Biologically Based Treatment Planning

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The classical way of quantifying dose-response relations for tumors and normal tissues and their dependence on the genetic make up of the patient is briefly reviewed. Response quantifiers such as quality of life and the probability of achieving a complication-free cure are helpful in solving many of the problems of radiation therapy planning. It is shown, through the use of these quantifiers, that by introducing radiobiologically optimized, intensity-modulated dose delivery, the treatment outcome can be improved by as much as 20%, and more in cases with a complex spread of the disease. The real strength of the radiobiological models is to serve as a scientific tool for the development of treatment optimization so that the models are modified when the clinical response systematically deviates from the predictions of the models. In this way, the biological models serve as a continuously updated historical database that later on may replace the control arm in clinical trials and allow all patients to benefit from the latest developments in radiobiologically optimized treatment techniques.

Radiation therapy today is at the dawn of a new era where radiation biology and molecular biology data are increasingly being used in clinical decision-making. Simultaneously, the new three-dimensional treatment optimization techniques that also have largely been developed during the past decades are becoming as important as the new biological tools for the development of improved treatment results. In fact, several of the new optimization algorithms will prove their greatest usefulness when they can be combined with reliable patient individual data on the radiation responsiveness to be expected by the tumor and surrounding normal tissues. Obviously, different types of predictive assays are of interest here but also the more readily and rapidly obtained status of molecular markers will play an increasingly important role in the future. For example, today there are already indications that certain point mutations on the tumor suppressor gene P_{53} make radiation therapy indicated for node-negative breast cancer patients (1).

When the new biological data and optimization tools can be combined with modern radiation therapy equipment with full 3-D capability in their dose delivery, the potential for substantially improved treatment results will become a reality. After a brief discussion of some of the molecular genetic factors determining the radiation responsiveness of tumors and normal tissues, their principal influence on the radiation response characteristics are discussed in this paper. Furthermore, different radiobiological treatment objectives are described for use in treatment optimization algorithms, making full clinical use of the power of intensity-modulated radiation therapy. Finally, the possible expectations on the improvement of the treatment outcome by including biological response models in the optimization process are presented.

MOLECULAR BIOLOGY OF RADIATION SENSITIVITY

A large number of genetic factors can influence the radiation sensitivity of tumors and normal tissues. Obviously, for the tumor the state of proto-oncogenes is most important, as they generally encode for proteins that are responsible for the signal transduction cascade of growth factors that normally stimulate cell division or differentiation. Most known proto-oncogenes (about 100) have therefore a positive stimulating function on cell proliferation and have therefore a dominant influence in relation to the other possibly normal alleles. There is also a second important group of tumor suppressor genes, which instead is recessive in relation to a normal allele since it promotes neoplasia by loss of function.

One of the most commonly mutated or lost genes in human cancers, P_{53}, belongs to the tumor suppressor group, as do many recently found tumor-specific genes such as BRCA1–4 (breast cancer susceptibility genes). The very interesting P_{53} gene product is a DNA-binding transcription factor that can induce apoptosis and cell-cycle arrest in the G1 phase of the cell cycle. It therefore seems to influence the decision of the cell whether to rest and repair induced DNA damage or to give in and eliminate itself by programmed cell death because of a too

severe level of damage (2). Owing to its central role in handling DNA damage, it should be no surprise that P_{53} is found mutated in many types of cancers, for example glioblastoma, astrocytoma, colorectal, breast, brain and lung carcinoma. It is interesting to note that if the tumor suppressor gene P_{53} was mutated in a cell, there is immediately an increased risk that this cell line may develop neoplasia since such cells will have greater difficulty in dealing with DNA damage to their genome. Fortunately, for the same reason, radiation therapy may be the ideal way of treating a tumor developed by such a process, since the tumor cells will generally still be associated with a poor ability to handle the DNA damage inflicted in a controlled way by the therapeutic beams. This mechanism may explain why radiation therapy has recently been shown to be very useful in node-negative breast cancer patients who have certain mutations on their P_{53} gene (1). The situation is not always as simple as this because P_{53} mutations can also decrease the ability of the cells to induce apoptosis. This may show up in an apparent increased survival of the cells since they are damaged and not repaired with a high degree of fidelity.

Besides the oncogenes and tumor suppressor genes that are largely responsible for tumor induction, a large number of other genes may also be affected to promote tumor development and alter the radiation sensitivity of the patient. A large number of gene families can be identified, such as cell-cycle control genes, DNA repair genes, DNA processing and topology genes, detoxification and stress-response genes, immediate early genes and modifier genes in general.

It is clear that if some of these genes have an impaired function, the processing of normal and damaged DNA may be affected. This may in turn promote genetic instability, tumor development and alter the radiation sensitivity of the cells. It is likely that the status of many of these genes with regard to polymorphism, amplification and transcription factors and mutations could be combined as useful genetic predictors for radiation sensitivity both for tumors and, probably even more importantly, for the normal tissues. Based on the status of such genetic markers in the tumor and normal tissues, it is likely that we in the near future can estimate the relative and absolute sensitivity of these tissue types and use it for response prediction.

OBJECTIVE FUNCTIONS FOR TREATMENT OPTIMIZATION

Quality of life

The primary objective of radiation oncology, and for all medical care for that matter, is to make the quality of life for the patient as high as is reasonably achievable from the time of his or her first contact with the medical system. In principle, some kind of integral measure of the quality of life would be a suitable objective function, since a long, healthy, and comfortable life, accounting for all steps of medical care, is most desirable (3). However, a very long life with severe loss of quality of life is not generally desirable (4), so some kind of weighted integral measure would therefore be most desirable. Obviously, the quality of life of a person has to be a subjective quantity (5) but from a medical point of view it also has a more strict and objective side as a general health index. This index can range from unity, corresponding to perfect health, to zero when the person in medical terms is dead or does not want to live any longer. There are several measures that are aimed at quantifying the condition of the patient, such as the Karnofsky status (6), but all of them are much too complex and difficult to relate to therapeutic actions to be used directly for therapy optimization. We will therefore first discuss some simplifications that need to be introduced to obtain an objective function that is useful for computed radiation therapy optimization.

In practice, two main groups of objective functions have been used, physical and biological as illustrated in Fig. 1. So far, the most commonly employed objective functions are physical and they often describe the desirable properties of the delivered dose distribution in the target volumes and affected normal tissues and organs at risk. In fact, the exact definition of these volumes is extremely important for how accurately and precisely a treatment can be performed. It is fundamental that the target volume and the organs at risk can be delineated with the narrowest possible safety margins in relation to the anatomical landmarks that are used for setting up the patient for external beam therapy.

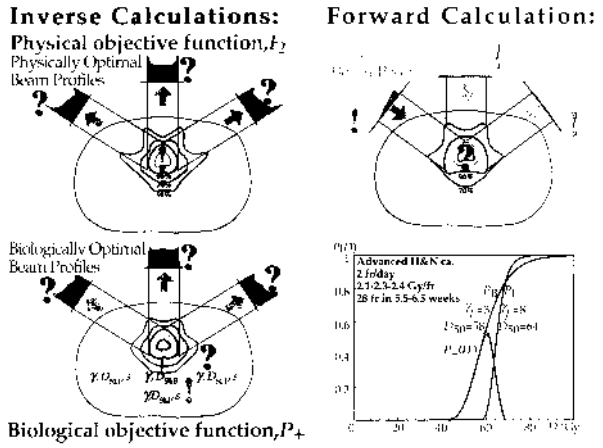


Fig. 1. Schematic illustration of the differences between conventional forward radiation therapy planning and inverse planning. Dose optimization using forward calculation based on classical beam profiles (a) is generally a trial-and-error process, whereas inverse planning directly results in optimal beam profiles for physically optimal beam profiles (b) optimal isodose distributions for biological optimal beam profiles, and (c). The exclamation marks indicate known quantities, whereas the question marks indicate the principal unknowns. The contours are for isodoses of 90%, 70% and 50%. The dose response curves in the lower right corner illustrate the kind of data used in the biological optimizations.

In principle, the target volume should include all the volumes and margins whose dimensions cannot be affected by changing or developing dose planning or treatment techniques (including fixation of the patient). Therefore the intrinsic or internal target volume is defined by adding a target margin to the clinical target volume to account for all internal shape changes of organs and their possible motions relative to the anatomical reference points (7–9). To this target volume, setup margins may later have to be added depending on the treatment technique and the quality of the treatment unit and the fixation method employed. It is fundamental that the internal target volume is used for dose prescription and reporting, as it is the most relevant one for the treatment outcome. The biological objective functions aim at quantifying the probability that the patient will have a desirable treatment outcome. From this point of view the radiobiological objective functions therefore to some extent do quantify the quality of life of the patient after therapy.

Dose-response relations

Until reliable patient individual molecular biologic and quality of life measures have been developed, clinically observed dose-response data for patient groups of relevant tumor stages have to be used. Data for local tumor control can generally be well described by binomial statistics, since each and every one of the clonogenic tumor cells has to be eradicated to control the entire tumor. If the tumor initially contains N_0 clonogens each of which having a mean survival probability $s(D)$ after irradiation to dose D, the probability of having exactly v surviving clonogens is according to the binomial theorem given by:

$$P_v = \frac{N_0!}{v!(N_0 - v)!} s^v (1 - s)^{N_0 - v} \quad [1]$$

as illustrated in Fig. 2. It is clearly seen how the linear quadratic-like cell survival dominates at low doses, whereas at high doses and low survival probabilities the sigmoidal dose-response relation describes the biological effects very well in comparison with the more clinically based Figs. 3 and 4. For beneficial outcome with full tumor control no tumor clonogens are allowed to survive ($v = 0$) and thus:

$$P_B = P_0 = (1 - s)^{N_0} \quad [2]$$

This expression can in the limit when N_0 is very large be approximated well by the Poisson expression (10–12)

$$P_B = \mathrm{e}^{-N_0 s} \quad [3]$$

When the survival of the cells is exponential or linear quadratic, the tumor control curve is well described by a relation of the type:

$$P_B = 2^{-\mathrm{e}^{\gamma \mathrm{e}\left(1 - \frac{D}{D_{50}}\right)}} \quad [4]$$

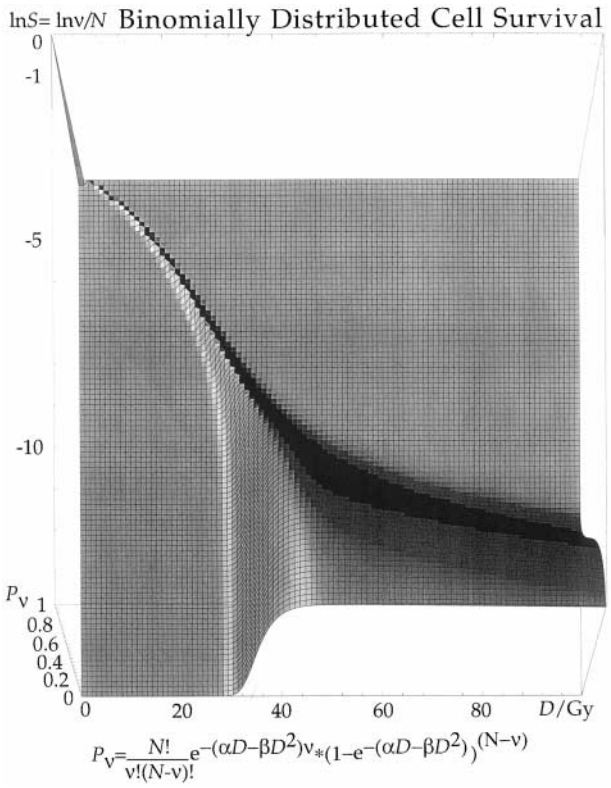


Fig. 2. The probability that a certain fraction of the cells survive at a given dose level. At zero dose 100% of the cells survive, whereas at high doses and low survival probabilities almost all the cells are eradicated leading to tumor control. Outside these areas the probability mass is spread out over a wider range of survival levels and the resultant probability is lower. At low doses the linear quadratic cell survival dominates, whereas at high doses the dose-response relation is the most useful concept to describe the radiation effects.

where $\gamma \approx \frac{\ln N_0}{\mathrm{e}}$ is the normalized slope of the dose response relation and D_{50} is the dose at which 50% of the tumors are controlled. It can be shown that a similar relation also holds well for the probability of injury (P_I) to normal tissue. So based on γ and D_{50} values for the tumor and the normal tissues, it is possible to estimate to probability for a totally positive treatment outcome, P_+; i.e. to cure the patient without inducing severe complications in normal tissues:

$$P_+ = P_B - P_{B \cap I} \approx P_B - P_I + \delta(1 - P_B) P_I \quad [5]$$

P_+ is thus a scalar quantity or function that can be used as a figure of merit of the treatment. The parameter δ is the portion of patients with an uncorrelated response and has often a value below 20% (13). The individual parameters of the P_B and P_I functions for a given patient are often based on the mean value of γ and D_{50} over a few hundred patients of the relevant tumor stage, age group, sex, etc. However, for a given patient the radiation sensitivity of the tumor and that of the normal tissues may vary consid-

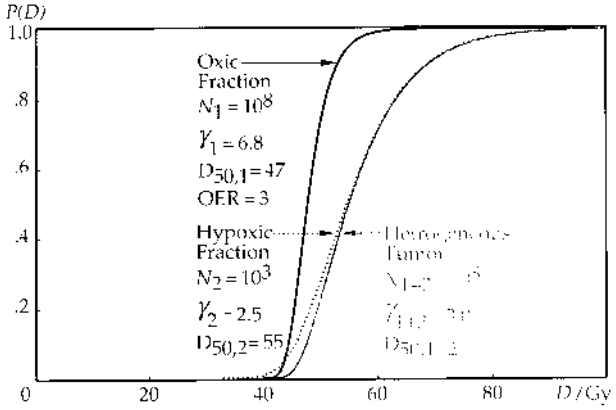
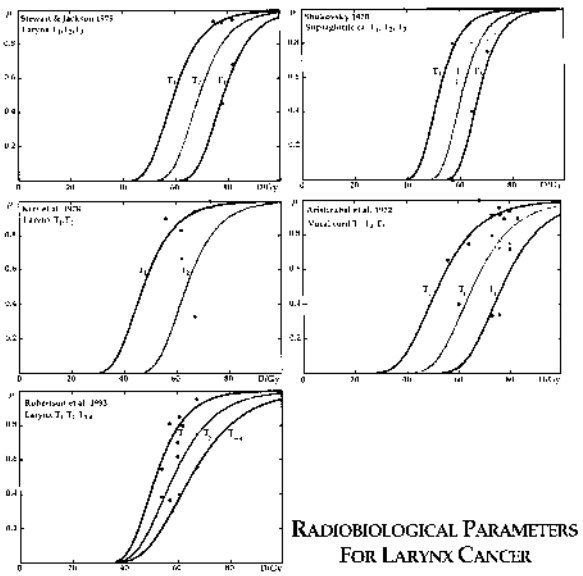


Fig. 3. Dose-response curves for a hypoxic tumor and its two constituent cell compartments, the anoxic and the well-oxygenated tumor cells. It is interesting to observe that the small anoxic cell compartment dominates the response at large doses.

erably from the mean value over the patient population and the individual γ value is also likely to be steeper than the mean value. To be on the safe side, it can be shown that it is reasonable to assume that the given patient has a more resistant tumor at the same time as the normal tissues are more sensitive (by about $0.5\sigma_{D_{50}}$; (14)) and that the γ value is steeper (10). It should also be taken into account that (5) holds strictly only when fatal or very severe complications are considered, since only then can patients lost because of their disease or late treatment-related side effects to some extent be compared. However, if there are milder side effects that the patient or physician is not willing to accept, it is still possible to use (5) as a first approximation since it will be almost equivalent to scoring the severity of such complications at the same level as fatal complications.

With the help of the radiobiological treatment objective, P_+ (Equation [5]) and the expectation value of P_+, EP_+, it is now possible to develop treatment optimization algorithms that can maximize these objectives so that the probability of curing the patient without inducing severe complications will be as high as possible. A more detailed discussion of the structure of such optimization algorithms is beyond the scope of this brief review and they have already been thoroughly discussed in the literature (15–20). From the structure of the objectives it can be seen that these optimizations could consider many degrees of freedom of the treatment technique such as: radiation beam modality (electrons, photons, protons, etc.) number of beam portals, beam orientations, beam cross-section, beam energy spectrum, beam intensity modulation, fractionation schedule, pulse structure, dose rate, etc. By far, the most important degree of freedom is the intensity modulation and in the last section some examples are presented of what can be achieved using biologically optimized intensity modulated beams. From this point of view it is an unfortunate fact that most of the first hundred years of radiation therapy were focused on producing uniform therapeutic beams.



RADIOBIOLOGICAL PARAMETERS FOR LARYNX CANCER

	T1			T2			T3			
	D_{50}	γ	v	D_{50}	γ	v	D_{50}	γ	v	h
Shukovsky -70	51.7	3.2	0.2	60.6	3.8	1.0	67.0	4.2	3.0	0
Stewart et al. -75	59.2	2.8	0.2	69.5	3.5	1.0	78.1	3.7	3.3	0
Aristizabal et al.72	52.0	1.7	0.3	65.6	2.2	1.0	77.1	2.6	2.9	0
Kim et al. -78	47.2	2.1	0.3	63.6	2.8	1.0	-	-	-	0
Slevin et al. -92	-	-	-	62.2	2.0	1.0	75.9	2.4	3.3	0
Robertson et al. -93	51.7	2.4	0.4	58.2	2.1	1.0	65.0	1.8	1.7	0.2
Mean Values	52.4	2.4	0.2	63.5	2.7	1.0	72.6	2.9	2.8	-
Standard deviation	3.9	0.5	0.1	3.9	0.7	-	5.5	0.9	0.6	-
Mean Values				59.9	2.9	1.0	(59.9Gy+0.35Gy/d above 41d at 2Gy/f)			
Standard deviation				2.1	0.3					

Fig. 4. Review of the clinically observed dose-response relations for T1, T2, T3 and T4 larynx tumors. When the clinical data are treated in a uniform way the agreement between the different data sets is quite good with a relative standard deviation of about 3% in D_{50} and 10% in γ for the T2 tumors, as seen in the inserted Table.

THE CLINICALLY OBSERVED RADIATION RESPONSIVENESS OF TUMORS AND NORMAL TISSUES

Clinical data on the radiation effect on tumors (21–24) and normal tissues have been collected at an increasing rate during the past decades (10, 15, 21–24). Despite the strong development of new response models, two main problems still exist. For the tumors it is important to be able to quantify the hypoxic or most resistant tumor cell compartment since it is fundamental for the responsiveness of the tumors even though that compartment is small (15, 25). Fig. 3 illustrates the strong influence of a small hypoxic population (1000 cells—dotted curve) even if the bulk of the clonogenic tumor cells is 100000 times larger (left solid curve). So even though the tumor physically is dominated by the well-oxygenated cells, the small hypoxic compartment totally dominates its radiation response at high doses where the right most solid curve illustrates the total tumor responses (hypoxic and well-oxygenated cells together). In Fig. 4 the clinically observed dose-response relation in five different larynx cancer materials are sum-

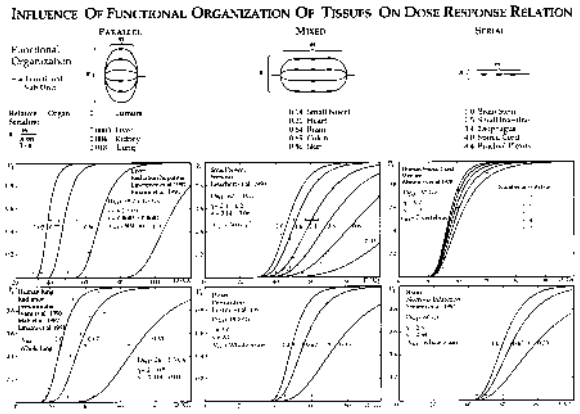


Fig. 5. Depending on the functional organization of the subunits of an organ, the dose-response relation will be strongly dependent on the volume being irradiated. For tissues with a parallel organization, small volumes can tolerate large doses without severe damage to the organ. Serial tissues, on the other hand, are severely damaged even when a small portion of the organ is irradiated.

marized (Ågren et al. 1995). After converting the different fractionation schemes to a standard 2 Gy/f and by introducing a 0.35 Gy/day dose addition for the treatment duration beyond 42 days, and as far as possible correcting the data to get actuarial survival, the 50% control dose was found to be 59.9 Gy with a standard deviation of 2.1 Gy or about 3% for the six data sets. The established γ value was 2.9 with a standard deviation of only 10% which is a much lower uncertainty than commonly observed in clinical materials. This indicates that the clinical data, when treated in a systematic way, can give us well-defined dose-response relations for use in treatment optimization.

For the normal tissues, the problem is more on the organizational side since the functional arrangement of the subunits of a tissue is fundamental for its response to heterogeneous or partial irradiation, as illustrated in Fig. 5 (15, 24, 26). The continued development of this field is very important both on a local and global basis because the spectrum of individual variations may vary from continent to continent and even between different countries or ethnic groups. It is also very important when reporting the result of clinical trials of radiation therapy for various tumor sites that the correlation and covariance of the responses of the tumor and the surrounding normal tissues are carefully studied, since it is crucial for finding the optimal dose level in radiation therapy. The customary practice of just reporting tumor response and complications separately is insufficient since knowledge about the correlation between these two endpoints is of utmost importance in order to estimate the probability of a truly positive outcome (25).

When the aim is not just to find the optimal relative dose distribution but also the best fractionation scheme and absolute dose level, a more extensive set of radiobiological parameters is needed. The old ICRU reports, 29 (27) and 50 (28), recommend the use of the so-called ICRU point dose central in the clinical target volume to be used for reporting radiotherapy dose delivery. The more recent NACP report (7) also includes the mean dose to the internal target and organ at risk volumes and the associated standard deviations so more clinically relevant dose and target concepts can be used for a truly conformal treatment optimization.

When more descriptive radiobiological models of different tumors and normal tissues are required, the dose needed to deliver a specified effect in 50% of the patients (D_{50}) and the normalized slope of the dose-response relation (γ) are often used. When the dose fractionation schedule is changed from the regular 2 Gy per day, a large number of other parameters are also needed such as the α/β value characterizing the shoulder of the dose response relation. To account for more fine details of the response the tumor repopulation rate (δ) the volume dependence of the response of normal tissues often described by the relative seriality (s) and the repair and reoxygenation rate (μ, ρ) should also be considered. Recent radiobiological results also indicate a need to consider the hypersensitivity at low doses when large volumes of normal tissues receive multiple low doses (α_{sen}, D_c). For the analysis of dose response data, it may also be desirable to utilize some of the new dose-effect measures such as the effective uniform doses (D_{eff}), (29–31).

As discussed in the previous section, the ultimate future tool for determining radiation sensitivity is to use molecular biology to scan for various genetic alterations in the tumor and the normal tissues. The new technology using silicon chips prepared with cDNA libraries to detect genetic alterations in the entire human genome of 50000–100000 genes is already available and may become a very useful assay for radiotherapy patients in the not too distant future (32).

RESULTS

The first clinical example on dose response optimization is presented in Fig. 6 and it clearly illustrates the considerable therapeutic advantages achieved by using intensity-modulated radiation beams. The figure compares the same central slice and isodose diagram through a head and neck target with classical quasi uniform and intensity-modulated beams and the associated dose-response curves for the two treatments. This allows a very clear-cut comparison of the two treatment techniques since the common dose axis is in units of the mean dose to the tumor or, more exactly, the internal target volume, which is identical in both cases. Therefore, the dose-response curves for the tumor will be practically the same in the two cases (left most solid sigmoidal curve). However, the normal tissue complication curves are different since in the intensity-modulated plan the dose to the tumor is significantly increased at the same time as the dose to the critical normal tissues is reduced somewhat.

Since all curves are related to the mean tumor dose and it has increased over the normal tissue dose by almost 15 Gy compared to the plan with essentially uniform dose delivery, the solid complication curve for the intensity-modulated plan has moved about 15 Gy to the right from its location with essentially uniform dose delivery (dotted sigmoidal curve). As a consequence, the therapeutic window has opened up substantially and the bell-shaped curve for complication-free cure (P_+) has increased from about 50% to 85%. This significant increase in treatment outcome is achieved because biologically optimized intensity-modulated dose delivery results in an increased dose to the tumor at the same time as the normal tissues are spared to a greater extent. This also implies that the classic problem of double trouble in dose escalation is converted to a double advantage. Not only is the relative dose to the normal tissues reduced, but the dose per fraction is also reduced and thus the risk of severe late complications. This simple comparison thus presents in a 'nut shell' the advantages that can be gained by biologically optimized intensity-modulated dose delivery.

To illustrate the merits of the new biologically based treatment optimization techniques, we also compare different external beam treatment configurations on an advanced tumor of the cervix. The calculations have been performed with one of the most advanced and flexible optimization algorithms available today (17, 20, 33). To illustrate the potential benefits of non-uniform dose delivery, the maximum possible complication-free tumor control P_+ is plotted in Fig. 7 as a function of the angle of incidence for a single beam irradiation of an advanced cervix tumor. Three types of beams have been used in the optimization: uniform (dotted line), wedged (dashed line) and generally non-uniform beams (dash–dotted line). It

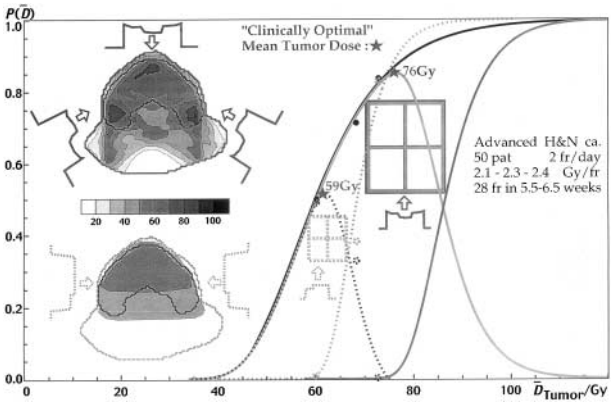


Fig. 6. Comparison of biologically optimized intensity-modulated plan (solid lines) with a more conventional essentially uniform dose delivery (dotted lines). The increase in complication-free cure resulting from intensity modulation is schematically illustrated by the widening of the therapeutic window. The underlying clinically based dose-response curves were taken from the work of Ågren et al. (13).

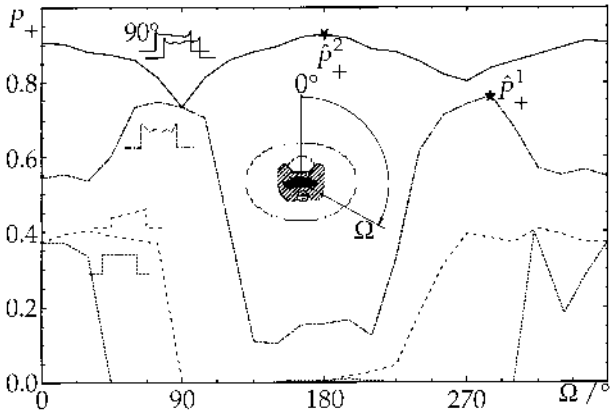


Fig. 7. The variation of P_+ with the o for treatment of an advanced cervix cancer using 10 MeV monoenergetic photons and different degrees of freedom in the optimized beam profiles. The dotted line (····) shows the result when the dose level of the uniform beam is the only free variable. The dashed line (----) shows the result with the beam weight and the wedge angle as the free variables for each optimized beam profile. The dash dotted line (–·–) shows the result if the beam has 64 free variables almost corresponding to fully non-uniform beams. The upper solid line (———) shows the further improvements with two beams, one of which is locked at 90°, the asterisk (*) represents the highest possible P_+ value with two fields.

can be clearly seen that non-uniform dose delivery has a considerable influence on the resultant P_+ value and the useful range of angles of incidence. With uniform beams the useful angular interval is approximately $\pm 45°$ around the forward direction with a maximal P_+ value of less than 40%.

With wedged beams, the feasible angular interval is more than doubled, but the P_+ value is only marginally increased above 40%. With optimized non-uniform beams, all directions of incidence are feasible with optimal directions around 90 and 270° and P_+ values reaching as high as 75%. The upper solid curve illustrates the result with the best possible first field of about 90° and all possible combinations of a second field with an optimum close to 180° and a P_+ value of more than 90%. With as many as 24 or 72 evenly spaced beams the P_+ value is only marginally increased ($\sim 0.5\%$) indicating that even in difficult cases, like this one, a few well-selected non-uniform beams are a very good treatment option.

To illustrate what can be achieved with one of the most advanced treatment optimization algorithms ORBIT (Optimization of Radiation Therapy by Iterative Techniques) (34), its ability to find locally optimal intensity-modulated beam directions is shown in Fig. 8. There is no doubt that the possibility to optimize the angle of incidence is an important clinical improvement of considerable practical value, since it allows the clinician to make a first choice and have it fine-adjusted by the algorithm. It is also important that all organs at risk in the neighborhood of the target are considered in the biological modeling to

make the algorithm as clinically relevant as possible. The new treatment optimization algorithm ORBIT is today incorporated in ADAC's dose-planning system Pinnacle and will, it is hoped, also be available in other dose-planning systems in the future.

The new algorithm is of general applicability, being able to optimize everything from fractionation schedules, radiation modality combinations, angles of incidence, collimator motions, scanning patterns, and intensity modulation in general, taking also stochastic processes into account such as uncertainties in radiation sensitivity and beam patient alignment (35). As seen in the figure, quite large angular adjustments are sometimes desirable depending on the exact shape of the tumor and the location and sensitivity of surrounding normal tissues, in the present case a prostate cancer with rectum as principal organ at risk. After the beams have been released by the algorithm from their preset 0°, 120° and 240° directions, the complication-free cure is increased by about 5% as a result of better alignment of the beams with the tumor and the organs at risk, as seen in Fig. 8.

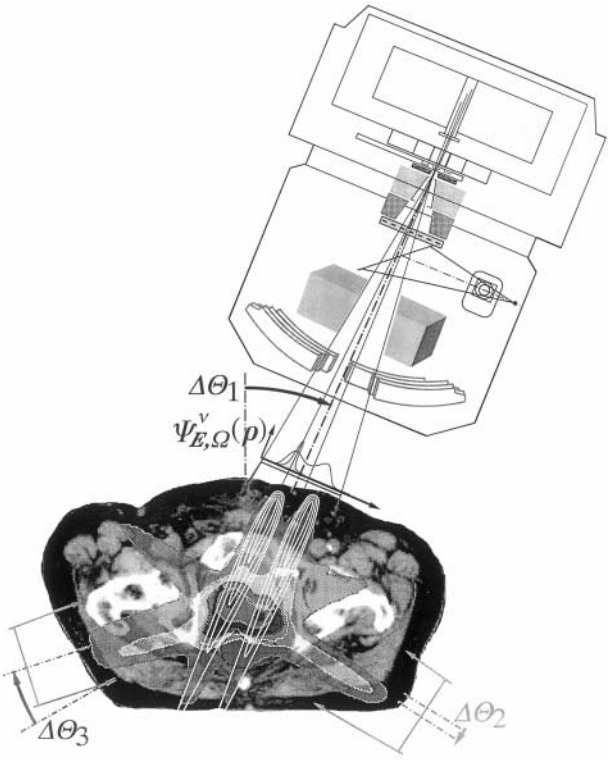


Fig. 8. Illustration of a local optimal treatment plan for a 3-field intensity-modulated treatment of a prostate cancer. The start proposal was three beams, all at a fixed 120° interval from each other. As seen, owing to the special shape of the target and the location of organs at risk, angular adjustments of the order of 5–25° can significantly increase the treatment outcome from a P_+ of about 61% at 120° intervals to 66% with angular optimization. The treatment outcome could be improved even further by including a couple of extra beams.

DISCUSSION AND CONCLUSIONS

There are a great many clinical problems that require serious radiobiological modeling in order to be solved in a satisfactory way. Every time the right balance between advantageous and detrimental radiation effects has to be found, good biological measures are required. Probably the most difficult case where biological models are needed is when severe tumor growth is located close to life-threatening critical structures. The models can then be used to accurately determine precisely how the tumor dose should be reduced near the critical structures and instead be increased at more distant locations of the target, thus maximizing the complication-free cure.

The optimal dose delivery in the border region of an invasively growing tumor is also best handled by biological models. The more common problem of setting the collimator shape or intensity profile around a tumor and the influence of dose heterogeneities all belong to the area where good biological models are the ideal tool. The more complex problems where stochastic processes influence the patient geometry and thus the dose delivery but also uncertainties in the exact biological response parameters can be accounted for by the new biological measures using the expectation value. By using stochastic optimization or safety margins many of the advantages of biological optimization can be used already today even if we do not have exact information about the absolute patient sensitivity. A further breakthrough in biological modeling will take place when accurate patient individual response data for each individual patient can be determined simply by analyzing the genetic profile of the tumor and the normal tissues, making radiation therapy optimization an exact science.

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