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Back to the Future: Reexploring Radiotherapy for Benign Disease

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It is always with the best of intentions that the worst work is done, or some remarks on the development of radiotherapy for benign disease.

For 50 years, before the advent of antibiotics, radiation was used to manage many infections [1]. In fact, moderate anti-inflammatory doses of irradiation were recommended in patients with pelvic inflammatory disease and carcinoma of the cervix, preceding the 'heavy' cancericidal doses. This practice went unchecked despite observations of damage to tissues of early radiation workers. A second wave of irradiation injuries became evident when patients (mostly children) who had been previously irradiated for benign conditions were diagnosed with carcinomas and sarcomas. This second wave of radiation injuries rang the bell for the wake-up call. As a result, physicians, mostly nonradiation oncologists, began worrying about radiation carcinogenesis. Two examples are the use of irradiation in serous otitis and obstetrical mastitis.

Nasopharyngeal irradiation was employed to treat serous otitis, by obliterating the lymphoid hyperplasia of the nasopharynx obstructing the eustachian orifice. Intranasal radium applications were inserted on 3 separate occasions for about 300 cGy to the mucosa of the eustachian tube. This method was highly effective in preventing permanent deafness and was used successfully for more than 25 years. Discontinuation of this type of therapy occurred with the advent of antibiotics and transtympanic drainage procedures. Sandler et al. [10], in 1982, studied the effects of nasopharyngeal irradiation on excess cancer rates. He compared 904 irradiated patients with 2,021 unirradiated patients.

He found 3 patients in the irradiated group who developed malignant brain tumors, compared to zero in the nonirradiated group. Four malignancies of the head and neck were found in the irradiated group compared to none in the nonirradiated group. From this, he concluded this procedure caused a twofold increase in benign and malignant neoplasms of the head and neck.

Shore [11] proposed that if 10,000 children were given intranasopharyngeal radium treatments, there would be an excess of 27 brain cancers, 44 thyroid cancers and 5 salivary gland cancers. Preservation of hearing is not mentioned. Verduijn [13] and Loeb [6] both reported on populations of children treated with this procedure. Neither was able to demonstrate a significant increase in cancer mortality. Verduijn noted a statistically significant twofold increase in cancer incidence at all sites studied; however, it should be noted that no one site showed a significant increase. Most studies are too small to detect significant increases.

The breast is one organ where relatively low radiation doses have been shown to cause cancer [5]. Obstetrical mastitis is a *Staphylococcus aureus* infection seen in nursing mothers within a few weeks after delivery. A segment of the breast is tender, warm and painful, corresponding to infection of a major duct. Abscess or fistula may occur. The diseased breast was typically irradiated with orthovoltage x-rays. A daily skin surface dose of 40–50 cGy was enough, if given within 48 h of the onset of symptoms. If symptoms and/or signs persisted or worsened, the dose was repeated, up to 200–400 cGy [3, 4]. Shore et al. [12] studied 601 irradiated women and compared them to 1,239 controls. Orthovoltage radiations of 300 cGy to 2.5 cm below the skin surface approximated the mean breast dose. Most patients had 10 fractions or less. Fifty cancers were observed in 601 irradiated patients with mastitis, whereas only 60 cancers were found in 1,239 control patients, indicating a relative risk of 2 for women who received breast irradiation.

Mole [8] in his discussion of ionizing irradiation as a carcinogen said: 'No dose of radiation, however small, is without some chance of causing cancer ... the increase in cancer with increasing radiation exposure is linearly proportional to dose ... and the cancer rate per unit dose is given directly by human experience ...'

I would like to add two other factors. The number of radiation-induced cancers in patients for any one site is small and the follow-up interval must extend over at least two generations. Both of these factors limit any conclusions that can be drawn in anyone's lifetime. Often mental gymnastics must be summoned to help instill radiobiological understanding in our minds.

Depending on the age of the patients and the site of the radiation-induced carcinoma, the incidence is closer to 1 in 10,000 rather than 1 in 1,000. In the final analysis, radiations used for therapy are weakly carcinogenic at worst.

Irradiation has a low carcinogenicity in the treatment volume because most cells are killed rather than transformed [9]. The use of megavoltage irradiation treatment planning and the moratorium on the treatment of benign disease in children has decreased the height of a third wave of radiation-induced cancers.

The practice of radiation oncology must provide effective treatment for the patient's problem with the least risk of complications. Nasopharyngeal irradiation prevented serous otitis and hearing loss. Irradiation of mastitis prevented abscess and allowed breast feeding [7]. Part of the highly flammable and negative criticism against radiations as therapy was voiced by epidemiologists and statisticians outside of our specialty, using radiation-induced tumors as a pivot. These nonclinicians have declared that radiations are a hazard to the patient's health. Admittendly, there are hazards with irradiation, but it may be a benefit to health if when used, it destroys pathology at a higher incidence than it causes complications.

It is of historical interest that within a short time of Roentgen's discovery, dermatitis and skin ulceration were being discovered in the early workers. Despite the importance of the roentgen ray, this finding elicited an adverse editorial in a daily newspaper, *The London Pall Mall Gazette* [2]:

'We are sick of the rontgen ray; ... you can see other people's bones with the naked eye, and also see through eight inches of solid wood. On the revolting indecency of this there is no need to dwell. But what we seriously put before the attention of the Government ... that it will call for legislative restriction of the severest kind. Perhaps the best thing would be for all civilised nations to combine to burn all works on the rontgen rays, to execute all the discoverers, and to corner all the tungstate in the world and whelm it in the middle of the ocean.'

The irradiation of benign disease has been through the scientific mill; it is now seasoned, battle-scarred and ready to take on new tasks: coronary artery disease, macular degeneration, cerebral arteriovenous malformation, to name a few. This time let us take the lead for recording complications. These may be nominal, but we, not the epidemiologists should record them. Only we can make the risks meaningful in the clinical setting. Finding cancers in a previously irradiated population is not enough to prove they are due to irradiation. The occurrence of cancers may be due to genetics or other factors other than irradiation which affect the natural history of the disease. A major step in this direction is to have a central registry for reporting untoward effects of patient irradiation for benign disease. Factors such as random variation due to sample size, multiple variables, limited time of follow-up, and problems of extrapolation are best accounted for in a prospective manner. By supporting a central registry, we would have more control over public opinion by having the data. Surprises on the Internet or in newspapers would be minimal.

Presently and in the future, we will find that the big decision to irradiate benign disease is not really a decision at all. The decision is a product of habit and momentum – things going on for long enough that they have built up their own speed and force and become difficult to stop or deflect. This time, unlike the first 50 years of this century, we should be in the know and in control of reporting late radiation complications.

The further radiation oncology advances, the more it detaches itself from the past is a truism which is believed by the present generation. But if we ignore the past we may jeopardize our exploration into benign disease. As John Cairns wrote: 'The moral of this story is obvious. All public pronouncements about risks and benefits, whether experimental or epidemiological in origin have to be cautious and great efforts have to be made to put the conclusions in their proper context'.

To conclude, we should quantitate our experience as a whole. In the past, we have had to put pieces of a jigsaw puzzle together to establish a database. We use the many epidemiological studies of radiation risks *and* a century of accumulated experience in radiation therapy to estimate the risk of once again treating benign conditions. The resulting database has been incomplete but has been better than nothing. I would ask for careful planning now to establish a central registry for complications in order to build a database for the future.

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References

1 Berk LB, Hodes PJ: Roentgen therapy for infections: An historical review. Yale J Biol Med 1991; 64:155–165.
2 Cade S: Radiation induced cancer in man. Br J Radiol 1957;356:393–402.
3 Elword JF, Dodek SM: Roentgen therapy in acute puerperal mastitis. Radiology 1940;34:166–170.
4 Harvey RA, Spendler HA, Dowdy AH: Roentgen therapy as an adjunct in the management of acute post-partum mastitis. Surg Gynecol Obstet 1945;80:396–403.
5 Land CE, Boice JD Jr, Shore RE, Norman JE, Tokunaga M: Breast cancer risk from low-dose exposures to ionizing radiation: Results of parallel analysis of three exposed populations of women. J Natl Cancer Inst 1980;65:353–376.
6 Loeb WJ: Radiation therapy of the nasopharynx: A 30 year view. Laryngoscope 1979;89:16–21.
7 Marshall BR, Hepper JK, Zirbel CC: Sporadic puerperal mastitis: An infection that need not interrupt lactation. JAMA 1975;233:1377–1379.
8 Mole RH: Ionizing radiation as a carcinogen: Practical questions and academic pursuits. Br J Radiol 1975;48:157–169.

9 Pizzarello DJ, Roses DF, Newall J, Barish RJ: The carcinogenicity of radiation therapy. Surg Gynecol Obstet 1984;159:189–200.
10 Sandler DP, Comstock GW, Matanoski GM: Neoplasms following childhood irradiation of the nasopharynx. J Natl Cancer Inst 1982;68:3–8.
11 Shore RE: Epidemiologic issues related to nasopharyngeal radium exposures. Otolaryngol-Head Neck Surg 1996;115:422–428.
12 Shore RE, Hildreth N, Woodard E, Dvoestsky P, Hempelmann L, Pasternak B: Breast cancer among women given X-ray therapy for acute postpartum mastitis. J Natl Cancer Inst 1986;77: 689–696.
13 Verduijn PG: Late health effects of radiation for eustachian tube dysfunction: Previous results and ongoing study in the Netherlands. Otolaryngol-Head Neck Surg 1996;115:417–421.

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