Physica Medica 43 (2017) 73–78

Contents lists available at ScienceDirect

Physica Medica

journal homepage: www.elsevier.com/locate/ejmp

Original paper

Radiotherapy for non-malignant shoulder syndrome: Is there a risk for radiation-induced carcinogenesis?

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ARTICLE INFO

Keywords:
Radiation therapy
Shoulder syndrome
Radiation-induced cancer

ABSTRACT

Purpose: To estimate the organ-specific probability for carcinogenesis following radiotherapy for non-malignant shoulder syndrome.
Methods: Photon-beam radiation therapy to 6 Gy for shoulder syndrome was simulated with a Monte Carlo code. An androgynous computational phantom representing a typical adult was used to calculate the radiation dose to out-of-field organs having a predilection for carcinogenesis. The organ-specific lifetime attributable risk (LAR) for out-of-field cancer induction was estimated by the organ dose calculations and the proper risk factors introduced by the BEIR-VII report. The average dose (D_{av}) and organ equivalent dose (OED) of lung, which was partially included within the treatment volume, was found from 3d-conformal radiotherapy plans. The D_{av} and OED were used to estimate the lung cancer risk with a linear and mechanistic models, respectively. All risk assessments were made for 50- and 60-year-old male and female patients.
Results: Monte Carlo simulations resulted in an out-of-field organ dose range of 0.7–48.4 mGy. The LARs for out-of-field cancer induction were (1.4×10^{-4})% to (2.8×10^{-2})%. These probabilities were at least 403 times lower than the respective lifetime intrinsic risk (LIR) values. The D_{av} and OED of lung was up to 164.9 and 142.3 mGy, respectively. The LAR for developing lung malignancies varied from 0.11 to 0.18% by the model used and the patient's age and gender. The lung cancer risks were 36–64 times smaller than the LIRs.
Conclusions: The estimated probabilities for developing malignancies due to radiotherapy for non-malignant shoulder syndrome are minor relative to the natural cancer occurrence rates.

1. Introduction

Shoulder syndrome affects the shoulder joint causing pain and a loss of motion [1]. This benign disease was described by Duplay in 1872 with the term periarthritis humeroscapularis [2]. The etiology of the shoulder syndrome has not been completely explained and it may be associated with mechanical stress, trauma, circulatory factors and infections [3]. The prevalence of this painful condition may reach up to 5% of the population [4]. Several conservative approaches starting from physiotherapy have been employed for the management of the shoulder syndrome. The treatment is often based on the administration of non-steroidal anti-inflammatory drugs which might cause gastrointestinal adverse effects [1]. The direct injection of steroids or analgesics in the shoulder usually results in a limited time period without pain [1]. The use of extracorpeal shock wave therapy (ESWT) in the region of shoulder may result in a complete resorption of the lesion in 43% of the patients with this benign disorder and in 72% when the ultrasound-guided needling is employed [5]. Kim et al. [6] reported a success rate of 30–85% with the application of ESWT in the shoulder joint. Open or arthroscopic surgery can be applied after the failure of the aforementioned conservative treatment options [1]. Physiotherapy should follow the operative procedures for a long time period up to 12 weeks [3].

Radiotherapy remains an alternative treatment option and it may be employed whenever the conservative approaches have been proved to be unsuccessful after a patient's follow-up of 3 months [1]. Several studies of the last decade with large series of subjects clearly revealed the effectiveness of external-beam radiotherapy [3,7,8]. Niewald et al. [3] reported a pain relief in 69% of the 141 participants directly after the end of irradiation. Adamietz et al. [7] found that the relief from painful symptoms was achieved in 94 of the 115 shoulder joints at a median follow-up of 18 months. Ott et al. [8] examined 312 irradiated patients and found an overall response rate of 85% in 6 weeks after radiotherapy. Therapeutic irradiation of the shoulder syndrome is not

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http://dx.doi.org/10.1016/j.ejmp.2017.10.021
Received 2 August 2017; Received in revised form 21 September 2017; Accepted 24 October 2017
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associated with the appearance of short-term side effects [1,9]. Despite the effectiveness of radiotherapy and the absence of acute toxicity, the exposure to ionizing radiation of subjects with this non-malignant condition may be in question due to the risk for carcinogenesis. The follow-up in previous studies [3,7–10] dealing with the irradiation of shoulder syndrome was rather limited with a mean value up to 6.9 years. This time interval should not be considered as enough for the detection of radiation-induced malignancies. It is well known that the latency for the development of solid tumors may vary from 10 years to 60 years [11].

This study was conducted to (a) calculate the radiation dose to critical organs of the human body, and, (b) estimate the relevant organ-dependent cancer risk from radiotherapy for the non-malignant shoulder syndrome.

2. Materials and methods

2.1. Monte Carlo study

2.1.1. Organ dose calculations

The Monte Carlo N-particle (MCNP) radiation transport code was previously employed to model a medical linear accelerator emitting 6 MV photon beams [12]. The target of the machine, primary collimators, flattening filter, flattening filter holder and secondary collimators were simulated in detail. The generated model also consisted of the surrounding shielding components of the head of the linear accelerator. The validity of this model was verified against radiation dose measurements performed inside and outside the treatment field borders [12].

The aforementioned model was combined with a computational androgynous phantom to represent patient's irradiation for non-malignant shoulder syndrome. The phantom simulated a typical adult patient of weight 73.5 kg and height 179 cm and it was produced with the aid of a commercially available software (Body Builder, White Rock Science, Los Alamos, NM) using the descriptions of Cristy and Eckerman [13]. A two-field isocentric technique was used to simulate the radiation therapy in the region of shoulder. Two opposing anteroposterior (AP) and a posteroanaterior (PA) treatment fields were modeled. The dimensions of the simulated treatment portals were equal to $10 \times 15\,cm^2$. The positions and dimensions of the fields were determined by a senior radiation oncologist.

Monte Carlo simulations were used to find the average radiation dose (D_{av}) received by all critical organs for which the BEIR-VII report [14] has provided an age- and gender-specific risk coefficient enabling the direct assessment of the probability for radiation carcinogenesis. The D_{av} was calculated for the following 10 organs: stomach, colon, liver, lung, prostate, urinary bladder, thyroid, female breast, uterus and ovary. The prostate gland was not included within the body of the computational phantom. The missing tissue was represented by adding a 3.6-cm-diameter sphere below the urinary bladder [15]. Monte Carlo calculations were made by assigning the necessary F6 tallies within the geometrical cells representing each critical organ of the phantom. For each organ comprising two or more geometrical cells, the D_{av} was taken as the mass weighted average of the calculated doses to the organ's cells. The obtained D_{av} values corresponded to a total target dose of 6 Gy which may be delivered in six fractions of 1 Gy [16]. The above fractionation scheme is often applied for the irradiation of patients with shoulder syndrome [3,8]. The target dose associated with each AP and PA field irradiation was 3 Gy. Additional Monte Carlo simulations were made to determine the effect of the dimensions of the AP and PA fields on the radiation dose to critical organs. The standard field size of $10 \times 15\,cm^2$ was decreased to $9 \times 14\,cm^2$ for these dosimetric calculations.

2.1.2. Cancer risk to organs excluded from the treatment fields

All critical organs of the mathematical phantom except a part of the lung were entirely excluded from the simulated AP and PA fields. The stomach, colon, liver, prostate, bladder, thyroid, female breast, uterus and ovary were characterized as out-of-field organs. These out-of-field structures of interest were exposed to scattered radiation and head leakage and, therefore, they received low doses of less than 2.5 Gy. For absorbed doses falling in the region of 0.1–2.5 Gy, the risk for carcinogenesis increases linearly with the dose [17]. The BEIR-VII committee [14] reported that the linear-no-threshold (LNT) model provides the most reasonable relationship between the exposure to low doses and the probability for solid cancer induction. The committee also suggested that the LNT hypothesis may be extended to radiation doses below 0.1 Gy. The data provided in the BEIR-VII report [14] enable the direct estimation of the lifetime attributable risk (LAR) of site-specific solid cancer incidence. The LAR for a particular site of an exposed patient corresponds to the probability that this patient will develop a radiogenic malignancy at this site at any time following the exposure to ionizing radiation.

The methodology of the BEIR-VII report, based on the LNT approach, has been extensively employed for estimating the out-of-field cancer risk from photon-beam radiotherapy [15,18,19]. For each out-of-field organ examined in this study, the lifetime attributable risk (LAR) for cancer development was found by multiplying the calculated D_{av} value by an organ- age- and gender-specific risk factor derived from the BEIR-VII report [14]. Cancer risk assessments were made by assuming 50- and 60-year-old male and female patients. Previous studies reported that the mean patient's age at the time of irradiation for shoulder syndrome was 57 [3] and 62 years old [8]. The LAR assessments were compared with the respective lifetime intrinsic risk (LIR) values derived from the most recent SEER Cancer Statistics Review [20].

2.2. Radiotherapy planning study

2.2.1. Calculation of the organ equivalent dose to lung

The estimation of the cancer risk to organs exposed to high therapeutic doses of more than 2.5 Gy can be made with the aid of non-linear models [21]. Schneider et al. [22] introduced a mechanistic model enabling the assessment of the probability for carcinogenesis at sites which are partly or entirely encompassed by the treatment fields. The organ-specific dose response relations for cancer development were defined by data derived from the Atomic bomb survivors and a Hodgkin cohort exposed to radiotherapy doses [22]. The model is based on the use of the organ equivalent dose (OED) which accounts for the target dose fractionation and the cell repopulation between dose fractions [22]. The mechanistic model has been successfully applied for estimating the cancer risk to organs exposed to therapeutic doses [23,24].

The OED of lung, which was partially encompassed by the treatment volume, was calculated in this study. The accurate knowledge of the dose distribution within the lung is a prerequisite for the OED calculation. The above dose distribution was defined with the aid of a differential dose volume histogram (DVH) derived from a three-dimensional radiotherapy planning system (XiO, CMS Inc., St Louis, USA). Two different treatment planning computed tomography (CT) examinations of a female and male patients, who were previously treated in our department, were used. The CT scans were performed on a 16-slice unit (Somatom Sensation 16, Forcheim, Germany). The patients were in the sixth decade of life and their lungs were normal. The contouring procedure was made by the same radiation oncologist who determined the primarily irradiation site for the Monte Carlo calculations. The target volume and the lungs were manually delineated on a slice-by-slice basis. The anatomical area encompassed by the target site in the two different patients' CT examinations was similar with that defined in the computational phantom used for the MCNP experiments. As a result, the dimensions of the treatment fields in the planning system were similar with those employed for Monte Carlo simulations. The three-dimensional conformal radiotherapy plans for shoulder

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