months, for pancreatic cancer patients. So there is a need for an adjuvant treatment that could provide a much longer survival without the severe side-effects of the current treatments.

HB LDI therapy is based on stimulating the patient's adaptive protection systems, including the immune system [16,17]. This treatment could be started immediately after the surgery because LDI given in this manner might promote healing of the surgical wounds [18]. Dose fractions of 15 cGy are delivered to the trunk of the body. Studies on humans have demonstrated that this dose is tolerated well, with no symptomatic non-hematologic side-effects [5,19,20]. The 3 day interval between radiation exposures is adequate time for the patient's protection systems to remediate the damage caused by the absorbed dose and for protections to become up-regulated and operate, before the subsequent dose is given. The total dose is 150 cGy, which is more than 30 times lower than the total dose of about 5000 cGy (200 cGy x 5/week x 5 weeks) that is delivered to the tumour area in the standard adjuvant radiation treatment. The probability of LDI causing cancer is discussed below.

The effectiveness of this treatment may be measured by monitoring the patient's CA 19-9 serum marker during and after HB LDI therapy. If the CA 19-9 level rises, the physician would revert to a standard adjuvant option. The delay would not exceed 5 weeks after resection, which is about the usual delay before starting adjuvant treatment.

Therefore, the likelihood of a significant benefit is high, and there is little risk to the patient.

Brief History of LDI Treatment for Cancer Patients

Two Harvard University clinical trials of TBI LDI on 25 and 39 non-Hodgkin's lymphoma patients, published in 1976 and 1979, were reviewed by Pollycove [20]. Both trials employed 150 cGy TBI therapy. The first trial used ten 15 cGy fractions, and the second fifteen 10 cGy fractions. Significant improvements in patient survival were achieved.

The results of one of Sakamoto's many experimental studies in mice, a lung metastasis model shown in Figure 5, demonstrates a very strong stimulation of the immune system by a single 15 cGy TBI exposure. (The authors are not aware of any studies performed on pancreatic cancer animal models.)

Subsequently, he treated more than 200 cancer patients in Japan. Although most were non-Hodgkin's lymphoma cases, Figure 6, his first patient was a colleague with advanced ovarian cancer. She received 150 cGy in 15 total-body irradiations of 10 cGy each. Following this course, the tumors disappeared in all regions of her body [5]. Dr. Sakamoto himself received HB LDI adjuvant therapy for metastatic colon cancer, in the late-1990s, after surgery. He received a repeat course of this treatment, six months later, as a booster. This treatment eliminated the extensive metastases and prevented cancer recurrence.

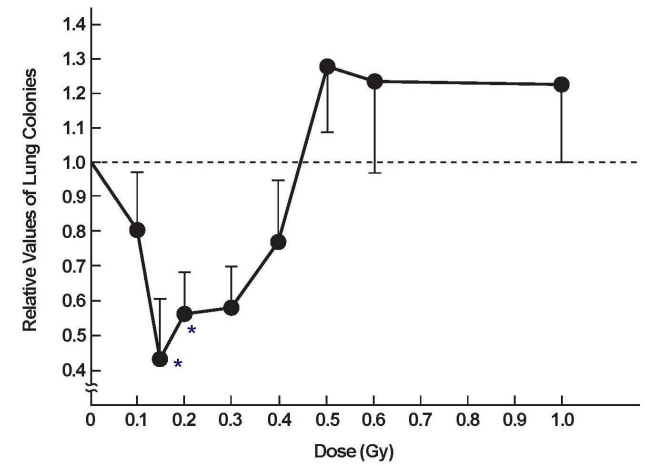

Figure 5: Effect of total body irradiation (TBI) X-ray dose on spontaneous lung metastasis in mice [5]. TBI was given 12 days after tumour-cell transplantation into groin; * $p \leq 0.05$.

In 1999, an 81 year old patient who had been suffering from Waldenstrom's macroglobulinemia since 1992 was treated by a five-week course of TB LDI, doses of 15 cGy twice weekly. This disease is cancerous proliferation of IgM plasma cells, which increase blood viscosity leading to fatigue and weakness. The chemotherapy that had started in 1998 was intolerable. The patient was informed about the LDI treatment being provided in Japan by Sakamoto and requested it. The patient's IgM level and serum viscosity declined strongly by the completion of treatment and he became symptom free. Other than transient thrombocytopenia, no acute or late side effects were noted [21].

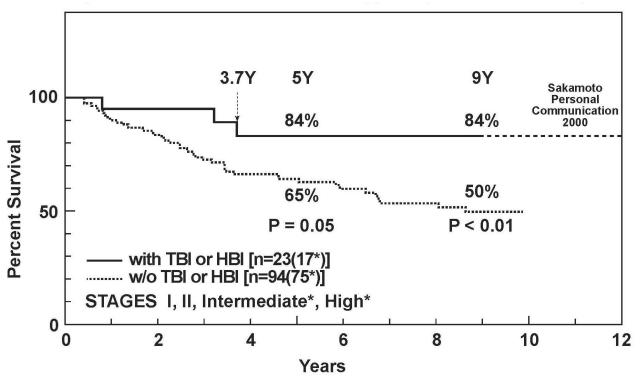

Figure 6: Improved survival of patients who received LDI following conventional NHL treatment Note: Patients in both groups received chemotherapy and localized tumor high-dose radiation. Adapted from Sakamoto et al. data by Pollycove [20].

Historical Background for LDI Treatments

Immediately after the discovery of X-rays in 1895 and radioactivity in 1896, it was apparent that low and moderate exposures to these radiations produced remarkable beneficial health effects in all biological organisms, including plants [22]. A large amount of data has accumulated from a wide variety of medical treatments using low radiation doses over the past 120 years. These include eradication of cancer metastases, treatments of wounds, cures of serious infections (gas gangrene, boils, sinus, inner ear, pneumonia), arthritis and other inflammations, and even asthma.

By 1903, animal studies had shown that radiation exposures could produce delayed effects, such as cancer [23]. But Mitchel [24] and others have demonstrated that low doses of radiation reduce cancer risk in animals. Many publications on medical treatments with low doses generally make no mention of any increase in cancer risk [10,14].

Cuttler and Pollycove questioned why treatments with low doses of radiation are not employed to treat cancer, based on the extensive, positive information available in the scientific literature [19]. Subsequently, Pollycove, in a detailed review, presented a strong case for clinical trials on breast, prostate and colorectal cancer [20].

Does a Low Dose of Radiation Increase Cancer Risk?

Radiation protection advice began to appear in 1913, and in 1921 the British Roentgen Society issued recommendations to radiologists. The 1934 standard of the International Commission on Radiological Protection (ICRP) recommended a "tolerance dose" limit of 0.2 roentgen per day (equivalent to about 70 cGy per year) [23,25]. This advice was satisfactory for more than 20 years.

Two key papers in Science in the 1950s revolutionized radiation protection, creating the world-wide radiation health scare. The first was the National Academy of Science paper in 1956. It recommended the use of a linear no-threshold (LNT) model for assessing the risk of radiation-induced mutations in germ cells [26]. Forty-five years later, the UNSCEAR 2001 report [27] invalidated this recommendation,

stating, "Radiation exposure has never been demonstrated to cause hereditary effects in human populations."

The second paper, in 1957, analyzed the Hiroshima-Nagasaki leukemia data and recommended using a LNT model to calculate the excess risk of cancer due to any radiation exposure [28]. A recent examination of this paper identified a very serious error [29]. This error was missed by the radiation regulators who adopted the LNT model. The 1957 study did not properly account for the incidence of leukemia among the "control population" (the people who were not exposed) [29].

To address the incidence among the control population, the author stated [28], "Since the majority of the population in zone D (from 2000 meters on) was beyond 2500 meters, the average dose is under 5 rem and is thus so low that zone D can be treated as if it were a "control" zone."However, the survivors who were in the band from 2000 to 3000 metres distance from the atomic bombs absorbed very significant radiation doses.

They should not have been combined with the non-exposed people who were located beyond 3000 metres. Averaging the data in low dose intervals concealed the evidence of the dose threshold, which would have invalidated the author's recommendation to use a LNT model for calculating the excess risk of radiation induced cancer [29].

The 1958 UNSCEAR report, Annex G, Table VII provides the leukemia data for the ~ 96,000 Hiroshima survivors, including ~ 33,000 who were in zone E, from 3000 metre and beyond [30]. These human data, are shown in (Figure 7).

The footnote for zone C in Table VII [30] states, "almost all cases of leukemia in this zone occurred in patients who had severe radiation complaints, indicating that their doses were greater than 50 rem." Hence, a point has been added in Figure 7 at 100 rem to account for the reported severe radiation complaints by the zone C patients.

The dashed line through this point strengthens the evidence of a threshold dose. These human data contradict the recommendation to use the LNT model to predict the excess risk of leukemia (and cancer in general). They suggest an acute radiation threshold at about 50 rem (500 mSv) for excess leukemia incidence.

Radiation Protection Issue

In spite of the scientific evidence and 120 years of human experience using low radiation doses in medicine, with no significant evidence of radiation-induced cancer, the National Council on Radiation Protection and Measurement (NCRP) and the other radiation protection organizations refuse to discard their LNT hypothesis, a precautionary assumption for radiation protection purposes. NCRP Report 121 [31] states, "Few experimental studies and essentially no human data can be said to prove or even provide direct support for the [LNT] concept. Ultimately, confidence in the linear no threshold dose-response at low doses is based on our understanding of the basic mechanism involved. [Cancer] could result from the passage of a single charged particle, causing damage to DNA that could be expressed as a mutation or small deletion." NCRP Report 136 [32] states, "It is important to note that the rates of cancer in most populations exposed to low-level radiation have not been found to be detectably increased, and in most cases the rates appear to be decreased." Taylor stated in 1980 [33], "No one has been identifiably injured by radiation while working within the first numerical standards set by the NCRP and the ICRP in 1934." "The theories about people being injured have still not led to the demonstration of injury and, if considered as facts by some, must only be looked upon as figments of the imagination." Cohen provided comprehensive reasons for physicians and surgeons to reject the LNT theory [34].

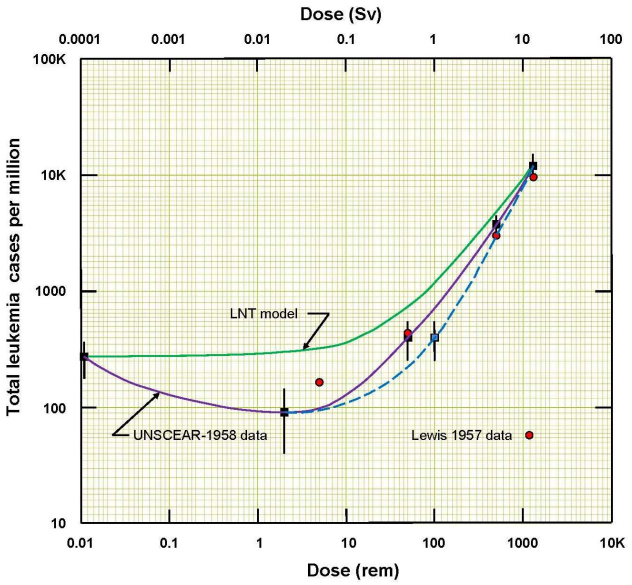

Figure 7: Leukemia incidence among the Hiroshima atomic bomb survivors, 1950-57 [29].

Conclusions

Cancer of the exocrine pancreas is the fourth leading cause of cancer death. Only 15 to 20 percent of patients are candidates for surgery, the only potentially curative treatment. Prognosis is poor even after a complete resection. Pancreatic cancer has an extremely high rate of systemic recurrence and a high rate of local recurrence. Adjuvant therapy, which is usually chemotherapy alone, prolongs median survival modestly (28 versus 15 months), presumably by eliminating many of the metastases.

Since low dose irradiation (LDI) has been used successfully to treat different types of cancer, including colon cancer, it may prove to be more effective than chemotherapy (and high-dose local irradiation) as an adjuvant treatment for pancreatic cancer. A single treatment, soon after surgery, could stimulate the patient's protection systems, accelerating recovery and removing cancer metastases. Repeated applications of LDI could up-regulate the adaptive protection systems, providing long-lasting protection against the recurrence of metastases. The typical course of treatment is 15 cGy half-body irradiations, twice each week, for five weeks (total dose is 150 cGy). A booster course after six months, could improve survival. In contrast to the harsh side-effects of conventional therapies, patients tolerate LDI well; there are no symptomatic side-effects.

In many cases, the effectiveness of LDI therapy could be measured by monitoring the CA 19-9 serum marker during and after the treatment. If the improvement in the patient's condition after LDI therapy is judged to be inadequate, then conventional adjuvant treatments could be administered without risk of a significant delay.

Recommendations

The option of providing HB LDI as an adjuvant treatment after resection for pancreatic cancer should be evaluated to determine whether it would provide a significantly better outcome for suitable pancreatic cancer patients. A clinical trial of this therapy could be carried out using existing facilities, with no risk to patient health.

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