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QUANTITATIVE CLINICAL RADIOBIOLOGY

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Based on a series of recent papers, a status is given of our current ability to quantify the radiobiology of human tumors and normal tissues. Progress has been made in the methods of analysis. This includes the introduction of 'direct' (maximum likelihood) analysis, incorporation of latent-time in the analyses, and statistical approaches to allow for the many factors of importance in predicting tumor-control probability or normal-tissue complications. Quantitative clinical radiobiology of normal tissues is reviewed with emphasis on fractionation sensitivity, repair kinetics, regeneration, latency, and the steepness of dose–response curves. In addition, combined modality treatment, functional endpoints, and the search for a correlation between the occurrence of different endpoints in the same individual are discussed. For tumors, quantitative analyses of fractionation sensitivity, repair kinetics, reoxygenation, and regeneration are reviewed. Other factors influencing local control are: tumor volume, histopathologic differentiation and hemoglobin concentration. Also, the steepness of the dose–response curve for tumors is discussed. Radiobiological strategies for improving radiotherapy are discussed with emphasis on non-standard fractionation and individualization of treatment schedules.

Wir finden also, daß für die Schädigungsgrenze nicht eine bestimmte Dosisgröße angegeben werden kann, sondern daß ein ganzer Bereich in Frage kommt, in dem die Wahrscheinlichkeit für die Entwicklung einer Dauerschädigung von 0 bis 100 ansteigt. . . . dann kann aber die Frage nach den Aussichten der Strahlentherapie unter Berücksichtigung der Gefahrengrenze nur durch eine statistische Betrachtung gefördert werden, nicht aber durch die kasuistische Betrachtung von Einzelfällen. (H. Holthusen 1936)

Clinical radiobiology is concerned with descriptions of the biologic response of human normal tissues and tumors, as derived from basic clinical observations, to doses of ionizing radiation in the range normally employed in radiotherapy. Valuable information has been gained from retrospective, descriptive studies or controlled clinical trials. Yet these studies provide only limited insight into biological mechanisms. In an attempt to further our understanding of clinical radiobiology, mathematical modeling techniques have been used for more than half a century. This approach, here referred to as quantitative clinical radiobiology (QCRB), involves at some level the assumption about an underlying quantitative relationship between patient and treatment characteristics on one hand and response to irradiation on the other.

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Some historical notes

Biological effect of ionizing radiation

Few months after Röntgen's discovery of the x-rays the first attempts were made to use this new radiation for treatment (see (1)). During the following 40 years, combined experimental and clinical observations accumulated until a consensus was reached in the 1930s that fractionated radiotherapy was superior to single irradiations (2). Baclesse (3) summarized in 1951 his and Coutards experience with the treatment of cancer of the larynx, where total treatment time and doses were systematically varied. In selecting the total dose, Coutard aimed for producing the skin reaction 'radioepidermitis', an intense moist desqua-

mation. Under these conditions he arrived at dose–time–fractionation schedules which were close to what is now regarded a standard fractionation schedule: 2 Gy per fraction, daily fractionation, over 6 to 7 weeks (1). An impression of the ideas about normal tissue radiobiology in the late 1930s is obtained from the 1936 paper by Holthusen (4) and the 1941 paper by Zuppinger (5). Here, there is a consistent distinction between early reactions ('Frühreaktion') and late reactions ('Spätwirkungen'). The irreversibility of the late reactions was recognized in the synonym 'Dauerveränderungen' and Holthusen recommended that late reactions were assessed after a minimum observation time of 2 years. Zuppinger (5) published his careful studies of telangiectasia after radiotherapy, describing its long latent period especially after low doses (up till 10 years) and the continuous progression in severity in some patients. Zuppinger also noted that telangiectasia became relatively more pronounced after high doses per fraction than the early reactions, erythema and moist desquamation.

Biologically, the distinction between these two categories of reactions is very important, a realization that has further been underlined by the developments in the last decade. Early reactions occur during or immediately after the treatment, although the actual time of onset varies considerably from one tissue to another. In the clinic, where the pathogenesis of a specific symptom is often unclear, a pragmatic criterion is often employed, defining 'early' as within 3 months after the end of treatment.

Dose–response relationships

The quantitative approach to the analysis of clinical radiobiological data was pioneered by Holthusen (4) and Strandqvist (6). Holthusen (4) plotted dose–response for local control of skin cancer and telangiectasia, and discussed the existence of a dose range where tumor control could be obtained with an acceptable incidence of severe complications. He interpreted the two dose–response curves as expressions of an underlying distribution of radiosensitivities for both tumor control and telangiectasia—an idea that has had somewhat of a renaissance in recent years. In many aspects, Holthusen's 1936 paper stands out as almost modern in its concepts.

Munro & Gilbert (7) suggested that the dose–response curve was an expression of the random nature of tumor-cell kill, and assumed that tumors can recur from a single surviving clonogenic cell. If the number of surviving clonogenic cells after irradiation has a Poisson distribution, the probability of tumor cure is easily calculated as the relative frequency of tumors with zero surviving clonogens after therapy. Although this hypothesis has not been rigorously tested, there is some indication that random cell kill can hardly be the sole cause of the clinical dose–response curve (see below).

Isoeffect formulae

Elaborating on the early work by Strandqvist (6) and Cohen (8), Ellis proposed in the late 1960s two isoeffect formulae, the Nominal Standard Dose (NSD) formulae, for tumors and normal tissues (9). The NSD concept was met with severe criticism almost immediately (10), but nevertheless it came in widespread use in the 1970s. It was soon realized that the data underlying the derivation of the NSD isoeffect formulae were shaky (10); and even worse that the difference in recovery exponents between normal tissues and tumors, which was a key element in the derivation of the formulae, was an artefact originating from inconsistent conventions on how to plot single doses on a double logarithmic dose-vs.-treatment-time scattergram. Probably the most severe fallacy of the NSD formulae for normal tissue tolerance was the hypothesis that early and late radiation sequelae were both the results of damage to 'connective tissue'. In other words the basic biology was flawed. A clear demonstration was provided from the M. D. Anderson Hospital (11), in a trial where the acute reactions were kept constant when changing the dose per fraction. Despite the equivalence of the incidence of acute reactions a marked increase in late sequelae was seen with increased dose per fraction. Bates & Peters (12) gave an early warning based on clinical observations that the NSD formula in general overestimates isoeffect doses for late reactions. Except for the (important) realization that the apparent 'time factor' in radiotherapy was a composite effect of both time and number of fractions, evidence was soon gathered that the biology underlying the NSD was all wrong (13, 14). Perhaps the most convincing evidence against these models came from clinical studies employing large doses per fraction, that were designed to be equivalent with standard dose per fraction schedules according to the NSD formula, but turned out to yield disastrous late normal-tissue complications (15–20).

The most remarkable feature of the NSD formula for tumors was the lack of an influence of overall treatment time on the isoeffect dose. At least for squamous cell carcinoma of the head and neck there is substantial support for the hypothesis that prolongation of overall treatment time leads to a reduced tumor control probability (21, 22).

In parallel with the evolution of the NSD formalism Cohen (23) developed a target-cell kinetics model. Although the Cohen model incorporates many sound biological assumptions, the main obstacle for its successful application in QCRB has been the large number of model parameters that has to be estimated from clinical data. In the basic formulation the model employed 7 parameters: the two-component model for cell killing contains 3 parameters (characterizing the initial and final slopes of the cell survival curve and the extrapolation number); the other 4 parameters are the growth rate of the target-cell population, the number of available cell cycles in the tissue

(a factor limiting repopulation), the critical threshold for cell depletion, and a field size correction for both tumors and normal tissues. The field size effect was meant as a correction for the number of target cells in the tumor, and as a representation of the (possibly) reduced normal-tissue tolerance from larger field sizes. The problem was that the complexity of the Cohen model did not match the biological resolution of clinical and experimental animal data. One prediction from the Cohen model was that split-course radiotherapy would yield a therapeutic gain (23, 24). But the clinical results (25, 26) showed that the protraction of treatment time gave little or no sparing of the late-responding normal tissues so that the extra dose required to compensate for tumor proliferation during the split gave a marked increase in late sequelae.

In hindsight, the most remarkable aspect of the introduction of both the NSD formalism and Cohens model was the sparse clinical data, from which model parameters were estimated, and the rather uncritical acceptance of these models for use in the clinic. On the positive side, these models led to attempted rational designs of new therapeutic regimens, instituted as consistent treatment policies. When these regimens came out disappointingly, they had at least contributed significantly to our knowledge on clinical radiobiology.

The linear-quadratic model.

In the early 1980s, a new set of concepts emerged (27), A cornerstone in this theory was the demonstration of systematic differences in fractionation sensitivity between early and late-responding normal tissues and the interpretation of this in terms of the curvature ('shoulder') of the dose-survival curve for the underlying target-cell population (27). This curvature was quantified by means of the ratio, α/β, of the parameters in the linear-quadratic (LQ) model (27–29): a low value of α/β for a particular endpoint (see below) indicates a high fractionation sensitivity of the underlying target cells, that is a steep relationship between the total dose needed to produce isoeffect and dose per fraction. Thus a basic concept is the target cell, defined as a renewing cell whose death following irradiation contributes to a reduction in tissue function. A unified presentation of the target-cell hypothesis in fractionated radiotherapy has been given in the monograph by Thames and Hendry (30). Consequences of the target-cell hypothesis important for this work are as follows. An endpoint is a specific expression of radiation injury in a given tissue. Various endpoints in the same tissue may depend on the killing of different target cells. Finally, the biological effects of various treatment and patient characteristics are assumed to be attributable to changes in the probability of target-cell survival.

The LQ model has been extended to the situation where repair of sublethal cellular damage is not complete between dose fractions, the so-called incomplete repair LQ-model, and to continuous low dose-rate irradiation (31).

Background and aim of the present studies

By the mid 1980s the LQ model had got a wide acceptance. Very large experimental animal studies all showed that this model provided a quite accurate means to quantify the response of tissues to changes in dose fractionation. However, with the Gothenburg study (19, 20) as a notable exception, few clinical studies available at that time were suited for quantitative radiobiological studies. And many people felt that the past experience had shown that human radiobiology was too complex to be described by simple mathematical models. Indeed, many patient and tumor characteristics of importance for outcome of radiotherapy were not included in the models.

The present studies were initiated in the mid 1980s. The aim was to improve the analysis and interpretation of clinical radiobiological data through (a) a systematic optimization of the methodology of quantitative clinical radiobiology involving clinical, dosimetrical, and statistical aspects, (b) more specifically to introduce state-of-the-art biostatistical tools in the analysis and interpretation of such data, and (c) by doing so, to add to our current knowledge on human normal-tissue and tumor radiobiology. Special emphasis was put on the introduction of methods that could incorporate not only dose-fractionation details but also the effects of latent time and of other patient and treatment characteristics in describing the radiobiology of normal tissues and tumors. In the following the main findings of these studies will be summarized, and their contribution to current attempts to improve clinical dose-fractionation schedules will be reviewed.

Clinical materials

The currently employed radiotherapy schedules have to some extent been optimized through a long empirical tradition. This constrains the variability in treatment characteristics that would be ethical. Therefore much of the work in clinical radiobiology is done on data from retrospective series. Furthermore, QCRB studies of late-responding normal tissues require prolonged observation, typically for at least 5 years after the end of treatment, in a sizeable group of patients. Many of the studies conducted so far have been on patients receiving postoperative radiotherapy for breast cancer, some of the reasons for this are given in Table 1.

The Aarhus postmastectomy radiotherapy study

From 1978 to 1982 the technique for postmastectomy radiotherapy remained essentially unchanged at the Department of Oncology in Aarhus. All patients were treated

Table 1

Features of postmastectomy radiotherapy as given in Aarhus 1978–1982 of interest in clinical radiobiology of late normal-tissue injury

Biological feature	Consequence
High incidence	A large series of patients treated in a consistent manner were collected in a relatively short time in a single institution
High loco-regional control, typically 90%	Observation of late normal-tissue injury possible without the confounding effect of progressing loco-regional disease
Relatively long life expectancy: crude survival in high-risk patients at 5 years is 50% or more	Late normal-tissue injury progresses over several years. Follow-up should continue for at least 3 to 5 years with a high proportion of the patients still under observation after 5 years
Standard radiotherapy techniques involve irradiation of a number of different tissues	Late normal-tissue injury may be evaluated in different tissues and/or using different endpoints in each individual
The DBCG radiotherapy technique applies different doses or radiation qualities to different areas in the patient, for example photons/electrons or a wax bolus covering the surgical scar	Dose–response relationships may be established. Relative biological effectiveness (RBE) may be estimated.

by an anterior 8 MV photon field covering the axillary and the infra- and supraclavicular areas (18). Individually shaped shielding blocks, positioned by means of skin marks drawn during fluoroscopy, protected the humerus from the level of the caput humeri, the larynx, and the lung below the level of the second rib. The shielded part of the chest wall was treated by an abutted electron field. The energy of the electron beam was chosen after ulstrasound measurement of the thickness of the chest wall in the inter-costal spaces. The surgical scar was covered by a 5 mm wax bolus with a margin of 3 cm. The area underneath the wax bolus (referred to as the axillary field), the open photon field (the supraclavicular field), and the electron field provided three independent scores of early and late radiation reactions.

Beginning in 1981 the fractionation schedule was changed from 2 to 5 fractions per week. In the 2-fractions-per-week group, 88 patients received a maximum absorbed dose of 51.4 Gy and 75 patients received a minimum target dose, specified at the level of the mid-axilla, of 36.6 Gy. In both cases the dose was delivered in 12 fractions over a period of 37 to 46 days. In the 5-fractions-per-week group, 66 patients received a minimum target dose of 40.9 Gy in 22 fractions in an overall time of 29 to 35 days. In addition to these 229 patients, another 90 patients received postmastectomy radiotherapy and adjuvant chemotherapy (32, 33). Inter-patient variations in the absorbed dose resulted in part from the two different dose prescriptions in the 12 fraction group, and partly from the patient-to-patient variation in the depth of the mid-axilla.

Acute reactions were evaluated routinely on the last day of treatment by staff or junior staff members. From the clinical description of the skin reaction, a retrospective scoring of the grade of erythema and moist desquamation was performed using arbitrary 4 point scales (18, 33, 34). Late endpoints studied in this thesis included telangiectasia (33–36), subcutaneous fibrosis (32–36), arm edema (17, 33), and impaired shoulder movement (17, 33). Scoring was done by the same physician on ordinal 4 point scales except for arm edema which was recorded as present if the difference between the circumference of the ipsilateral and the contralateral arms exceeded 2 cm.

The Gothenburg postoperative radiotherapy study

The analysis comprised scores of telangiectasia from 401 treatment fields in 335 patients treated with postoperative radiotherapy of the internal mammary nodes at the Department of Oncology in Gothenburg. They are part of a systematic prospective study (19, 20, 37) of dose-fractionation and received 1, 2 or 5 fractions per week, the total number of fractions ranging from 4 to 30. Telangiectasia was scored from photographs of the irradiated fields taken every 3 months for the first 5 years and twice per year thereafter. Two observers scored the telangiectasia blindly, using an arbitrary 4-point scale defined as no, minimal, distinct, and very marked telangiectasia.

The Aarhus oropharynx study

Local tumor control was evaluated in 181 consecutive patients receiving definitive mega-voltage radiotherapy for histologically proven SQCA of the oropharynx at the Department of Oncology in Aarhus. The patients were treated between 1959 and 1985 with ^{60}Co or 4–8 MV photons from linear accelerators. Dose-fractionation prescriptions were standardized for all patients, but changed with a changing treatment policy throughout the period. A considerable variation in overall treatment time was caused by the employment of split-course regimens from 1977–1985. Ninety percent of the patients received close-to-standard doses per fraction in the range 1.7 to 2.2 Gy. The major deviation from this was in a group of 10 patients who received split-course radiotherapy with

33.04 Gy in 8 fractions (4.13 Gy per fraction, 2 fractions per week) before the break followed by an additional 26 or 28 Gy with 2 Gy per fraction.

The endpoint used was local control in the T position after primary radiotherapy irrespective of the status of neck disease.

The melanoma study

This series comprised 239 histologically proven recurrent or metastatic lymph node (47%) or cutaneous (53%) melanomas in 121 patients. Cutaneous lesions were treated by single electron beams, while more deeply seated tumors received ^{60}Co or 4–8 MV x-rays. The maximum absorbed dose on the central axis was used as the tumor dose in the study. Lesions involving the skin were covered by a wax bolus to increase the surface dose. There was a considerable variation in total dose, dose per fraction (1.8 to 10 Gy, most of them 2.5, 5.0, and 9.0 Gy), and overall treatment time (from a few days to more than 60 days). Tumor size, expressed as maximum diameter, was available for all tumors.

The endpoint for treatment response was complete response, that is complete tumor clearance after a minimum follow-up of 2 months. This is not an ideal endpoint for tumor radiobiology studies but was necessitated by the short life expectancy in many of these patients. Also, studies by Overgaard have shown that a complete response is associated with a high probability of a persistent disappearance of the tumor (38, 39).

Physical aspects

The physical absorbed dose to a tumor or a tissue is obviously a fundamental parameter in QCRB. However, the dose prescribed by the radiotherapist is not necessarily a very good measure of physical dose in clinical radiobiology.

Dosimetric reference point

The standard practice of dose prescription is to specify the absorbed dose to a single point, which, in many cases, is geometrically defined and only indirectly tumor related. Examples are the specification of a mid-plane dose in case of two parallel opposing fields (or in general, at the intersection of the central axes of a multiple field arrangement), the specification of a minimum dose at a given depth in the patient, or simply specification of the maximum absorbed dose. With the introduction of computed-tomography-based dose-planning systems, more refined dose prescriptions are possible, for example the average target dose, or a dose-volume histogram for the target volume (40). Either way, these prescribed doses may be of little value in QCRB.

For tumors, the prescribed dose will often be representative. The reason is, that the goal in radiotherapy has been to obtain a homogeneous tumor dose, which in most cases is accomplished with modern megavoltage multiple-field techniques.

For normal tissue radiobiology prescribed doses are in many situations of limited value, because the critical cells or tissues may be located in the build-up region (35) or they may be only partially irradiated. But not only that, close to the surface even open-field depth dose data at the relevant tissue depth may be underestimated by 10–12% (35) due to scattered irradiation from the treatment machine or from block-supporting trays etc. This contribution depends on field-size and is mainly due to secondary electrons with a relatively short range.

Relative biological efficiency

The RBE is defined for a specific biological endpoint as the ratio between the isoeffect doses for a reference radiation quality and the test radiation quality, provided that all radiobiologically relevant factors except dose and linear energy transfer (LET) are identical. The latter requirement is rarely fulfilled in practice, and as a consequence the RBE is often used in an operational manner simply defined for a specific endpoint as the empirical dose-modifying factor the test radiation relative to the standard radiation with explicit reference to the particular treatment conditions.

Megavoltage electrons have been in clinical use for more than 30 years. Except for a few early studies (41–43), there is a scarcity of clinical RBE determinations for high-energy electrons, and technical aspects of these early studies weaken their conclusions (35).

From the postmastectomy radiotherapy data (34), where high energy electrons were used for treating the chest wall above the lung, the RBE of 6–10 MeV electrons relative to 8 MV photons was estimated to be 0.89 (95% c.l. (0.85, 0.93)) for telangiectasia and 0.88 (95% c.l. (0.86, 0.91)) for fibrosis, at the depths of 0.1 mm and 4.1 mm (5.1 mm and 9.1 mm underneath the wax bolus), respectively. If these dose-modifying factors are applied, dose–response data from the electron and photon fields fall on the same curve (34).

These RBE estimates are obtained for superficial points where electron equilibrium is not established. They may not apply to more deeply situated reference points. Yet they illustrate that data obtained from fields treated with the two different radiation qualities can not be pooled without appropriate correction for RBE. Progress in microdosimetry, especially the introduction of variance-covariance measurements, could improve the ability to characterize local radiation-quality differences between therapeutic beams (44).

Quality assurance

A large number of factors influence the precision by which radiotherapy is delivered, and thereby possibly the

absorbed dose to normal tissues and the tumor. A fundamental distinction is between on one hand random fluctuations in treatment-machine output, positioning of the patient, and the precise setting of the treatment parameters, and on the other hand systematic errors. The former may to some extent cancel out when the average over a large number of fractions, say 30, is considered. The systematic errors may include geographical misses or miscalculated doses. Also dosimetric errors on the treatment machine may be a problem.

Reviews of simulator and port films may reveal some of these problems, while others, like a wrong AP measure, in general can not be checked and/or corrected.

It is a special concern in many retrospective series extending over several years, that technical routines in the radiotherapy departments in general have improved over time, which could introduce a bias: 'new' treatments would come out better than 'old' treatments. One example, is the transition from ortho- to megavoltage radiotherapy which substantially improved the homogeneity of the tumor dose distributions. To allow for this patients treated with 250 kVp x-rays were excluded from the analysis of oropharynx cancer patients in Aarhus (45).

Models and direct analysis

Fractionation models

The systematic difference in α/β for early- and late-responding normal tissues, originally observed in experimental animals, has been shown to hold in clinical radiobiology as well (see below). This has made the complete- or incomplete-repair LQ model the basis for most current QCRB analyses. Deviations from the simple LQ expression are found in experimental animal and cellular systems at very low and very high doses (46). Nevertheless, over the range of typical clinical doses the LQ model provides a reasonable fit to the data. Admittedly, very little has been done on actually testing the goodness-of-fit of these models in the clinic (or for that sake in experimental animals); but at the time of writing, there are no compelling reasons for leaving the simple LQ formalism for late-responding normal tissues.

Attempts have been made to modify the LQ model by including a time-factor to represent regeneration in early-responding tissues (47). So far, the suggested modifications have been oversimplistic (48, 49) and the development of more realistic models is hampered by the complexity of the homeostatic control mechanisms in early-responding normal tissues.

Also for tumors the LQ-model must be modified to allow for overall treatment time. The approach taken so far, has been to assume simple exponential growth during treatment (45, 50, 51). This growth rate probably exceeds the pre-treatment rate, a phenomenon termed accelerated regeneration. A 3 to 5 week lag time before the onset of accelerated regeneration have been suggested by Withers (52). However, in most clinical series with conventional fractionation schedules this lag time can not be resolved as very few patients are treated in such short times (except for patients who do not complete treatment), and in fact the available clinical data are consistent with an interpretation in which the lag time, if any, is shorter than 1–2 weeks (53–55). In addition to the time factor, tumor size must be allowed for in the model together with other patient and tumor characteristics (45, 50, 51). Multivariate methods of analysis are therefore required.

Maximum likelihood estimation

Maximum likelihood estimation is a standard method in statistics and the basic idea is as follows. Assume that we have a mathematical model that for a given set of variables, say, treatment and patient characteristics, allows us to calculate the probability of an event, in our case, a specific biological response. Assume further, that the model has a number of parameters, like the α/β ratio, that determine this probability. The ordinary point of view is that for the 'true' population values of the model parameters, we can calculate the probability of any particular outcome. With maximum likelihood estimation this is given a twist: suppose instead that we vary the parameter values. Then for each choice of parameters we can compare the observed and the predicted outcome. The maximum likelihood estimate of the parameters are the values that maximize the probability of the actually observed result. An example of how different sets of parameters give rise to likelihood surfaces (or in the two-dimensional case, likelihood contours) have been given in (51).

Standard computer code is available for solving this maximization problem (56), and this has been implemented in programs especially designed for the analysis of radiobiological data (57, 58). Standard errors of the parameter estimates, and from these 95% confidence limits, are available from the variance-covariance matrix.

Direct analysis offers a number of advantages relative to the traditional two-step methods (Table 2).

Mixture models

In contrast to early reactions, which appear in a relatively narrow time interval, both late normal tissue injury and tumor recurrence are technically response-time or failure-time data. Such data arise, when in each individual we know either the time of response or a maximum observation time at which the endpoint has still not been reached. There is an extensive statistical literature on the analysis of such data, but traditional failure-time statistics does not distinguish between incidence and latency of the event (59). Contrary to this, mixture models are specified

Table 2

Advantages of using direct analysis in comparison with two-step methods

Property of direct analysis	Consequence	Two-step methods
Inherently multivariate	Correction for latency (36, 60) and other patient/treatment characteristics possible (17, 32, 34, 45, 50)	Time-window approach (60) necessary; stratification for other covariates necessary
No grouping of data required	Data from infrequently applied schedules or patients with rare characteristics may be included (45)	In each stratum a considerable no. pts. with variation in total dose is needed to obtain isoeffect dose estimates Reliable dose estimates for a common isoeffect should be available
Confidence limit estimation	Indispensable in judging the significance of results	Simple estimates of confidence intervals are invalid with this method (57, 97)
May be extended to graded responses	More detailed biological information available (61, 98)	No natural extension to graded-response analyses possible
Statistically efficient	Fewer patients needed with this method than with its alternatives to obtain a certain width of the 95% confidence interval (99)	Requires more patients for same accuracy
Unbiased	Estimates on the average centered on the 'true' values for the underlying population (57, 99)	Bias may exist (57) (see however (99))

in terms of the ultimate probability of expressing the endpoint, p_∞, and the parameters of the latent-time distribution (60). Intuitively, the mixture model applies to situations where some subjects never reach the endpoint even at very long follow-up time, for example in the case where a subset of patients obtain a persistent local control or they never express a specific type of normal tissue injury. The basic concept is that latency is only meaningful in these individuals that actually reach the endpoint, but with allowance for incomplete follow-up (censoring). One attractive feature of the mixture model is that the standard radiobiological models like the LQ-model are embedded in this framework in a natural way, as they are taken to represent the p_∞ (60).

Extensions of the mixture model

Two extensions of the mixture model are of special interest in QCRB: analysis of single-follow-up data (36) and of graded-response data (61).

Single-follow-up studies are those, in which the status of the patient is examined at one occasion only. On that particular time the status of the patient with respect to the endpoint in question is known, thus in a responder, the event (expressing the injury) has happened at some unknown time between the end of treatment and the time of examination. In this case the cumulative probability distribution may be used in the likelihood function in place of the standard density function (36).

Graded responses are seen with non-stochastic radiation effects like early and late skin reactions. The method used has been to dichotomize such data by analyzing the proportion of patients whose reaction exceeds an arbitrarily chosen threshold (57). However, by doing so information is lost. Furthermore, various grades of reaction may have different dose-latency relationships, a phenomenon of interest in itself. Using an approach suggested by McCullagh (62), the mixture model has been extended to analyze graded responses. This method was applied to the Gothenburg telangiectasia data (61).

Clinical radiobiology of normal tissues

Fractionation sensitivity and repair kinetics

Ten years ago Thames & Withers (27) pointed out that in experimental animals early- and late-responding normal tissues may be grouped according to their α/β ratio. This picture holds for human tissues as well (17, 32–36, 61, 63). Rather than a whole spectrum of α/β ratios, values in the range 1–5 Gy have consistently been found for late-responding tissues, whereas α/β for early-responding tissues center around 10 Gy. Many of the available estimates stem from studies of postmastectomy radiotherapy (Table 3).

While the overall picture strongly supports the systematic difference between the fractionation sensitivities of early- and late-responding tissues, the α/β ratios for specific endpoints still have relatively wide confidence limits. If

Table 3

α/β-ratios and latency for late-responding tissues after post-mastectomy radiotherapy

Tissue	Endpoint	α/β (Gy)	LT_{90} (years)	Ref.
Subcutis	fibrosis	1.9 [0.8, 3.0]	3.2 [2.3, 3.9]	(36)
Vasculature	telangiectasia	2.8 [−0.1, 8.1]	4.7 [2.8, 6.5]	(34)
		2.8 [1.7, 3.8]	?	(37)
		3.9 [2.7, 4.8][a]	?	(37)
		2.6 [2.2, 3.3][b]	2.0–15[c]	(61)
Lung	fibrosis	3.6 [?]	?	(100)
	pneumonitis	6.9 [?]	?	(100)
Bone	necrosis	≈3 [–, –]	< 3 [?]	(101)
Muscle/ vasculature/ cartilage	impaired shoulder movement	3.5 [0.7, 6.2]	3.9 [3.1, 4.6]	(17)
Subcutis/ muscle	nipple retraction	2.5 [?]	?	(102)
Lymphatic system	late arm edema	?[d]	?	
Nerve	brachial plexopathy	< 5.3	?	

?: not available
[?]: 95% confidence limits not available
[–, –]: 95% confidence limits too large to be estimated by standard methods
[a] with correction for overall treatment time, see (37)
[b] reanalysis of graded response data from (37) with latent-time correction
[c] depends on grade of reaction and toxicity of treatment (61)
[d] confounded by extent of axillary dissection (17)

these values are applied directly in estimating isoeffective treatment schedules in the clinic, the confidence intervals for the isoeffective doses become disappointingly wide (33).

Clinical data on repair kinetics are sparse. With the exception of the study by Turesson & Thames on telangiectasia (37), for which the authors suggested that repair may be biphasic with half-times of 0.4 and 3–4 h, repair half times for most endpoints are only tentative (63). At present, a conservative attitude is justified in designing clinical fractionation schedules, which means that interfraction intervals of less that 6 hours are discouraged.

The time factor

Early reactions depend not only on total dose and dose per fraction but also on overall treatment time. While early reactions are more readily made the subject for prospective clinical studies, few quantitative analyses have been made (35, 37).

There is only negligible sparing of late reactions from protracting overall treatment time, at least up till 10 weeks. This is supported by the data from split course radiotherapy in head and neck patients (26) and also by a preliminary analysis of late proctitis requiring treatment after combined external and intracavitary radiotherapy (64). In the latter study, two groups of patients were treated to estimated biologically equivalent dose in 2 Gy fractions to the ventral rectal wall of 64 and 65 Gy in overall treatment times of 4.5 and 11 weeks, respectively. The actuarial incidence of late proctitis at 5 years was $26 \pm 7\%$ and $27 \pm 6\%$ in the two groups, thus no detectable sparing was observed.

Latency

The latent period is the time from irradiation until a specific endpoint is reached. Latency has been studied in some detail for telangiectasia (36, 61, 65), subcutaneous fibrosis (36), and impaired shoulder movement (17) (see Table 3). The main findings are as follows. The expression of late radiation injury is a time dependent process, with increasing grades of reaction expressed at increasing time after treatment, and with the proportion of patients, expressing any given grade of reaction, increasing over time. Thus the incidence of a specific grade of reaction is time dependent, with 90% of the ultimately expected incidence of the reaction seen after 2 to 4 years (subcutaneous fibrosis, impaired shoulder movement), or for telangiectasia after 10 years or more (depending on grade of reaction (61)). Furthermore the latent period shows a

strong dose dependency: grade 3 telangiectasia in the Gothenburg series had an estimated median latent time decreasing from 11 to 5 years as the total dose increased from 40 to 70 Gy with 2 Gy per fraction (61).

Combined treatment modalities

Combined treatment modalities are frequently used in oncology, which may cause problems when analyzing treatment-related morbidity. For instance late arm edema after post-mastectomy radiotherapy is a clinical problem and its incidence does indeed increase with increasing dose and dose per fraction; but it is also strongly dependent on the extent of the axillary dissection (17), thus the surgery and the radiotherapy both contribute to the overall treatment toxicity. Also combination chemotherapy with cyclophosphamide, methotrexate and 5-fluorouracil (CMF) resulted in a left-shift of the dose-response curve for subcutaneous fibrosis (33, 34). This was not seen for cyclophosphamide used as a single agent (33), one possible interpretation being that the target cells for radiation induced fibrosis are not damaged notably by the cylophosphamide. Clinically, this means that two chemotherapy regimens with equal tumor activity may or may not be equitoxic with respect to a specific late endpoint. Again these interactions are of interest in themselves. At the same time they constitute a problem in any univariate analysis because they will confound the results.

Consequential late reactions

Peters et al. (66) introduced the distinction between on one hand 'classical' late reactions, most likely arising from cell killing to the mesenchymal tissues, and on the other hand, consequential late reactions, caused by prolonged epithelial denudation. This was suggested as the likely explanation for the unexpectedly high incidence of bone and soft-tissue necroses seen in the accelerated fractionation study by Peracchia & Salti (67).

Similarly, the risk of developing telangiectasia after a given course of radiotherapy was significantly higher in a treament field with previous moist desquamation compared with fields without this early reaction (34). Thus the radiation pathogenesis of telangiectasia may involve a component of consequential late reaction. As suggested by Hopewell (personal communication), this observation is most likely explained by the temporary lack of epidermal protection of the endothelium in patients with moist desquamation. Another explanation, namely that both types of injury would occur with a higher probability in patients who were particularly sensitive to radiation, is not likely because a similar predisposition after moist desquamation could not be seen for subcutaneous fibrosis and no increased incidence of telangiectasia was noted after severe erythema. Consequential late reactions may be a growing problem with the introduction of accelerated fractionation schedules, treating to the limits of early normal tissue tolerance.

Patient-to-patient variability in response to radiotherapy

Age above 60 years has been identified as a predisposing factor in developing reduced mobility of the ipsilateral shoulder relative to that of the contralateral shoulder after post-mastectomy radiotherapy (17). It should be noted, that this is an functional endpoint, most likely having a complex pathogenesis (17). No predisposing factors were identified for subcutaneous fibrosis in patients treated with radiotherapy alone in the Aarhus series, thus the occurrence of this complication appears to be predicted from dose-fractionation characteristics alone. However, a significantly increased risk of developing this complication was seen after CMF chemotherapy combined with radiotherapy.

Compared to tumors, there appears to be less variability in the response of normal tissues to radiotherapy in an unselected population of humans. Indirect support for this is found in the quite steep dose–response curves that have been seen for late-responding normal tissues (33). Still, there appears to be a host factor in the expression of late normal-tissue injury. A correlation between the expression of subcutaneous fibrosis and/or telangiectasia in different fields in the same patient was tested by Bentzen et al. (68). This was done by looking at weaker- or stronger-than-expected reactions in two fields using the technique of residuals (34, 50). Residuals for the same endpoint in different treated areas in the same patients are highly significantly correlated ($p < 2 \cdot 10^{-5}$). Contrary to this, no significant correlations could be detected between the residuals when comparing two different endpoints in the same patient. The lack of correlation between early and late endpoints in individual patients (34) has been supported by a recent study (69). No significant correlation was found between erythema and telangiectasia whereas a high grade of telangiectasia in one field was correlated with a high grade of telantiectasia in another field in the same patient. Thus a predictive assay, for example an in vitro radio-sensitivity test of a specific type of human normal cells, would be a clinically useful predictor for a specific type of late normal-tissue injury only, but not for tumor control or normal-tissue reactions in general.

Some genetic syndromes, like ataxia telangiectasia (AT), have been shown to be associated with a strongly increased sensitivity to radiotherapy (70). While these are rare diseases, also AT heterozygotes, who according to some estimates may constitute 8% of all breast cancer patients (71), have been shown to have an increased in vitro radiosensitivity of their fibroblasts (72, 73). However, the lack of significant correlation between various endpoints in individuals, suggests that any predictive assay of radiosen-

sitivity would have to be aimed at a specific clinical endpoint.

Clinical tumor radiobiology

Overall, human tumors exhibit more biological diversity than human normal tissues, not only when comparing tumors of different histology but also within a specific tumor type.

Fractionation sensitivity and repair kinetics

Few estimates of α/β are available for human tumors (63), and from these there appears to be a considerable variation between different tumor histologies. For SQCA of the head and neck, α/β values have been estimated at 7–10 Gy, but with relatively wide confidence intervals (74). In the oropharynx study (45) only 10 patients received larger-than-standard doses per fraction, namely 4.13 Gy, and only for part of treatment. This precluded direct estimation of α/β. However, $\alpha/\beta = 10$ Gy gave a better fit to the data than the $\alpha/\beta = 25$ Gy suggested by others (74).

In contrast, malignant melanoma is very sensitive to changes in dose per fraction, characterized by a low α/β value of 0.6 Gy with 96% c.l. (−1.1, 2.5) Gy (50). However, in a recent randomized study (75) complete response were seen in the same proportion of tumors after 4×8.0 Gy and 20×2.5 Gy. This would indicate an α/β of about 7 Gy. It is difficult to assess the confidence limits on this value but the trial most likely can not rule out that α/β is considerably lower than this value (76).

There are no clinical data on tumor repair kinetics. The conservative attitude is to assume that tumor SLD repair half times are shorter than those for late-responding normal tissues. This means that short intervals between fractions would be a therapeutic disadvantage.

The time factor

A number of studies (22, 52, 77) have shown a detrimental effect on local control from protracted overall treatment time in squamous cell carcinomas. However, most of these studies are subject to methodological problems hampering their interpretation (21, 53, 54). So far, the most convincing demonstrations of the treatment-time effect are from split-course studies where all patients during a period of time were given protracted treatment as a consistent treatment policy. A typical value was estimated in (45), where the dose needed to compensate one extra day of treatment was found to be 0.68 Gy with 95% c.l. (0.05, 1.3) Gy.

For malignant melanoma, the probability of obtaining a complete response did not change as a function of overall treatment time (50). The times ranged between 1 and 10 weeks.

Tumor volume

Tumor volume is a major determinant of outcome in radiotherapy. This was also demonstrated in SQCA of the orophanyx (45) and in malignant malanoma (50). In the latter case, maximum tumor diameter was a strong confounder of the dose–response relationship, a significant relationship becoming evident only when size was accounted for (50). The number of target cells does not simply scale in proportion to tumor volume (45, 50). While there might be good biological reasons for this, new analyses have shown that this could be an artefact arising from a considerable patient-to-patient variability in tumor radiosensitivity (51).

Histopathology

Poor differentiation of the tumor cells is associated with a poor prognosis with respect to disease-free survival. This is possibly because of a more aggressive natural history of the tumor. Use of actuarial methods, permits studying local control as the endpoint even when observation time is limited in some patients because of death from a competing cause, for example death from an out-of-field relapse. A mixture-model analysis of local control in SQCA of the oropharynx revealed that low differentiated tumors were more susceptible to treatment (45).

The oxygen effect

Overgaard (78) has reviewed the current data indicating the hypoxia may be a cause of radio-resistance. Although attempts have been made to measure hypoxia in the clinic, these techniques have not been used routinely. Here, hemoglobin concentration has been used as a rough indicator for hypoxia in QCRB studies. In a multivariate analysis, after correcting for time-dose-fractionation, tumor size and histopathological differentiation, decreasing hemoglobin concentration still had an independent profound negative influence on local control probability (45).

Patient-to-patient variability

Very shallow tumor dose–response curves are observed in the clinic. As a consequence the estimates of the number of target cells in human tumors become unrealistically low, typically in the order of less than 100 target cells per cm^3. There are several possible explanations for this finding, the most likely, at least in this authors view, is that a considerable patient-to-patient variability flattens the dose–response curve. In the melanoma data (50) there was less variability between the response of multiple lesions in an individual patient than between identically treated lesions in different patients. This is an indication that either a tumor factor, like intrinsic radiosensitivity, or a host factor, like immune competence of the patient, play a role in

determining the outcome of a given treatment. None of the current models take such an effect explicitly into account.

One of the proposed sources (79) of patient-to-patient variability in tumor response to radiation is the intrinsic radiosensitivity as quantified by the in vitro SF_2. Indeed this measure has been shown to be significantly correlated with local tumor control in patients treated by definite radiotherapy for cancer of the uterine cervix (80). In two recent studies (51, 81) we have looked at the observed variation in SF_2 for human melanoma and head-and-neck SQCA cell lines assayed in vitro to see if this variation alone could explain the shallow clinical dose-response curves. For melanoma the observed variation in SF_2 contributed significantly to this flattening, but a considerable additional variation in radiosensitivity and/or clonogenic density had to be assumed in order to remove the discrepancy between the observed and expected dose–response curves (81).

For SQCA of the head and neck (51), variability in the in vitro intrinsic radiosensitivity was forced into a direct analysis of tumor control data for oropharyngeal carcinomas. A dose-modifying factor was needed to correct for the apparent difference between in vitro and clinically realistic radiosensitivities. The value of this factor is estimated at 2.4 with approximate 95% c.l. (1.3, 5.9), suggesting that hypoxia may play a role in reducing the radiosensitivity of human tumors. After this correction, the target-cell doubling time during treatment was estimated at 3.2 days with 95% c.i. (1.7, 8.7) days. Estimates of the target cell density in a tumor with typical characteristics varied between $1.8 \cdot 10^{-6}$ and $6.6 \cdot 10^{-4}$ per cm^3 as the delay before onset of accelerated tumor growth was assumed to vary between 0 and 28 days. Thus the clinical dose–response curves may be interpreted as a superposition of quite steep dose–response relationships in individual patients.

Radiobiological strategies for improving radiotherapy

Several research areas in clinical oncology are aimed at improving radiotherapy. The rationales for two of these, altered fractionation and individualization of treatment, are largely based on, or strongly supported by, QCRB studies, and these will be discussed in some detail below. Two other research fields should briefly be commented from the current point of view. One is conformal therapy, where the rationale is to allow escalation of the target dose and/or minimization of the irradiated normal-tissue volume. This strategy has become feasible with the new medical imaging techniques, whereby the target volume can be better defined. This is combined with progress in radiation physics and technology, such as improved computer algorithms for dose-planning, automated set-up of treatment fields, and new radiations (e.g. proton beams). From the high steepness of dose–response curves for late normal-tissue injury this should indeed be a promising approach. The missing link from a radiobiological perspective is that so little is known about dose–volume relationships (82). Looking at tumor control, on the other hand, the very shallow dose–response curves mean that quite substantial dose escalations may be needed to produce a detectable advantage in a realistic size clinical trial. The other research field is the use of biological response modifiers in radiotherapy. Although this field is still mainly experimental and dominated by a good deal of empiricism, one basic rationale is to apply cytokines or growth factors to reduce normal-tissue injury through stimulation of target-cell growth. The news here is that late normal-tissue injury up till now has been regarded as an almost inevitable price for intensified treatment to be reduced only by utilizing the radiobiological differential between NT and tumors. This could drastically change as methods of direct intervention become available.

Non-standard fractionation

A standard fractionation schedule employs 1.8 to 2.2 Gy per fraction, 1 fraction per day, 5 days per week. Any deviation from this scheme is termed non-standard fractionation. There are four major types of alterations of the standard schedule, and they are summarized in Table 4. In practice, many fractionation schedules involve a mixture of these ideas. Of the 4 prototypical strategies, hypofractionation will in general lower the therapeutic ratio between tumor and late-responding NT because of the high fractionation sensitivity of the latter. There is only one exception, namely in tumors with a very low α/β (for example melanoma (50, 83)) where hypofractionation may be as good as or even better than standard fractionation. A slightly different situation may occur for rapidly proliferating tumors where the advantage of shortening overall time in principle could allow a sufficiently large reduction in total dose to keep down the incidence of late sequelae despite the high doses per fraction. Large dose fractions would still represent a therapeutic disadvantage in theory, while in practice the incidence of clinically manifest injury may be kept below the acceptable limit. Whether this is actually the case in some tumors remains to be proven, although Fowler (84) has suggested that this could be the reason why the Manchester schedule, employing 54 Gy in 16 fractions over 3 weeks, is doing relatively well with respect to tumor control and late sequelae in the treatment of head and neck SQCA.

A second clinical case for hypofractionation may be in palliative treatments where the palliation obtained from using a few or even a single large dose fraction may be the same as that obtained after multiple fractions to higher total doses (85). Here the rationale for large doses per fraction is not biological but rather patient convenience and cost of treatment.

Table 4

Prototypical strategies for altered fractionation

Strategy	Characteristics	Basic rationale	Therapeutic gain?
Hypofractionation	Dose per fraction exceeds 2.2 Gy	Economical/patient convenience: reduced total number of fractions Cost reduced	SQCA: NO! The dose reduction possible without compromising tumor control probability is insufficient to allow for the increased biological effect on the LNT. Melanoma:? Large doses per fraction probability yields a therapeutic gain. Uncertainty in α/β for melanoma and LNT prevents a firm conclusion.
Split-course	Treatment-free interval is included	Regeneration in early-responding normal tissues improves treatment tolerance. This allows an increase of total dose. Cost neutral	SQCA: NO! Tumor regeneration cancel the effect of the dose increment whereas no appreciable regeneration occurs in LNT. As a consequence, the increased total dose leads to increased LNT injury. Melanoma: NO! There is no appreciable time effect for melanoma. On the other hand early reactions are rare.
Hyperfractionation	Dose per fraction less than 1.8 Gy	Differential between fractionation sensitivity of LNT and tumors allows tumor BED to be increased while keeping LNT BED constant. Cost increased	SQCA: YES! Early reactions are slightly increased, but a gain in tumor control is seen for a constant incidence of LNT sequelae. Melanoma: ? See comment on hypofractionation.
Accelerated fractionation	Rate of dose accumulation exceeds 10 Gy per week	Differential between regeneration rate in tumor and LNT allows tumor effect to be increased while maintaining the effect on LNT. Cost neutral	SQCA: PROBABLY! Early reactions and consequential late reactions may be dose limiting. If total dose is reduced tumor control may go down in slowly growing tumors. Melanoma: NO! No appreciable time factor for melanoma.

BED: biological equivalent dose; LNT: late-responding normal tissue
SQCA: squamous cell carcinoma

Split-course regimens using conventional doses per fraction are probably disadvantageous at least for SQCA as the protracted treatment will allow considerable tumor regeneration (25, 26, 45, 52) while late-responding normal tissues would not be spared to a similar degree (26, 64). The only place for split-course treatment might be in accelerated radiotherapy where the split has been proposed as a means of sparing the early responding normal tissues (86). The other two strategies, accelerated fractionation and hyperfractionation, are promising candidates for improved treatment of at least some tumors. A comparison of some 'new' fractionation schedules currently under trial with three standard schedules (Table 5) has been done for a typical patient with a T3 oropharyngeal carcinoma using the local tumor-control model derived from an analysis of clinical data (45).

Accelerated fractionation is in a way the opposite of split-course regimens. If prolongation of overall treatment time is detrimental to the therapeutic differential between tumors and late-responding normal tissues, then shortening the treatment time might be beneficial. Several strategies are currently under clinical trial (66), three schedules with slightly different philosophies are: CHART (87), concomitant boost (88, 89), and accelerated split course (86).

Table 5

*Evaluation of treatment strategies in SQCA of the oropharynx**

	Dose (Gy)	No fx	time (d)	TCP	Biol. D (Gy)**
Conventional					
US	66.6	37	51	57%	63–64
Europe I	60.0	30	42	58%	60
Europe II	66.0	33	45	63%	66
Accelerated					
Acc. split	64.0	40	40	62%	57–60
CHART	50.4	36	12	69%	42–45
Conc. boost	69.0	38	40	70%	65–67
EORTC acc.	72.0	45	32	77%	64–67
DAHANCA 6/7	66.0	33	38	70%	66
Hyperfract.					
EORTC	80.5	70	47	73%	62–69

* Male patient, 17.3 cm^3 poorly differentiated tumor, hemoglobin concentration 8.8 mmol/l.

** Equiv. dose in 2 Gy/fx assuming α/β = 1.8 Gy and 4.0 Gy, respectively.

In the Danish Head and Neck (DAHANCA) trial a somewhat more conservative approach is taken. Although pre-treatment cellular kinetics is a candidate for predicting which patients might benefit from a shortened total time (90), routine application of this method is premature and as a consequence the biological effective dose should not be reduced. In the DAHANCA trial the same total dose and dose per fraction are used in the accelerated and the standard treatment arms. A one week acceleration of the schedule is obtained by treating with six instead of five fractions per week.

To avoid the use of larger-than-standard doses per fraction acceleration is best achieved by using multiple fractions per day (MFD). One of the current problems in designing MFD trials is that recommendations for a 'safe' interfraction interval rely on scarce data. There is some indication that the interval should be at least 6 h, preferably 8 h or more, between fractions (63, 91). Thus schedules employing more than two fractions per day run into practical difficulties.

The rationale behind hyperfractionation is to take advantage of the preferential sparing of late-responding normal tissues relative to tumors by reducing the dose per fraction. Usually hyperfractionation is accompanied by a significant increase in total dose so that, for equal late effects, an increase in tumor control is expected. To avoid an increase in overall treatment time, this type of schedule also involves MFD. There are currently two areas where more clinical radiobiological work could strengthen the argumentation of hyperfractionation. While normal tissue α/β ratios are relatively well established, tumor α/β ratios from clinical studies are sparse. Furthermore relatively little clinical experience has been gathered with doses per fraction below 1.8 Gy, thus the validity of the LQ model will have to be assumed to allow extrapolation of results down to lower doses per fraction. And once again information on repair kinetics is urgently needed.

From experience with MFD treatments it has emerged that acute reactions can become dose limiting, particularly when the treatment fields involve significant volumes of mucosa in head and neck treatments (92). The difficulty is to quantify the effect of compensatory proliferation in the oral mucosa. Data are lacking on the dose equivalent of proliferation in this situation, but it appears that healing occurs after 4 weeks treatment in most patients treated with 1.8 Gy/day, but not with 2.5 Gy/day (63).

When all this is said, hyperfractionation has been tested clinically in a large randomized trial (EORTC protocol 22791 (93)) and has come out to be beneficial compared to standard fractionation with respect to 5-year loco-regional control (59% vs 40%, $p = 0.02$) and with a trend towards an improved survival ($p = 0.08$) (94). It further strengthens the case in favor of hyperfractionation that the standard arm chosen for the randomized study was a quite 'hot' schedule: 70 Gy in 35 fractions over 7 weeks. Applying the oropharynx TCP model (45) (with patients characteristics as in Table 5) yields an expected 9% higher local TCP in the hyperfractionated arm. This is for control in T-position alone and is somewhat lower than the observed increase in loco-regional control seen in the EORTC study (94).

Individual assignment of treatment schedules

Individualization of treatment regimens is of great potential value in cancer therapy. It is important first of all to try to characterize the high-risk patients and also to establish whether the problem is local tumor failure, regional (nodal) disease and/or distant metastases. Therefore clinical radiobiology should be seen in relation to general prognostic/descriptive studies of the natural history of the disease. Even in patients with loco-regional disease as their main problem further stratification is warranted. Patients who are judged to have low probability of tumor control from a specific treatment may be spared the inconveniences and hazards of developing sequelae from that treatment and may be considered for experimental treatment modalities. On the other hand, if a patient has a high probability of cure from a low-toxicity therapy, intensified treatment may not be justified. Similarly, in testing potentially improved treatment strategies, subsets of patients are likely not to show any appreciable improvement from the new therapy because they do not have the biological problem that the therapy tries to address (95, 96). Such patients would obviously dilute the detection of any improvement in outcome from the use of the new therapy.

Reduction of the normal-tissue high-dose volume by using more treatment portals or selecting radiation-qualities with different depth-dose distributions would be justified in patients with increased normal-tissue radiosen-

sitivity. Combined modality treatment, with less intensive radiotherapy, would also be indicated in this situation.

Conclusion

Modeling is an integrated part of most sciences. Models may be concrete, as in the case of a murine tumor as a human tumor model, or abstract, as in deriving a mathematical model from a set of biological assumptions. Any model has a limited field of application and the past history of modeling in clinical radiobiology, where models were used without knowing their limitations, has produced a lot of justifiable skepticism. On the other hand, the attitude that human biological phenomena are too complex to allow modeling is to a large extent a self-fulfilling prophecy. In the 1980s radiobiological models have been instrumental in providing new insights in human radiobiology and in critically defining the limitations of our current knowledge. This is, at least in this author's view, the role of modeling in clinical radiobiology: as a tool for research rather than as an end result in themselves.

The studies described here were aimed at a systematic optimization of the methodology used in QCRB. This included clinical, dosimetrical, and statistical aspects. The focus has been on the introduction of multivariate maximum-likelihood based statistical methods. Such methods are of particular value in clinical radiobiology, where large variability in patient and treatment characteristics makes two-step methods much less efficient, as the latter require dose–response relationships in homogeneous strata to be established. Furthermore, multivariate mathematical modeling techniques constitute a general framework for analysis, interpretation, and hypothesis generation and testing. The introduction of these methods have allowed statistically valid analyses of the clinical radiobiology of normal tissues and tumors.

Radiotherapy has gradually been refined through a long historical tradition. It should be realized, however, that many historical studies have been conducted with non-optimal treatment techniques, and have been designed and interpreted from biological concepts that we now know are inconsistent with clinical data. The renewed interest in clinical radiobiology, aided by the powerful modern methods of analysis, open up the perspective of optimizing the relationship between tumor control and treatment related long-term morbidity. Late sequelae have been thought of by many therapists as being the inescapable price for cure of cancer. Unfortunately, in the past this price has often been higher than necessary. It is appropriate to give the final word to Holthusen. Although more than half a century has passed, the concluding remark from his 1936 paper still presents one of the goals for clinical radiobiology: '*Es ist zu hoffen, daß mit fortschreitender Erfahrung auch bei der Behandlung von Tumorkranken die Möglichkeiten der Schädigung immer mehr eingeschränkt werden können.*'

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