Development of Radiation Therapy Optimization

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The principal radiobiological problems in the treatment of advanced tumors and the solution of many of them by radiobiologically optimized intensity-modulated radiation therapy are presented. Considerable improvements of the treatment outcome using radiobiologically optimized intensity-modulated treatments are achieved by: (a) increasing the tumor dose and dose per fraction; (b) keeping constant or even reducing slightly the dose and dose per fraction to organs at risk; (c) reducing the overall treatment time and the number of treatment fractions. The merits of the new radiation modalities and advanced intensity-modulated treatment techniques are compared in terms of equipment costs per patient cured. It is predicted that the new development of radiobiologically optimized intensity-modulated radiation therapy will rapidly become an important clinical tool, increasing the efficiency of the collaboration between radiation physicists, radiation biologists and radiation oncologists. Not only does it allow the optimal treatment of every patient, but it also promotes an efficient feedback of treatment outcome and complication data to improve the accuracy of known dose response relations to further augment future treatment results. Equipment costs may go up during a transition period until efficient interfaces between new diagnostic equipment, treatment-planning systems and intensity-modulated treatment units are fully developed. From then onwards the cost of high quality biologically optimized intensity-modulated treatments will decrease and so will the treatment time and personnel requirements, at the same time as the treatment quality is greatly improved particularly for more advanced tumors.

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During the first century of radiation therapy many dramatic advances have taken place. The improvements of treatment outcome have mainly been linked to developments in the areas of molecular and clinical oncology, radiation biology and radiation physics. The present discussion will concentrate mainly on the radiation aspects even though in recent years an important potential for improvements is emerging in the area of molecular oncology. The radiobiological developments have been numerous in areas like dose fractionation, understanding of the role of hypoxic tumor cells and the relative biological efficiency of different radiation modalities at low and high doses. The increased understanding of the mechanisms behind cell cycle progression and check point control, cell survival curves and dose response relations for different tumors and normal tissues, as well as different repair mechanisms of damaged DNA has been important. In the area of radiation physics the development includes accurate dosimetry, treatment planning and diagnostic techniques in addition to the development of a large number of new radiation modalities. Almost all radiation sources that have been developed by accelerator physicists have been tested with regard to their possible advantages in the treatment of cancer. A nice historical review was given by Milford Schulz in his 1974 Janeway Lecture: 'The supervoltage story' (1). To illustrate the broad range of devices that have been used throughout the years some of the main radiation sources are given in Table 1.

It is surprising that even though such a multitude of radiation devices have been used there are very few randomized clinical trials that have been performed in order to quantify the possible clinical merits of each new treatment modality. This is generally explained by the rather modest and obvious clinical improvements expected so a large-scale randomized study would not really be feasible. For example the improvements with regard to skin sparing going from low or medium energy x-rays to megavoltage photons like ^{60}Co and above are generally accepted by most people. Often the publications of Allt (2) and Bush (3) are cited with regard to the improvements obtained going from ^{60}Co to betatron bremsstrahlung. However, it is not clear which property of the betatron beam that is responsible for the improvement. Allt (2) suggested the increased field size used with the betatron but that is not linked to the new higher photon energy unless it was feasible just because the integral dose was lower with the high-energy beam.

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More recently some clear-cut evidence for the advantage of multileaf collimation compared to more conventional beam blocking was demonstrated in the American neutron therapy trial where a considerable reduction of the complications was seen with the isocentric double focused multileaf collimator in Seattle as compared to the more conventional collimation techniques used at the other US centers (4). Such a large influence could be expected with neutrons, because normal tissue damage is a major problem since the repair potential of neutron induced damage to normal tissues is very low. In photon beams the gain would probably be smaller and more difficult to detect in a clinical trial.

Even though one preferably would like to test most new treatment modalities and irradiation techniques by randomized clinical trials, small improvements in irradiation techniques may be more accurately quantified by well designed radiobiological models. Holthusen (5) was one of the first to discuss the role of dose response relations for tumors and normal tissues. A few decades ago some researchers did not even believe in the existence of dose response relations and there are still those who question their relevance (6, 7). However, today when we can account for most factors that influence the radiation response, like actuarial survival, total dose, dose per fraction, dose rate and total treatment duration accurate dose response relations can be established. For example, in the study by Ågren-Cronqvist et al. (8) the tumor control of five different larynx data sets was studied as a function of tumor stage. After bringing all the data sets together on the same response format the standard deviation of the 50% control dose, D_{50}, was as small as 3% around 60 Gy in 2 Gy fractions in 6 weeks. For each day beyond this time, the dose should be increased by 0.35 Gy to compensate for accelerated tumor cell proliferation. If we go through all the troubles to make the clinical data sets compatible well defined dose response relations exist for most tumors and normal tissues and can be determined and used as an invaluable historical reference data set for treatment prediction and optimization. The aim of the present review is to discuss the clinical possibilities and the cost effectiveness of the different new intensity-modulated treatment techniques that are rapidly being developed and introduced in the clinic today.

THE RADIOBIOLOGICAL BASIS FOR THE DEVELOPMENT OF RADIATION THERAPY

In order to accurately quantify the relative merits of new treatment modalities and treatment techniques clinically relevant radiobiological response models are needed. For that purpose it is important to adopt biologically sound cell survival models for tumors and normal tissues to clinically observed dose response data so that the model describes the response of standard radiation therapy. As mentioned in the introduction and discussed in great detail in a number of publications (9–11) a large amount of clinical dose response data is being accumulated. Several introductions to the modeling of tumors and normal tissues have recently been published, so the reader is referred to them for more details about the underlying radiobiology and the fundamental properties of the biological models (12–19). The present focus is therefore on the major challenges of curative therapy of advanced disease.

A typical dose response data set (19) is illustrated in Fig. 1, where the dose response curves for small and advanced head and neck tumors and the associated fatal complica-

Table 1

Radiation modalities for radiation therapy

Radiation modalities used for radiation therapy	Approximate year of introduction	Approximate cost range (M$)
X-ray tube and high voltage source combinations	1896	~0.2–0.5
Radionuclides for Brachy and external beam therapy Radium–^{60}Co–^{137}Cs–^{127}I–^{252}Cf–^{103}Pl	1900	~0.5–1
Bremsstrahlung and electrons Cascade transformers Van de Graaff generators Betatrons Synchrotrons Traveling and standing wave linear accelerators Circular microtrons Racetrack accelerators	1930	~1–5
π mesons, neutrons, protons and light ions D-T generators Cyclotrons Proton linear accelerators Synchrotrons	1935	~5–40
Heavy ions from various ion sources Radiofrequency quadruple, linear accelerator and synchrotron combinations	1975	~40–150

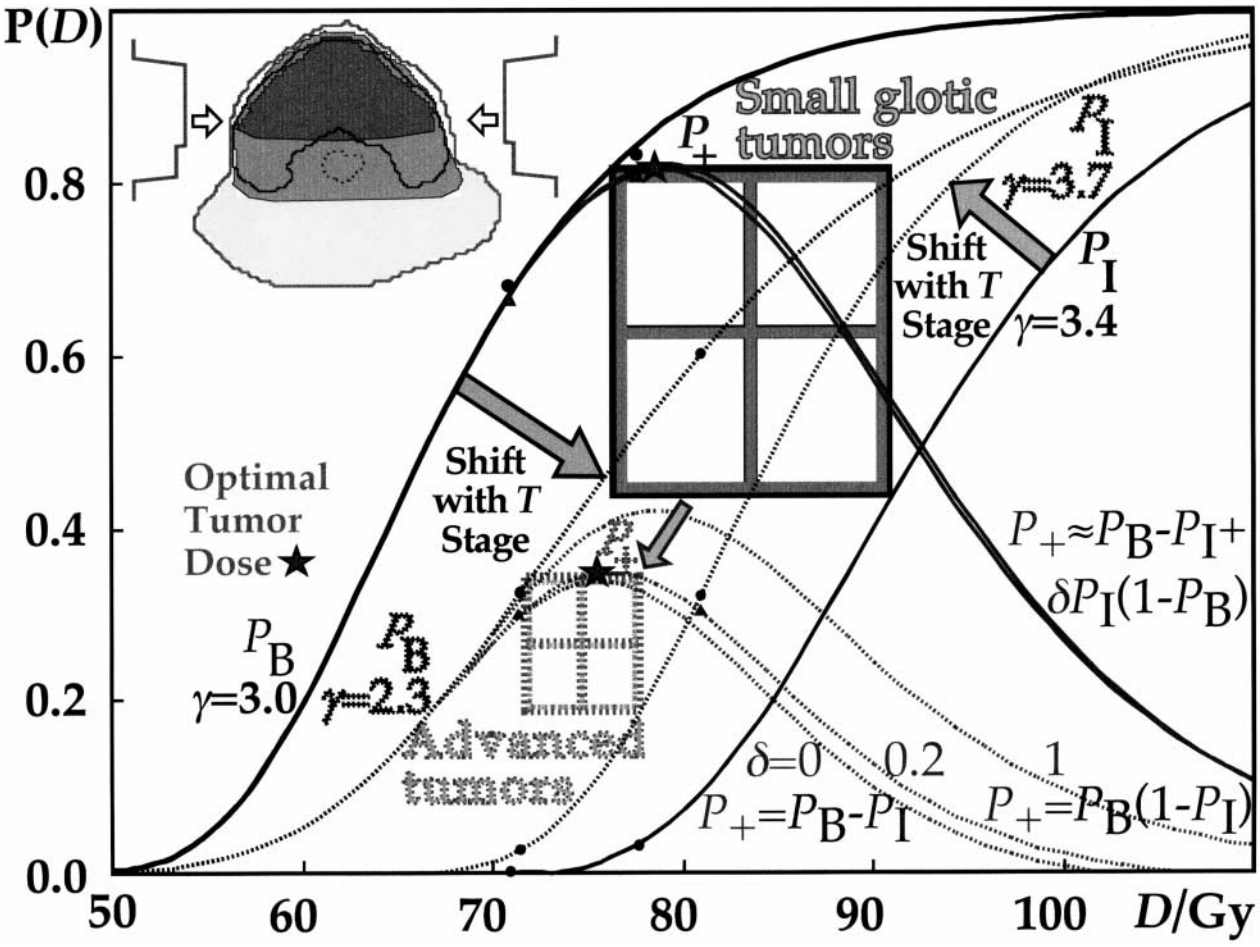

Fig. 1. The problem of the diminishing therapeutic window in curative radiation therapy of small glottic and advanced head and neck tumors. The large horizontal arrows illustrate the shift of the tumor control (P_B) and normal tissue complication curves (P_I) as the tumor stage is increased from small glottic tumors to larger more advanced tumors (19). The insert illustrates one slice of the approximately uniform dose delivery used to obtain the clinically observed data points.

tions are plotted. The mean dose to the tumor, or more precisely the internal target volume (20), is used as independent dose variable. This data set, in a nutshell, illustrates the main problem of radiation therapy of advanced tumors. For the small glottic tumors (solid curves) the therapeutic window between tumor control (P_B and left most sigmoid curve) and fatal normal tissue damage (P_I and right most sigmoid) is very large. For this reason the probability to achieve complication free cure (almost 85% at the optimal dose level) is very high. However, for the advanced tumors (dotted curves) the therapeutic window has shrunk and the optimal complication free cure is now about 35%. Figure 1 illustrates the case of more or less standard uniform beam radiation treatments where the increased tumor burden for the larger tumors requires substantially larger radiation fields and tumor doses to be eradicated, in accordance with most existing radiobiological dose response models. Therefore, the tumor control curve (P_B, the probability for beneficial treatment) is shifted to the right to higher doses (left most dotted curve). However, as the larger tumor is irradiated to higher doses the fatal normal tissue reactions increase substantially and the complication curve (P_I, the probability for fatal injury) moves instead to the left or lower doses. Thus, for advanced disease the therapeutic window is substantially decreased making it very difficult to cure all patients. This is the key problem of curative radiation therapy and we have to solve it in order to cure patients who present with advanced disease.

Figure 1 also illustrates a few other interesting phenomena that are common in many clinical materials. Not only are the dose response curves for the larger tumors shifted to larger doses but their dose response slopes, as expressed by their normalized dose response gradient, γ, are decreased. Conversely, the slope is increased for the normal tissues making it even more difficult to achieve a high probability of complication free cure. This further reduction of the therapeutic window for advanced tumors is

owing to an increased tumor heterogeneity and increased mass of normal tissues being irradiated resulting in more shallow and steeper slopes, respectively (16, 19, 20).

Furthermore, for the advanced tumor stages the clinically observed complication free cure (solid triangles on the middle dashed bell-shaped curve) is lower than most traditional response models predict (upper dashed bell-shaped curve). This is so since the traditional models assume that cure and fatal complications are statistically independent processes resulting in a complication free cure or positive treatment outcome given by the product of the probability for cure and no fatal injury or $P_+ = P_B(1 - P_I)$. However, in the clinical material almost all patients ($\sim 80\%$) who suffer fatal complications are also cured so the clinically observed P_+ is much closer to the totally correlated response with $P_+ = P_B - P_I$ (lowest dashed bell-shaped curve). The main reason why the tumor control and severe normal tissue complications often are strongly correlated in clinical trials is that both are caused by high uniform dose levels both in the tumor and the normal tissues, for example when parallel opposed beam techniques are being used. However, the correlation may also depend on that most genetic alterations in the normal tissues are preserved in the tumor, such as for example the ATM gene, which makes both the tumor and the normal tissues more sensitive than usual (19, 21). To be able to use clinical dose response data for treatment optimization it is therefore important to record not only tumor cure and normal tissue damage but also to register the degree of correlation between these two major endpoints as it strongly influences the location of the optimal dose level as seen by the dashed bell-shaped curves in Fig. 1, cf. Ågren et al. (19).

In order to illustrate how the merits of the new biologically based treatment optimization techniques using intensity-modulated beams can handle these problems, we will now compare them with standard uniform external beam treatment configurations on an advanced head and neck tumor similar to that of the dotted curves in Fig. 1. The intensity-modulated dose distributions have been calculated with one of the most advanced and flexible optimization algorithms available today (22–25).

The resultant dose response relations are presented in Fig. 2 and they illustrate the considerable therapeutic

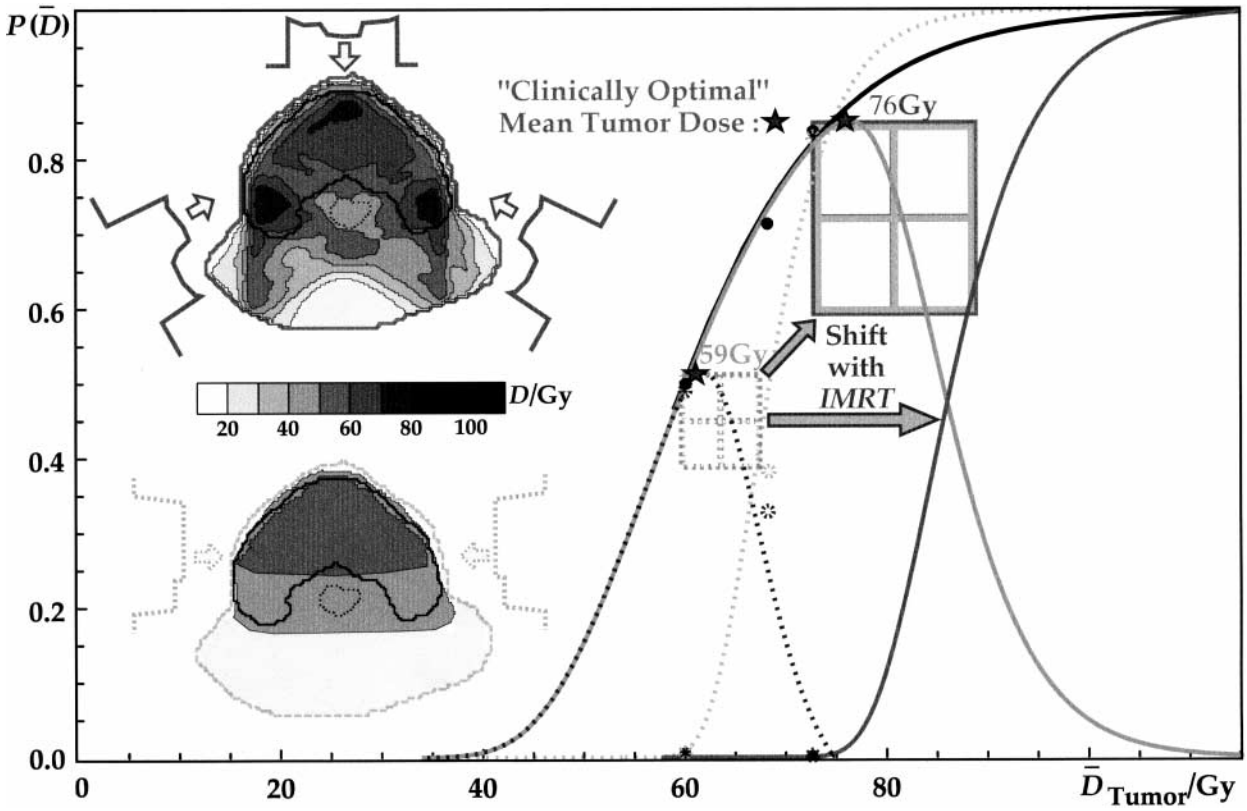

Fig. 2. Illustration of the possible improvement of the therapeutic window and the clinical outcome by using biologically optimized intensity-modulated treatments. By three-dimensional intensity-modulation the dose to the tumor is increased at the same time as it is reduced to the normal tissues. It should be pointed out that this figure is based on a more uniform subset of the advanced head and neck tumors in Fig. 1 with shorter treatment time and, in addition, the dose per fraction was increased instead of the number of fractions. Therefore, the observed steepnesses of the response curves and the cure (dotted lines) are higher than in Fig. 1 (cf. 14, 26). The considerable increase of the therapeutic window and complication free cure by using intensity-modulated dose delivery is clearly seen (solid curves).

advantages achieved by using intensity-modulated radiation beams. The inserted isodose diagrams compare in the same slice of a head and neck target classical and intensity-modulated beams and the associated dose response curves for the two treatments (dotted and solid curves, respectively). This figure allows a comparison of the two treatment techniques since the horizontal dose axis expresses the mean dose to the tumor or more exactly the internal target volume. Therefore, the dose-response curves for the tumor will practically be 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, the solid complication curve for the intensity-modulated plan has thus moved about 15 Gy to the right from its location with essentially uniform dose delivery (right most 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 almost 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. By comparison of Figs. 1 and 2 it is seen that with intensity-modulation the treatment outcome for advanced tumors can be brought up to the level of small tumors and uniform dose delivery and even somewhat further, provided the disease is well localized.

This also implies that the classic problem of double trouble in dose escalation is converted to a double or even triple advantage. Not only is the relative dose to the normal tissues reduced, but the dose per fraction and the dose rate are also reduced and thus the risk for severe late complications is substantially reduced. As mentioned in the figure caption the response curves in Fig. 2 were derived with a varying dose per fraction rather than with varying the number of 2 Gy fractions as in Fig. 1. This data set is therefore well suited for use with non-uniform dose delivery where the dose per fraction will vary with the intensity-modulation (26). The comparison in Fig. 2 thus illustrates the clinical advantages that can be gained by biologically optimized intensity-modulated dose delivery.

A schematic view of the different steps in the development of treatment techniques that took place during the first century of radiation therapy is illustrated in Fig. 3. Obviously, all radiation therapy aims at being conformal: that is to wrap the 'therapeutic' isodose as close as possible around the tumor, or more exactly, around the internal target volume. In the present review the term conformal is used to describe this aim similar to the conformation therapy technique developed by Wright et al. (27) and Takahashi (28). Simultaneously, the first optimization algorithms with essentially uniform or wedged beams shaped according to the projection of the target volume were developed (29, 30). This is also the method used by most workers today saying they are doing conformal radiation therapy. However, from Fig. 3 it is clear that considerable improvements in treatment outcome are not assured until we enter the area of full intensity-modulation and physically and preferably biologically optimized treatments. It is well known today that the considerable dose optimization effort that took place from the mid-sixties throughout the seventies was not so successful due to the low number of free variables used, cf. Brahme (31). We need thousands of free variables whereas in the sixties a few dozen of fields with or without wedges were used. However, when radiobiological dose optimization is used it is even possible to reduce the number of free variables using few field multi-segmented treatments, cf. Svensson et al. (32).

As important as the dose level delivered to the target tissues is the fractionation schedule employed. Considerable advances have taken place during the last few decades. First, it was understood that large doses per fraction are not tolerated by the late responding normal tissues that normally set a limit to what can be achieved by radiation therapy. It is well proven today that this phenomenon is linked to the extended shoulder region of the cell survival curve (33) which often is due to a larger compartment of resting G_0 cells in such organs. Late responding organs therefore have a longer recovery phase after irradiation allowing them to repair a larger fraction of the sub-lethal injury induced by each treatment. The late response of such organs may also be due to multi-step processes where the radiation effect on the microscopic capillary vasculature in addition to direct damage to tissue specific cells may contribute.

The shape of the shoulder of the cell survival curve is often described by the α/β ratio of the linear quadratic cell survival model:

$$s = e^{-\alpha D\left(1+\frac{D}{\alpha/\beta}\right)} \quad [1]$$

An α/β value of 3 Gy is common for late responding tissues which means that at 3 Gy the linear cell kill is equal to the quadratic repairable kill of the D^2 term. Tumors and acutely responding normal tissues have an α/β of about 10 Gy and large doses per fraction are better tolerated.

It has been known for a very long time that the cell kill is purely exponential (34) at very large doses and not quadratic as equation 1 indicates. More recently it has been shown that the linear quadratic model is not so well suited to describe the response at low doses either, even though it works quite well in the standard clinical 2 Gy/fraction range. At low doses the cell kill seems to be

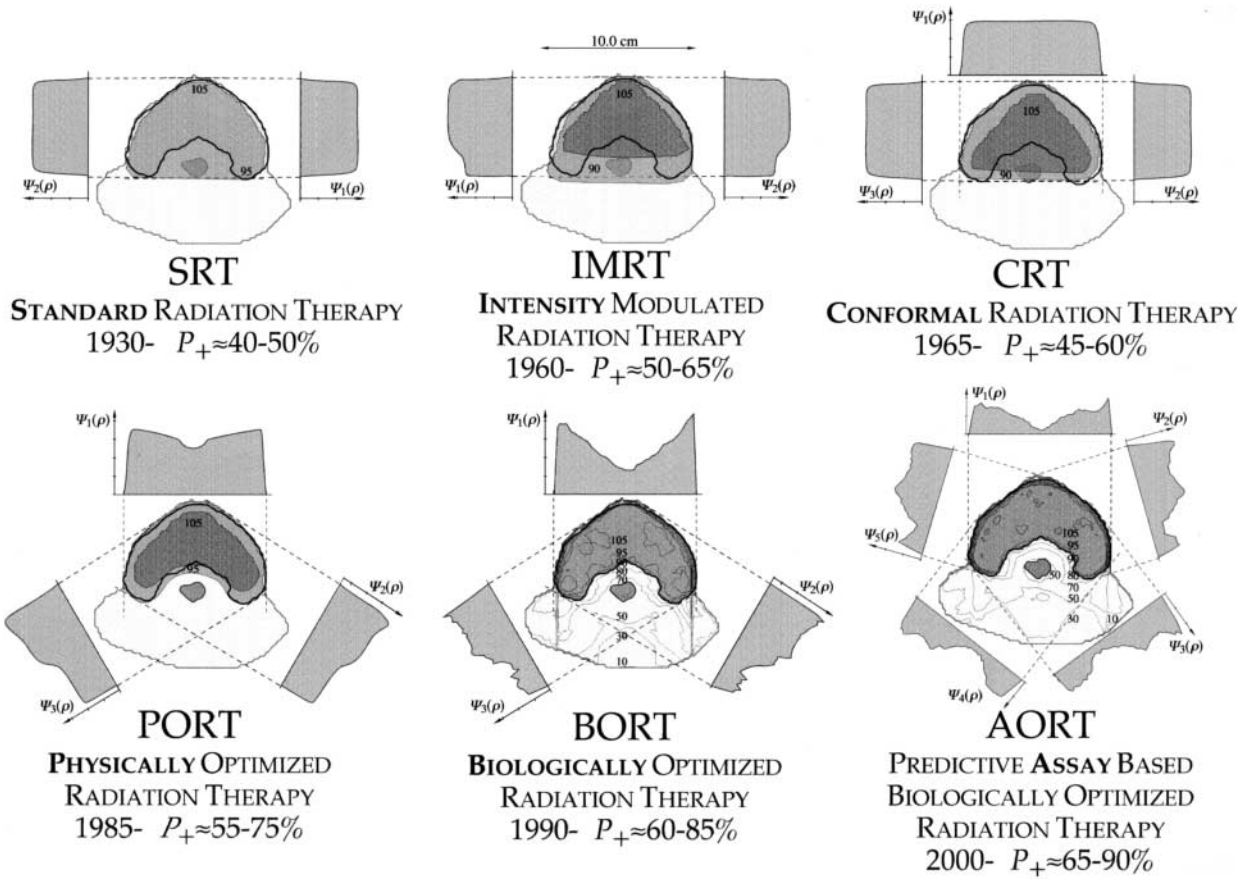

Fig. 3. Schematic overview of the development of modern radiation therapy techniques. Approximate year of introduction and the resultant complication free cure, P_+, compared to that of standard radiation therapy are also indicated. It is seen that the commonly used term *conformal therapy* does not necessarily imply a very large improvement in P_+. Obviously the whole lower row of panels are special cases of IMRT and CRT but in general such high degrees of conformity is rarely obtained just by absorbers or dynamic collimation, respectively.

much steeper than previously realized. The increased sensitivity at low doses as shown in Fig. 4 is more pronounced when the shoulder of the cell survival curve is large (35) such as for late responding tissues with a low α/β value. There are already indications that this low dose hypersensitivity phenomenon may be clinically relevant since low and high doses per fraction to the skin may cause similar skin reactions even if the total skin doses differ substantially (36). From the above points of view a better description of the cell survival curve is obtained by an expression of the type:

$$s = e^{-\alpha D} + bD^2 e^{-\beta D} \qquad [2]$$

where the α term describes the irreparable cell kill and the b term the potentially lethal part which can be repaired if the right environmental conditions for repair prevail. The thick solid curve in Fig. 4 is from equation 2 and the dots with error bars are experimental data for lung epithelial cells (35). By comparing with the dashed linear quadratic curve due to equation 1 the improved fitting particularly at low but also at high doses outside the figure are obvious. A very interesting effect of clinical relevance can be seen in Fig. 4 by studying the shallowest possible secant of the survival curve through the origin to find the smallest effective cell kill for a given dose to the tissue in question. For the lung epithelial cells in Fig. 4 this is the tangent close to the 2 Gy per fraction dose which means that this dose per fraction is the one which produces the least possible cell kill per unit dose to the tissue. Thus, the low dose hypersensitivity not only makes the tissue quite sensitive for low doses per fraction but it also forms a fractionation window where a certain dose level per fraction produces the least possible damage to a given tissue per unit dose when trying to irradiate an underlying tumor. It is very likely that this mechanism is responsible for the observation in most clinical trials that the best possible therapeutic effect is obtained in the dose per fraction range around 2 Gy per fraction.

At higher doses per fraction the late responding tissues introduce more complications (32) whereas at lower doses per fraction the low dose hypersensitivity may cause more complications as indicated in Fig. 4. Thus, when introduc-

ing optimized intensity-modulated radiation therapy to increase the dose in the tumor and often simultaneously reduce it to the normal tissues (cf. Fig. 2) we should make sure that the dose per fraction to the normal tissues is largely left unchanged to ensure a substantially increased tumor cure and an unchanged level of damage. Since the low dose hypersensitivity is most pronounced in late responding tissues with broad shouldered survival curves ($\alpha/\beta \approx 3$) one would expect that this phenomenon is not very pronounced for the tumors ($\alpha/\beta \geq 10$) in fair agreement with existing experimental data, cf. Lambin et al. (35).

A further conclusion of high relevance to some forms of modern conformal treatments may be drawn, since the dose is often spread out from a large number of beam portals covering a large part of the body volume. This will make the dose per fraction to a large percentage of the patient's normal tissues low and an increased cell kill due to the low dose hypersensitivity may increase complications. It may therefore be desirable to increase the dose per fraction to the normal tissues back to the classically established level of around or just below 2 Gy per fraction. These problems of intensity-modulated and multi-portal conformal therapy may therefore partly be solved in the clinic by one and the same approach: a shortening of the overall treatment time by a reduction of the number of fractions when using optimized intensity-modulated beams.

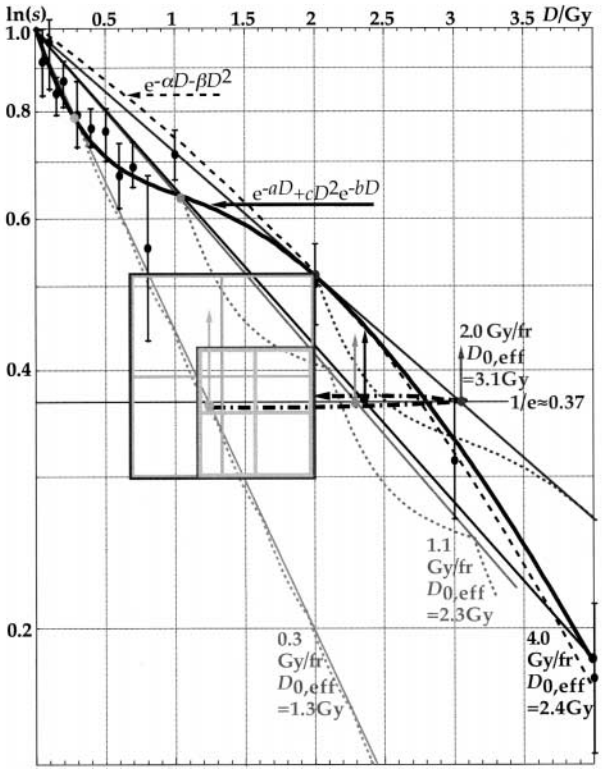

Fig. 4. Illustration of the normal tissue fractionation window caused by low dose hypersensitivity. Both at lower doses and higher doses per fraction the normal tissue damage is increased over that at the standard 2 Gy/fraction level used in classical radiotherapy. For simplicity a fixed survival fraction at 2 Gy of 0.3 is assumed for the tumor.

Even if the reduction is not more than a few fractions it represents a new kind of advantage since the effect of accelerated tumor repopulation that often sets in after the first 2–3 weeks of treatment will be less of a problem when the total treatment time is reduced (37). In general, the delivered dose could be reduced by 0.4–0.6 Gy per day of shortening of the total duration of the treatment compared to the reference situation of 30 fractions in 6 weeks. Therefore, if the total dose is left unchanged, an equivalent tumor boost of about 0.5 Gy times the number of days of treatment time reduction is obtained.

In conclusion, there are basically five kinds of improvement of the treatment outcome possible when using biologically optimized intensity-modulation:

- Increase of the tumor dose and dose rate
- Increase of the tumor dose per fraction
- Unchanged or slightly reduced dose per fraction to the normal tissues
- A reduced treatment time and an associated additional tumor boost
- Less work in the clinic as fewer treatment fractions are used.

All of these advantages can simultaneously be effective at a varying degree or all the advantages may be focused on one or two of them making the remaining largely unaffected leaving considerable room for advanced radiobiological treatment optimization.

It is often claimed by physicians that radiation therapy in the future will be replaced by molecular biology approaches and gene therapy. Surely we will see considerable improvements in these areas. However, they will also augment the power of radiation therapy as we can use the new genetic markers for radiation responsiveness and radio-resistance. Furthermore, gene therapy will probably fail on large bulky solid tumors and could gain considerably by combination with radiation therapy. We should therefore also expect considerable improvements in radiation therapy when these new tools come into clinical use as indicated by the last step of development in Fig. 3. It is likely that patient individual predictive assay based on molecular or cellular methods when combined with biologically based therapy optimization can improve the treatment outcome by 5–15% compared to using the average value of the response over a population, at least for locally advanced tumors (12, 13, 19).

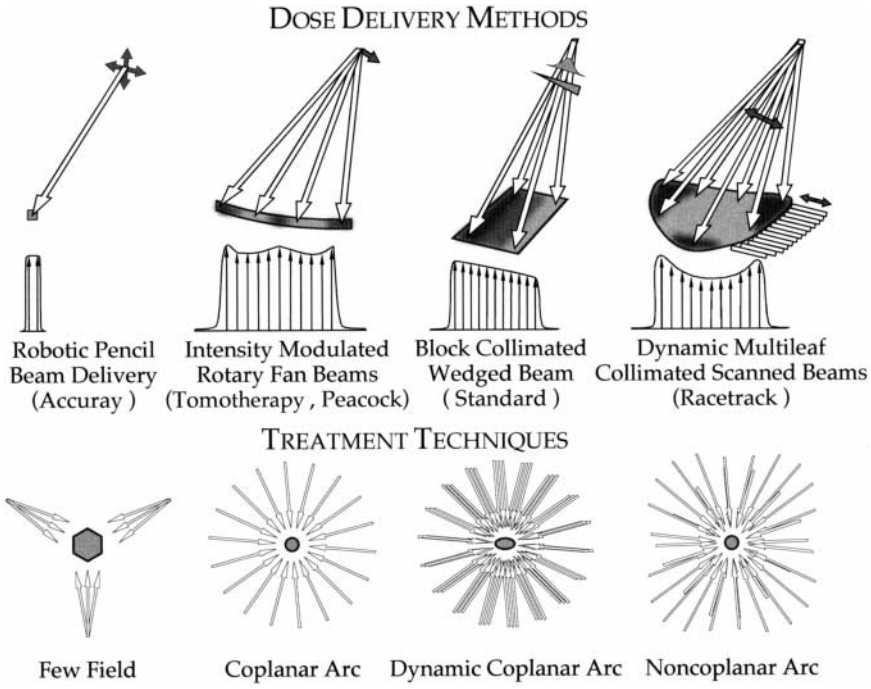

Fig. 5. Illustration of the main types of beam shaping and dose delivery systems developed today. The greater flexibility in dose delivery with the narrow pencil beam and fan beam approaches is obtained at the cost of an increased treatment time. This time loss is not obtained if dynamic multileaf collimation is combined with scanned narrow photon beams that are directed only where the collimator is opened.

COMPARISON OF NEW RADIATION MODALITIES AND IRRADIATION TECHNIQUES

As seen from Table 1 a large number of radiation therapy modalities have been developed and used over the years. The majority of the dose delivery systems have been of the classical type using block collimation sometimes combined with wedge or compensator filters as illustrated by the third panel in Fig. 5. However, in recent years most new radiation modalities are linked to more flexible beam shaping or intensity-modulation. The other three panels in the top row of Fig. 5 illustrate various approaches from robot mounted linear accelerators producing fairly narrow photon beams that can be moved around the patient, via intensity-modulated fan beams like in the tomotherapy and peacock devices to full dynamic multileaf collimation in the fourth panel of Fig. 5. Obviously, this last approach has the greatest flexibility since by almost closing all the collimator leaves a narrow slit beam and the fan beam geometry is obtained and by further closing all but one leaf pair completely a pencil beam delivery is possible. The lower set of panels in Fig. 5 illustrates the few field treatment techniques employed with standard and dynamic multileaf collimation and the arc techniques of tomotherapy and robotic dose delivery.

From the above description it is immediately clear that the treatment time will be significantly increased as the collimator is closed down and only a narrow fan or pencil beam is delivered. The effective increase in treatment time may not be as large as the reduction of the beam area since the narrow beam approaches may be used without beam flattening filter thus increasing the output by a factor of two. Still the treatment time with a fan beam is about 5–10 times larger than for conventional treatments and almost 100 times larger for the narrow pencil beam approaches unless the beam current and speed of motion of the accelerator are substantially decreased. The treatment time can also be increased by removing the filter when using the dynamic leaf collimation approach. If scanned beams are used, the treatment time can be brought back to standard uniform beam values or even faster when substantial intensity-modulation of the beam is required. It is therefore clear that dynamic multileaf collimation is here to stay as a practical and cost effective way of realizing intensity-modulation.

Today multileaf collimation combined with scanned beams is available for clinical electron and photon therapy through the Racetrack accelerator (38), but it has also been developed for ion beam therapy (39) proton therapy (40, 41) and been proposed for neutron therapy (42). It is clear that such techniques have important advantages with regard to the speed and quality of the treatment and may be increasingly implemented and used for radiation therapy in the new millennium. The large number of new treatment techniques that are being developed today covers the entire spectrum of radiation modalities in Table 1 and their radiobiological and dose distributional properties

are summarized in Fig. 6. It is no major surprise that the time and cost axia are running parallel in Table 1 since the most costly techniques have been developed most recently.

After the extensive and very interesting test period of heavy ion beams Berkeley was closed down in 1992, only the advanced developmental projects at Chiba, Japan and Darmstadt, Germany, are being used. It is clear from a cost/effectiveness point of view (in this context: equipment cost per patient cured) that these projects still need to be clinically proven. They have probably their most important role in the study and development of high LET radiobiology for a deeper understanding of the role of ions in radiation therapy. However, since the optimistic days of the late seventies (43) the role of high LET heavy ions has not really met up to the expectations largely due to the increased normal tissue damage in microscopically invasive parts of the tumor. Today this is at least partly understood since high LET beams have a high RBE at low doses. However, at curative doses the high microscopic heterogeneity makes the low dose RBE misleading since tumor clonogens will survive in microscopic cold spots (44). This microscopic heterogeneity is understandable as the high ionization density of the heavy ions and the low dose delivered (~ 20 Gy) by necessity will make some tumor clonogens escape lethal hits. Therefore, to be curative with high LET beams considerably larger doses must be delivered than indicated by the low dose RBE, causing severe acute and late reactions in the normal tissues. This normal tissue problem, augmented by the poor repair of high LET damage, sometimes overshadows the advantage of a high LET in hypoxic tumors.

This normal tissue damage syndrome is present particularly in neutron beams due to their high LET, being almost as high as for heavy ions as seen in Fig. 6. This also explains why combined neutron and photon treatments have shown interesting results in clinical trials (45, 46). The microscopically more uniform low LET photon part helps remove microscopic regions with too low dose associated with high LET dose delivery. Owing to their extensive use, neutron beams have shown more clear-cut evidence that they are advantageous for some largely hypoxic tumors, such as salivary glands, prostate and sarcomas. In fact, the optimal use of a high LET beams of neutrons or heavy ions should combine with low LET beams in the often well-oxygenated microscopically invasive part of the tumor as illustrated in Fig. 7. The high LET component should thus be focused only on the gross tumor. This radiobiologically optimized photon and neutron beam combination was based on experimental cell survival data for the two beam components for well-oxygenated and hypoxic cells (47). Still the cost effectiveness of neutrons is a problem owing to the high installation cost and the high expertise of the personal required for dosimetry and the handling of normal tissue reactions. The interest in boron capture therapy in recent years using epithermal neutrons from nuclear reactors that otherwise had been dismantled may reduce the cost but will still suffer from the microscopic heterogeneity, specially in invasive regions with low boron uptake and low neutron fluence.

Today π mesons are not really realistic either, partly due to the high accelerator costs involved. They do have some interesting therapeutic properties though, since they like

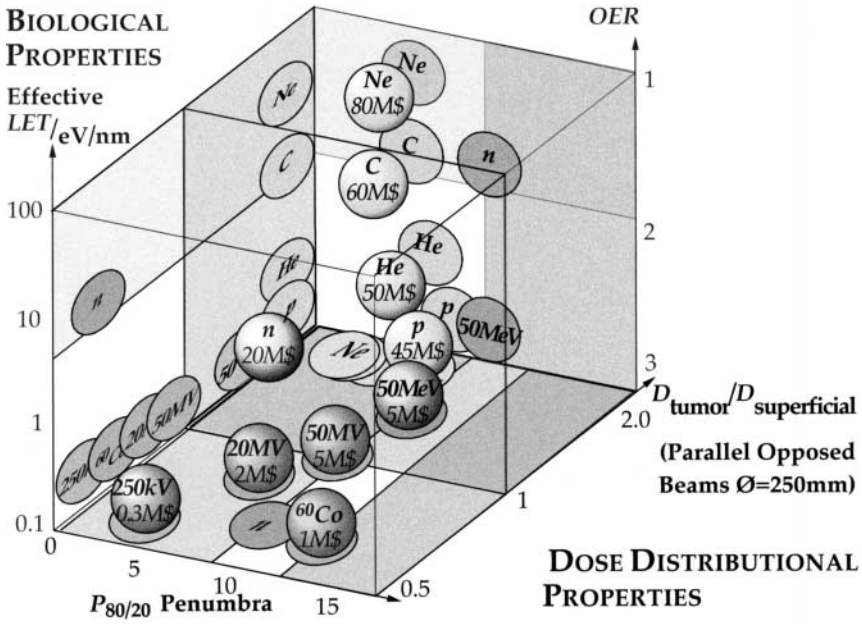

Fig. 6. Comparison of the radiobiological (effective LET and OER) and the dose distributional properties (penumbra and tumor to superficial tissue dose ratio for a parallel opposed beam pelvic irradiation) of different radiation beam modalities. The approximate cost per typical installation is also indicated (cf. 46).

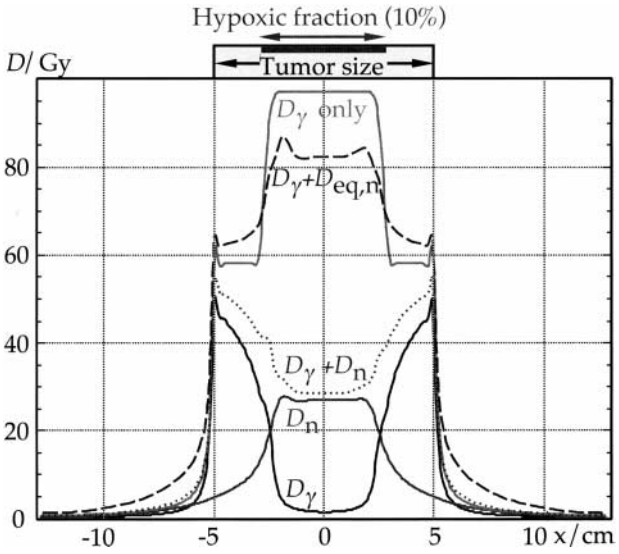

Fig. 7. The radiobiologically optimized combination of high LET neutrons and low LET photons on a hypoxic tumor. Neutrons dominate over the hypoxic region whereas photons dominate in the well-oxygenated microscopically invasive region. The complication free cure with only photons (upper solid curve) is inferior to that with neutron addition owing to the high survival of the hypoxic cell fraction in a pure photon beam.

the light ions He, Li and Be combine low and high LET dose delivery in one single modality. Of the more costly radiation modalities light ions and protons are most interesting, since they combine advanced precise dose delivery with a not too high LET and efficient repair in normal tissues. However, the rapid development of intensity-modulated dose delivery with electrons and photons has reduced the number of tumors where protons are required. Because the cost of a proton installation is about 10 times higher than for advanced photon and electron therapy units with intensity-modulation, mainly very difficult tumor sites are indicated for proton therapy. Among tumors that are of interest for proton and light ion application are those located close to serially organized tissues where a small local overdose can cause fatal complication such as most tumors close to the spinal cord. The steep dose gradients outside the target volume make protons and light ions an interesting alternative in such cases (cf. Fig. 6).

To quantify the merits of high-energy proton therapy as compared to radiobiologically optimized intensity-modulated photon and electron beams some comparisons have been made as illustrated in Figs. 8 and 9. For an advanced cervix cancer with extensive nodal involvement all the three radiation modalities were compared using radiobiologically optimized intensity-modulation. In Fig. 8 the angular variation of the maximum achievable level of complication free cure (P_+) is plotted as a function of the angle of incidence for a single intensity-modulated beam portal. Obviously, this target would never be treated with a single portal of any of the tested modalities since the inevitable dose reduction from most directions can be improved considerably from other directions (cf. Fig. 9). Since every proton portal generally requires multiple range shifted proton beams we have compared them with electrons and photons alone or in combination with multiple beam energies through one and the same beam portal.

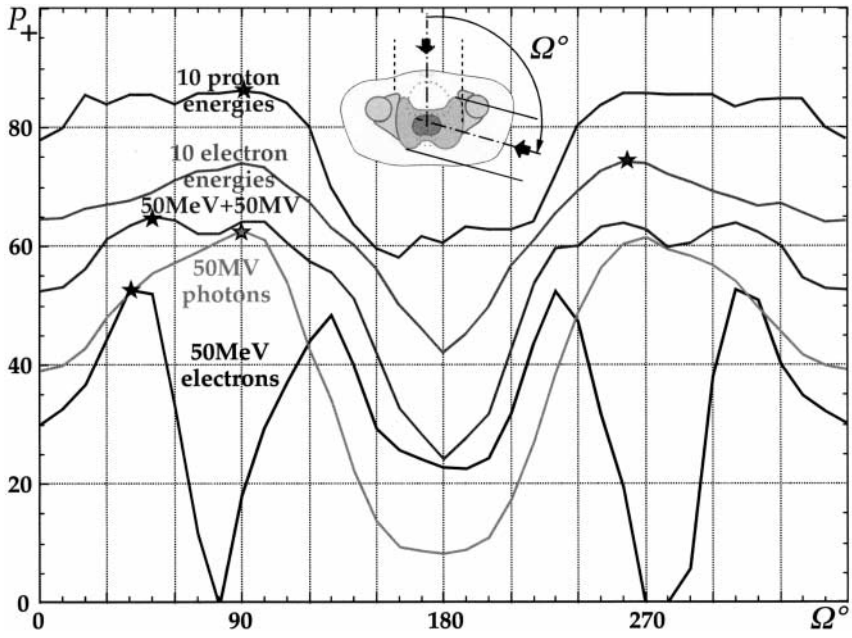

Fig. 8. Comparison of the single beam portal complication free cure of some of the main low LET radiation modalities in Fig. 6 as a function of the angle of incidence while treating an advanced cervix tumor. The optimal angle of each treatment modality is indicated by a star.

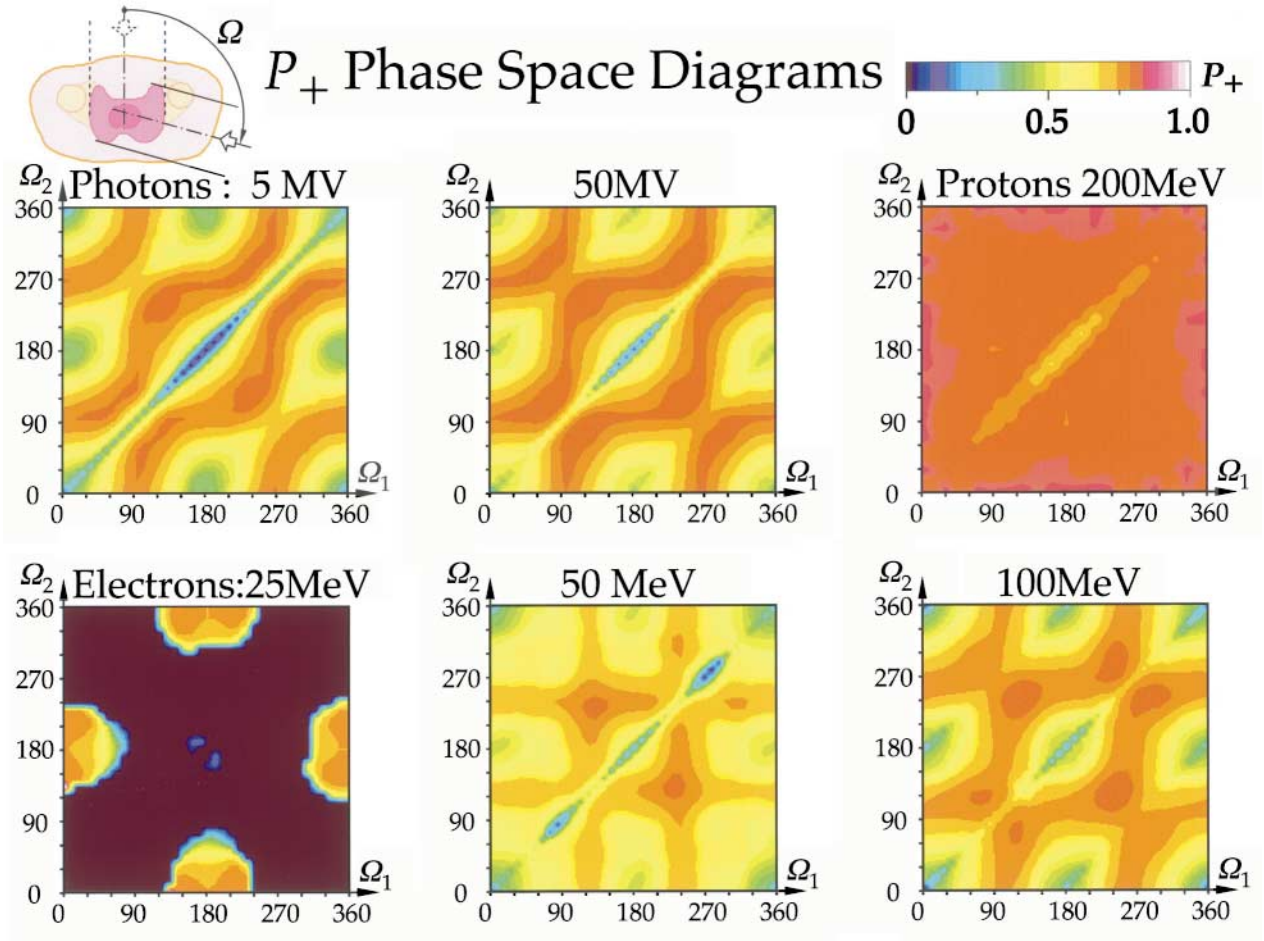

Fig. 9. Same as Fig. 8 but now considering two beams and plotting the resultant complication free cure, (P_+), using color coding. It is striking that all the radiation modalities reach approximately the same maximum complication free cure but for greatly differing angles of incidence.

Owing to their very different depth dose characteristics (cf. Fig. 6) the beam direction, where photons and electrons alone have their most interesting use (highest P_+ value), differs considerably as seen in the lower part of Fig. 8. For 50 MeV electrons the therapeutic range is not enough for lateral irradiation but for some anterior and all posterior directions intensity-modulated electrons do much better than photons owing to the finite range and low exit dose of the electrons. The high complication free cure with lateral 50 MV photon beams is owing to the high photon energy with a deep extended dose maximum and the possibility to give a high dose to the gross tumor without damaging rectum. To see the improvement in dose delivery through a single portal the proceeding curve is for 50 MeV and 50 MV combined from the same direction by biologically optimizing the total dose distribution delivered by simultaneous intensity-modulating of both the electron and photon components (cf. 48, 49). The resultant improvement is considerable from some directions specially anterially but the best P_+ value is only increased by 3% to 65% from 62% with photons alone and 53% with electrons alone. The optimal direction is now around 45° close to the maximum with only electrons. If we now combine 10 pre-selected electron beam energies, the P_+ is increased by 21% over the single 50 MeV electron energy and 12% over photons alone to 74% indicating the high value of simultaneous intensity- and energy-modulation with electrons (see also Fig. 10).

If we similarly use 10 pre-selected proton energies uniformly covering the maximum depth range of the tumor, a further increase by 12% is seen to a total of 86%. If higher energy electrons were allowed such that their therapeutic range covered the maximum tumor depth better over 70% would be achieved with 100 MeV alone (cf. Fig. 9) and at least 80–82% would be reached combining 10 different lower electron energies and probably a few percent more if a single high-energy photon beam was replacing one of the electron energies (not shown). In conclusion, with a single beam portal 10 intensity-modulated proton beams probably give some 3–5% higher P_+ than 10 electron and photon beams combined through one portal.

It should be pointed out that all of this proton advantage would be lost if not biologically optimized three-dimen-

sional Bragg peak spot scanning would be used for the protons and it is thus a fundamental prerequisite for future proton installations, cf. Brahme (46). Unfortunately, this is not yet done systematically at any proton therapy center to date and significantly lower values would be obtained by most standard fixed range modulation techniques presently in use.

If we now switch from one to arbitrary two beam portal combinations the situation becomes much more complex as we need to optimize some 650 dose plans covering all possible beam combinations used in Fig. 9 instead of the 36 in Fig. 8 (at even 10° intervals). For this reason we have changed from $P_+(\Omega)$ to plotting $P_+(\Omega_1, \Omega_2)$ as function of the two angles of incidence Ω_1 and Ω_2 in the (Ω_1, Ω_2) plane with P_+ color coded using the Sucholov color table starting with black as zero going through dark blue, green, yellow, orange, red, pink and white as unity.

In Fig. 9 six such phase space diagrams for 5 and 50 MV photons, 25, 50 and 100 MeV electrons and 200 MeV protons are summarized. Some very interesting conclusions can be drawn from these diagrams. First of all, the diagonals of each diagram in Fig. 9, where $\Omega_1 \equiv \Omega_2$, correspond strictly to single beam treatments as they are the degenerate cases where the two beams coincide and are thus equal the corresponding modality in Fig. 8 (since $P_+(\Omega) \equiv P_+(\Omega, \Omega)$). The color coding of diagonals in Fig. 9 thus corresponds to P_+ curves in Fig. 8 as seen by comparing the curves and colors for 50 MeV and 50 MV for example. It is clear that for most modalities it is important to avoid the region around $\Omega_1 \approx \Omega_2$ since the resultant P_+ is decreased when the intensity-modulating components become more and more aligned and dependent. From the small 'side valleys' parallel to the deep central diagonal valley it is also seen that parallel opposed photon beams ($\Omega_2 = \Omega_1 \pm 180°$) should for the same reason be avoided using intensity-modulated dose delivery. It is for this reason unfortunate that the majority of all uniform beam photon therapy is performed with parallel opposed or four-field box techniques where the entrance and exit portals coincide and give a high dose to the normal tissues. Perpendicular beams or most preferably 100°–120° beams and symmetric three-field techniques are generally more advantageous for photons (50). However, for electron and proton beams the situation is different as they have almost zero exit dose and therefore less interaction with the normal tissues. At an electron energy of 25 MeV for example anterior-posterior almost parallel short opposed beams are the only possibility owing to their short therapeutic range.

The other very striking result seen in Fig. 9 is that independent of radiation modality the highest peak is always at the same P_+ level close to 90%. However, the optimal beam angle combination varies considerably with the radiation modality. For protons the selection of beam directions is not important, even parallel opposed beams work well due to the low exit dose. All the electron and photon beams however have a few discrete regions where the incident beams should preferably be located to maximize P_+. From this we may draw the conclusion that with biologically optimized intensity-modulated proton beams a rotary gantry is no more necessary since we can always rotate the patient in the horizontal plane to get 90° and 270° beam portals. However, it should be pointed out that this study for reasons of treatment planning time consumption was made with a two-dimensional patient where every slice through the patient is the same. Therefore, in some advanced treatments where the ideal beam directions vary considerably from slice to slice the extra flexibility of a rotary gantry may be desirable as seen from Fig. 8. However, the proton P_+ does not vary much with the single beam portal direction except possibly for beams entering from the very sensitive rectal side ($\Omega \approx 180°$ in Fig. 8).

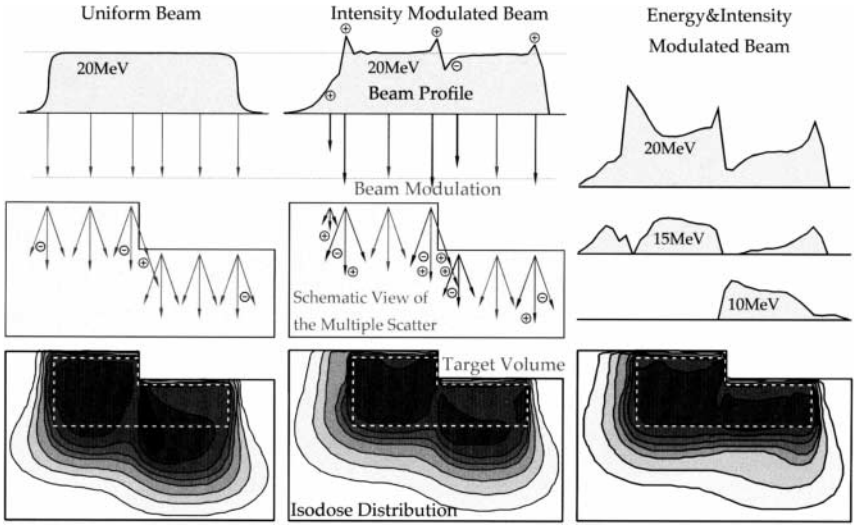

Fig. 10. Schematic illustration of the clinical advantages of combining electron energy- and intensity-modulation for complex heterogeneous target volumes.

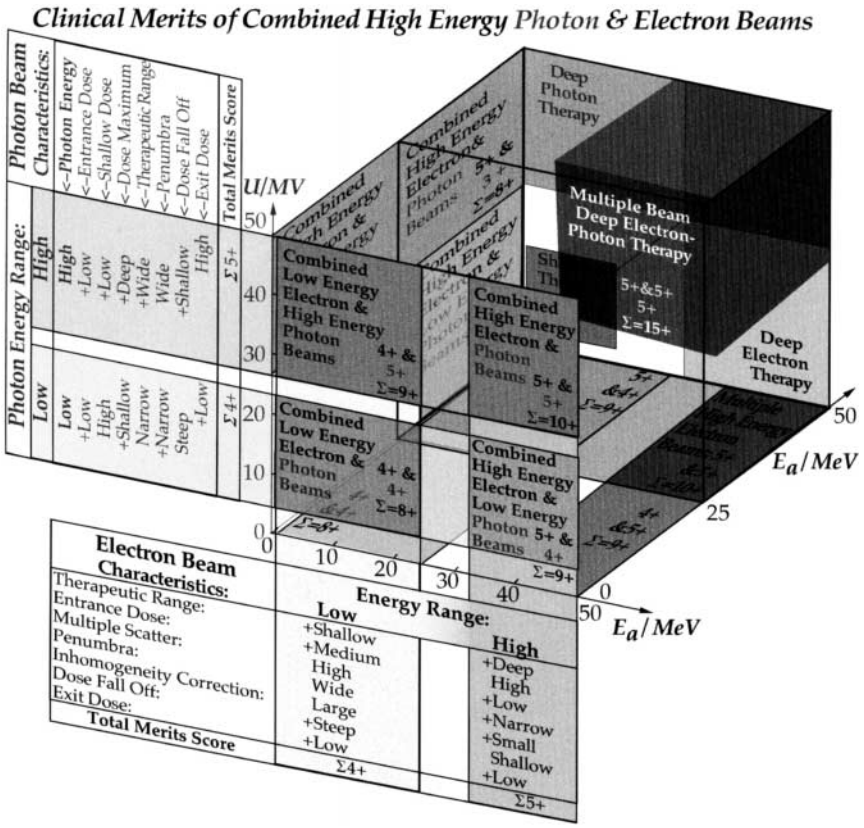

Fig. 11. Comparison of the different dose distributional properties of high- and low-energy electron and photon beams. A simplistic score of counting only positive factors was used to compare the merits of different electron and photon beam combinations.

A way to get 360° coplanar rotation with a fixed horizontal proton beam port would be to treat the patient seated as commonly done in non-hospital based accelerators. It therefore is still worthwhile to consider using radiobiologically optimized three-dimensional intensity-modulated proton beams with fixed beam delivery to bring down the cost from, maybe 40–45 million USD for two rooms to maybe 25–30 million USD for three rooms without rotary gantries. This would reduce the cost per treatment room to about 40% of that with rotary gantries.

Some of the main reasons why high-energy electron and photon beams do almost as well as high-energy protons when intensity-modulation is used are illustrated in Fig. 10 where a heterogeneous step phantom and target are irradiated by uniform but also energy and intensity-modulated electron beams. This heterogeneity problem is also relevant for proton beams which suffer similar multiple scatter interactions in the patient and to a lesser extent also to the secondary electron and photon scatter in photon beams. The first third of the figure shows what happens with a uniform beam producing a cold spot under the 'nose' and a severe hotspot just outside it due to out scatter. The middle portion illustrates how the fluence profile of the incident beam could be adjusted to correct for the dosimetric problems with uniform beams. It is clearly seen in the middle isodose diagram how the dose distribution in the target has been improved and made more uniform. The improvement is achieved partly by irradiating less sensitive structures outside the target to get in scatter to the tumor. However, most of the hot and cold spots have been eliminated by the intensity-modulation as indicated by + and − in the middle panel of Fig. 10. In the last third of Fig. 10 local energy- and intensity-modulation are used to enclose the target by a high uniform dose distribution. The lowest energy is predominantly used over the shallow target portion to avoid irradiating normal tissues beyond the tumor, whereas high energy is used to sharpen the dose distribution near the heterogeneities.

In Fig. 11 the various dose distributional advantages of combined high- and low-energy electron and photon beam treatments are compared schematically. A number of interesting modality combinations can be distinguished in this figure primarily adopted to classical uniform beam delivery. Starting with plain electron therapy, two regions can be distinguished directly: the classical one, where a patch work of different low-energy beams generally below 20 MeV are used to save underlying tissues largely owing to the steep dose fall-off along the depth axis of such beams. Normally the low-energy electrons are not really safe in multiple non-parallel beam configurations in more shallow

tumor regions due to the steep dose gradients at the end of their range. However, in the high-energy region the dose fall-off is less steep and the exit dose is still low so multiple beam combinations with either electrons or photons become very useful. The narrower penumbra in high-energy electron beams is also useful in such cases as seen from the beam characteristics tabulated in Fig. 11. By combining parallel or perpendicular electron and photon beams a sharpening of the target volume dose distribution is also possible (49).

The low-energy photons have their greatest value for shallow to deep-seated tumors of small sizes. This is so since a narrow penumbra is most important for small targets and it is narrowest in low MV photon beams. When the tumor diameter increases to about 5 cm the entrance dose becomes more and more of a problem for deep seated tumors requiring beams with broadest possible build-up region and highest possible photon energy, cf. Söderström et al. (51). Deep therapy with combined high-energy electron and photon beams is most useful when the penumbra and entrance and exit dose regions can be optimally combined e.g. using perpendicular beam configurations. For lung tumors with a high density surrounded by low-density lung also parallel beam portals of electrons and photons have an interesting role to sharpen up the dose delivery at the periphery of the tumor. Obviously, many of these advantages, most relevant for uniform dose delivery, will benefit considerably by combination with intensity-modulated electron and photon beams as illustrated in Fig. 10.

Beside the main road of development of few field intensity-modulated treatments that are safe and easy to verify (52) a large number of special techniques have been developed for various target locations (53). Elongated tumors following the lymph nodes or other extended organs of the body are well treated by tomotherapy. For targets in the head the new dynamic γ-knife using an automatic patient positioning system and biological optimization of the motion of the patient head opens new unprecedented possibilities for complex intra-cranial targets. In such devices the biological advantage of multiple concomitant beams on the target, cf. Svensson (54), are likely to improve the cure of large complex lesions.

To illustrate the power of radiobiological treatment optimization with multiple conventional photon beams, a

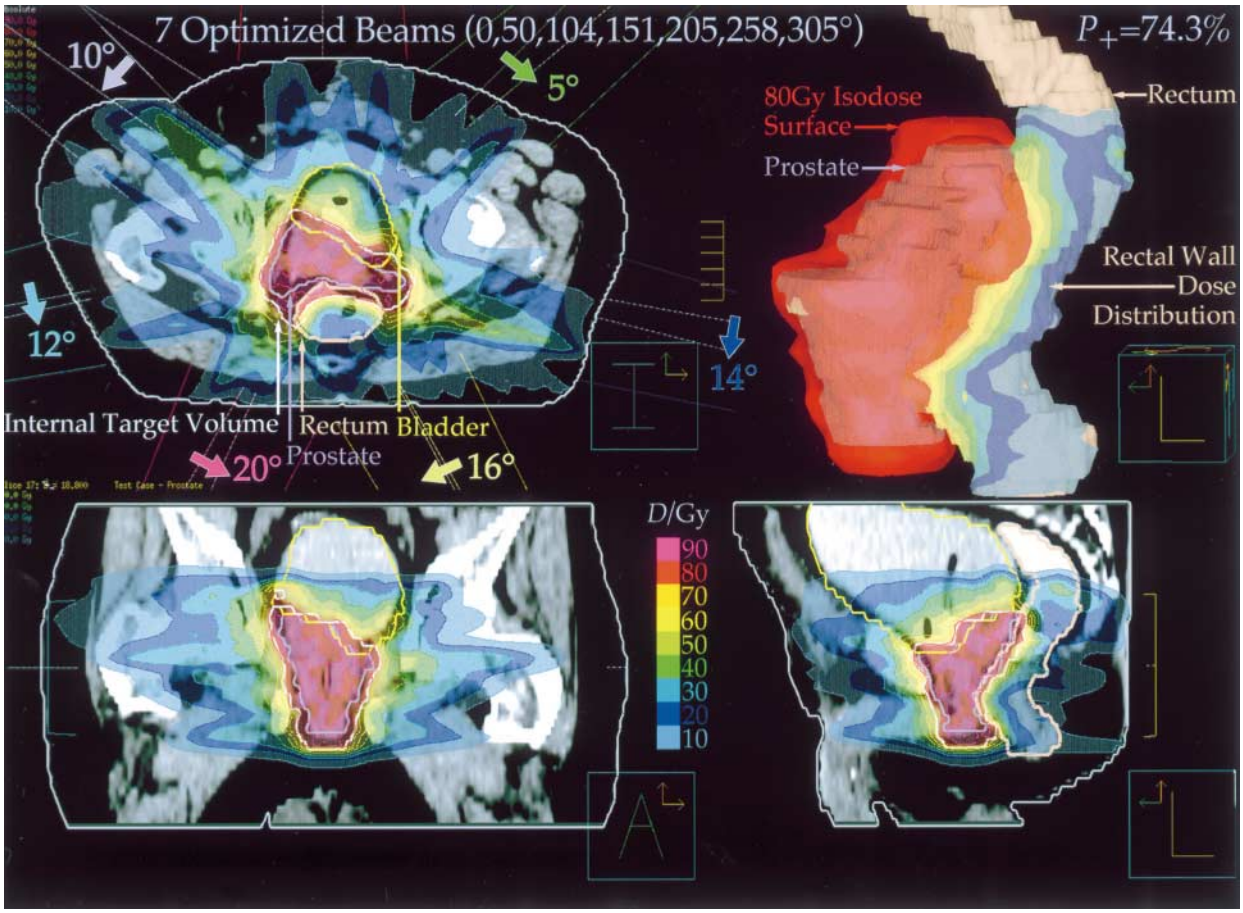

Fig. 12. A seven-field treatment plan of a prostate tumor where the intensity distribution and the angle of incidence of the beams have been radiobiologically optimized using the universal optimization algorithm ORBIT within the Pinnacle dose planning system. The perfect encloser of the target volume and significant sparing of organs at risk are striking.

treatment plan where the angles of incidence are optimized together with their intensity-modulation, is shown in Fig. 12. This is a seven-field plan for a prostate tumor where the initial suggestion was seven nearly equally spaced beam portals. An almost 6% improvement in the complication free cure could be achieved by fine adjusting the angles of incidence so they better separate the dose delivery to the prostate from the 'spill-over' to rectum and bladder. The optimized beam directions are better aligned to the shape of the tumor at the same time as they reduce unnecessary irradiation of organs at risk as shown in Fig. 12. This ability to radiobiologically optimize the directions of incidence is very useful clinically as it performs a fine adjustment of the angle of incidence to a degree, which is hard to achieve by ocular inspection even by a trained clinician. The treatment plan in Fig. 12 was developed using one of the most advanced and flexible radiobiological optimization algorithms that is available today, called ORBIT (Optimization of Radiation therapy Beams by Iterative Techniques (25, 55)) here shown fully integrated in the Pinnacle treatment planning system. It allows optimum combination of different radiation modalities or beam energies as in Figs. 8 and 9, but also optimization of the fractionation schedule considering low dose hypersensitivity such that the optimal dose level per treatment fraction is achieved in the late responding organs at risk as discussed above. The ultimate application of this type of algorithm would be to combine different types of low and high LET modalities such as protons, light and heavy ions, to really cure advanced hypoxic tumors by optimized 3D dose delivery using the latest form of multi-particle synchrotrons (41).

It is obvious that all patients do not really need the full power of efficient intensity-modulation. For example, many of the early-diagnosed small T1–T2 tumors are already treated very well with ordinary uniform beams of rectangular cross-section. As the tumor (T), nodal (N) and metastatic (M) stages gradually deteriorate the need for individual beam shaping and intensity-modulation increases rapidly. This is illustrated in Fig. 13 indicating the volumes in TNM-space where the different treatment modalities are most cost effective. Depending on the tumor site different percentages of the patients will require more advanced intensity-modulated treatments. However, even if uniform beams are sufficient for a curative outcome for some smaller tumors, intensity-modulation may still be of interest, especially if the patient is young and has a considerable life expectancy after a successful treatment. It is then important to ensure the lowest possible risk for late adverse reactions making advanced intensity-modulation the most attractive method to maximize the long-term complication free cure.

CONCLUSIONS AND FUTURE DEVELOPMENTS

It is absolutely clear that many of the new developments in radiation therapy have the potential to considerably improve the treatment outcome for many target sites. This does not mean that we need to implement the most advanced form of intensity-modulated radiation therapy on all treatment units in every clinic. Most small tumors can be treated very effectively by standard treatment techniques even though biologically optimization still may reduce late morbidity in some of these tumors. However, when the new optimized treatment techniques have been fully integrated in modern equipment with full computer control and biologically based treatment planning it will not be more complex to make advanced optimized intensity-modulated treatment plans for all patients and deliver them using computer controlled intensity-modulation. In fact, it will be much simpler since most of the new methods are ideally suited for full automation using fully computer controlled equipment in the clinic. In the transition period we now are living in costs will temporarily go up, since we have to improvise until most existing treatment units and planning systems are fully developed and well integrated. This obstacle should be gradually resolved, hopefully some 5 years from now. After that time it should be much easier to get fully integrated equipment and equipment costs may also start to reduce slowly as the technology evolves.

In a 5- to 10-year perspective we will not only have well functioning and integrated treatment units and planning systems but also many rather accurate genetically based assay techniques to better predict optimal treatment strategies for the individual patient. In fact, the new biological

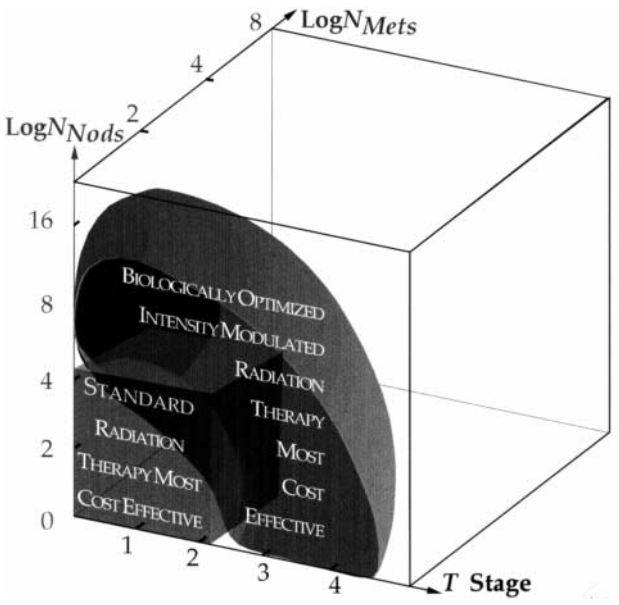

Fig. 13. Schematic illustration of how different tumor (T), nodal (N) and metastatic (M) stages (N_{nods} and N_{mets} are the numbers of positive nodes and discrete metastasis respectively), are most cost effectively treated by standard radiation therapy and by the more advanced new techniques including biological optimization of the complication free cure. Obviously cases with discrete metastatic spread may not be curative with radiation alone.

optimization methods will become a central tool for the development of improved dose response models and predictive assays. This is because the new biological models and optimization technique are the ideal tools for radiation biologists, radiation oncologists and radiation physicists, to work together for the development of our profession. Not only will they help optimizing the outcome of a given treatment, they will also indicate those organs and sites where the treatment is most likely to produce adverse reactions to simplify follow-up and improve feedback of response data to the models. In fact it is likely that all the new optimization methods that are now becoming available may even alter the way randomized clinical trials are performed. The improved knowledge about the patient and the substantially improved therapeutic modalities and methods of follow-up will make the treatment of every patient with advanced disease a radiobiological optimization challenge. The treatment outcome will then be compared with the accumulated historical experience which is contained in the predictions of the biological models, and fewer and fewer patients are likely to be randomized to sub-optimal treatment arms (56). The large historical data sets (8–13) built into the biological models will ensure a minimal contribution from patient individual variations, which can not be avoided in classical randomized trials. Furthermore, model-based techniques will not only result in optimized treatment plans for each patient, but also ensure the most efficient feedback for the development of the radiobiological models and to the fastest possible benefit of future patients. Recently a powerful Bayesian algorithm has been developed to rapidly feedback data to the radiobiological models from all patients being treated at a clinic or group of clinics (56). This algorithm ensures a much faster and continuous feedback of clinical results to the benefit of currently treated patients than waiting for 5–10 years to make a retrospective analysis. From this point of view it is important to have as large and uniform patient recruitment population as possible to further speed up data acquisition and improve the accuracy of follow-up in the interest of future patients.

It is becoming increasingly clear that we have essentially one real chance to cure a patient, namely at the time of the first treatment. Many tumors, where the initial treatment was not radical enough, seem when they reoccur locally several years after the treatment, to have progressed in severity and often metastasized. Some theories explain this to be owing to radiation induced genetic changes during the treatment (57) even though the probability for such positive events, from the tumors point of view, should be rather small. Independent of the real reason it is therefore important, not least from a cost effectiveness point of view, to be really radical at the first treatment and make use of the tolerance of the patient and his own judgement of acceptable side effects to really maximize the complication free cure and to some extent the quality of life. Such arguments will increase the use of advanced treatment techniques and may be our best way to improve the efficacy of radiation therapy. There is therefore no doubt that the new powerful tools of intensity-modulated radiotherapy will be rapidly introduced in the first decade of the new millennium, not least for cost effectiveness reasons but also to speed up the systematic feedback of radiobiological data from each patient treated to the benefit of future patients. Efficient intensity-modulated treatment units, radiobiological treatment optimization, fast statistical analysis and a continued search for molecular markers of radiation sensitivity and tumor characterization are the key to the future.

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