ESTIMATES OF RADIATION DOSES IN TISSUE AND ORGANS AND RISK OF EXCESS CANCER IN THE SINGLE-COURSE RADIOTHERAPY PATIENTS TREATED FOR ANKYLOSING SPONDYLITIS IN ENGLAND AND WALES[1,2]

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INTRODUCTION

Available data on patients with ankylosing spondylitis who received a single treatment course with x rays in the Doll-Smith study (4,5) were reviewed to estimate radiation doses in tissues and organs giving rise to excess leukemias and cancers of heavily irradiated sites. It was not possible to review radiotherapy charts of each patient; it was therefore necessary to make assumptions on selection of patients, extent and severity of disease, method of therapy, radiotherapy dosimetry, exposures, tissues irradiated, and doses absorbed. Selection of patients and clinical courses of treatment chosen by radiotherapists in individual cases were, understandably, extremely variable. In spite of these limitations, it was possible to make reasonable assumptions to develop a model of the radiotherapy planning and treatment of patients with conventional orthovoltage radiotherapy of the 1930s-1950s. Estimates of radiation doses absorbed thus derived are imprecise and must be further corrected as new information becomes available, not only with respect to assumptions made, but also to information still lacking, as on location of organs during treatment and on the fraction of the organ or tissue irradiated.

PATIENTS STUDIED

Of the original 14,558 patients in the ankylosing-spondylitis study group, 4,421 (30.4%) patients who had received only one course of treatment were studied by Doll-Smith (4,5). The average period of followup for these single-course patients who had one course was 16.2 yr. In addition, histories and clinical courses of 52 patients who developed leukemia after either single or multiple courses of x-ray therapy were detailed in the MRC 295 Report (3); these patients had all developed leukemia after either single or multiple courses of x-ray therapy.

RADIOTHERAPY DOSIMETRY AND TREATMENT PLANNING

Radiotherapy dosimetry of patients was reviewed and reconstructed in MRC 295 Report (3). Most likely treatment ports, x ray qualities, dose fractions, etc, were used; depth-

dose data for conventional orthovoltage x-ray therapy was used (2). It was assumed that one-third of the patients were treated in late 1930s and early 1940s, and two-thirds were treated in late 1940s and early 1950s. For the earlier patients in the series it was assumed equipment used was 100-kVp radiotherapy x-ray machine, HVL of 2 mm Al, 30-cm focus-skin distance (FSD). For the later patients it was assumed equipment used was 200-kVp radiotherapy x-ray machine, HVL of 1 mm Cu, 50-cm FSD. It was assumed the entire cervical, thoracic, lumbar, and sacral spine and sacroiliac joints were treated in the single course of radiotherapy. On the basis of the range of rectangular skin-field dimensions for spinal and sacroiliac fields described in MRC 295 Report (App. B) (3) and that multiple fields were used, it was assumed in this analysis depth-dose data for a 200-cm^2 field would be appropriate to estimate organ-dose characteristics. Positions of cervical, thoracic, lumbar, and sacral spine were determined (1) on the assumption that all ankylosing-spondylitis patients were treated in the prone position. Positions of various organs and tissues of the thorax, abdomen, and pelvis were determined from contours and relationships from computerized-tomography images, cadaver correlative anatomy (6), and anatomical descriptions (7); it was recognized that CT patients and cadaver transverse sections are examined in the supine position.

PATIENT SELECTION, TREATMENT, AND CLINICAL COURSE

Review of the histories of the 52 ankylosing-spondylitis patients who developed leukemia outlined in MRC 295 Report (3) demonstrated that no process of patient selection could be ascertained with regard to severity of disease at time of first course of radiotherapy, nor for failure of palliation that warranted second or additional courses of therapy. Thus, it was assumed these leukemia patients were no different from all other ankylosing-spondylitis patients when they began radiotherapy. For the following analysis, it was assumed these patients were not selected on the basis of severity of their disease or of any other predisposing factors and were therefore representative of all 14,558 patients in the study at the start of their radiotherapy.

It was further assumed the group of patients who required retreatment (7,453, or 51.2%) (4,5) did not enter their initial course of radiotherapy with a plan for retreatment. In other words, all patients were treated in the hope of palliating their disease in the first course. There was no way for the radiotherapist to predict that a given patient would require more than a single course for palliation, and thus each patient who received multiple courses of radiotherapy was initially judged to be a single-course patient and treated accordingly. This would obtain for all 14,558 patients, and therefore for the 52 patients who ultimately developed leukemia. It is of interest that 34 (65.4%) of the 52 patients who developed leukemia did receive additional courses of treatment.

ESTIMATION OF MEAN EXPOSURE OF THE SPINAL BONE MARROW

On the basis of radiotherapeutic histories of the 52 ankylosing-spondylitis patients, it was assumed the clinical trend was to begin with single-course treatment. This resulted in a mean spinal bone-marrow exposure for the initial course for all 52 patients of 542±355 R. Thereafter, if a patient returned for additional radiotherapy because of recurring disease, each additional course up through the fourth course resulted in an increment of 346±319 R in mean spinal marrow exposure. Both in the initial treatment course and in later courses, standard deviations were extremely large. It was assumed, therefore, that the average spinal marrow exposure for all 4,421 patients who received a single course of therapy was 542±355 R. The average exposure of the spinal bone marrow represented a very wide spectrum of exposures selected by the radiotherapist. This suggested extreme variability in treatment techniques and in clinical response of patients. The average exposure of the spinal marrow in the 18 single-course patients who developed leukemia (3) was 668±325 R. This value is not significantly different from the mean spinal marrow exposure of all 52 patients after the first course of radiotherapy.

DETERMINATION OF PERSON-YEARS AT RISK

Doll and Smith (4) suggested that the data for individual irradiated sites, other than for CNS tumors, showed little variation in the ratio of observed to expected numbers of cancer deaths during the first 5 years of follow-up. Most CNS cancers caused death within 5 years after treatment, and could have caused the clinical symptoms that were ascribed to ankylosing spondylitis. Several other cancers, such as pancreas and colon, may have presented similarly. Thus, in the absence of information on such patients who may have been treated when they had cancer mimicking the symptoms of ankylosing spondylitis, Doll and Smith (4) excluded the early observations from analysis of the carcinogenic effects of radiation treatment. Since the risk ratios (observed/expected cancer deaths) by time since the first treatment for all neoplasms except leukemia fell preogressively from 0-2 years (O/E=1.71), to 3-5 years (O/E=1.68), to 6-8 years (O/E=1.27) years after radiation treatment, and began to rise after 9+ years, all observations made during the first 5 years after treatment were not included in their analysis of cancers of heavily irradiated sites. The number of person-years (PY) at risk from 6+ years on was 77,494 PY for cancers of heavily irradiated sites (4, Table 5). In the case of leukemia, on the other hand, their analysis includes the risk of death 2 or more years after the first treatment; here, the total is 112,970 PY at risk (Doll and Smith (4), Table 4A). The present analysis (Table 1), therefore, has also excluded for this purpose, all observations during the first 5 years after treatment.

Table 1. Estimates of Radiation Doses in Tissues and Organs and Absolute Risk of Excess Leukemias and Cancers Arising in Heavily Irradiated Sites in Patients with Ankylosing Spondylitis Following a Single Treatment Course with X Rays

Site of Cancer	Excess Deaths	Person Years	Dose (rads)	Risk
Leukemia (bone marrow)	29.15	112,970	214	1.2
Lymphoma (mediastinal lymph nodes) excl. Hodgkin's Disease	7.65	77,494	306	0.3
Esophagus	4.73	77,494	306	0.2
Stomach	11.43	77,494	67	2.2
Colon	5.44	77,494	57	1.2
Pancreas	4.53	77,494	90	0.7
Bronchus	31.51	77,494	197	2.1
Bone	2.27	77,494	1950;505	0.02
CNS (spinal cord & nerves)	1.56	77,494	698	0.03
Kidney	3.88	77,494	46	1.1
Bladder	2.02	77,494	31	0.8

a) From Doll and Smith (4), Table 4A, 5 and 6; b) From Doll and Smith (4), Table 4A; for excess risk of leukemia, all patients followed 2 or more years after first treatment including patients with leukemia whose primary cause of death was not classified as leukemia. Tables 3, 5, and 6; for excess risk of cancer of heavily irradiated (and lightly irradiated) sites 6 or more years since the first treatment; c) Based on average spinal marrow dose of 505 rads; d) Absolute risk estimated from linear dose-response and expressed as excess cancer deaths per 10^6 PY per rad.

ESTIMATION OF RADIATION DOSES ABSORBED AND EXCESS RISK OF CANCER IN TISSUES AND ORGANS IN HEAVILY IRRADIATED SITES

On the basis of the above assumptions, the average radiation doses to the spinal bone marrow and to the organs and tissues in heavily irradiated sites have been calculated (Table 1). It was assumed that all leukemias and cancers arose in irradiated tissues and organs. The absolute risk estimate calculated is based on linearity of dose-response and is expressed as excess cancer deaths per million person-years per rad. ¶ The estimated absorbed dose for leukemia was based on the assumption that spinal bone marrow constitutes 42.3% of active bone marrow and the assumption that leukemia arose in irradiated bone marrow in the spine. ¶ The estimated absorbed dose for lymphoma (excluding Hodgkin's disease) was based only on the position of the most prominent lymph nodes in the mediastinum of the thorax. These included lymph nodes lying in and around the trachea and the bifurcation of the main bronchi. If lymphomas arose in the lymph nodes of the posterior mediastinum, the dose would have been much higher, and the risk would be reduced; if the lymph nodes of the anterior mediastinum

were involved, the risk would be increased. ¶The position of the esophagus varies considerably in the thorax; and kyphosis in ankylosing-spondylitis patients would affect its position. If neoplasms arose in the upper esophagus, the radiation dose could have been higher, and the risk lower. Because many patients received lumbar spine irradiation, it is possible that the distal esophagus, although more anterior (and thus receiving a smaller dose), could have been in the irradiated fields more frequently. The cervical portion of the esophagus was not included in this analysis. ¶The lower value for the absorbed dose in stomach assumed half of it was irradiated: this may have occurred in hypersthenic patients. The higher value assumed two-thirds of the stomach was irradiated; this may have occurred in asthenic patients. ¶The absorbed dose in the colon was based on the assumption that one-third to one-half the colon was in the irradiated field, primarily the transverse colon, the sigmoid, and the rectum. The dose in the pancreas assumed irradiation of the head and the portion of the body of the pancreas anterior to the lumbar spine; this accounts for two-thirds of the organ. ¶The dose estimated in the bronchus assumed that bronchial cancers arose in the primary and secondary branches. Further branching--say, to the tertiary portions--would increase the amount of bronchial epithelium, but decrease the probability of the epithelium's being situated in the irradiated field. It was assumed that 80% of the bronchial epithelium was irradiated. ¶The absorbed dose in bone was low, with a large range. Corrections were made for x ray absorption in bone relative to soft tissue, i.e., for osteocyte lacunae and bone-marrow cell spaces. The lower dose estimate refers to the bone marrow of the vertebral bodies, transverse and spinous processes, pedicles, etc. The higher estimate refers to the apatite (calcium-protein matrix). It was assumed that only the spine and the sacroiliac joints were irradiated, and no corrections were made for irradiation of other bony structures, such as ribs.

The absorbed dose estimated in the spinal cord and spinal nerves (nerve root and dorsal and ventral branches) originating from the cord assumed that these structures were in the field of irradiation. A dose of 505 rads is estimated to the spinal bone marrow cells and endosteal lung cells of bone marrow cavities. The dose to the nervous system tissues could have been higher, because the cord and the origins of the spinal nerves are closely related to the surrounding bone of the spinal column. ¶The values for the kidney and bladder (lightly irradiated sites) assumed 10% of both kidneys and 33% of the bladder were in the irradiated fields.

CONCLUSIONS

The estimates of absorbed doses of x rays in tissues and organs and excess risk of cancer in bone marrow and heavily irradiated sites in the radiotherapy patients with ankylosing spondylitis in England and Wales after a single treatment course of x rays are extremely crude and are based on very limited data and on a number of assumptions. Some of these assumptions may later prove to be incorrect, but the general principles are valid and are probably reasonably appropriate. It is therefore important to place these estimates of absorbed dose into perspective, recognizing that they may be somewhat inaccurate, but no grossly so. It is probable that they are correct to within a factor of 2. The excess cancer risk estimates calculated compare well with the most reliable epidemiological surveys thus far studied and reviewed in ICRP Report 26 (8) and the National Research Council's BEIR Report (9). This is particularly important for cancers of heavily irradiated sites with long latent periods. The mean followup period for the single-treatment-course ankylosing-spondylitis patients was 16.2 yr, and an increase in cancers of heavily irradiated sites may appear in these patients in the 1970s in tissues and organs with long latent periods for the induction of cancer.

The accuracy of these estimates is severely limited by the inadequacy of information on doses absorbed by the tissues at risk in the irradiated patients. The information on absorbed dose is essential for an accurate assessment of dose-cancer incidence analysis, which could provide valuable insights into the mechanisms of cancer induction in man. Furthermore, in this unusually valuable human series of irradiated patients, the information on radiation dosimetry entered on the clinical radiotherapy charts is central to any reliable determination of somatic risks of radiation with regard to carcinogenesis in man. The work necessary to obtain these data is under way in England; only when they are available can more precise estimates of risk of cancer induction by radiation in man obtained.

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REFERENCES

(1) Brinkley D, Master HE The depth of the spinal cord below the skin. Brit J Radiol 40:66-67 (1967) (2) Central Axis Depth Dose Data for X-Radiation of Half Value Layers from 0.01 mm Al to 15.0 mm Cu, Cobalt-60 Radiation, HVL 11 mm Pb, and Beta Radiation, 22 MeV, Scientific Subcommittee of the Hospital Physicists' Association. Brit J Radiol NS Suppl. 5 (1953) (3) Court-Brown, Wm, Doll R Leukemia and Aplastic Anemia in