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A COHORT STUDY WITH REGARD TO THE RISK OF HAEMATOLOGICAL MALIGNANCIES IN PATIENTS TREATED WITH X-RAYS FOR BENIGN LESIONS IN THE LOCOMOTOR SYSTEM

II. Estimation of absorbed dose in the red bone marrow

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A cohort study with regard to the risk of haematological malignancies was performed on about 20 000 patients who in 1950–1964 received roentgen treatment for benign conditions in the locomotor system. In order to estimate the mean absorbed red bone marrow dose the treatments were classified as concerning 10 sites (cervical spine, thoracic spine, lumbar spine, sacral region, shoulder, hip, elbow, wrist, knee and ankle). The four last-mentioned sites do not normally contain red bone marrow in adults and their contribution to the mean absorbed dose was regarded as zero. For the other 6 sites random samples consisting of 30 patients for each site were drawn from the cohort. By use of the treatment records and data from the literature on some physical parameters and red bone marrow distribution in normal adult persons, average conversion factors were calculated by which the subscribed surface dose could be converted into mean absorbed dose in red bone marrow. These conversion factors were then applied on the whole cohort and used for stratification of it according to different levels of exposure.

Epidemiological studies are essential for assessing the carcinogenic effect in man of ionising radiation. In supplement to the Japanese A-bomb survivors, several groups exposed to radiation for medical reasons have given important contribution to the knowledge (1). The present work deals with a cohort of about 20 000 patients who 1950–1964 received roentgen treatment of painful benign conditions in the locomotor system as arthrosis, spondylosis, etc. (2). The cohort is in a way similar to the British series of x-ray-treated ankylosing spondylitis (3, 4) but as a rule smaller parts of the body were exposed and lower radiation doses were applied.

In order to assess the risk of radiation-induced leukaemia and other haematological malignancies in quantitative terms there is a need to estimate the absorbed dose in the irradiated red bone marrow. In the present cohort detailed treatment records were available for all patients. These records contained data on skin dose, radiation quality, field size, and location. Other parameters of importance for a more exact individual estimation of the bone marrow dose was, however, lacking as for instance depth from skin to the exposed part of the bone marrow. For such parameters reasonable assumptions had to be made, referring to assumed average conditions. From estimates of local absorbed doses the mean absorbed bone marrow dose can be calculated. The aim of the present paper is to describe the methods used for these estimations.

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Material and Methods

General comments

The mean absorbed dose in the red bone marrow is defined as the total energy absorbed in the red marrow divided by its mass. For the type of radiation of interest

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the numerical value of the equivalent dose measured in sievert (Sv) equals the absorbed dose in gray (Gy). The energy can be absorbed either in the directly irradiated parts of the marrow or via scattered radiation reaching other parts of the bone marrow. For the assessment of the mean absorbed dose it is necessary to estimate both the local absorbed dose in the part of the red marrow directly irradiated and the fraction of the total red marrow irradiated in this way.

Treatment data for all patients were recorded in a computer and used for estimation of the mean absorbed dose in the red bone marrow. The latter was accomplished by deriving a factor by which the surface exposure could be converted into mean absorbed dose in the red bone marrow. The method presumes that the conversion factors represent correct averages for the relevant types of treatments. The surface exposure ('skin dose') which is the prescribed dose is usually given in terms of 'surface equivalent exposure', in units of roentgen (R). This implies that the x-ray tube has been calibrated through measurements with an ionisation chamber, in the presence of a back-scattering media. To transform this into absorbed dose expressed in rad (cGy) a factor of approximately 0.9 should be applied.

For the analysis of the distribution of the mean red bone marrow dose in the cohort, the treatments were grouped into ten categories according to the irradiated site. For six of those sites a fraction of the red bone marrow was located in the direct beam. To estimate an average conversion factor for each of these sites, 30 patients for each site were randomly selected. For these patients the mean absorbed dose in the red marrow was estimated, based on the detailed treatment data in the patient records. Within the remaining four sites no red bone marrow is normally found in adults. These sites (knee, ankle, elbow, wrist) encompass the distal parts of the extremities, and it was assumed that the absorbed dose in the red bone marrow was negligible and thus set to zero.

Estimation of local absorbed dose

In order to estimate the absorbed dose in the red marrow knowledge of a number of physical, biological and geometrical parameters is needed. The physical parameters described the output from the x-ray tube and the scattering and attenuating properties of the irradiated tissues. The biological parameters of interest are those describing the distribution of the red marrow within the skeleton, as well as the location and depth of the red marrow in relation to the skin surface. Since these biological parameters are not known for individuals a 'standard' patient was defined by use of data from the literature.

The two most important parameters influencing the local absorbed dose in the red marrow are the surface exposure and the depth of the red marrow in the irradiated volume. Additionally the radiation quality (i.e. photon energy distribution), and the focus to skin distance will influence the local absorbed dose, but to a smaller degree. Except for the depth of the red marrow, data on these parameters were registered in the treatment records.

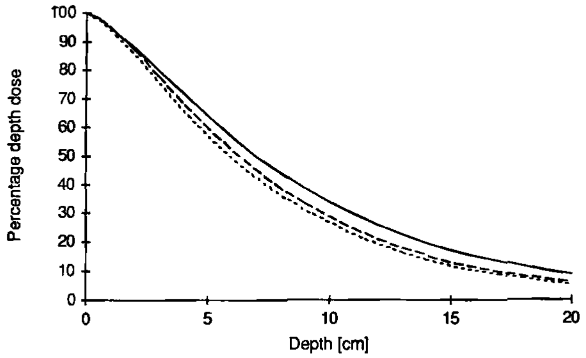

Fig. 1. Percentage depth dose for different radiation qualities (from ref. 7). ——: HVL 3 mm Cu (50 cm SSD). – – – –: HVL 1 mm Cu (50 mm SSD). · · · · · ·: HVL 1 mm Cu (40 cm SSD).

The major parameters determining the radiation quality are filtration and peak voltage. The peak voltage varied between 155 and 205 kV_p and the treatment was usually given with a tin filter (so-called Thoraeus filter) or a filter made up by copper and aluminium. Filters labelled 'CuAl' or '1/2Cu' in the records were regarded as corresponding to an HVL of 1 mm Cu, which approximately is equivalent to 12 mm Al (5, 6). Tin filter results in an HVL of 3 mm Cu, which approximately corresponds to 18 mm Al (5, 6). These data were assumed to be independent of the peak voltage. Fig. 1 illustrates the depth dose curves for these radiation qualities, using data from the literature (7), and shows their minor differences. For the assessment of the local absorbed dose, data published by Ellis et al. (8) were utilized. For a given radiation quality, focus-to-skin distance and field size give the absorbed dose per unit surface exposure at different points of a skeleton and are based on measurements in a soft tissue equivalent phantom which contains a human dried skeleton.

Estimation of the irradiated fraction of the total red bone marrow

For the assessment of the mean absorbed dose in the red marrow it is essential to estimate what fraction of red marrow is irradiated. In the treatment records the field size was given. In many cases, however, not only the size, but also the shape of the field is of interest. Thus the length of a rectangular field can be more important than its width; this applies especially to the spine where the length of the organ included in the beam determines the amount of red bone marrow exposed. On the other hand, when the

Table 1

Distribution of the active red marrow among different bones. The label ×2 indicates that the given figure should be divided equally between the left and right bone. (Data taken from ref. 9, 10 and 11)

Bone	Percentage of red marrow
Humerus (×2)	2.29
Clavicles (×2)	0.79
Scapulae (×2)	2.85
Mandibles	0.8
Skull	7.8
Vertebrae	32.3
Sternum	3.1
Ribs	16.1
Sacrum	9.9
Os coxae	17.5
Femur, head (×2)	3.0
Femur, shaft (×2)	3.35

treatment area is located at the periphery of the body, e.g. hip joint or shoulder, a fraction of the direct beam may pass outside the body but still be included in the recorded field size. The registered field size was in such cases corrected by a factor of standard type. The fraction of red marrow included in the direct radiation field depends also on the concentration of red marrow at the specific skeletal site. The distribution of red bone marrow in adult persons is given in Table 1, with data compiled from the literature (9–11).

Correction factors

Scattered radiation also gives some contribution to the mean absorbed red bone marrow dose, depending on the distribution of red marrow outside the beam. To allow for this a standard correction factor of 1.22 has been used as recommended by Ellis et al. (8). In order to obtain the bone marrow dose a correction should also be made for the higher electron flux in the marrow cavities caused by the surrounding bone tissue. This correction factor depends on the radiation quality and the structure of the bone, which may vary from one part of the skeleton to another. In the present study a factor of 1.07 was used in all cases, which is a reasonable approximation with regard to the used radiation qualities.

Estimation of absorbed dose in the red marrow

Shoulder. For the shoulder it was assumed that the irradiated volume included all red bone marrow in humerus, which is entirely located in the proximal part of the bone. In addition half of the red bone marrow in the clavicle and one-third of that in the scapula were also included. In total this corresponded to 1.8% of the red bone marrow mass. This assumption applied to a typical field size of 150 cm^2. For other field sizes the relative amount of irradiated red bone marrow was assumed to be proportional to the square root of the area. The square root dependence was motivated since the active bone marrow is not homogeneously distributed over the area, but rather linearly elongated.

Hip joint. It was assumed that all active marrow present in the femur head was included in the irradiation field. An additionally size-dependent fraction was assumed to derive from the pelvic bone and the remaining part of the upper half of the femur. For a 150 cm^2 field it was assumed that 40% of the marrow in the ipsilateral half of the pelvic bone and 33% of that in the shaft of the femur were included. This gave a total fraction corresponding to 5.6% of the red bone marrow mass, of which 1.6% derived from the femur head, while the remaining 4% were regarded as proportional to the square root of the area and accordingly adjusted for deviating field sizes.

Spinal column. Each treatment of the spine was classified as concerning either the cervical, the thoracic or the lumbar spine. The active bone marrow content of the different parts was derived from Cristy (9) and their extension from Snyder et al. (12). These data were combined to obtain the relative bone marrow content per cm of spine for the different regions (Table 2). If, from the field size in a sample case, it seemed obvious that also a proportion of an adjacent part of the spine was included (e.g. upper part of thoracic spine when cervical spine was irradiated) this was taken into account.

Cervical spine. C1 was regarded as defining the upper boundary of the field and no adjustment was made for the possible inclusion of some part of the skull.

Thoracic spine. Concerning thoracic spine also the sternum and the anterior-medial part of the ribs were included; due to the P-A beam direction this contribution was small and accounted for c. 10% of the total

Table 2

Characteristics for the different parts of the spine (compiled from ref. 9 and 12)

Region No.	Location	Length (cm)	Red marrow (%)	Red marrow (% cm^{-1})
I	C1–C5	13.1	2.7	0.20
II	C6–Th12	34.9	17.4	0.50
III	L1–L4	10.5	9.8	0.93
IV	Sacrum + L5	15.0	12.4	0.83

Table 3

Characteristics for different parts of the rib cage (compiled from ref. 9 and 12)

Rib No.	Length (cm)	Red marrow (%)	Red marrow ($\% \ cm^{-1}$)	Circumference* (cm)
1–4	10.7	4.3	0.41	81.7
5–9	13.4	9.3	0.69	81.7
10–12	8.1	2.5	0.31	42.9

* Only the part of the circumference with bone present is included, ribs No. 10–12 are presumed to fill out only the posterior half of the rib cage.

absorbed red marrow dose. Also the exposure of the posterior-medial parts of the ribs were taken into account and contributed with another c. 10% of the total dose. For the purpose of dosimetry the rib cage was divided into three regions (Table 3). The dimensions of the rib cage were taken from Snyder et al. (12). The red marrow in the ribs was considered as evenly distributed over the rib cage. The fraction of marrow included in the direct irradiation field was determined by the length and width of the beam area. For the sternum and the anterior part of the ribs the correction due to beam divergence was considered. The centre of the beam was normally assumed to be Th6.

Lumbar spine. When the lumbar spine was treated often also sacrum or a part of it was included in the field; this was accounted for in the dose estimation. The centre or the field was usually assumed to be located at L4. Literature data on absorbed dose per unit surface dose are available for a number of different spots in the vertebral spine (8). For each field (cervical, thoracic or lumbar) the closest spot was used for the dose estimation in the spine.

Sacrum. The bones in this region have a higher concentration of red marrow than any other bone in the body. When sacrum was irradiated often a part of the lumbar spine was included. It was assumed that sacrum and L5 were irradiated together and that the length of sacrum + L5 was 15 cm. It was further assumed that 20% of the pelvic bone was included in the direct irradiation field. This figure was supposed to refer to a 15 cm × 10 cm field. For other field areas the fraction was assumed to be directly proportional to the area; however, the fraction was maximized to 25% of the total content of red marrow in the pelvic bone.

Distribution of mean absorbed red bone marrow dose in the total material

The dose estimation in the mentioned samples of patients were used to define the dose distribution in the total cohort. By use of the estimated average conversion factors the mean absorbed red bone marrow dose were calculated for all patients. For some statistical analysis the cohort was stratified, with regard to mean absorbed red bone marrow dose, in three groups: <0.2 Gy, 0.2–0.5 Gy and >0.5 Gy.

Results

The averages of the estimated conversion factors and the calculated mean absorbed red bone marrow dose are presented in Table 4 for the six selected sites normally containing red bone marrow. The table is based on the previously mentioned random samples of 30 patients drawn for each site. For the four sites not mentioned in the table (knee, ankle, elbow and wrist) the mean absorbed bone marrow dose was regarded as zero. Fig. 2 shows the distribution of mean dose in red bone marrow in the whole cohort after application of the average conversion factors derived from the sample study.

In the 180 sample cases representing sites normally containing red marrow, the local absorbed dose was in

Table 4

Average mean absorbed dose in red bone marrow from treatments of different parts of the skeleton, and average factors (range) for conversion of skin dose to red bone marrow dose. Data are based on a random sample of 30 patients for each site

Skeletal site	Mean absorbed dose in red marrow (Gy)	Average conversion factor (10^{-4} Gy R^{-1})	
Shoulder	0.11	1.35	(0.80–1.76)
Hip joint	0.27	2.63	(1.5–4.0)
Cervical spine	0.22	3.85	(0.93–6.6)
Thoracic spine	0.36	6.45	(2.7–13.8)
Lumbar spine	0.51	8.02	(4.4–13.8)
Sacrum	0.82	12.60	(5.4–15.8)

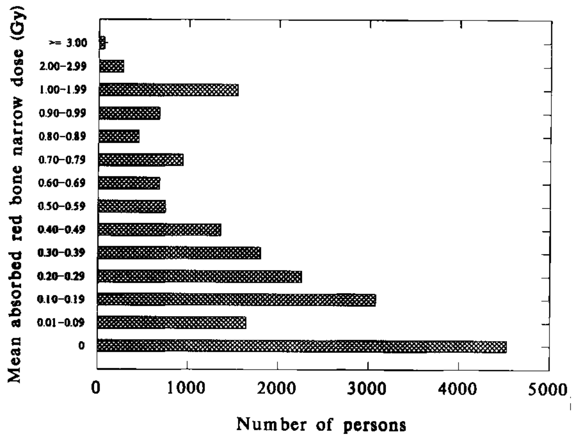

Fig. 2. Distribution of the mean absorbed dose in red bone marrow for the entire cohort. Note that the strata for the 3 highest dose levels for graphical reasons are wider than the others!

practically all cases below 8 Gy. After weighing of the sites with respect to their frequency of abundance the local absorbed dose was less than 4 Gy in about 70% of the cases. Since local doses had been delivered by a number of smaller fractions it seems reasonable to assume that no essential effect had been caused by increased cell death within the directly irradiated red bone marrow. Such cell death may cause a reduction of the cancerogenic risk when expressed in relation to the absorbed dose (1).

Discussion

One advantage of radiotherapy cohorts is the prospective registration of the exposure data. In cancer treatment this registration has often a very high degree of exactness. In the present cohort, however, which concerned rather small radiation doses for benign conditions the registration was of course less detailed. Data concerning the exact dimensions of the treated volume, depth from skin to the exposed part of the skeleton, etc. were, for instance, lacking which introduced some uncertainty when the local and the mean absorbed red bone marrow doses were estimated.

Different radiation qualities had been used, but the influence of this factor was minor and the uncertainty can be assumed to be less than 10%. Other causes of uncertainty are the assumptions concerning local anatomy and bone marow distribution in the 'average' adult person that had to be made. In reality there are considerable biological variations which cannot be taken into account in a study of the present kind. The uncertainty introduced by the use of a 'standard' man has been discussed by Cristy (9) and is in general said to be about 5% but might of course in individual cases be considerably larger.

The use of standard correction factors is another source of uncertainty. Maybe the most remarkable effect is that the mean absorbed dose in red marrow is estimated at zero for patients in whom only distal parts of the extremities were irradiated. This is due to the assumption that scattered radiation increases the mean red bone marrow dose with a certain fraction (22%). Actually some bone marrow dose must be caused by scattered radiation also when the distal parts of the extremities are irradiated. This dose is, however, very small and the used type of correction may be justified since in patients where central parts of the body are irradiated there is also a high concentration of red marrow in the immediate vicinity of the treated volume.

When these factors are considered it seems likely that the overall uncertainty in the mean bone marrow dose estimate is dominated by the estimated fraction of red bone marrow directly irradiated. This uncertainty is probably especially great when the pelvic regions are treated. In such cases the error in the mean red bone marrow dose is probably in general less than 25% but could in extreme individual cases reach 30–40%. Further uncertainty is introduced by the use of conversion factors calculated from limited random samples of the cohort. However, for epidemiological purposes this seems justified and the procedure as a whole sufficiently accurate.

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REFERENCES

1. UNSCEAR. Sources and effects of ionizing radiation. Annex A. Epidemiological studies of radiation carcinogenesis. United Nations Scientific Committee on the Effects of Atomic Radiation. New York: United Nations, 1994: 11–183.
2. Damber L, Larsson LG, Johansson L, Norin T. A cohort study with regard to the risk of haematological malignancies in patients treated with x-rays for benign lesions in the locomotor system. I. Epidemiological analyses. Acta Oncol 1995; 34: 00–00.
3. Darby SC, Doll R, Gill SK, Smith PG. Long-term mortality after a single treatment course with x-rays in patients treated for ankylosing spondylitis. Br J Cancer 1987; 55: 179–90.
4. Lewis CA, Smith PG, Stratton IM, Darby SC, Doll R. Estimated radiation doses to different organs among patients treated for ankylosing spondylitis with a single course of x-rays. Br J Radiol 1988; 61: 212–20.
5. Smith CAW, Sutherland H. X-rays half-value layer range 0.5 mm–4.0 mm Cu. Br J Radiol 1983; (Suppl. 17): 23–6.
6. Burns JOE. Equivalent half-value layers. Br J Radiol 1983; (Suppl. 17 Appendix C): 121–4.
7. Johns HE, Aspin N, Skarsgard LD, Cohen M. X-rays: HVT range 0.5–3.0 mm of Cu diaphragm-limited fields. Section 3. In: Cohen M, Jones DEA, Greene D, eds. Central axis depth dose data for use in radiotherapy. Br J Radiol 1972; (Suppl. 11): 25–37.
8. Ellis RE, Healy MJR, Shleien B, Tucker T. A system for estimation of mean active bone marrow dose. DHEW Publication (FDA) 76–8015. Washington, 1976.

9. Cristy M. Active bone marrow distribution as a function of age in humans. Phys Med Biol 1981; 26: 389–400.
10. Ellis RE. The distribution of active bone marrow in the adult. Phys Med Biol 1961; 5: 255–8.
11. International Commission on Radiological Protection. Reference man: Anatomical physiological and metabolic characteristics. ICRP Publication 23; Oxford: Pergamon Press, 1975.
12. Snyder WR, Ford MR, Warner GG, Watson SB. MIRD pamphlet No 11: 'S' absorbed dose per unit cumulated activity for selected radionuclides and organs. New York: Society of Nuclear Medicine, 1975.