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Review paper

Cancer risk after radiotherapy for benign diseases

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ABSTRACT

Radiotherapy with low to intermediate doses has been historically employed for the management of several benign diseases. The exposure to ionizing radiation may increase the probability for carcinogenesis. The knowledge of this probability is of value for weighting the benefits and risks of radiotherapy against different therapeutic approaches. This study initially reviews the epidemiologic data associated with the cancer induction due to radiotherapy for non-malignant conditions in previous decades. Most of these data were derived from patients irradiated with conventional techniques, which are no longer applied, for some benign diseases not treated with radiotherapy nowadays. The follow-up of a series of patients undergoing modern radiotherapy for benign disorders may be used for estimating the radiation-induced cancer risk. The realization of this process is often difficult due to the relatively small number of patients undergoing radiation therapy for such diseases in many countries and due to long latent period for the appearance of a malignancy after exposure. The combination of dosimetric data, which can be obtained by phantom measurements or treatment planning systems or Monte Carlo calculations, with the appropriate linear and non-linear risk models may lead to theoretical estimates of the radiotherapy-induced cancer risks. The limitations of the method providing a whole-body cancer risk based on the effective dose concept are presented. The theoretical organ-specific risks for carcinogenesis give useful information about the development of malignancies at any in-field, partially in-field and out-of-field critical site. The uncertainties of the organ-dependent cancer risk estimates are discussed.

Contents

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1. Introduction

Radiation therapy has been historically employed in patients with various non-malignant diseases [1]. The anti-inflammatory effects of radiotherapy with low target doses of 2–6 Gy may be used for the management of several inflammations and painful disorders [2]. Higher target doses are required to influence cellular differentiation and proliferation for the effective treatment of proliferative benign diseases [2]. The use of radiotherapy may expose all healthy tissues of the human body inside or outside the applied treatment fields to ionizing radiation. This unavoidable organ exposure during radiation therapy may elevate the probability for the development of deterministic and/or stochastic effects. One of the most serious effects is the cancer induction in irradiated patients.

In 1965, Court-Brown and Doll [3] reported an elevated mortality risk from leukemia attributable to radiation therapy for ankylosing spondylitis. An increased radiotherapy-induced cancer risk was also found by subsequent publications [4–6] dealing with other non-malignant conditions. The awareness about the possible carcinogenesis and the introduction of new treatment approaches during the last decades has affected considerably the therapeutic use of ionizing radiation in patients with benign diseases. However, there are still considerable geographic differences in the use of radiotherapy for non-malignant disorders.

In Germany, about 50,000 patients suffering from a wide variety of benign diseases are subjected to radiotherapy annually in more than 300 centers [7]. The number of patients undergoing this type of treatment in this country increased by 86.3% from 1999 to 2004 [7]. Radiotherapy for non-malignant conditions is less commonly applied in the United States than in Germany [1]. This declined use of irradiation nowadays is in contrast with the common practice adopted between 1920 and 1960 where more than one million Americans were subjected to X-ray treatment for benign diseases in the region of head and neck [1]. A limited use of radiation therapy for non-malignant conditions in UK has also been recently reported [8].

This study provides a review of the epidemiologic evidence related with the cancer development from irradiation of non-malignant conditions. The methods enabling the direct assessment of the probability for cancer development following radiotherapy for benign diseases are presented. The advantages and limitations of these methods are described.

2. Radiotherapy for benign diseases

The treatment of a non-malignant disease is indicated when this disease is symptomatic or potentially symptomatic [1]. The role of radiation therapy is of great importance when other therapeutic options are not available or have been proved ineffective. The irradiation of a benign disease in patients with long life expectancy is a dilemma for physicians due to the potential early or late complications of radiotherapy. The European Society of Therapeutic Radiology and Oncology organized a consensus meeting in 2007 to define the clinical evidence of radiation therapy in benign disorders [9]. These guidelines were recently reviewed by the Royal College of Radiologists in order to determine an evidence-based strategy about the irradiation of non-malignant conditions across UK [10]. Similar updated evidence-based practice guidelines was recently published by the German Cooperative Group on Radiotherapy for Non-Malignant Diseases in 2015 [7]. In accordance with the German Working Group [7], radiotherapy should be performed (level of recommendation = A) for painful plantar fasciitis and heterotopic ossification (HO). Irradiation shall be performed (level of recommendation = B) for painful benign disorders such as gonarthrosis, shoulder syndrome and elbow syndrome. The same level of recommendation is for Morbus Dupuyten, keloids, Peyronie's disease, desmoids tumors, symptomatic vertebral hemangiomas, pigmented villonodular synovitis, Gorham Stout syndrome and Graves orbitopathy. Radiation therapy might be performed (level of recommendation = C) for the management of, trochanteritic bursitis and arthrosis in the hand or finger joints. The effective management of the majority of benign diseases with radiotherapy requires low to intermediate radiation doses of 3–50 Gy [8].

3. Epidemiologic data of cancer induction

3.1. Head and neck malignancies

In a study including 10,834 patients treated for tinea capitis from 1948 to 1960, the authors found sixty neural tumors in exposed subjects leading to a relative risk of 8.4 for neural tumors in the head and neck region [11]. Radiation doses of 1–2 Gy were found to considerably elevate the probability for the appearance of neural tumors. Sadetzki et al. [12] showed that the excess relative risk for developing both malignant brain tumors and benign meningiomas remains increased even at 30 or more years after irradiation of tinea capitis during childhood.

Modan et al. [4] showed that the risk of thyroid cancer induction in 10,902 children subjected to irradiation for scalp tinea was six times higher than that in matched control groups. Favus et al. [13] also found a correlation between radiation exposure and the appearance of benign and malignant thyroid malignancies in subjects irradiated in the nasopharyngeal and tonsillar regions for non-malignant diseases. Shore et al. [14] studied 2650 infants irradiated with X-rays for purported enlarged thymuses. They found an excess radiogenic risk of developing thyroid tumors for at least 40 years following treatment. A pooled analysis of seven studies including 58,000 persons exposed for benign and malignant conditions and 61,000 nonexposed subjects revealed that radiation doses as low as 0.1 Gy may lead to thyroid tumors [15].

3.2. Thoracic malignancies

Shore et al. [6] studied 601 females who underwent X-ray treatment for acute postpartum mastitis during the 1940s and 1950s and 1239 controls. The average follow-up time was 29 years. The relative risk for breast cancer induction was found to be 3.2. In a cohort of 1216 women irradiated for benign breast diseases between 1920 and 1950 in Sweden, 198 cases with breast cancer were observed versus 101 in the unexposed cohort [16]. An excess relative risk of 0.33 per Gy was also found in a Swedish cohort of 17,202 infants treated for skin hemangioma before 1965 [17].

Darby et al. [18] studied 14,106 patients subjected to X-ray treatment for ankylosing spondylitis between 1935 and 1954. They observed 224 deaths because of lung cancer whereas only 184 deaths were expected. A subsequent study dealing with irradiation of the above disease found that the risk for mortality from lung malignancies disappears after a period of 35 years from the initial exposure [19]. The study of Griem et al. [20] included 1831 patients irradiated with a mean dose of 14.8 Gy for peptic ulcer and 1778 treated with different methods. The relative risk of dying from lung cancer was 1.70. A similar probability of 1.50 was also reported later [21].

3.3. Abdominopelvic malignancies

Carr et al. [21] studied 3719 patients with peptic ulcer who underwent radiation therapy and/or surgery and medication

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