Chapter 23

Radiation and Telomere Biology Disorders

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Introduction

Individuals with dyskeratosis congenita (DC) and related telomere biology disorders (TBDs) have very short telomeres for their age caused by pathogenic germline variants mutations in genes essential in telomere maintenance (see also Chapter 2, Why Telomeres Matter and Chapter 4, The Genetics of Dyskeratosis Congenita and Telomere Biology Disorders) [1-3]. Telomeres are long repeats of DNA nucleotides [$(TTAGGG)_n$] and a protein complex at chromosome ends essential for chromosomal stability. In general, the telomeric DNA repeats are sensitive to DNA damage caused by radiation and oxidative stress [4-6]. Since individuals with DC/TBDs have very short telomeres from birth, they may also be more sensitive to the effects of both ionizing and non-ionizing ultraviolet radiation [7, 8].

When therapeutic or interventional radiation [1] is being considered for patients with DC/TBDs, precautions should be taken to prevent or minimize harm. It should be noted that there are very little data on radiation effects in these individuals. The radiation risk from clinically indicated medical imaging is extremely low. Diagnostic exams should be performed if the information obtained from medical imaging is important for patient care. This chapter reviews the types of radiation that may be of clinical importance in DC/TBDs.

Types of Radiation

Ionizing radiation is radiation that can pass through the body. It carries enough energy to liberate electrons from atoms, creating ions, which can in turn damage DNA and cause cell death. Examples include X-rays and gamma rays used in medical imaging and certain interventional or therapeutic procedures.

Diagnostic radiation, such as x-rays used in bone density scans, radiography, diagnostic fluoroscopy, computed tomography (CT), and gamma rays used in single photon emission tomography (SPECT) and positron emission tomography (PET), typically use very low levels of ionizing radiation. Interventional radiation is sometimes used in interventional radiology, cardiology, and operating room procedures, and uses moderate levels of X-ray ionizing radiation. Therapeutic radiation involves much higher doses of ionizing radiation, including X-rays and gamma rays, and is designed to treat cancer or prepare a patient for hematopoietic cell transplant (HCT).

Ultraviolet radiation consists of light rays slightly more energetic than the color violet and can excite electrons to move to a higher energy state. However, such radiation does not carry enough energy to produce charged ions, so ultraviolet radiation is considered “non-ionizing”. For protection from ultraviolet radiation, individuals with DC/TBDs need to avoid tanning beds and take precautions to minimize sun exposure as much as reasonable (see also Chapter 6, Dermatologic Manifestations) [1].

Ultrasounds (sonograms) and magnetic resonance imaging (MRI) do not use ionizing radiation, have no known ill effects specific to patients with DC/TBDs, and are not discussed in this chapter.

Effects of Radiation

There are two types of radiation effects: tissue reactions and stochastic effects.

Tissue Reactions

Tissue reactions are defined as those that cause cell death or an injury in populations of cells. The type of tissue reaction is based on the dose of radiation, sensitivity of the specific tissue type exposed, and the individual’s underlying sensitivity to radiation. There is a threshold dose to producing a tissue reaction such that there are doses below a certain level in which there is no reaction, and above which the harm to tissue reaction increases as the dose increases [9].

Therapeutic radiation (generally thought of as higher-dose radiation) is used to create a tissue reaction in order to kill cancer cells. It is also used as part of some hematopoietic cell transplantation (HCT, see also Chapter 13, Hematopoietic Stem Cell Transplantation) preparation regimens to eliminate the patient’s bone marrow cells so they can receive donor cells. Tissue reactions can also occur in healthy tissue near the area of the body targeted by therapeutic radiation. Very rarely, tissue reactions occur when using moderate dose interventional radiation as part of a procedure that requires X-rays to see inside the body.

Stochastic Effects

Stochastic (random) effects generally refer to the potential occurrence of cancer in an individual who received radiation therapy, or after radiation exposure from medical imaging or interventional imaging or procedures [9]. Stochastic effects of radiation might occur years after exposure to ionizing radiation. They can be thought of as the long-term consequences of radiation exposure. It is often difficult to know whether stochastic effects are caused by radiation, lifestyle choices, or from natural biological or environmental causes. The risk of cancer is believed to increase with increasing radiation dose, although this has not yet been definitively proven for effective doses less than 100 mSv [9].

Therapeutic Radiation

Therapeutic radiation is high dose radiation used to create controlled tissue reactions as part of a clinical protocol. Examples where this type of radiation is used include cancer radiotherapy and total body irradiation for HCT.

Patients with DC/TBDs appear to have a lower threshold for tissue reactions than other patients when exposed to therapeutic radiation [1, 8, 10, 11]. However, detailed studies of ionizing radiation in DC/TBDs have not been conducted to better define these lower thresholds. Even though tissue sparing techniques like proton therapy show promise [11], more studies are needed to better determine optimal use of therapeutic radiation for cancer in patients with DC/TBDs [1].

HCT protocols for patients with DC/TBDs are being developed that use reduced intensity total body irradiation, or none at all, and have improved clinical outcomes compared with full dose irradiation procedures (see also Chapter 13, Hematopoietic Stem Cell Transplantation) [12-14].

Interventional Radiation

Interventional radiation is moderate dose radiation used in minimally invasive procedures to see inside the body while performing certain treatments or surgeries. For complex cases, there is a chance of exceeding a threshold dose that can cause unintentional tissue reactions [15].

Based on what has been observed from therapeutic radiation for patients with DC/TBD, there is reason to believe that tissue reactions might occur at a lower threshold than in the general population for interventional radiation. Examples of interventional radiation include certain cardiology, urology, and angiography procedures.

It is important to know if X-rays are used for these types of clinical procedures, and to know where X-rays enter the body. This information will help patients identify potential rashes from the interventional radiation exposure, which is often the first sign of a tissue reaction. Patients should report any rashes of concern to their primary provider.

Diagnostic Radiation

Diagnostic radiation (low dose radiation) is used for medical imaging. This type of radiation includes X-rays used in mammography, bone density scans, radiography, diagnostic fluoroscopy, computed tomography (CT), and gamma rays used in nuclear medicine (NM) studies, including single photon emission computed tomography (SPECT) and positron emission tomography (PET). The doses used in diagnostic procedures are far too low to cause tissue reactions but could cause stochastic effects in patient populations.

Diagnostic radiation doses can be compared to natural background radiation (see Table 1). For diagnostic imaging, the chances of stochastic effects are so low that they cannot be measured in an individual patient, but are estimated for patient populations. In fact, many radiation safety professional organizations now clearly state that there could very well be no effect for effective doses below 100 mSv [16, 17]. However, the medical imaging community continues to assume there is some risk from radiation at these lower doses, to be conservatively safe.

Although patients with DC/TBDs might be more sensitive to stochastic effects from ionizing radiation than the general population, the doses required for diagnostic purposes are very low. Clinically indicated exams should be performed when needed. One must always weigh the benefit of proceeding with care using information from imaging against the very low, and possibly non-existent, harm from the imaging exam, as well as the harm in proceeding with care without appropriate imaging.

Summary

Radiation exposure of individuals with DC/TBDs should be managed proactively. Patients with DC/TBDs are more sensitive to therapeutic radiation (high dose radiation) than the general population, but the degree of this sensitivity has not been established. Clinically indicated interventional procedures (interventional radiation) and medical imaging (low dose radiation) should be performed when clinically appropriate for optimal patient care since the benefit of performing these clinically indicated procedures or exams far outweighs the potential harm from radiation effects.

Table 1. Patient dose from diagnostic X-ray exams [18, 19] compared to natural background radiation to provide context. Background radiation dose varies from 1 to 10 mSv per year [20] depending on where one lives. This table compares medical imaging effective doses to the natural background radiation level of 4 mSv per year.

Diagnostic Exam	X-ray Dose	Amount of Time to Receive Similar Dose from Natural Background Radiation
Knee X-ray, Dental X-ray	0.005 mSv	11 hrs
Dental panoramic X-ray	0.01 mSv	22 hrs
Bone Density Scan	0.015 mSv	1.5 days
Chest X-ray	0.02 mSv	2 days
Lumbar spine X-ray	1.5 mSv	4.5 months
Head CT	2 mSv	6 months
Chest CT	7 mSv	21 months
Abdomen/Pelvis CT	14 mSv	42 months

Abbreviations: millisievert (mSv), a measure of the effective dose of radiation. Effective dose is used to estimate stochastic risk in patient populations.

Table 2. Summary of Chapter Terminology

Types of Radiation	
Ultraviolet Radiation	• Ultraviolet (UV) light (UV radiation) is invisible to the human eye. It is not energetic enough to ionize atoms and is therefore considered non-ionizing radiation. It can, however, damage overexposed skin. • A beneficial effect of UV radiation exposure is vitamin D production in the body. • UV radiation comes from the sun and is filtered by the atmosphere. UV radiation is also produced by electrical arcs (like welding), tanning lamps, and blacklights.

Ionizing Radiation	● Ionizing radiation is powerful enough to remove electrons from atoms (ionize atoms), which can damage DNA and cause cell death. ● Ionizing radiation can cause tissue reactions and stochastic effects (see below). ● Most cosmic ionizing radiation is absorbed by the atmosphere. ● Diagnostic, interventional, and therapeutic radiation in medicine eases pain and saves lives.
Patient Exposure to Ionizing Radiation	
Background Radiation	● Low dose radiation. ● Background radiation comes from the sky, the soil, and what we eat. We naturally live in a bath of radiation.
Diagnostic Radiation	● Low dose radiation. ● Medical uses include X-rays and gamma rays used for medical imaging. ● Ionizing radiation is used to see inside the body to aid with important diagnosis and monitor function. ● Stochastic effects might occur from diagnostic radiation. ● Patients with DC/TBDs might be more sensitive to stochastic effects than the general population, but not so sensitive that clinicians should avoid clinically appropriate medical imaging.

Interventional Radiation	● Moderate dose radiation. ● Ionizing radiation is used in minimally invasive procedures to see inside the body while performing treatments or surgeries. ● Very rarely, radiation levels exceed a threshold where tissue reactions occur. ● Based on what has been observed from therapeutic radiation, there is reason to believe that tissue reactions might occur at a lower threshold for patients with DC/TBDs than in the general population for interventional radiation.
Therapeutic Radiation	● High dose radiation. ● The purpose of therapeutic radiation is to create controlled tissue reactions as part of a clinical protocol. ● Examples where this type of radiation is used include cancer radiotherapy for cancer treatment and total body irradiation for hematopoietic stem cell transplants. ● Case studies of cancer therapy in patients with DC/TBDs have shown that tissue reactions occur in non-cancerous tissue at lower doses than the general population. Total body irradiation is more toxic to these patients, which has led to the development of reduced intensity or elimination of radiation in conditioning in hematopoietic cell transplant protocols.
Radiation Effects	
Stochastic Effects	● Effects that can occur by chance, especially malignancies or genetic mutations. The probability of occurrence increases with radiation dose, but the severity is independent of dose. ● There is no threshold; severity of effect is not dose-dependent.

Tissue Reactions	●	Injury in populations of cells or cell death.
	●	There is a threshold dose. Once above the threshold, the severity of the reaction increases as dose is increased.

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