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A STUDY OF PREDICTED BONE MARROW DISTRIBUTION ON CALCULATED MARROW DOSE FROM EXTERNAL RADIATION EXPOSURES USING TWO SETS OF IMAGE DATA FOR THE SAME INDIVIDUAL

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Abstract

Red bone marrow is among the tissues of the human body that are most sensitive to ionizing radiation, but red bone marrow cannot be distinguished from yellow bone marrow by normal radiographic means. When using a computational model of the body constructed from computed tomography (CT) images for radiation dose, assumptions must be applied to calculate the dose to the red bone marrow. This paper presents an analysis of two methods of calculating red bone marrow distribution: 1) a homogeneous mixture of red and yellow bone marrow throughout the skeleton, and 2) International Commission on Radiological Protection cellularity factors applied to each bone segment. A computational dose model was constructed from the CT image set of the Visible Human Project and compared to the VIP-Man model, which was derived from color photographs of the same individual. These two data sets for the same individual provide the unique opportunity to compare the methods applied to the CT-based model against the observed distribution of red bone marrow for that individual. The mass of red bone marrow in each bone segment was calculated using both methods. The effect of the different red bone marrow distributions was analyzed by calculating the red bone marrow dose using the EGS4 Monte Carlo code for parallel beams of monoenergetic photons over an energy range of 30 keV to 6 MeV, cylindrical (simplified CT) sources centered about the head and abdomen over an energy range of 30 keV to 1 MeV, and a whole-body electron irradiation treatment protocol for 3.9 MeV electrons. Applying the method with cellularity factors improves the average difference in the estimation of mass in each bone segment as compared to the mass in VIP-Man by 45% over the homogeneous mixture method. Red bone marrow doses calculated by the two methods are similar for parallel photon beams at high energy (above about 200 keV), but differ by as much as 40% at lower energies. The calculated red bone marrow doses differ significantly for simplified CT and electron beam irradiation, since the computed red bone marrow dose is a strong function of the cellularity factor applied to bone segments within the primary radiation beam. These results demonstrate the importance of properly applying realistic cellularity factors to computation dose models of the human body.

Keywords

bone marrow; computed tomography; dosimetry; Monte Carlo

INTRODUCTION

Computational models of the human body are essential tools for the understanding of radiation dose distribution for different exposure geometries. Calculation of the effective dose, as a marker for comparative risk assessment, requires the determination of equivalent dose to many individual organs in the body. Most of the organs important in radiation dosimetry are well defined by computed tomography (CT) images, but one radiosensitive tissue that is not easily observable is the red bone marrow. Since it is difficult to directly identify this structure in the body of an individual, theoretical assumptions must be applied to properly incorporate the anatomical information into computational models of the human body.

The objective of this study is to evaluate different algorithms for predicting the distribution of the red bone marrow in an adult male. This is completed using the two data sets available from the Visible Human Project (VHP)—the color images and the CT images of the same individual. The color images were previously used to construct the VIP-Man (VIsible Photographic-Man) model that defines red bone marrow directly from the color information (Xu et al. 2000). The CT images represent the kind of images that are clinically available medical images. Since the two sets of images have identical anatomy, it is possible to study various assumptions about red bone marrow distribution and to evaluate the accuracy of the computed dose to the red bone marrow in Monte Carlo simulations. This paper then presents results of testing the algorithms in three different dosimetry applications: 1) external photon beams, 2) CT examinations, and 3) whole-body electron-beam irradiation for cancer treatment.

Bone tissue and structure

Bone and marrow have unique properties. Bone tissue can be formed into two main types of bone structure, classified primarily by differences in hardness, porosity, and soft tissue content: compact (also called cortical) bone and trabecular bone. Compact bone is the dense solid tissue that forms the outer walls of all of the bones. Trabecular bone has a spongy appearance, consisting of a complex latticework of thin structures of hard bone. Trabecular bone is located throughout the interior of the flat bones and is found at the ends of the long bones. The cavities between the bone trabeculae are filled with soft tissue known as the bone marrow. The region that consists of trabecular bone and bone marrow is known as the spongiosa. In addition, the center of some bones, particularly the long bones of the arms and legs, contains a region in the interior of the compact bone where no bone trabeculae or red bone marrow is present, known as the medullary cavity.

Bone marrow is composed of red and yellow bone marrow. Red and yellow bone marrow is alternatively classified as active and inactive bone marrow, and the terms are interchangeable. The terms “active” and “inactive” refer to the hematopoietic function. Red bone marrow gets its color from the large quantities of red blood cells (erythrocytes) being produced. In addition to the red blood cells, the red bone marrow produces most of the white blood cells and all of the platelets found in the blood stream. Yellow bone marrow gets its color from the deposits of adipose or fatty tissue that take up the majority of the space in the tissue. Red and yellow bone marrow differs only slightly in chemical makeup, mostly due to the iron content in the hemoglobin of red blood cells, but they have very similar densities and are therefore indistinguishable through normal radiographic methods.

Red bone marrow distribution

The quantity of hematopoietically active cells in the bone marrow is known as the marrow cellularity, and is defined as the volume fraction of marrow occupied by hematopoietic cells. The cellularity of the bone marrow in an individual bone varies depending upon the type of

bone and the age of the individual (Cristy 1981). These values of marrow cellularity have been adopted by the International Commission in Radiological Protection (ICRP) in Publication 70 “Radiological Protection Data: The Skeleton” (ICRP 1995). The reference cellularity values for an adult range from a minimum of 0.25 for the upper half of the humeri and femora, to a maximum of 0.7 for the ribs, spine, sacrum, and sternum. These reference values attempt to reflect the characteristics of the average population, but the degree of variability within the population has not been well quantified.

Previous methods of calculating dose to the red bone marrow

Over time, a variety of methods have been applied to the calculation of red bone marrow dose when a Monte Carlo method is used. For assessing dose from external sources (external to the bone, not necessarily to the body), the methods used fall into two major categories: those that treat the bone or spongiosa as a homogenous tissue and those that approximate the complex heterogeneous mixture of bone tissues.

The first category of techniques for dose estimates treats the bone as a single tissue for purposes of inclusion in Monte Carlo simulations. The tissue is defined as consisting of the average composition and density of all bone tissues (hard bone, red bone marrow, and yellow bone marrow) in the body. The simplest of estimates assumes that bone marrow absorbs energy per unit mass as efficiently as hard bone does, and therefore applies a factor equal to the mass fraction of red bone marrow in the bone to the energy deposited in the mixture. This method was applied to the original MIRD5 (Snyder et al. 1969) and MIRD5-Revised (Snyder et al. 1978) models for photon dose calculations. The authors recognized at the time that this assumption would result in an overestimation in the red bone marrow dose for photon energies below about 200 keV. Katagiri et al. (2000) used a similar process in the calculation of energy deposition from external electron exposures.

To account for the preferential energy absorption in hard bone at low photon energies, other authors included a second scaling factor to this partitioning technique (Kramer et al. 1982; Rosenstein 1976). The second factor is the ratio of the mass-energy absorption coefficient in red bone marrow to that of the homogeneous bone tissue. The two-factor technique improves dose estimates at the lower photon energies, but it presumes the existence of charged-particle equilibrium within the spongiosa. In reality, photoelectrons produced in the trabeculae would be expected to increase the absorbed dose to the marrow tissues of the spongiosa. These authors also proposed the use of a third factor, the dose enhancement factor as tabulated from experimental studies by Spiers (1969), to further improve the marrow dose estimate. However, Lee et al. (2006) demonstrates that the dose enhancement factors do not greatly contribute to the overall red bone marrow dose except in the case of the cranium. The original Spiers data have been updated by King and Spiers (1985) for use in this type of model. For electron exposures, a similar technique was used by Schultz and Zoetelief (1996) involving the relative mass stopping powers of red bone marrow and homogeneous bone. In principle, these techniques could be applied to both stylized models and to image-based models, as long as the bone tissue was modeled as a homogeneous substance.

An alternate approach to photon dosimetry of red bone marrow and of the bone endosteum, or bone surface tissue, was adopted by Cristy and Eckerman (1987) in the Oak Ridge National Laboratory (ORNL) series of stylized models. In this technique, rather than calculating the energy deposited in the Monte Carlo simulation, the energy-dependent photon fluences within the skeletal regions of the model are tallied. Then, fluence to absorbed dose response functions are utilized to assign values of absorbed dose to each tissue region. These values are derived using previous studies of path-length distributions of bone trabeculae and marrow cavities (Darley 1972; Whitwell 1973; Beddoe 1976).

The second class of techniques directly considers the heterogeneity of bone in the Monte Carlo radiation transport simulation using an image-based phantom. Many of these methods utilize the density information present in CT images to define the structure of the bone. This CT-based method was first proposed by Zankl and Wittmann (2001) for a family of tomographic phantoms, and has also been adopted by others including Kramer et al. (2003) in the Male Adult voXel (MAX) and Female Adult voXel (FAX) phantoms. In this approach, voxels corresponding to a mixture of bone and marrow are identified by linear interpolation between two threshold CT numbers representing pure marrow and pure hard bone.

The calculated CT number for a voxel in a CT image slice represents the derived photon attenuation coefficient, or relative electron density, of the material at that location. The linear dimensions of the marrow cavities and bone trabeculae are distributed around the most probable values of about 500 μm for the marrow cavities and 200 μm for the trabeculae (Rajon et al. 2000). Since the voxel size in CT images are usually much larger than this, most voxels located in the spongiosa will include a mixture of the hard bone tissue of the trabeculae and bone marrow. Unless CT resolution for human in vivo images is drastically improved, we will have to continue to deal with this challenge in clinical practice of identifying the bone tissues. The volume fraction of the marrow (or bone) in the voxel can be computed by performing linear interpolation between the CT number values corresponding to a bone voxel and a marrow voxel (Zankl and Wittmann 2001).

To perform the linear interpolation of CT numbers, the thresholds for pure marrow and pure hard bone must be predetermined. Threshold values for voxels of hard bone and marrow are chosen by inspection of the grey value distribution of the bones in the CT images. A lower level threshold, GV_{marrow} , is chosen such that a voxel with a grey value below this value is assumed to consist only of marrow, and an upper level threshold, GV_{bone} , is chosen such that a voxel with a grey value above this value is assumed to consist only of hard bone.

The values of GV_{bone} and GV_{marrow} are unique to an individual set of images, and depend upon several factors, including the type and model of CT machine and parameters used to obtain the images. Zankl and Wittmann (2001) report using values of 2,040 and 800, respectively, in their initial work with this method. Kramer et al. (2003) applied the method to CT images that had been converted to 8-bit numbers from 12-bit numbers (which reduces the precision of the CT numbers by a factor of 16), and used threshold values of 170 and 65. When the grey value for a voxel falls between these two thresholds, the fraction of marrow in a given voxel is computed by

$$f_{\text{marrow}} = \frac{GV_{\text{bone}} - GV}{GV_{\text{bone}} - GV_{\text{marrow}}}. \quad (1)$$

Eqn (1) only defines the fractions of hard bone and bone marrow. Red bone marrow and yellow bone marrow cannot be distinguished in the same manner because they differ in density by less than 5%, which is much lower than the deviation caused by the partial volume effect. An additional factor is applied to f_{marrow} to estimate the content of red bone marrow present in the voxel. Zankl and Wittmann (2001) applied a simple algorithm to the voxels, assuming that 50% of the marrow is active ($f_{\text{RBM}} \times f_{\text{marrow}} \times 0.5$), except in the lower extremities ($f_{\text{RBM}} = 0$), implying that the effect of red bone marrow distribution on the calculated dose is minimal.

They reported that, using this method, the whole-body red bone marrow mass of the Golem phantom was sufficiently close to the value of red bone marrow mass adopted by ICRP 70 (Zankl and Wittmann 2001). However, in comparison with the values given by Cristy (1981), that calculation can differ by as much as 30% from the expected marrow cellularity.

This method has been applied to many different computational models derived from CT data (Fill et al. 2004; Sato et al. 2007).

Kramer et al. (2003) proposed a similar method for use with the MAX and FAX models. In that application, the red and yellow bone marrow was partitioned based upon the cellularity factors adopted in ICRP 70 to achieve a better estimate of red bone marrow dose. In the MAX model, the upper and lower GV thresholds and the skeletal tissue distribution in specific bones were adjusted to achieve the desired quantity of red bone marrow (Kramer et al. 2003).

A related advanced method involves introducing high resolution images of microCT scans of excised bone segments into the spongiosa region of skeletal model (Jokisch et al. 1998; Kramer et al. 2006, 2007). This method provides a detailed microstructure of the marrow cavities and bone trabeculae. If the entire skeleton is filled with a model from microCT images, an untenable strain on computer memory and processor speed would result (Kramer et al. 2006). In principle, a two-scale model could be constructed to cover both micro- and macroscopic information (Shah et al. 2005). Multi-scale geometric models may eventually be implemented using advanced geometry tools such as those reported by Xu et al. (2007). This type of model is critically important for understanding the dosimetry of internal emitters (Sgouros 2005). However, microCT also is unable to differentiate between active and inactive marrow, so the methods of calculating red bone marrow dose described in this paper are still required.

VIP-Man anatomical model and the VHP

Another technique that treats the heterogeneity of the bone was implemented in the VIP-Man model, previously constructed at Rensselaer from the color photographic data of the VHP. VIP-Man is a high-resolution and highly detailed model, with nearly 1,400 individual structures initially segmented, and many others specifically identified for dosimetric purposes (Spitzer and Whitlock 1998; Xu et al. 2000). To date this is the only model of red bone marrow spatial distribution derived directly from image analysis.

Since color, rather than electron density as seen in CT images, was the basis for segmentation, it was possible to delineate red bone marrow from other components of the bone such as the yellow marrow. Marrow cellularity is commonly determined using visual observation of biopsy samples, so such direct image analysis is a realistic method for identifying red bone marrow from VHP color photographs (Ho-Yen and Slidders 1978). It was recognized that the $0.33 \text{ mm} \times 0.33 \text{ mm} \times 1 \text{ mm}$ voxel size of VIP-Man is larger than the size of active bone marrow sites, so each voxel may contain a mixture of red bone marrow, yellow bone marrow, and hard bone. As a voxel may only be identified by a single tissue type, the voxel is assigned to the dominant bone tissue by considering the composite color of a voxel and by applying an algorithm to identify its contents (Xu et al. 2000).

For analysis of the color photographs, a quantifiable value must be used to differentiate red bone marrow from the surrounding tissue. The VIP-Man model uses the value of 'redness' of a voxel, defined as the degree to which the red channel contributed to the total intensity of the voxel, or

$$\text{Redness} = \frac{R}{R+G+B}, \quad (2)$$

where R , G , and B are the values of the red, green, and blue channels respectively, ranging from 0 to 255 (Chao 2001). Redness is related to the concept of hue in the Hue, Saturation, Value color space, but is more straightforward to compute and evaluate in our application.

Color saturation was also investigated but was not found to be descriptive of red bone marrow location.

The total mass of red bone marrow in the body is sensitive to the choice of redness threshold for assigning a particular voxel to the red bone marrow. To choose the correct threshold, the critical value that separates the red bone marrow from the non-red bone marrow voxels is chosen through histogram analysis using Otsu's method (Otsu 1979). The redness of hard bone and yellow bone marrow are similar in value, so an excess of hard bone voxels can confound the selection of a threshold value, since Otsu's method is less reliable when the number of "background" (or bone and yellow marrow) and "foreground" (or red bone marrow) pixels differs too greatly (Sezgin and Sankur 2004). To minimize this effect, only bone segments containing a significant quantity of red bone marrow (ribs, spine, sacrum, and sternum) are included, and voxels more than five pixels in any direction from a red bone marrow voxel were not counted, so as to eliminate large regions of cortical bone. Fig. 1 presents the histogram of the redness of the voxels in the selected bones of the VIP-Man skeleton (a discontinuity in the curve at 0.5, presumably due to an image processing artifact, has been smoothed in the figure, but does not affect the threshold calculation). The histogram has a bin width of 1/256 due to the discrete nature of the RGB source images. The threshold value between the visible peaks obtained using Otsu's threshold selection method has a value of 0.47. Therefore, voxels of bone where the redness exceeded 0.47 were identified as red bone marrow.

The accuracy of this segmentation is limited by the voxel size in VIP-Man. The data from Spiers (1969) indicate that the mean path-length through a marrow cavity (in this case, for a cervical vertebra) is 909 μm , with a most probable value of about 500 μm . This is the same order of magnitude as the size of the VIP-Man voxel. Red bone marrow will be undercounted when a small amount is present in a voxel not assigned to red bone marrow and overcounted when a small amount of other tissue is present in a voxel that is assigned to the red bone marrow. The total skeletal red bone marrow mass in VIP-Man is close to the quantity in ICRP Reference Man, and the masses of red bone marrow in the various bone segments of the VIP-Man compare favorably with ICRP Reference Man, indicating that the errors from the segmentation are small or cancel each other out (ICRP 1995, 1975).

The VHP image sets include a set of CT images for the same subject that was used to create the VIP-Man model. The CT images were taken after the freezing of the cadaver, so the position of the limbs and organs corresponds exactly to the positions seen in the color photographs used to create the VIP-Man, although the CT's view field was too small to cover a portion of the arms (Spitzer and Whitlock 1998). Furthermore, the slice thickness of the CT scan is the same (1 mm) as the thickness of the slice in the color photographic data.

By performing the color image analysis of the bone interior using the VHP color photograph data set, we have a unique "gold standard" for this individual against which to compare the red bone marrow mass derived from analysis of CT images of this same individual. Since no in vivo technique exists to measure the distribution of red bone marrow throughout the body, this standard provides an opportunity to compare different methods of calculating red bone marrow dose from CT-based computational models.

MATERIALS AND METHODS

VHP—CT images

The segmented color photography data of the VHP provide a convenient resource for segmenting the bone segments in the CT data set. The voxels that are part of the skeleton must be identified and distinguished from the surrounding soft tissue. The bone segments in the

Visible Human Project Computed Tomography (VHPCT) data set are identified by a three step process:

1. Each CT image slice was registered against the segmented color image corresponding to the same position in the body with corresponding and nearby pixels labeled with the proper bone segment;
2. Due to minor distortions in the CT image, some soft tissue on the exterior of the bone was identified as bone in step 1, so soft tissue was iteratively eroded down to the hard bone voxels using three-point connectedness of a threshold CT number; and
3. Manual corrections were made for errors that remained after step 2, mostly in locations where non-bone soft tissue was completely surrounded by bone, such as in the spinal column and portions of the sacrum, and other rare locations.

Grey value thresholds for VHPCT were chosen by analyzing the CT image set. The lower level threshold, GV_{marrow} , is the average of the grey values in the medullary cavities of the long bones. The upper threshold, GV_{bone} , is selected as the point of the local minimum between the grey values population corresponding to the spongiosa and those corresponding to the cortical bone. Due to the statistical fluctuations among grey values, a histogram of grey values is not a smooth function, so a strict mathematical treatment of the histogram is not possible. The best approximation for GV_{marrow} is 975 and for GV_{bone} is 2,250.

The first method applied to VHPCT to compare the red bone marrow distribution and dose values is equivalent to the method described by Zankl and Whittmann (2001). Except for the bones in the extremities, all bone marrow is assumed to consist of 50% cellularity. We designate this assumption as Method 1.

We have also implemented a method similar to that described by Kramer et al. (2003) to apply cellularity factors in a way as applicable to arbitrary CT-based models as Method 1. In this method

$$f_{\text{RBM}} = f_{\text{marrow}} \times CF_{\text{seg}}, \quad (3)$$

where CF_{seg} is the cellularity factor for the bone segment from Cristy (1981). We designate this approach as Method 2 for comparison of red bone marrow distribution and dose.

Using the VHPCT data set with the bones identified and the VHP color photograph data set as segmented in VIP-Man, three values of red bone marrow mass for the whole body and for individual bone segments are compared:

1. the mass of the red bone marrow as calculated from the CT data set under the assumptions of Method 1;
2. the mass of the red bone marrow as calculated from the CT data set under the assumptions of Method 2; and
3. the mass derived from VIP-Man, which provides the “gold standard,” or the best available representation of the red bone marrow whole-body distribution for this individual.

Monte Carlo implementation

Monte Carlo simulations for this work were performed using the Electron-Gamma-Shower 4 (EGS4) code (Nelson et al. 1985) with the PRESTA electron transport models (Rogers 1988) on a 3.4 GHz Pentium 4 running Slackware Linux. An EGS4 user code is used to carry out the

simulations, which we have called VHPCT, and which was adapted from the EGS4-VLSI used with VIP-Man (Chao 2001). Bone segment identification numbers were converted into 4-bit values and combined with the 12-bit CT numbers to form a single 16-bit value that is passed to the EGS4 code (Caracappa 2006).

Material information for the EGS4 simulation is precompiled using the PEGS4 subroutines. Elemental composition of bone/marrow mixtures is broken into 51 groups, ranging from 100% bone to 100% marrow in 2% increments and generated based upon International Commission on Radiation Units and Measurements (ICRU) data. Density of a particular voxel is calculated at run-time to the precision of the CT number using a linear interpolation between the average ICRU marrow density and the ICRU compact bone density, as

$$\rho = 1.005 + [(1 - f_{\text{marrow}}) \times 0.915] \text{ g cm}^{-3}, \quad (4)$$

where f_{marrow} is the fraction of marrow corresponding to the grey value of the voxel as calculated in eqn (2). Absorbed dose to organs other than the bone is not considered for this work, so other organs are not segmented from the VHPCT data. However, radiation interactions in the other body tissues are necessary in realistic dose calculations, so the methodology described in Schneider et al. (2000) is used to determine material composition and density for all voxels in the CT images not identified as bone. This method is commonly used in Monte Carlo-based treatment planning.

To calculate the marrow dose from the energy deposited in the bone/marrow mixture by the Monte Carlo simulations, we applied the three-factor correction method on a voxel-by-voxel basis as described in Kramer et al. (2003). Although the voxel size in VHPCT is somewhat smaller than for MAX and FAX, we chose to maintain the same kerma approximation limit of 200 keV, since the range for 200 keV electrons in marrow is still small compared to the size of the voxel. The tally of energy deposited in red bone marrow is calculated by

$$E_{\text{RBM}} = E_{\text{VOX}} \times f_{\text{RBM}} \times \frac{\left[\frac{\mu_{\text{en}}}{\rho}(E) \right]_{\text{RBM}}}{\left[\frac{\mu_{\text{en}}}{\rho}(E) \right]_{\text{VOX}}} \times S_{\text{KS}}(E), \quad (5)$$

where f_{RBM} is the fraction of red bone marrow as calculated by either Method 1 or Method 2, and S_{KS} is the King-Spiers dose enhancement factor.

Three dosimetry applications are considered in this work: 1) parallel photon beams representing typically encountered sources in occupation exposures, 2) CT examinations of patients, and 3) electron-beam irradiation of the type used for cancer treatments. The parallel beam is representative of either a large source or a finite source at sufficient distance from the body that the radiation field is essentially uniform over the entire area of the body. In this situation, the entire body is exposed to the incident radiation field. Four different source directions are considered: anterior-posterior (AP), posterior-anterior (PA), left-lateral (LLAT), and right-lateral (RLAT). Fig. 2 illustrates the orientation of the radiation source and the VHPCT body in these exposure scenarios. The photons are modeled with photon energies that span the range from those corresponding to common radioactive material gamma rays through high-energy machine generated x-rays. The photon energies modeled are 30, 60, 68 (60 and 68 keV

represent the characteristic x-ray lines of a tungsten target x-ray source), 80, 100, 120, 150 and 200 keV, and 0.5, 1, 2, 4, and 6 MeV.

In contrast, a CT procedure covers only a portion of the body and thus offers a test for how the marrow distribution might affect the dosimetry of a partial-body exposure. A cylindrical source of photons centered about two typical CT scan areas have been chosen in this study to illustrate the effect of scan position on calculated red bone marrow dose, as shown in Fig. 3. The head scan covers 14 cm of the head, starting approximately 3 cm below the top of the crown. The abdominal scan is 19 cm long from the lower ribs to the upper pelvis.

A cylindrical source of photons is chosen to represent a simplification of a true CT machine. Monoenergetic photons of energies 30, 50, 60, 68, 100, 150, and 1,000 keV are modeled. A linear combination of the results from monoenergetic photons could be used to predict the result for a realistic x-ray energy distribution, if desired. Also, all photons are directed towards the isocenter, as opposed to being arrayed in an x-ray fan beam. Since the fan beam is not included, the flattening filter is also absent from the simulation. Our purpose is to examine the effects of limited field size on the model instead of details in the CT source.

In addition to photons that are very penetrating, it is of interest to also consider less penetrating radiation, such as high-energy electrons. The third application considered for this study is the so-called “Whole-Body Irradiation” (WBI) electron beam treatment plan for *mycosis fungoides* (a skin cancer form of non-Hodgkin’s lymphoma). The dose to red bone marrow in such medical treatments must be assessed in the treatment planning to minimize the potential for secondary leukemia. The treatment protocol described by Fraass et al. (1983) involves whole-body exposure to 3.9 MeV electrons in six fields. In that protocol, a beam of 4.5 MeV electrons is reduced in energy to 3.9 MeV through a Plexiglass scatterer. Since the scatterer is designed to generate a reasonably uniform electron field, a point source of electrons at the position of the scatterer has been modeled in this simulation for simplicity. In the exposure protocol, the patient is exposed to the electron source in the anterior and posterior directions, and at oblique angles from the left and right for both the anterior and posterior sides. Additional localized treatments are subsequently applied to inaccessible or under-irradiated skin segments such as the scalp, soles, and perineum, but those are not considered in this study. Because of the limited range of electrons in tissue, one would expect red bone marrow dose to be most significant in the bones that are nearest to the surface of the body, such as the cranium.

RESULTS AND DISCUSSION

Red bone marrow mass

The values of the mass of red bone marrow in each bone segment are presented in Table 1. A comparison of the three different red bone marrow mass values is shown graphically in Fig. 4 and the ratios of masses from Method 1 and Method 2 to VIP-Man are shown in Fig. 5. In this figure, “Method 1” and “Method 2” are the ratio of the mass calculated by that method to the mass calculated from VIP-Man for each bone segment. Bone segments in the CT images of the Visible Human where no red bone marrow is expected to be present are omitted, as the mass calculated from either method would be zero. In truth, the segmentation of color photograph-based VIP-Man identified very small amounts of red bone marrow in the lower arm and leg bones. No other category of bones contains more than 2 g of red bone marrow, and the fraction of the whole-body red bone marrow from VIP-Man not included in the figures is less than three-quarters of 1%.

The mass of red bone marrow as calculated by Method 1 differs significantly from the mass observed in the VIP-Man data. Despite the fact that total body red bone marrow mass differs by less than 4%, only the mass in the scapulae, cervical spine, and thoracic spine are within

20% of the observed values. Method 1 overestimates the red bone marrow in the humeri, femora, and mandible (although the mandible contains only a very small amount of red bone marrow) of the VIP-Man by more than double.

By using the weighting of the ICRP cellularity factors in Method 2, red bone marrow masses are much improved overall. The total body red bone marrow mass is slightly closer to the observed value, differing by less than one percent. Additionally, the mass in the humeri, ribs, lumbar spine, sacrum, and sternum as calculated with Method 2 are all within 10% of the values from the VIP-Man images, as shown in Fig. 5. The greatest relative difference is found in the mandible, which exceeds the observed value by 161%, but the mandible has the smallest absolute mass of red bone marrow, so the effect of the difference on dosimetry is minimal.

Method 2 results in red bone marrow mass that is closer than Method 1 to the value calculated from VIP-Man data in all bone segments except the pelvis, scapulae, cervical spine, and thoracic spine. The differences for the scapulae are similar (14.3% underestimation by Method 2 vs. 12.7% overestimate by Method 1), and the mass in the cervical spine is smallest of the bone segments next to the mandible and clavicles. Both methods underestimated the red bone marrow mass in the pelvis by a similar percentage. By using Method 2 the average absolute difference in red bone marrow mass between each bone segment in the CT image calculations and VIP-Man improves from 33.97 g for Method 1 to 18.85 g for a 45% improvement.

Dose to red bone marrow

The absorbed dose to the red bone marrow has been calculated for the three exposure scenarios described above. Fig. 6 illustrates the ratio of red bone marrow dose calculated using Method 2 to dose calculated using Method 1 for each direction. At low energies, below about 200 keV, red bone marrow dose for Method 1 diverges significantly from Method 2. At low photon energies, tissues nearer the source of radiation will receive much higher doses than those deeper in the body. Therefore, the bones near the surface of the body on the side of the photon source will receive a greater dose than those for other parts of the body, and the differences in the cellularity factors applied to those bone segments will be amplified. At energies greater than about 200 keV, there are not large differences in the red bone marrow dose as calculated by the two methods. When the body is exposed to a broad field of high-energy photons, the photon fluence and absorbed dose to the marrow will be relatively uniform throughout the body. Therefore, the cellularity factors applied will have little influence on the predicted red bone marrow dose.

In addition, Fig. 7 presents a comparison between the red bone marrow dose per unit air kerma as calculated using Method 2 in VHPCT for photons in the AP direction compared with the values reported for several other models. Included in Fig. 7 is MAX (Kramer et al. 2003), which applies Method 2, Golem (Zankl et al. 2002), which applies Method 1, NORMAN-05 (Ferrari and Gualdrini 2005), which applies something like Method 1, but to a homogeneous bone, and MAX06 (Kramer et al. 2006), which is based upon microCT images. The VHPCT red bone marrow doses compare very closely with these models. Variation in dose between models may be due to physical differences in the individual models or their implementation in the Monte Carlo codes (Kramer et al. 2003,2006). The use of approximated density and composition values for non-skeletal tissues in VHPCT may also have impacted skeletal dose.

The cylindrical photon geometry is presented as one example of a situation where partial-body irradiation may occur. Monoenergetic photons in the range of diagnostic x-rays are modeled for both scan protocols. The equivalent dose to red bone marrow per unit air kerma for each energy is presented in Table 2 for the head region and in Table 3 for the abdominal region. The statistical error in each Monte Carlo calculation is less than 0.2%, and is not shown in the tables. In each case, the whole-body red bone marrow dose is primarily contributed by those bone

segments that are located inside the exposure region, and is therefore highly dependent upon the differences in cellularity factors applied to those bones in the field of view. Tables 2 and 3 show that the red bone marrow dose as calculated by Method 1 can differ significantly from Method 2. In the head region, where the dose to the cranium is the major contributor to the overall dose, the Method 1 red bone marrow dose is greater than Method 2 by about 33%. In the abdominal region, the red bone marrow dose from Method 1 is less than Method 2 by 25%. Although the results of the two methods differ significantly, the degrees of the discrepancy are not significantly influenced by the energy of the incident photons. Because the body is irradiated from all directions in this type of simulation, the geometric effects seen in the parallel beam photons at low energies are less evident.

For radiation protection purposes, over- or underestimating the dose to the red bone marrow by 25% to 30% or more for dose estimates of diagnostic procedures may not make a significant difference because of the relatively low dose level. However, these cylindrical geometries are only two examples of the types of procedures that could result in a mis-estimated red bone marrow dose. External beam radiation treatments and nuclear medicine will inevitably deliver doses to the healthy tissues outside the treatment volume. Since the red bone marrow dose is often the Organ at Risk (OAR) and therefore becomes the limiting factor in the radiation treatment plan, a significant mis-estimate of the red bone marrow content of the surrounding bones can impact the effectiveness of radiation therapies. For example, Lujan et al. (2003) and Gershkevitch et al. (2005) have previously assessed the dose to red bone marrow from intensity-modulated radiotherapy (IMRT) treatments using available techniques, which would seem to have an uncertainty according to our results.

The final exposure scenario considered involves an electron beam whole-body irradiation procedure. The red bone marrow doses from each projection, along with the average red bone marrow dose for the whole-body skin treatment, are presented in Table 4. Fig. 8 illustrates the marrow dose in each bone segment for each projection in this procedure, per ampere of incident electron beam. As the figure shows, the largest bone marrow dose in all projections is received by the cranium. This is due to the relatively thin sheath of soft tissue that surrounds the cranium, allowing possible penetration of the electron beam to the bone tissue and greater bremsstrahlung production in the bone. For similar reasons, the sternum shows increased dose in the directly anterior projection as compared to all other projections, although the cranium remains the most significant contributor to red bone marrow dose. For this application, the Method 1 red bone marrow dose exceeds that for Method 2 in each projection by 24% to 56%, and the average whole-body red bone marrow dose from the treatment by 39%. The red bone marrow dose from skin tumor treatment plans that utilize direct electron beams, such as the procedure modeled here, are generally low and do not limit the clinical application. Nonetheless, these results suggest that the distribution of red bone marrow should be considered when calculating the red bone marrow dose from charged particles.

CONCLUSION

We implemented and evaluated methods for modeling the red bone marrow and for determining the radiation dose in a computational phantom derived from CT images. CT images and color photographs of the same individual allowed detailed comparison to be made in order to draw conclusions regarding the appropriateness of these methods. Method 2, which combines ICRP marrow cellularity factors, or active marrow fractions, with the CT number or gray value of a bone voxel to estimate the red bone marrow mass have proven to show better agreement with the standard derived from color images. Results from three different exposure scenarios suggest that low energy and partial body irradiations benefit the greatest from the cellularity factor-weighted model, although for high-energy photons, the effect proves to be small.

Method 1 is found to have small uncertainty when applied to irradiation geometries that result in relatively uniform dose distribution throughout the body. For radiation protection purposes, the homogenous marrow mixture assumption of that method may be acceptable for most situations. However, for medical applications which involve high doses and irradiation of limited field size or charged particles, significant error up to 40% in the calculated red bone marrow dose has been shown to arise. Therefore, the cellularity of the marrow in different bones must be accounted for, and incorporating the cellularity factor weights of Cristy (Method 2) into future CT-based computational models is recommended.

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Fig. 1.
Histogram of the redness of the voxels in the VIP-Man skeleton.

Fig. 2.
Illustrations of external beam photon irradiation geometries.

Fig. 3.
Illustration of cylindrical irradiation geometries for (a) head and (b) abdomen.

Fig. 4.

Red bone marrow mass comparison of Method 1, Method 2, and VIP-Man images.

Fig. 5.
Ratio of red bone marrow mass as calculated by Method 1 and Method 2 to the mass from the VIP-Man images.

Fig. 6. Ratio of mass-averaged whole-body red bone marrow dose as calculated by Method 1 to dose calculated by Method 2 for photons.

Fig. 7. Red bone marrow equivalent dose per air kerma as a function of the photon energy for AP-incidence for VHPCT and several previous models.

Fig. 8. Marrow dose to each bone segment from each projection of whole-body electron beam treatment, normalized to highest overall dose.

Table 1

Mass of red bone marrow in various bone segments as calculated by Method 1, Method 2, and VIP-Man, and the cellularity factors used to find the red bone marrow mass in Method 2 (from Cristy 1981).

Bone segment	Cellularity factor	RBM mass (g)		
		Method 1	Method 2	VIP-Man images
Humeri	0.25	80.412	40.206	37.083
Clavicles	0.33	16.777	11.073	13.754
Cranium	0.38	93.52	71.075	48.285
Femora	0.25	138.22	69.108	42.588
Mandible	0.38	9.6106	6.343	2.429
Pelvis	0.48	231.08	221.84	325.165
Ribs	0.70	122.88	172.04	164.663
Scapulae	0.38	53.716	40.824	47.654
Cervical spine	0.70	25.919	36.286	23.508
Thoracic spine	0.70	132.7	185.78	149.991
Lumbar spine	0.70	105.79	148.11	139.323
Sacrum	0.48	73.622	103.07	113.468
Sternum	0.70	32.199	45.079	44.404
Total mass		1116.446	1150.834	1152.316 ^a

^aThe VIP-Man images contain an additional 8.766 g of red bone marrow in other bone segments not represented in this table or considered in either Method 1 or Method 2.

Table 2

Dose to red bone marrow as calculated by Method 1 and Method 2 for monoenergetic photons in cylindrical sources centered about the head.

Photon energy (keV)	Red bone marrow equivalent dose/kerma in air (Sv Gy ⁻¹)		Method 1 to Method 2 ratio of RBM dose
	Method 1	Method 2	
30	1.15	0.85	1.36
50	3.09	2.31	1.34
60	3.32	2.49	1.33
68	3.08	2.32	1.32
100	2.39	1.82	1.31
150	1.73	1.32	1.31
1,000	1.23	0.91	1.35

Table 3

Dose to red bone marrow as calculated by Method 1 and Method 2 for monoenergetic photons in cylindrical sources centered about the abdomen.

Red bone marrow equivalent dose/kerma in air (Sv Gy ⁻¹)			
Photon energy (keV)	Method 1	Method 2	Method 1 to Method 2 ratio of RBM dose
30	0.40	0.54	0.74
50	2.26	3.01	0.75
60	2.90	3.84	0.75
68	3.04	4.03	0.75
100	3.05	4.00	0.76
150	2.62	3.43	0.76
1,000	2.61	3.50	0.75

Table 4

Red bone marrow dose calculated by Method 1 and Method 2 applied to whole-body skin treatment with 3.9 MeV electrons.

Electron beam direction	Red bone marrow equivalent dose/electron beam current (Sv A ⁻¹)		
	Method 1	Method 2	Method 1 to Method 2 ratio of RBM dose
Anterior	8.30	6.74	1.24
Anterior left oblique	10.30	7.49	1.37
Anterior right oblique	7.05	5.20	1.35
Posterior	7.80	6.22	1.25
Posterior left oblique	15.61	10.99	1.42
Posterior right oblique	15.73	10.05	1.56
Total average for entire procedure	10.80	7.80	1.39