Acta Oncologica Vol. 33, No. 3, pp. 251–259, 1994

THE CLINICAL RBE AND MICRODOSIMETRIC CHARACTERIZATION OF RADIATION QUALITY IN FAST NEUTRON THERAPY

HANS G. MENZEL, ANDRE WAMBERSIE and PASCAL PIHET

High-LET radiation therapy using fast neutrons is being applied regularly at several centres worldwide and in the future, other types of radiation qualities, such as protons and heavier ions and boron neutron capture therapy (BNCT) are likely to be used. The neutron beams used are of considerably varying energy and thus considerable variations in the relative biological effectiveness (RBE) have been found. At present, no generally accepted method exists for the quantitative specification of these differences in radiation quality for clinical purposes. This is in clear discrepancy with the accuracy requirements in clinical dosimetry. An approach is presented which is based on a single parameter radiation quality characterization determined in combined microdosimetric and radiobiological experiments. It is shown that the method can meet the accuracy requirements of clinical dosimetry and that it is applicable within a concept of formalized procedure of clinical practice and experience ('clinical RBE').

For a given absorbed dose, biological system and endpoint, the effects of ionizing radiation on biological structures depend on the spatial (and temporal) distribution of individual energy transfers, i.e. on primary physical processes on molecular and cellular levels. In radiation biology, this observation is described quantitatively by the relative biological effectiveness (RBE), the biological effectiveness of one radiation compared with that of a reference radiation. Usually the term 'radiation quality' is used to refer to the differences in the effectiveness of different types of energies of radiation.

In radiation therapy, the RBE was introduced when conventional 200 kV x-rays were replaced by ^{60}Co gamma-rays and high-energy photons and electrons. It was assumed for a long time that an empirical conversion factor of 0.85 was sufficient to take account of the radiation quality differences. Although this factor appeared to be a reasonable approximation for the clinical situations (1), it has been shown that the RBE of 200 kV x-rays, relative to high-energy (>1 MeV) gamma-rays, photons or electrons could reach values of 2 and more at low doses (RBE_{max}), i.e., in the dose range which is relevant in radiation protection (2).

In fast neutron therapy, radiation quality is of much greater relevance when treatment doses have to be described. The RBE values, relative to gamma-rays, are large (ranging from 2 to 5) and depend inter alia on neutron energy and on the biological system. In fact, any therapeutic gain can only result from an RBE being larger for the effects on the tumour than for the effects on the normal tissues at risk. The same is true in boron neutron capture therapy (BNCT). The RBE concept continues to be important in radiation protection where radiation quality has to be taken account of for exposures to different types of radiations, such as gamma-rays and fission neutrons. Indeed, the concepts of equivalent dose and effective dose, or dose equivalent and effective dose equivalent, take into account experimentally observed RBE values through radiation weighting factors, w_R, or the radiation quality fac-

Received 25 November 1993.
Accepted 27 November 1993.
From the Commission of the European Communities, Radiation Protection Research Action, DG XII-F-6, ARTS 3/61, B-1049 Brussels, Belgium (H. G. Menzel), l'Université Catholique de Louvain, Cliniques Universitaires St-Luc, Dept. of Radiotherapy, Neutron- and Curietherapy, av. Hippocrate 10, B-1200 Brussels, Belgium (A. Wambersie), and l'Institut de Protection et de Sûreté Nucléaire, DPHD/SDOS, CEA, F-92265 Fontenay-aux-Roses, France (P. Pihet).
Correspondence to: H. G. Menzel, address as above.
Presented at the Nordic Conference on Neutrons in Research and Cancer Therapy, 29–30 April, 1993, Linköping, Sweden.

 ISSN 0284-186X

tors, Q respectively (2–4). The values for these factors are based on the consensus of experts on their suitability and adequacy for radiation protection purposes. This approach is considered acceptable due to the practised principle of conservatism, i.e. because of the unavoidable acceptance of relatively high uncertainties as long as the chosen values provide a conservative estimate.

In high-LET therapy the situation is fundamentally different. The standard requirement for accuracy in the absorbed dose delivered to the target volume during photon or neutron therapy is $\pm 3.5\%$ expressed one standard deviation (5). Any quantitative specification of radiation quality to be used in dose prescriptions and reporting for high-LET therapy must fulfil comparable accuracy requirements (6). This paper describes an approach based on experimental microdosimetry and correlated radiobiological experiments which has the potential for meeting the accuracy requirement of radiation therapy. First, the paper describes briefly the radiation quality in high-LET therapy and a rationale for the specification of radiation quality for radiation therapy purpose, the 'clinical RBE'.

The radiation quality issue in high-LET therapy

The radiation quality problem in fast neutron therapy is composed of three distinct aspects: 1) the RBE of neutrons compared with that of photons, 2) the difference of RBE between neutron beams of different energy used at different therapy centres and 3) the variation of radiation quality with respect to different irradiation conditions.

Historically, the first aspect has been considered as the most important one since neutron therapy beams have relatively high RBE values compared with gamma-rays due to the large fraction of absorbed dose delivered by high-LET secondaries. The problem was investigated by means of radiobiological experiments using various biological endpoints relevant for therapy (early and late effects in normal tissues). The second aspect is an urgent present problem of neutron therapy owing to the increasing number of neutron therapy centres and to the widely differing energies used (7). The necessity arises to compare clinical results and therapeutic protocols between different centres and therefore to take into account the differences in radiation quality for the specification of the absorbed dose delivered. The third problem was recognized very early on (8). Initially, these investigations were focused on radiation quality variations within the irradiated patient or phantom. With the first generation of neutron therapy facilities (mean neutron energies < 10 MeV) the observed variations of radiation quality and RBE were rather small, at least compared with the RBE difference between neutrons and photons, so that ignoring the variation of radiation quality in tissue (except taking account of variations of the gamma-dose fraction) was considered acceptable. However, considering the accuracy requirement for dose delivery, variations in radiation quality of the order of 5% may not be neglected any more and are relevant for treatment planning calculations.

Furthermore, with the new generation of high-energy neutron therapy facilities (neutron beams produced using high-energy protons on Be-targets), significant (5–10%) RBE variations within patients can no longer be excluded (9, 10). The neutron beams used by various therapy centres are of widely differing energies and, correspondingly, variations of up to 50% in the RBE between different beams have been found in radiobiological experiments (11–13). In addition, at some facilities RBE variations have been observed inside irradiated phantoms, in particular with increasing depth (14, 15). In spite of this radiobiological evidence, there is no quantitative and widely accepted specification of radiation quality used in neutron therapy practice (16). This obvious discrepancy between the accuracy requirement for absorbed dose delivery and the lack of an adequate method for accounting for radiation quality differences and variations calls for a practical solution of this problem. The requirement of high accuracy in the delivery of absorbed dose to the target volume in radiation therapy is determined by the steepness of the dose–response curves for tumour control and complications in normal tissues (17). With respect to the quality control of therapeutic irradiations, it also includes the requirement of reproducibility. Furthermore, in cancer therapy one needs to be able to transfer clinical experience from one centre to another in order to optimize treatment procedures. In photon and electron therapy the accuracy requirements can be met by optimization of dosimetry, irradiation techniques and treatment procedures. In neutron therapy, and in general in high-LET therapy, the difference in radiation quality between various beams and its potential variation within the patient raise additional problems with regard to the dose prescription.

The clinical RBE

Experimental values

When comparing two radiation qualities, one identifies the test radiation and the reference radiation. If D_{test} and D_{ref} are the absorbed doses necessary to reach a given biological effect for the test radiation and the reference radiation respectively, the relative biological effectiveness, RBE, of the test radiation, R_{test}, relative to the reference radiation R_{ref} is given by:

$$RBE_{test/ref} = D_{ref}/D_{test}$$

An RBE value is the result of an experiment and is thus associated with an experimental uncertainty. The RBE is a clear, unambiguous and well-defined concept. However, the biological system, type and level of effect, the dose and the experimental conditions, in which a given RBE value has been obtained, have to be specified.

Strictly speaking, the commonly used jargon that a certain radiation, e.g. fast neutrons from a given nuclear reaction, have a certain RBE is fundamentally incorrect and misleading. RBE values cited in this way are usually not the result of a given experiment but are judgements based on experimental RBEs and sometimes clinical experience. Although this practice is widely spread and reflects some convenience of procedure for a complex issue, it has to be stressed very clearly that the use of such comparative values for different types of radiations should not be confused with RBE values. When comparing two radiation qualities there is no single but a large number of RBE values, i.e. one RBE value for every set of system, effect, and experimental condition (with the corresponding confidence intervals). Since the beginning of fast neutron therapy and even before, a large number of determinations of RBE values for a variety of systems and endpoints were made. In some centres, comprehensive sets of RBE measurements were performed, e.g., the full RBE/dose relationships for different normal tissues and different types of tumours.

Some general conclusions can be derived from the available experimental data:

- large differences in RBE values are observed (ranging from about 2 to 5),
- the neutron RBE increases with decreasing dose,
- the neutron RBE values are larger for late responding tissues than for early responding tissues. In other words, the neutron RBEs are higher for late complications than for early tolerance,
- the RBE also varies to a large extent with neutron energy, in the energy range used in therapy (about 40% for some systems).

The reference RBE

Due to the wide variation of RBE with the biological system and criterion, dose, and experimental conditions, it is necessary to select reference conditions for RBE specification when transferring or exchanging clinical information. These reference conditions should be as indicative as possible for the clinical situations. The following conditions appear to be relevant:

- dose level: 2 Gy (photon equivalent) per fraction,
- biological system: a system and endpoint 'representative' of the RBE for average or overall late tolerance of normal tissues.

The RBE defined in such reference conditions could be called reference RBE ($_{ref}RBE_{n/\gamma}$).

The reference RBE is a radiobiological approach and, in principle, there should be only one reference RBE value for a given neutron beam. This implies that a single RBE value can be defined for an 'overall' or 'average' late tolerance for the normal tissues in patients. The fact that the alpha/beta ratios for late tolerance of different normal tissues are similar supports this approach.

Most of the RBE determinations performed during the radiobiological pretherapeutic experiments and during the radiobiological intercomparisons were using biological systems chosen since they were suitable for the type of experiment and not necessarily since they were representative: well codified, reliable, easy to transport, providing reproducible results (e.g., mammalian cells in vitro, Vicia faba, intestinal crypt cell systems, etc.) (11, 18). A general and formal agreement does not exist as yet. However, comprehensive RBE/dose relationships have been measured recently for late effects on some normal tissues (19–22).

The clinical RBE

In contrast to the reference RBE, the clinical RBE is a clinical and operational concept. The term 'clinical RBE' has been used especially in the U.S. and it is understood as a ratio of the absorbed dose which would be given in a photon treatment and of the neutron dose which is actually prescribed at a given neutron therapy facility (and for a given tumour localisation) (23, 24). Dose prescription and treatment planning depend also on other factors, such as beam penetration or, in general, geometrical factors. If the physical selectivity of the neutron beams used is significantly inferior to that achieved with photons, the neutron dose obtained by simply dividing the photon dose by the reference RBE often cannot be delivered because the expected doses to the normal tissues at risk would exceed the tolerance level. Therefore, first different and more complex beam arrangements have to be investigated for neutrons. If the doses to the normal tissues at risk are still too high, a dose reduction factor taking into account the inferior physical selectivity of the neutrons has to be applied.

At a given neutron facility, there could be several clinical RBEs depending on the tumour site, especially when poorly penetrating beams are used. However, at modern facilities, the physical selectivity of neutrons is comparable to that of photons, and the clinical RBE tends to become close to the reference RBE (25). The 'clinical RBE' can be defined as the ratio of the photon and neutron doses which are actually delivered to the patient in a given neutron therapy facility and in a given therapeutic protocol. It is the quantity the radiotherapist has to select when prescribing the irradiation (e.g., in terms of monitor units). Although it is a dose ratio for two radiation qualities, it is not in a strict sense an RBE: it is the reference RBE (as defined above) weighted by empirical account of the physical selectivity (when needed) and the clinical experience (when available). It implies a value based on the judgement of the radiotherapist.

The microdosimetric approach to specifying radiation quality in fast neutron therapy

Microdosimetric data

The introduction of neutron therapy led to a large number of radiation quality investigations using biological and physical approaches. Radiation quality specifications in radiation therapy must meet specific criteria. The main criterion is derived from the accuracy requirement for absorbed dose delivery. Any weighting factor to be evaluated from biological or physical experiments and to be applied to the absorbed dose must fulfil comparable accuracy requirements. The method to evaluate the weighting factor needs to be valid only within the range of neutron energies used in therapy. The weighting factor would have to be used in support of establishing reference RBEs with increased reliability and to enable to take into account RBE variations of clinical relevance at a given facility.

Radiobiological experiments in neutron therapy beams have been used to determine RBE values and RBE ratios. Such experiments were aimed at providing the basis for the reference RBE approach. These radiobiological investigations are absolutely necessary for the determination of the reference RBE and are required in any attempt to find a suitable radiation quality specification. However, their usefulness is limited by the inherently large uncertainties and unavoidable experimental difficulties. An alternative approach is to identify physical beam parameters which can be determined relatively easily and which can be related to RBE. These parameters include the neutron energy, either measured by spectroscopic methods or assessed on the basis of the neutron-producing reaction, such as (d + Be) or (p + Be) taking into account neutron target geometry and other geometrical parameters. As in current practice, single parameters appear more useful than complete spectral information. The mean neutron energy or related parameters, such as the half value thickness (HVT), are often used.

The neutron energy, in terms of spectrum or average value, is primary information. Neutrons deposit energy through secondary charged particles whose distributions critically depend on the shape of the neutron spectrum and on the types and thresholds of nuclear reactions. The biological properties of neutron beams are therefore more directly correlated to the secondary radiation spectra and only indirectly to the neutron energy. However, the spectra of secondary charged particles are not an easily accessible piece of information, especially for high-energy neutron beams. Furthermore, there exists no biophysical model that describes adequately biological observations relevant for therapy. The measurement of microdosimetric spectra offers, at least for the restricted field of neutron therapy, a sufficiently accurate description of the secondary radiation components and provides a comprehensive and detailed information on radiation quality.

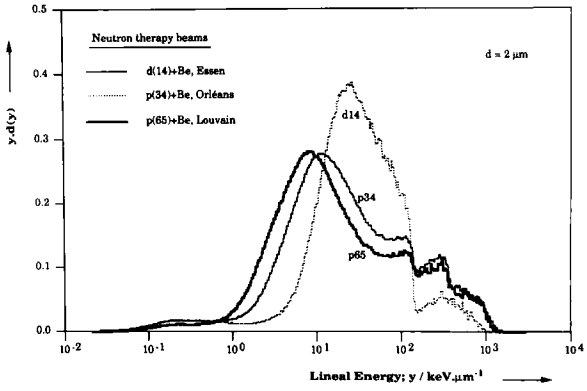

Fig. 1. Microdosimetric intercomparison of neutron therapy beams at European facilities. Comparison of the linear energy spectra obtained for a low-energy neutron beam and for two beams of the new generation (high-energy proton on Be-targets) neutron beams is shown. Modified from Pihet et al. (5).

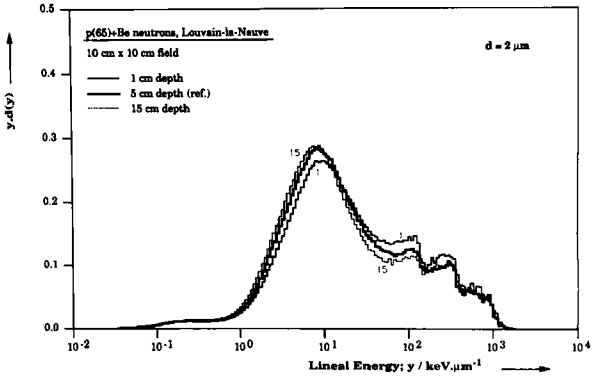

Fig. 2. Comparison of microdosimetric spectra measured at different depths in a phantom on the axis of the (p(65) + Be) neutron therapy beam used at Louvain-la-Neuve. From Pihet (6).

Several microdosimetric studies have been carried out by different groups since the early 1970s in close connection with the development of neutron therapy (8–10, 12, 26–42). These studies were aimed at the investigation of changes in radiation quality between different neutron therapy beams and for a given beam between different irradiation conditions. Figs 1 to 4 show typical examples of the results obtained from these investigations: Comparison of the dose distributions in lineal energy measured in similar conditions for neutron beams of different energies at various therapy facilities (Fig. 1); Comparison of microdosimetric spectra obtained in a neutron beam with a given energy at different depths in a phantom, on the axis of a standard 10 cm × 10 cm field (Fig. 2); Comparison of microdosimetric spectra obtained in a neutron beam with a given energy, at the same depth in the phantom, on the beam axis, and for different field sizes (Fig. 3); Comparison of microdosimetric spectra obtained in a neutron beam with a given energy, outside the geometrical beam, and by using collimators made of different materials (Fig. 4).

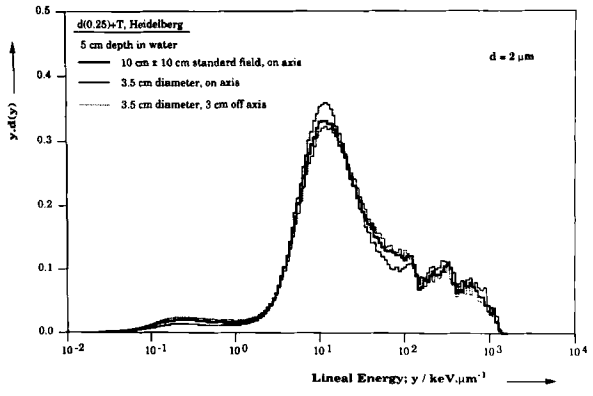

Fig. 3. Comparison of microdosimetric spectra measured for the 14 MeV d + T neutron beam in Heidelberg for different field sizes. From Pihet (6).

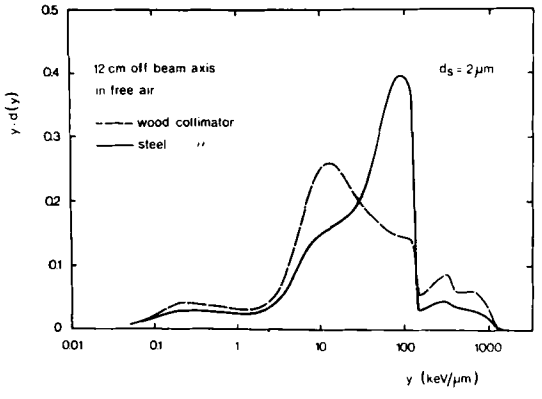

Fig. 4. Comparison of microdosimetric spectra measured for 14 MeV d + T neutrons (DKFZ Heidelberg) outside the geometrical beam for different types of collimator. From Menzel (30).

These examples illustrate the potential of the microdosimetric approach to account implicitly for any factor related to the current clinical practice that may influence radiation quality.

Although the correlation between the shape of the lineal energy spectra and the quality of the neutron beams appears obvious for neutron beams with widely differing energies, the use of microdosimetric spectra for quantifying the variation of radiation quality between different neutron beams by simply using purely physical parameters, such as mean lineal energies, presents, in general, difficult problems. The lineal energy spectra for fast neutrons show large overlapping components. The variation of radiation quality between neutron beams of different energy therefore depends on competing changes in the components of the spectra. In addition, RBE versus LET curves for many biological endpoints show a maximum at around 100 keV μm^{-1}. Consequently, the contribution of each lineal energy component to the average radiation quality for a given neutron beam critically depends on both their contribution to the total absorbed dose and on their relative biological weight. This problem is particularly

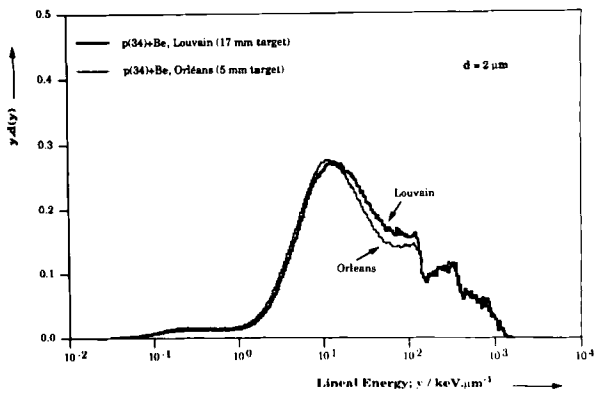

Fig. 5. Comparison of the microdosimetric distributions obtained in identical conditions for (p(34) + Be) neutron beams produced at Louvain-la-Neuve (17 mm thick Be target) and in Orleans (5 mm thick Be target). From Pihet et al. (38).

difficult if neutron beams with small differences in their neutron energy spectra are considered. Such small variations may lead to significant change in intervals where their contribution to RBE is high, i.e., around the peak of the RBE versus LET or y curve. As an example, in Fig. 5, the microdosimetric spectra measured for two neutron beams produced at two different facilities by using the same reaction and energy are compared. The major difference occurs between 20 and 100 keV μm^{-1} which is mainly due to the contribution of protons with relatively low energy. This variation is physically explained by the different target thickness used in the two centres. Biologically, an RBE difference of 6% has been observed between these two neutron beams. This difference is not negligible considering the biological intercomparison of the two facilities. Another example is given by the comparison of microdosimetric spectra measured for the same neutron beam, e.g. (p(65) + Be) in Fig. 2, at different depths in a phantom. Here again the differences between the spectra are relatively small but they affect the lineal energy interval where the biological weight of the events is most important. Related differences in RBE, however, may be detected in biological experiments only if large efforts are made in order to achieve sufficiently small experimental uncertainties.

In order to solve the problem of specifying radiation quality in neutron therapy, it would be useful to identify a parameter with a relative variation similar to that of RBE. It would then be necessary to prove that such a parameter could be determined with sufficiently low uncertainty.

Empirical biological weighting function

The approach presented here was developed by Pihet (10). It is based on the principle of using a weighting biological function applied to the dose distribution in lineal energy for a given radiation field in order to determine a single parameter that estimates its quality. This

procedure is well known in microdosimetry and was applied, for example, in radiation protection for determining the mean quality factor for a given radiation field (43):

$$\bar{Q} = \int q(y) \times d(y) \times dy \qquad [1]$$

Applying this principle to the field of neutron therapy, the problem of specifying the radiation quality for a neutron beam with a given energy compared with that of another neutron beam chosen as a reference may be solved by optimizing a weighting function r(y) so that the integral R:

$$R = \int r(y) \times d(y) \times dy \qquad [2]$$

reproduced the RBE ratio between the two neutron beams (42). This approach only assumes a correlation between the RBE of a given neutron beam and the shape of its microdosimetric dose distribution. It does not require further assumption regarding the biophysical meaning of the energy actually deposited in the site.

The specification of radiation quality for neutron therapy beams requires that the parameter R is determined with an uncertainty of about 3%. The crucial problem therefore remains as to how accurately the weighting function r(y) can be optimized in order to fulfil this requirement. During the 1980s, biological intercomparisons of neutron therapy facilities were limited most often to two neutron beams of different energy (12, 15, 44). Later, systematic biological intercomparisons of neutron therapy beams in the energy range between (d(14) + Be) and (p(65) + Be) became available (13). At the same time, a microdosimetric intercomparison carried out by the EORTC (European Organization on Research and Treatment of Cancer) enabled the measurement of the microdosimetric characteristics for 14 different neutron beams including those used in the biological experiments (9). By using the microdosimetric spectra and the RBE ratios determined for the same neutron beams as input data, the weighting function r(y) could be optimized numerically by an iterative procedure. This unfolding method has been applied several times in microdosimetry to evaluate empirically biological weighting functions (45, 46). Assuming an initial guess function, the parameters of the function r(y) are optimized by successive iterations (Eq. [2]) in order to match the calculated parameter type R and the experimental RBE ratio for each neutron beam. The main limitations of this approach are the energy range, the biological endpoint and the dose level for the RBE values used as input data. This calculation could be performed using the data for nine neutron beams of different energies ranging from (d(4) + Be) to (p(65) + Be) (42). The optimized weighting functions found by using two different series of RBE ratios are shown in Fig. 6. Their shapes are similar to that of the RBE versus LET curves. The effect of the weighting function on the dose distribution in lineal energy

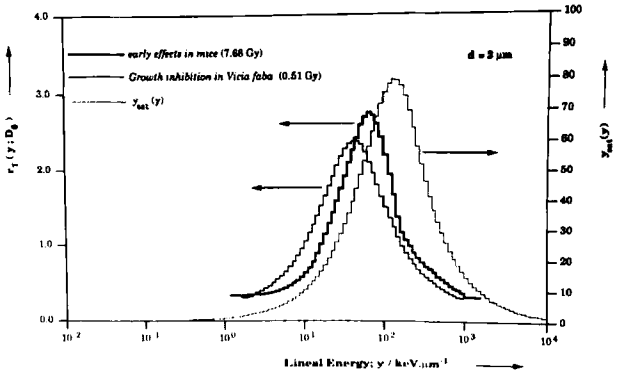

Fig. 6. Biological weighting functions obtained numerically by unfolding calculation using RBE ratios and microdosimetric distributions obtained for the same neutron beams as experimental input data. The functions depend on the biological system and the dose level corresponding to the input RBE values. The curves are compared with the function $y_{sat}(y)$ used for the calculation of y* introduced by Kellerer & Rossi (48). From Pihet et al. (38).

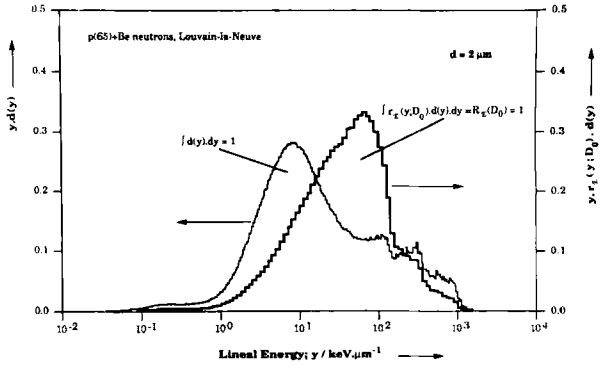

Fig. 7. Comparison of the dose distribution in lineal energy d(y) for (p(65) + Be) neutrons and the corresponding weighted distributions r(y)d(y) (for early effects). The integral under the weighted curve gives an estimate of the RBE of the neutron beam. This integral is equal to 1 for (p(65) + Be) neutrons since this beam has been used as reference in the related biological experiments. From Pihet (6).

is shown in Fig. 7 for (p(65) + Be) neutrons. The integral of the weighted dose distribution, R, gives an estimate of the RBE of the beam. In the case of (p(65) + Be) neutrons, this integral is equal to 1 as this neutron beam was taken as reference radiation according to the biological experiments (RBE ratio = 1). The weighted dose distributions enable the identification of the secondary radiation components that are mainly responsible for the differences in RBE. This is illustrated in Fig. 8 in comparison to Fig. 5; the RBE ratio of (p(34) + Be) neutrons in Louvain-la-Neuve compared with (p(34) + Be) neutrons in Orleans was found to be about 1.06, which agrees well with the difference between the weighted spectra in the interval between 50 and 150 keV μm^{-1}.

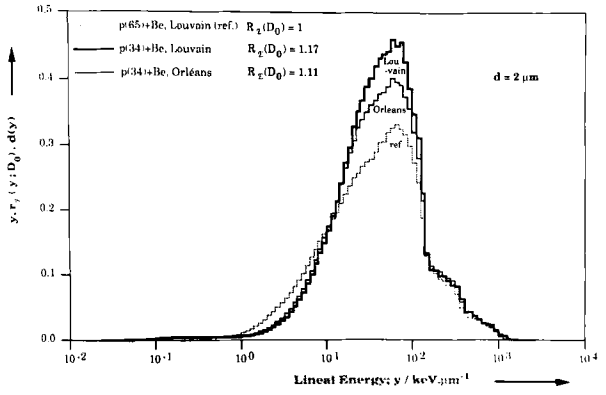

Fig. 8. Comparison of the weighted dose distribution (for early effects) in lineal energy obtained for (p(34) + Be) neutron beams produced at two different facilities and for the (p(65) + Be) neutron beam taken as a reference. The corresponding unweighted distributions were compared in Fig. 5. From Pihet et al. (38).

Uncertainty

The numerical procedure used enables the determination of the uncertainty of the weighting function and the parameter R according to the uncertainties of RBE input data. Assuming that the ideal weighting function r(y) has been found, the ratio of experimental RBE and calculated R parameters would be expected to be equal to 1. The statistical analysis of the curve RBE/R versus R therefore indicates the accuracy achievable in estimating the RBE ratio for a given neutron beam from the microdosimetric

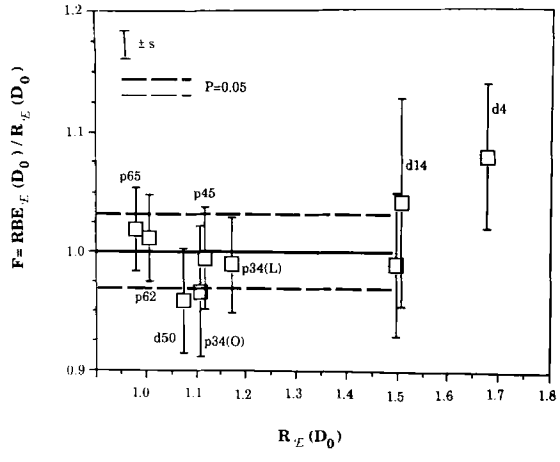

Fig. 9. Statistical analysis for the results of the unfolding calculation of the biological weighting function R. The integral (R) of the weighted dose distribution in lineal energy for each beam is compared with the corresponding experimental RBE ratio used as input data. The mean value of their ratio F is expected to be 1. The hypothesis F = 1 is acceptable for the entire range based on a χ^2 analysis. Reported standard deviations take into account only uncertainties of input RBE values. In the energy range of neutron therapy beams, the related standard deviation on the mean over F and thus the best estimate of the standard deviation over R is found to be ±1.5%; the confidence region (p = 0.05) is indicated. The deviation at low neutron energy implies at these energies (not used in therapy) larger uncertainties. From Pihet (6).

parameter R (Fig. 9). With the RBE values and microdosimetric data available at present, the overall uncertainty of R is found to be <3% (±1 SD), including the uncertainty of input RBE values and uncertainties of microdosimetric measurements. The empirical procedure proposed for the determination of the biological weighting function therefore gives an adequate solution of the problem of accounting for differences in radiation quality between different neutron therapy facilities. The calculation of the weighting function may be improved if further progress in biological data including data for different endpoints (early and late effects) is achieved.

Concluding remarks

High-LET radiation therapy using fast neutrons is at present being applied regularly at several centres in the world (25). In the future, BNCT, proton, and heavy ions are other types of high-LET radiations to be used for therapy. According to an assessment by Wambersie et al. (7) approximately 40–50 000 cancer patients per year, both in Europe and in the USA, could benefit from high-LET radiation therapy. These figures illustrate that the problem of radiation quality specification is a question of immediate practical relevance. It may be part of the principal problem of fast neutron therapy in finding its role in the spectrum of radiation treatment modalities, or at least an illustration of the complexity encountered, that after more than 25 years of clinical trials the central question of radiation quality specification has not been solved adequately for clinical purposes. In practice, very pragmatic and probably not sufficient procedures are applied which do not offer perspectives for future uses of other high-LET radiation.

The proposed microdosimetric approach takes account of clinically relevant criteria and provides a suitable tool for the application of the concepts of reference and clinical RBE. The main criterion, the requirement of high accuracy, has been met mainly by limiting the range of applicability and validity of the procedure to the neutron energies relevant to neutron therapy. Although the proposed procedure for radiation quality specification appears in principle to be very suitable for neutron and others high-LET therapy, there is still the problem of lack of sufficient and adequate radiobiological data suited for the type of analysis presented in the present paper. This is mainly due to the fact that there is no adequate characterization of the radiation field available for most of the large amount of published radiobiological results for fast neutrons.

The present paper has discussed practical ways to specify the relative biological effectiveness of fast neutrons in radiation therapy using the approaches of reference RBE and clinical RBE. These approaches attempt to formalize procedures of clinical practice and experience. The presented microdosimetric approach to determine a single

parameter characterization of radiation quality is closely related to the clinical approach and appears to be promising in providing a tool with an accuracy commensurate with that required in clinical dosimetry. Recent investigations by Loncol et al. (47) have shown that this approach can be extended to the use of protons in therapy.

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