A NOVEL METHOD TO ESTIMATE LYMPHOCYTE DOSE AND APPLICATION TO PEDIATRIC AND YOUNG ADULT CT PATIENTS IN THE UNITED KINGDOM

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Despite decades of epidemiological research, it remains uncertain whether ionizing radiation can cause lymphomas. Most epidemiological studies of lymphoma risk following non-uniform exposure used dose to red bone marrow (RBM), constituting a small fraction of the lymphocytes, as a surrogate of dose to the lymphocytes. We developed a method to estimate dose to the lymphocytes using the reference distribution of lymphocytes throughout the body and Monte Carlo simulations of computational human phantoms. We applied our method to estimating lymphocyte doses for a pediatric CT patient cohort in the United Kingdom. Estimated dose to the RBM was greater than lymphocyte dose for most scan types (up to 2.6-fold higher, a 5-year-old brain scan) except abdomen scan (RBM dose was about half the lymphocyte dose, a 5-year-old abdomen scan). The lymphocyte dose in the UK cohort showed that T-spine and whole body scans delivered the highest lymphocyte doses (up to 22.4 mGy).

INTRODUCTION

Despite decades of epidemiological research, it remains uncertain whether ionizing radiation can cause lymphomas[1–5]. Most of the previous epidemiological studies of lymphoma risk used radiation dose to red bone marrow (RBM) as a surrogate of radiation dose to lymphocytes, from which lymphomas derive. Because the RBM only constitutes a small fraction (3–7%)[6, 7] of the lymphocyte distribution throughout the body, it may be a relatively poor surrogate for exposure, which could have reduced the power of previous epidemiological studies of non-uniform exposures to detect a dose-response for lymphomas.

The lymphatic system is composed of lymphatic vessels, patches of lymphatic tissue, lymphatic organs, and isolated lymphocytes[7]. Computational human phantoms simulating human anatomy coupled with Monte Carlo radiation transport techniques have made it possible to precisely estimate radiation dose delivered to some organs within the lymphatic system exposed to a variety of radiation source. However, it is still complex to derive dose to other remaining tissues. To our knowledge, no dosimetry methods for the lymphatic system have been reported that fit.

In the current study, we developed a new method to estimate lymphocyte dose by using reference data for lymphocyte distribution throughout the body and Monte Carlo radiation transport in human anatomy represented by a series of computational human phantoms. We then applied the method to estimate lymphocyte dose for the pediatric and young adult patients who underwent computed tomography (CT) examinations in the United Kingdom.

MATERIALS AND METHODS

Lymphocyte dosimetry model

International Commission on Radiological Protection (ICRP) Publication 23[6] and 89[7] report the distribution of lymphocytes across four major tissue sites in human anatomy as a function of age as summarized in Table 1: RBM, lymphatic organs (spleen, lymph node, thymus and small intestine), blood and outside hematopoietic tissues (i.e. lymphocytes circulating throughout the body). Once radiation dose to each of the four components is estimated in any radiation exposure scenarios, lymphocyte dose can be derived through weighting dose to the four components by the distribution of lymphocytes in each component.

This approach requires computational human phantoms coupled with Monte Carlo radiation transport technique to estimate radiation dose delivered to specific organs in human anatomy. We adopted a series of computational human phantoms[8] representing newborn, 1-, 5-, 10-, 15-year old, and adult male and female reference individuals where the ICRP reference organ mass[7], the ICRP reference dimension of alimentary tract[9], and the reference elemental composition[7, 10] are incorporated. The anatomy of the male and female phantoms from

newborn to 10-year old is identical except for the urinary bladder and the gender-specific organs such as gonads, uterus, and prostate. For Monte Carlo radiation transport, we used a general purpose Monte Carlo code, MCNPX Version 2.7[11].

First, dose to RBM can be estimated by using the skeletal anatomy models built in the computational human phantom series and Monte Carlo code. Radiation fluence (particle/m^2) to spongiosa within each bone site is estimated through Monte Carlo method for computational phantoms and converted to absorbed dose (Gy) to RBM by multiplying them by pre-calculated dose coefficients called response function (Gy m^2)[12]. Dose to RBM calculated for different bone sites is then weighted by the distribution of RBM across bone sites[7] to estimate whole body RBM dose.

Dose to blood, the second component in the lymphocyte distribution (Table 1), can be derived by using organ doses computed from the computational human phantoms and reference blood distribution. ICRP Publication 89[7] provides the reference values for regional blood volumes for adult male and female across about 30 different organs and tissues. Once doses to the organs and tissues are calculated, the blood volume distribution data can be used for weighting the doses to derive average blood dose. We assumed that children have the same blood volume distribution as the reference adult data because ICRP Publication 89 only provides adult data.

Third, all lymphatic organs are available from computational human phantoms, including a lymph node model[13] that we previously published. The lymph nodes in the phantoms are distributed across the 16 cluster sites identified from the literature: extrathoracic, cervical, thoracic (upper and lower), breast (left and right), mesentery (left and right), axillary (left and right), cubital (left and right), inguinal

Table 1. Distribution of lymphocyte (%) across the four components in children and adults (ICRP Publication 89[7]).

Age	Mass (g)	Distribution of lymphocytes (%)			
		Red bone marrow	Blood	Lymphatic organs[a]	Outside hematopoietic tissues
Newborn	150	5.0	0.3	16.0	78.7
1 year	650	3.0	0.2	12.0	84.8
5 years	650	3.0	0.2	12.0	84.8
10 years	900	4.5	0.2	9.5	85.8
15 years	1250	6.0	0.2	7.5	86.3
Adult female	1500	7.0	0.2	7.0	85.8
Adult male	1300	7.0	0.2	7.0	85.8

[a]Lymphatic organs include spleen, lymph node, thymus and small intestine.

Table 2. Organ dose per unit CTDI$_{vol}$ (mGy/mGy) for the four major tissue sites and the lymphocyte in the pediatric and adult male and female phantoms simulated for brain, chest, and abdomen CT scans.

Scan type	Organs and tissues	Age (year) and gender (M/F) of phantoms							
		00 MF	01 MF	05 MF	10 MF	15 F	15 M	Adult F	Adult M
Brain scan	Red bone marrow	0.30	0.35	0.30	0.16	0.10	0.11	0.05	0.05
	Blood	0.10	0.11	0.08	0.05	0.04	0.04	0.04	0.03
	Lymphatic organs	0.03	0.02	0.02	0.01	0.01	0.01	0.01	0.01
	Outside hematopoietic tissue	0.20	0.18	0.12	0.07	0.05	0.05	0.05	0.03
	Lymphocyte	0.17	0.17	0.11	0.07	0.05	0.05	0.04	0.03
Chest scan	Red bone marrow	0.84	0.69	0.39	0.40	0.35	0.35	0.39	0.31
	Blood	1.10	0.86	0.69	0.63	0.52	0.53	0.47	0.45
	Lymphatic organs	1.04	0.72	0.44	0.35	0.32	0.27	0.21	0.21
	Outside hematopoietic tissue	0.67	0.39	0.36	0.38	0.29	0.37	0.26	0.28
	Lymphocyte	0.74	0.44	0.37	0.38	0.29	0.36	0.27	0.27
Abdomen scan	Red bone marrow	0.47	0.33	0.23	0.26	0.27	0.23	0.25	0.22
	Blood	0.81	0.53	0.54	0.44	0.41	0.37	0.32	0.35
	Lymphatic organs	1.36	1.00	1.00	1.07	0.88	0.73	0.81	0.67
	Outside hematopoietic tissue	0.59	0.32	0.38	0.34	0.25	0.27	0.21	0.26
	Lymphocyte	0.71	0.40	0.45	0.40	0.30	0.31	0.25	0.28

(left and right) and popliteal (left and right). Dose to each organ and tissue including lymph nodes can be calculated from phantoms and weighted by organ volumes to obtain average lymphatic organ dose.

Finally, as a surrogate for lymphocytes circulating outside hematopoietic tissues, we used volume-weighted dose to all organs and tissues except for the lymphatic organs and skeleton.

Lymphocyte dose for the UK CT patients

We applied our lymphocyte dosimetry method to the UK CT retrospective epidemiological study[14]. The cohort includes a total of 180 000 children and young adults who underwent CT scans in the UK between 1980 and 2002. The numerous CT scan types in the cohort were grouped into 15 different scan regions: brain, partial brain, facial bone, neck, chest, high-resolution CT, abdomen, pelvis, hip, cervical spine, thoracic spine, lumbosacral spine, shoulder, whole body and extremity. To estimate lymphocyte dose to the patient cohort, we first calculated dose coefficients, which convert CT scanner output (CTDI$_{vol}$) to organ dose[15, 16], and then multiply them by a set of CTDI$_{vol}$ values[17] previously established from surveys[18, 19] conducted in the UK.

First, we calculated overall lymphocyte dose coefficients after estimating dose coefficients for the four tissue components in Table 1 for six age groups (newborn, 1, 5, 10, 15 years and adult) undergoing the 15 CT examinations by using an in-house CT organ dose calculator, National Cancer Institute dosimetry system for CT (NCICT)[15]. NCICT is based on a comprehensive library of dose coefficients for 33 organs and tissues calculated from the computational phantom series coupled with Monte Carlo radiation transport code, MCNPX2.7[11]. Dose to blood was derived from organ doses calculated by NCICT and weighted by the blood volume distribution as described in the previous section. Since NCICT does not provide lymph node dose, it was additionally calculated using Monte Carlo simulation of a reference CT scanner[20] coupled with the lymph node-implemented computational human phantom series[13].

Second, we multiplied the CTDI$_{vol}$ collected from two UK surveys[18, 19] by the lymphocyte dose coefficients for the 15 scan types as described in the following equation.

$$D_{lymph}(A, G, T, Y) = \sum_{Z=SS}^{Z=SE} DC_{lymph}(A, G, Z) \times CTDI_{vol, UK}(A, T, Y)$$

(1)

where $D_{lymph}(A, G, T, Y)$ is the dose to lymphocyte for a given age A and gender G of patients scanned for the scan type T in the year Y, SS is the slice
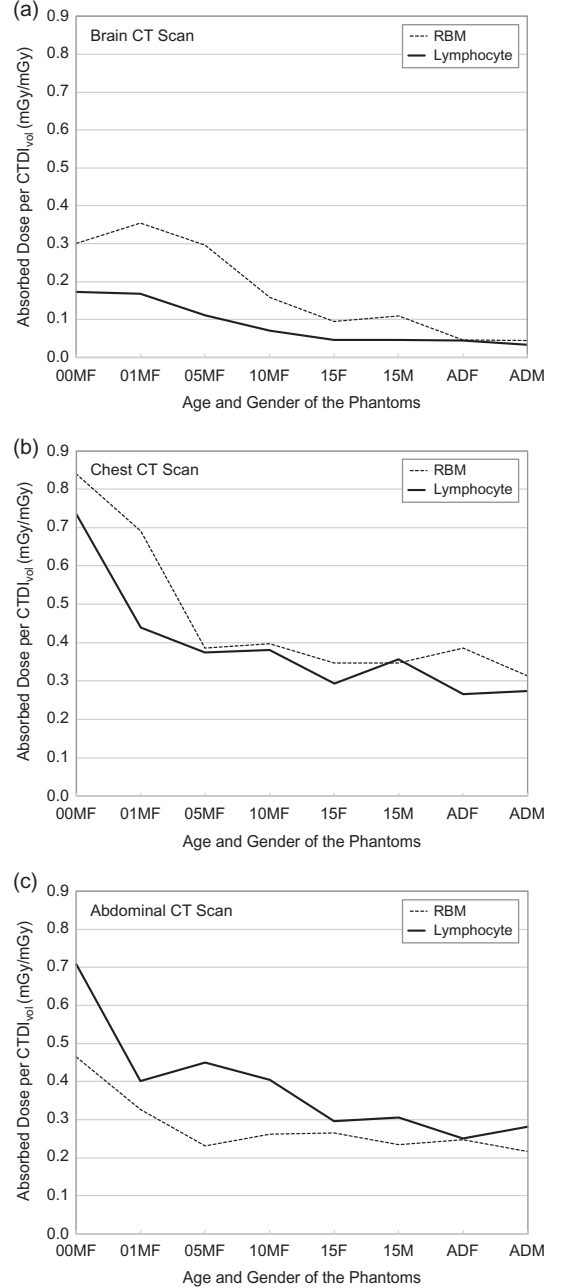

Figure 1. Comparison of age-dependent absorbed dose per CTDI$_{vol}$ (mGy/mGy) to red bone marrow (RBM) and lymphocyte in (a) brain, (b) chest and (c) abdominal CT scans.

number where scanning starts, and SE is the slice number where scanning ends, $DC_{lymph}(A, G, Z)$ is the dose coefficients for the patient of age A and gender G at the slice Z, and $CTDI_{vol, UK}(A, T, Y)$ is

Table 3. Lymphocyte dose (mGy) for the patients in the United Kingdom for different ages (newborn to 20 years old) and scan types in the two time periods (before and after 2001).

Scan type	0 MF	1 MF	5 MF	10 MF	15 F	15 M	ADF	ADM
Before 2001								
Brain	8.9	8.6	5.7	3.6	2.4	2.4	2.3	1.7
Partial brain	4.7	5.5	4.4	2.7	1.9	1.9	1.9	1.4
Facial bone	8.7	7.0	5.1	3.5	2.5	2.9	2.6	2.3
Neck	7.1	7.1	5.4	4.3	3.0	3.5	3.4	2.9
Chest	12.5	7.5	6.4	6.5	5.0	6.1	4.5	4.7
HRCT	2.9	1.8	1.5	1.5	1.2	1.4	1.1	1.1
Abdomen	12.7	7.2	8.1	7.3	5.3	5.5	4.5	5.1
Pelvis	8.9	8.6	9.1	8.6	6.3	7.4	6.2	6.3
Hip	4.1	4.3	5.7	5.8	4.5	4.5	3.9	5.1
C-spine	4.3	5.5	4.2	3.6	2.5	3.2	2.9	2.5
T-spine	22.4	14.0	13.1	14.0	8.3	8.9	8.2	9.1
L-spine	17.9	11.3	14.0	13.0	10.5	12.3	9.0	9.6
Shoulder	7.4	5.4	5.8	7.0	5.7	6.3	4.7	4.3
Whole body	21.6	16.3	17.2	16.6	12.1	14.0	12.0	12.4
Extremity	7.0	5.2	10.1	9.9	9.6	10.5	9.1	9.5
Unknown	8.1	7.0	5.6	4.3	3.1	3.3	3.0	2.7
After 2001								
Brain	4.3	4.2	3.8	3.1	2.6	2.6	2.5	1.8
Partial brain	1.9	2.2	2.4	1.9	1.7	1.7	1.7	1.2
Facial bone	3.9	3.2	3.2	2.8	2.5	2.9	2.6	2.3
Neck	1.3	1.4	1.0	1.0	0.5	0.6	1.2	1.0
Chest	4.1	2.4	2.1	2.7	1.4	1.8	2.7	2.7
HRCT	0.8	0.4	0.4	0.6	0.3	0.4	0.5	0.5
Abdomen	4.7	2.6	2.9	3.4	1.8	1.8	3.0	3.4
Pelvis	2.2	2.1	2.2	2.6	1.4	1.7	2.7	2.8
Hip	1.0	1.2	1.4	1.8	1.0	1.0	1.7	2.2
C-spine	1.2	1.5	1.2	1.3	0.6	0.8	1.4	1.2
T-spine	5.9	3.6	3.3	4.8	1.8	2.0	3.7	4.1
L-spine	4.6	2.8	3.5	4.1	2.4	2.8	4.0	4.2
Shoulder	1.4	1.0	1.1	1.6	1.0	1.1	1.6	1.5
Whole body	7.2	5.3	5.6	6.8	3.5	4.1	7.0	7.3
Extremity	1.9	1.4	2.8	3.5	2.3	2.5	4.3	4.5
Unknown	3.4	3.0	2.9	2.6	2.0	2.0	2.3	2.0

the $CTDI_{vol}$ for the age A of a patient, the scan type T and in the year Y collected from the UK survey. Based on previous studies[21–23], we divided the period of the UK CT study (1980–2002) into two time periods, before and after 2001, assuming that CT scan protocols for adults were also used for children before 2001 and age-specific protocols began to be used since then. For the patients with 'unknown' scan type (no information on CT scan region was given), average doses weighted by the frequency of the other 15 CT scan types were used for the dose estimates[17].

RESULTS AND DISCUSSION

We tabulated dose coefficients (mGy/mGy) of the four major tissue sites and lymphocytes for three major scan types calculated using the protocol assumed to be used before 2001 (adult scan protocol was used for children)

in Table 2. As expected from the distribution of lymphocytes across the four tissue sites in Table 1, the doses to outside hematopoietic tissues are overall similar to the lymphocyte doses for all ages except for newborns, for whom dose to outside hematopoietic tissues is 13% greater than lymphocyte dose for a brain scan, 10% smaller for a chest scan, and 17% smaller for an abdominal scan. The phantoms representing younger ages show greater lymphocyte dose coefficients than those for older ages. For example, the newborn phantom showed greater lymphocyte dose coefficients than the adult male phantom by a factor of 5.3, 2.7 and 2.5 times for brain, chest and abdomen scans, respectively. The chest scan delivers a higher dose to the lymphocytes compared with other scans when $CTDI_{vol}$ is fixed. In case of the adult male, the lymphocytes in chest scan receive about 8.4 times greater dose than brain scan.

Figure 1 shows the comparison of age-dependent doses coefficients to the RBM, which is usually used

as a surrogate for lymphocyte in epidemiological studies, versus overall lymphocyte dose for (a) brain, (b) chest and (c) abdomen scans. RBM dose coefficients overall overestimate lymphocyte dose coefficients except for abdomen scan. RBM dose coefficients are up to 2.6 (5-year old) and 1.6 (1-year old) times greater than lymphocyte dose in brain and chest scans, respectively. In contrast, RBM dose coefficients are about half the lymphocyte dose coefficients in the abdomen scan of 5-year-old phantoms.

Estimated age-dependent lymphocyte doses for the UK CT cohort are tabulated in Table 3 for the two time periods: before and after 2001. Lymphocyte doses (mGy) show different trends from the lymphocyte dose coefficients (Table 2) because the absolute dose was derived by multiplying the dose coefficients by the CTDI$_{vol}$ from the UK CT cohort. The lymphocyte doses from the newborn to 10-year old are identical between male and female because gender-specific organs (e.g. gonads and urinary bladder) contribute only 0.04% (male) and 0.02% (female)[7] of the blood dose, which again contributes to about 0.2% of the lymphocyte dose (Table 1). However, for both 15-year olds and adults, the male phantoms receive slightly greater dose than the female phantoms for torso CT scans because the volume ratio of muscle (more than 50% of the total body volume) is greater in the male phantoms than the female phantoms[7]. T-spine and whole body scans deliver major lymphocyte doses, up to 22.4 mGy for newborns, which are followed by L-spine, abdomen, and chest scans that deliver 17.9, 12.7 and 12.5 mGy, respectively, in newborns before 2001. Similar to the trends in other organ doses that were reported by Kim et al.[17], the lymphocyte dose significantly decreased after 2001. The lymphocyte dose of newborn scanned for T-spine examinations decrease from 22.4 before 2001 to 5.9 mGy since 2001.

CONCLUSION

We developed a method to estimate dose to lymphocytes by using the reference distribution of lymphocytes throughout the body reported by the ICRP and Monte Carlo simulations of computational human phantoms. We applied the method to estimating lymphocyte doses for the UK CT patient cohort to enable evaluation of the association between lymphocyte doses and subsequent lymphoma risk. RBM dose coefficients are overall greater than lymphocyte dose for most scan types (up to 2.6 times for 5-year-old brain scan) except in the abdomen scan where RBM dose coefficients are about half the lymphocyte dose. The dosimetry method and lymphocyte dose coefficients can be used for other epidemiological investigations analyzing the risk of lymphoma following non-uniform exposures. Improved dosimetry is essential to help clarify whether lymphomas can be induced by ionizing radiation.

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