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Epidemiological designs in radioepidemiological research

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Much of the interest in radiation research today focuses on the effects of chronic exposure to low levels of ionizing radiation such as are received from the environment or at work. However, at present most of the available information on the effects of radiation comes from the studies of atomic bomb survivors [1] and of populations who have received medical radiation therapy [2–6]: in both cases exposure was to fairly high doses, received either as the result of a single event (as with an atomic bomb), or in fractions over a fairly short period of time (radiotherapy). Attempts have been made to estimate the effects of low doses and low dose-rate exposures from these data by carrying out extrapolations across doses and dose-rates [7]. However, there are uncertainties about the adequacy of the extrapolation models used, and these uncertainties are unlikely to be resolved on theoretical grounds only. Direct epidemiological studies of the effects of these exposures (in the environment or at work) are therefore needed.

Because the effects which we want to quantify are likely to be small, if new studies are to result in data of sufficient quality to resolve the risk assessment controversy about the effect of low doses and low dose-rates, extreme care must be put into their design. Areas of particular importance designing the studies include the choice of the study population, and the accuracy of the dosimetry and of the disease diagnosis. In this paper we will review the limitations and advantages of various study designs, and the problems and importance of dosimetry for radiation risk assessment. The discussion will be illustrated with a number of examples from the recent epidemiologic literature.

Study designs: Limitations and advantages

The main problems in studies of the effects of low levels of ionizing radiation are due to the facts that: 1) the risks being studied are often quite small; 2) exposure to ionizing radiation is ubiquitous and quite variable in the natural environment; 3) the exposures under study may often represent only a small fraction of natural background radiation; 4) the cancers of interest may not be well characterized: although epidemiologic studies at high dose levels have permitted the identification of a large number of cancer types associated with ionizing radiation, chronic low level exposures could conceivably induce cancer in entirely different organs or cell types. Such a phenomenon has been observed in experimental studies of animals exposed to chemicals, for example to N-nitrosodimethyl nitrosamine, and is attributed to the dose-dependence of DNA repair and detoxification pathways [8]. Finally, especially in the case of environmental epidemiologic studies, the actual population at risk of exposure may often be quite small and badly characterized.

Cohort studies of exposed individuals

Large cohort studies with adequate follow-up (at least 20 years) and accurate individual exposure information are without doubt the most informative studies for evaluating the risk associated with different patterns of exposure to ionizing radiation. Such studies are, however, extremely expensive and time-consuming. The published studies meeting these requirements are those that constitute the basis of current radiation risk estimates. They include studies of atomic bomb survivors (for which active follow-up and periodical medical examinations of parts of the cohort are still being carried out), and some studies of medical exposures and of uranium miners.

The most informative cohort study until now has been that of the atomic bomb survivors [1]. In the latest follow-up, covering 35 years (from 1950 to 1985), cancer mortality was reported for approximately 76000 persons (men and women of all ages in both cities) for whom new dose estimates are available. A total of 5936 cancer deaths occurred, and over 2000000 person-years were accumulated during the follow-up period. The cancer sites for which significant excesses were observed, as well as the estimated excess risks, and the number of deaths on which they are based, are presented in Table 1. Although the dose equivalents in this study range from 0 to more than 4 Sv, most of the statistically significant increases are observed at fairly high dose levels (i.e. 1 Sv and above); approximately 3000 survivors received such doses.

The largest study designed to assess directly the effects of protracted, low-dose occupational exposures was a combined analysis of cancer mortality by level of individual exposure among 36000 white males employed at three nuclear

Tab. 1. Atomic bomb survivor study: cancer sites for which significant mortality excesses were oberserved[1].

Type of cancer	Excess deaths per 10^4 PY Gy[a]	Observed Number
Leukemia	2.94(2.4–3.5)[b]	202
Esophagus	0.45(0.1–0.9)	176
Stomach	2.42(1.3–3.7)	2007
Colon	0.81(0.4–1.8)	232
Lung	1.68(1.0–2.5)	638
Female breast	1.20(0.6–1.9)	155
Ovary	0.71(0.2–1.3)	82
Urinary	0.68(0.3–1.1)	133
Multiple myeloma	0.26(0.09–0.5)	36

[a] Based on organ doses.
[b] 90% confidence interval.

Tab. 3. Second cancer after radiotherapy for cancer of the cervix: cancer sites for which significant increased risks were observed[6].

Type of cancer	Relative risk[a]	Number of cases	Average organ dose (Gy)
Rectum	1.83(1.2–2.8)[b]	488	30–60
Vagina	2.65(1.0–6.3)	105	65
Bladder	4.05(1.9–8.5)	273	30–60
Stomach	2.08(1.1–4.0)	348	2
Leukemia[c]	2.02(1.0–4.2)	141	7

[a] For radiotherapy vs. no radiotherapy.
[b] 90% confidence interval.
[c] Excluding chronic lymphocytic leukemia.

facilities – the Hanford site, Oak Ridge National Laboratory and the Rocky Flats nuclear weapons plant[9]. It covered 1036 cancer deaths and 640000 person-years, with an average follow-up ranging between 14 and 21 years, depending on the facility. The average cumulative dose level (over a working lifetime) ranged between 20 and 40 mSv. Numbers of deaths and relative risks observed in this study for cancer types which were radiation-related in atomic bomb survivors are shown in Table 2. Only for multiple myeloma was mortality observed to be dose-related. For other cancer types, confidence intervals for risk estimates are consistent with a range of possibilities: from a protective effect of radiation exposure to a risk several times greater than that predicted by extrapolation from the data on atomic bomb survivors[9]. In order for studies of low-level exposures to be informative for risk assessment purposes, therefore, the sample size must be considerably larger; extending the follow-up in this study would also be informative, since these cohorts are still young.

Cohort studies without individual dose estimates provide little information for the purpose of radiation risk assessment. If the exposures under study result in very high doses, these studies may be useful in confirming increases at sites also observed in other epidemiological studies. If, however, the exposures of interest result in very low doses, the results of these studies are likely to be difficult to interpret: differences in exposures between "exposed" and "non-exposed" individuals within the study can result in small increases in risk which may be entirely obscured by much larger risk variations; these are attributable to the fact that exposed individuals are also often selected for other factors which influence their risk of cancer.

Tab. 2. US Combined study of nuclear industry workers: distribution of cancer deaths for sites at which an increased risk was observed in atomic bomb survivors[9].

Type of cancer	Relative risk[a]	Observed number of deaths	
		Total	above 100 mSv
Leukemia (non CLL)	0.98(0.2–5.3)[b]	42	3
Stomach	0.84(0.1–5.9)	52	2
Colon	0.91(0.2–4.3)	95	3
Multiple myeloma	10.0[c](0.1–750)	12	2
Bladder	– (0–15.3)	19	0
Lung	1.02(0.5–2.0)	326	16

[a] Ratio of internally standardized SMR for doses of 100 mSv or more compared to less than 10 mSv.
[b] 95% confidence interval.
[c] Dose-related ($p < 0.01$).

Case-control studies

The case-control study approach is generally very powerful since it allows collection of detailed data on each subject's dosimetry and on many potential confounding variables. Radiation exposure assessment must often be retrospective, however, except for case-control studies carried out within existing cohorts for which good individual dosimetric data have been collected routinely.

This is the case, for example, for the studies of second cancers following radiotherapy for cancer of the cervix[6]. In that study, the 4188 incident cases of 20 types of cancer and 6880 matched controls were identified from a cohort of approximately 150000 women treated for cancer of the cervix in 14 countries. Dosimetric data were then abstracted retrospectively from the treatment records of the cases and controls. Cancer sites were divided by degree of irradiation (> 3 Gy, 1–3 Gy, < 1 Gy). The cancer sites for which significant increases were observed are listed in Table 3, together with the relative risk, the number of cases and the average radiation doses received at each organ. The only increase observed in the lowest-dose range (< 1 Gy) was for cancer of the thyroid (average dose 0.11 Gy; RR = 2.35 (90% confidence interval: 0.6–8.7)). No increase in risk of breast cancer (average dose 0.31 Gy) was observed, although 838 cases were identified. The interpretation of these results for risk assessment is not clear: although organ doses at sites far from the cervix are quite low, it is unclear what the role of possible systemic effects (due to extremely high doses of radiation targeted at the cervix in persons with cancer of that site) may be in the induction of second cancers.

For studies carried out in populations for which dosimetry has not been carefully recorded through time (medical treatment or monitoring of occupational exposures), retrospective assessment of exposure may be quite difficult and early efforts should therefore be made to collect prospectively the information which will eventually be used to assess exposure, as part of a surveillance programme.

For case-control studies in the general population, it is important to ensure that the studies are carried out in regions with sufficient variation of exposure. Otherwise, the study will not have the statistical power to allow estimation of an increased risk. In these studies, additionally, the problem of correct choice of controls may be quite difficult.

Often, case-control studies focus only on one type of cancer. Such studies may fail to reveal any increases that exist in the risk for other cancer types not currently thought to be related to radiation, which may only occur when exposures result in low doses and dose-rates.

For all the above reasons, the most informative case-control studies for risk assessment in the low dose range will tend to be those that are carried out within cohort studies of persons exposed to a range of levels of ionizing radiation; these studies, moreover, permit direct estimation of excess risk and examination of the temporal aspects of radiation-induced risk.

Geographical correlation studies

An interesting approach to the study the effects of environmental radiation exposures, and one which has recently given rise to much controversy, is that of geographical correlation studies (also called ecological studies). In these studies, mortality or morbidity for specific cancers is compared between regions differing by exposure level or by the presence or absence of a source of potential contamination (such as a nuclear installation). Geographical correlation studies could be informative for risk assessment only if it were possible to divide the geographical region concerned into subregions with fairly homogeneous exposures determined by a random phenomenon (i.e. no age, sex, socio-economic or other important difference between subregions). In this type of study, both the likelihood of ecological fallacy and that of confounding (because of the randomness of exposure) would be minimized. A circumstance in which such a study could be set up is that of an accident like that in Chernobyl, if reliable average dose estimates were available at the level of sufficiently small geographical areas.

Geographical correlation studies are often criticized, in particular because it is nearly impossible to ensure an adequate choice of the geographical areas to be compared, or to adjust for potential confounding factors or population movements. Additionally, information on levels of the exposure of interest is very seldom available. In the best of cases, crude estimates by subregions might be available, or subregions could be classified as a function of their distance from a point contaminating source. Distance may not be a good surrogate for exposure level, however: this depends on the mode of environmental contamination.

A very large geographical study of cancer around US nuclear facilities has recently been completed[10]. Cancer mortality rates (and in some areas, cancer incidence rates) were compared between 107 counties with – or adjacent to – 62 nuclear facilities, and 292 counties carefully matched for a number of demographic and lifestyle factors. Cancer rates were based on 900 000 cancer deaths in the study counties, and 1 800 000 cancer deaths in the control counties occurring in men and women of all ages between 1950 and 1984. Comparisons were made by type of facilities and over time (before and after start-up, taking into account possible latent periods). No consistent increase in cancer at any site was observed. This study effectively rules out the existence, at the population level, of a very large excess of cancer resulting from the presence of a nuclear facility in a county. In terms of risk assessment, however, it can provide little more than an upper bound for the risk, because of the absence of exposure/dose information, and because of the large size of most of the counties and of their populations (large compared to the size of the area and of the population potentially "at risk" of exposures from the facilities).

In most instances, therefore, a negative geographical correlation study (i.e. a study in which no increase in risk is observed) cannot be interpreted to say that no risk exists but only to give an upper bound for a risk. A positive correlation study, on the other hand, may be difficult to interpret because of potential biases and confounding. Geographical correlation studies are therefore an approach which may be useful (because usually inexpensive and quick) to identify high risks, but cannot be used to rule out the existence of a public health problem.

The use of mortality and morbidity statistics based on much smaller geographical areas could, however, be quite useful. Researchers of the Small Area Statistics Health Unit of the London School of Hygiene and Tropical Medicine have set up a network of very detailed local statistics for the whole of the UK. This approach may be very useful in studying geographical variations of diseases and in providing quick answers to questions about public health risk around point sources, if it allows the setting up of studies satisfying the above criteria. Setting up a network is, however, costly and time-consuming. The difficulties associated with the determination of the denominators and the statistical treatment of random variation in rates in small areas also increase the complexity of this approach. Results from this UK programme will help to assess its value. The cost will of course depend on the availability and assessibility, at the national level, of computerized data bases on vital statistics, exposures and occupations. These networks may be set up easily in some countries, while the cost and effort involved may be prohibitive in others.

Problems and importance of dosimetry for risk assessment

Radiation exposure tends to be one of the best-measured exposures to environmental carcinogens. Dosimetric data used in epidemiologic studies, however, have come from different sources and are dependent on a number of assumptions and on practices which vary both over time and between studies. The accuracy of these estimates is therefore a function of time, place and radiation quality. Accuracy of estimates may not be essential in the first step of epidemiologic studies aimed at identifying the existence of a cancer risk; it is, however, of prime importance when comparing risk estimates across studies, over time and between populations, especially where the risk is expected to be small and the magnitude of the errors in dose (often dose-related) is large compared to that of the doses themselves. The sources and magnitude of uncertainties in dosimetry will depend on the context of exposure. These are reviewed below.

Environmental dosimetry reconstruction

For environmental exposures, environmental transport models will play an important role in estimating the exposure of populations and of individuals in a population. These transport models attempt to describe quantitatively the physical, chemical and biological processes involved between the release of radioactive substances or radiation and the resultant doses received by individuals. For radioactive releases, complicated models of their transport through air, water and the food chain must be postulated. Such models have mainly been used up till now for screening of exposures for public health decision-making, rather than for epidemiological exposure assessment[11]. Such screening may be "conservative" or "non-conservative". Conservative screening is based on a deliberate over-estimation of potential exposures: it may be useful for setting upper limits on possible health hazards from environmental contamination. Non-conservative screening is, on the contrary, the identification of exposures that clearly exceed a level of concern. Screening calculations are appealing because they need to be based only on a limited knowledge of site-specific conditions. They are, however, not useful for epidemiologic studies and a more precise risk assessment.

After the reactor accident at Chernobyl in 1986, extensive long-term monitoring programmes were set up in the USSR and elsewhere[12]. The aim was to determine the extent and the degree of contamination from released radionuclides. Samples of air, water, vegetables, milk and meat were taken; deposition densities were estimated; thyroid and whole body counts were carried out. Data on the size and characteristics of different areas and of their populations, on food production and consumption, as well as on weather and geography were also compiled. Finally, transfer factors were used to estimate committed dose equivalents from estimated deposition patterns, through dose equivalent estimations from both external and internal (from depositions to food, ingestion and the body) exposures[12]. The uncertainties involved at every step are not negligible.

Complicated environmental transport models are now also being used, and associated uncertainties are being estimated, in specific cases where epidemiologic studies will be carried out: environmental dose reconstruction studies have recently been carried out in the United States in Utah (for assessing the health effects associated with follow-up from atmospheric weapons testing in the 1950s[13]); and in Washington State, around the Hanford site (in order to assess the health impact of iodine releases, also in the 1950s[14]). An important aspect of this work is the assessment of uncertainties in exposure estimates. Monte-Carlo simulations are being used for examining the effects of uncertainties at various stages of the transportation models used. This implies postulating probability distributions for the uncertainties of each parameter in a model; ideally, the uncertainty in the choice of the model itself should also be taken into account.

Occupational dosimetry

An area in which more documentation of estimated doses is available is that of occupational exposures to ionizing radiation, in particular to low linear energy transfer radiation such as X- and γ-rays. Radiation exposures in the nuclear

industry and in radiation medicine have been assessed much more precisely than exposure to most other occupational carcinogens, because since the 1940s workers have been required by law, in most places, to wear personal dosimeters. The accuracy and the precision of these individual dose estimates is, however, dependent on a number of factors. These include: time, place, radiation quality, the type of dosimeter, the geometry of the radiation source, and the placement of the dosimeter on the body of the worker.
In the international study of cancer risk among nuclear industry workers carried out at the International Agency for Research on Cancer, a descriptive study of dosimetric practices in each study facility is being carried out by a small committee of epidemiologists and dosimetry experts. The aim of this study is to identify potential sources of bias and uncertainty in dosimetry, in an attempt to quantify the errors in recorded dose estimates and take them into account in the statistical analyses of cancer risk. This study is necessary since the errors in dose estimation are thought to be large relative to the actual doses, especially since dosimetric records were established to ensure compliance with contemporary radiation protection guidelines, and not for epidemiologic purposes. Recording practices have been shown to have a large effect on the dose estimates, especially in the early years of the industry [15].
A questionnaire requesting information on dosimetry design and dose assessment methodology is being used as the basis for this study [16], as well as monitoring of recording practices in each facility over time. It is supplemented by information from historical documents describing radiation protection requirements in individual facilities, by dosimeter intercomparison studies and by consultations with experts in individual facilities. In general, dose estimates for exposures received before 1960 are subject to great uncertainty because of the relatively high threshold values and poor precision of the dosimeters, and because, in some cases, of the practices used for recording exposure in the case of missing dosimeters or below-threshold readings. Uncertainties introduced by differences in methods of dosimeter calibration between the various facilities are also a source of concern, particularly at low dose levels, as are the geometry of the exposure and the spatial relationship of the dosimeter to the wearer and the source of exposure. Recorded dose estimates, moreover, were meant to estimate different quantities over time, varying from exposure, measured in Roentgens, to deep dose (absorbed energy one centimeter below the skin) recorded in mSv. Inter-laboratory differences in chemical processing, reading and interpretation of films may further increase the uncertainty of dose estimates.
Attempts to identify facility-specific and time-specific biases in recorded dose estimates, and to quantify the uncertainties as a function of dose, time and place, are currently being carried out for workers whose predominant exposure is to radiations of high energy (photons of greater than 100 keV). For the purpose of comparison with results from other radiation studies, an attempt is being made to derive organ dose estimates. For workers receiving significant parts of their exposure from radiations of low energies or from internal contamination, uncertainties in estimating actual deep or organ dose from recorded external dose are much greater [17].

Medical dosimetry

One exposure situation in which great effort has been invested in the accurate estimation of organ doses is medical (therapeutic or diagnostic) exposure. Radiation dose estimates following medical exposure are known to be relatively accurate (compared to environmental and even occupational doses), because of the quality of existing documentation in radiotherapy records. The uncertainties in these estimates are, moreover, much smaller relative to the level of exposure.
Estimates of radiation dose to individual patients or to individual organs can be calculated from direct measurements made during the treatment, from dosimetric experiments carried out on anthropomorphic or water phantoms in simulated exposure conditions, from extrapolation from experiments on phantoms and also by using computer simulation techniques. Account must also be taken of the type of machine used for the radiation treatment, the radiation energy and the size of the field. This information is normally available in the treatment records.
A number of important parameters affect the estimate of doses to various organs from these radiation treatments. They include: the orientation of the field, the shielding, the patient's position, patient movements and the physical attributes of the patient (size, weight). Variability of dose estimates as a function of these parameters has been the object of extensive studies [18]. These uncertainty estimates must be developed further, be compiled, and be taken into account in studies of cancer risk as a function of medical exposures, in order for these studies to be more informative for risk assessment purposes.

Biological dosimetry

Extensive work has gone into identifying cytogenetic and molecular biological techniques, as well as biochemical techniques, which could allow retrospective dose assessment. Among these are the examination of various type of chromosomal aberrations in circulating lymphocytes: dicentrics, micronuclei, and some stable aberrations. A number of somatic mutation analyses have also been proposed; they include an assay for loss of hypoxanthine guanine phosphoribosyl transferase (HPRT) in T-lymphocytes, an assay for a single base substitution in erythroblasts using specific antibody labelling, an assay for loss of expression of specific HLA-types, and an assay for the loss of expression of the glycophorin A allele. In the near future, oncogene mutation assays may also be developed. These various assays have different limits of detection (both in time and in doses), different levels of specificity, different costs, and different levels of automation.

Biological dosimetry has the potential to replace physical dosimetry and environmental transport models and to provide, a posteriori, an assessment of effective dose to a target cell, taking into account interindividual variability in metabolism, repair and exposure. What is needed for risk assessment purposes is a radiation-specific, automated, biological assay which permits precise estimation of doses below 100 mGy or resulting from exposures 20 years ago. At this time no such assay exists; in particular, markers such as chromosome aberrations are nonspecific, and may be misleading if potential confounders, such as tobacco smoke, are not considered. Biological dosimetry techniques are therefore not yet useful for quantitative risk assessment for radiation-induced carcinogenesis.

Discussion

In order to improve current radiation risk estimates, it is important to focus much attention on the study design and the dosimetry. The use of uncertainty estimates for doses of ionizing radiation in risk estimation is only now becoming more prevalent.

Systematic biases and random errors in exposure estimates are known to affect risk estimates. In general, non-differential random misclassification will bias the measures of risk towards the null point and distort the shape of the dose response; in the case of presumed small risks, this may have the effect of obscuring a risk altogether. Systematic biases in the doses can have a wide range of consequences for the risk estimates; these will depend on the magnitude and the direction of each individual bias.

Available records will not always provide the information which would ideally be required to correct recorded or estimated doses; the sources of bias and uncertainty, such as those mentioned above, should however be identified and the size of biases and uncertainties estimated if dose estimates are to be used for risk assessment. This is particularly important since uncertainties will tend in most situations to be dose-related, and therefore the misclassification will be dose-related. It is also particularly important since the exposures of interest result in very small doses and the uncertainties may in some cases be much greater than the doses.

Although geographical correlation studies may be useful in identifying fairly large risks, their contribution to radiation risk assessment will usually be limited to providing an upper bound for a risk estimate. In order to increase our knowledge about the magnitude of radiation-induced cancer risk, especially at the levels of exposure which are currently of interest for the environment, very large and very meticulous cohort studies are required, with extensive individual dosimetric information, at the very least such as to permit a case-control-within-cohort study to be done.

Summary

Most of the information currently available on radiation effects comes from the observation of individuals who received high doses, either from one acute exposure or a series of exposures. Because of the uncertainties in extrapolating risks from these studies to the exposure circumstances of most cancers today (in particular, low-level environmental exposure), direct epidemiologic studies of populations receiving low doses chronically are needed.

The effects which we want to quantify are likely to be small, however, and extreme care must therefore be put into the design of such studies if they are to be informative for risk assessment purposes. The areas of particular importance in designing risk assessment studies are reviewed. The advantages and limitations of various epidemiological study designs, and the problems and importance of dosimetry are discussed. Examples from the recent epidemiological literature are presented to illustrate the discussion.

Résumé

Typologie des études radioépidémiologiques

Les informations actuellement disponibles sur les effets sanitaires des radiations ionisantes proviennent, en majeure partie, de l'observation de groupes d'individus ayant reçu de fortes doses de manière ponctuelle ou fractionnée. Il existe des incertitudes concernant la pertinence des extrapolations proposées pour estimer, à partir de ces données, l'effet des circonstances d'exposition qui nous intéressent aujourd'hui (en particulier les faibles expositions présentes dans l'environnement). Des études épidémiologiques directes de populations soumises à des expositions chroniques, mais faibles, sont donc nécessaires. Les effets à quantifier sont faibles, cependant, et il est essentiel de planifier de nouvelles études épidémiologiques avec soin par obtenir des informations utiles pour l'estimation de risque. Les problèmes principaux des études d'estimation de risque sont discutés. Les avantages et limites des différents types d'étudés épidémiologiques ainsi que les problèmes et l'importance de la dosimétrie sont présentés. La discussion est illustrée d'exemples tirés de la littérature épidémiologique récente.

Zusammenfassung

Studienansätze in der strahlenepidemiologischen Forschung

Unsere heutigen Kenntnisse über Krebsentstehung durch ionisierende Strahlung stammt von Beobachtungen an Individuen nach Exposition mit höheren Dosen, die auf einmal erlitten oder über die Zeit verteilt (fraktioniert) angesammelt wurden. Aussagen über die Effekte niedriger Strahlendosen, wobei vor allem auch die Auswirkung der natürlichen Strahlenbelastung interessiert, sind nur via Extrapolation möglich, mit all den Unsicherheiten eines solchen Vorgehens. Direktere Angaben wären erwünscht; hierfür sind epidemiologische Studien an Populationen mit langdauernder Exposition gegenüber niedrigen Strahlendosen erforderlich. Die Effekte, die es so nachzuweisen gilt, sind höchst wahrscheinlich gering. Nur sehr sorgfältige Studienplanung wird, wenn überhaupt, verlässliche Risikoaussagen ermöglichen. Wir besprechen die hauptsächlichen Probleme sowie die Vor- und Nachteile bei den verschiedenen epidemiologischen Studienansätzen anhand von Beispielen aus der neueren strahlenepidemiologischen Forschung. Neben den epidemiologisch-methodischen Ansätzen wird die Bedeutung adäquater Erhebung und Dokumentation der dosimetrischen Daten betont.

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