Radiotherapy in Scandinavia

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This issue of *Acta Oncologica* contains some of the papers submitted to the first conference on radiation oncology held in Rosendal, 24–28 May 1997. The aim was to stimulate an interest in and to improve the quality of radiation oncology within the Nordic countries, by:

- discussing current issues of clinical importance in radiobiology;
- reviewing the state-of-the-art in radiotherapy;
- focusing on the value of radiation in oncology, a field of increasing importance;
- initiating a dialogue between the Scandinavian radiotherapy community and the leading experts in other countries;
- paving the way for closer international collaboration in the field and for exchange of ideas between young scientists at different centres.

The location chosen for this first symposium, Rosendal, is indeed a special place, being Norway's only Barony; located on the coast, south-east of Bergen, in a scenic area in the middle of the fjordland, surrounded by steep mountains, waterfalls and glaciers. The symposium attracted 110 participants, mostly from the Scandinavian countries. The invited faculty included 14 speakers, from 8 different countries, all well-known scientists in their respective fields.

A broad range of topics were addressed during the symposium:

- The radiobiological rationale for dose escalation.
- The use of boost modalities.
- Methods to improve the therapeutic ratio.
- The role of targeted radio-isotope therapy.
- Comparison between high, low and pulsed dose rate brachytherapy.
- The role of radiotherapy among paediatric cancer patients.
- The status of conformal radiotherapy.
- The biological rationale and clinical significance of palliative radiotherapy.

With this conference our aim was to bring the benefits of modern radiotherapy into the limelight, primarily for an audience of oncologists but also for the medical profession in general. Moreover, we sought to convey this message to the public and to politicians.

THE ROLE OF MODERN RADIOTHERAPY IN THE MANAGEMENT OF CANCER

Next to surgery, radiotherapy is the most important modality in the treatment of cancer. The significance of radiation therapy has, to some extent, been overshadowed by the extensive focus on chemotherapy. Although chemotherapy indeed has had some impressive results, it has failed to fulfil expectations in the common forms of solid cancers. Hence, radiotherapy is likely to play a major part in the management of cancer also in the decades to come. The field of oncology, as a clinical speciality in the Nordic countries, covers both 'medical oncology' and 'radiation oncology'. There is insufficient education, training, recruitment and research in the field of clinical radiotherapy, partly due to the emphasis on chemotherapy. The research carried out in many oncology departments is predominantly through clinical trials initiated by the drug companies. Furthermore, the liberal economic support from the pharmaceutical industry for conference attendance has strengthened the interest of young clinicians in drug-based treatment rather than radiotherapy. It is also a deplorable fact that in a rich country like Norway, radiotherapy is used in only about 25% of all cancer cases, whereas according to an international consensus (1), 45–50% of cancer patients can benefit from such treatment.

The first session was dedicated to the clinical role of radiotherapy. H. Suit from Massachusetts General Hospital, Boston, reviewed the rationale for radiation dose escalation. He stressed that most technological development efforts in radiation oncology are aimed at reducing the treatment volume. The resulting increase in patient tolerance level makes the escalation of doses to the target feasible, leading to improved local tumour control. The increase in response rate with progressively higher doses is shown for all solid tumour systems in the laboratory including xenografted human tumours. Obviously, complete response curves are not available from clinical experience. The relation between overall survival and tumour response was discussed on the basis of clinical trials yielding differences in local tumour control (2).

The importance of hypoxic modification and overall treatment time in radiotherapy was reviewed by J. Overgaard, Aarhus, based on his 20-years' experience treating head and neck carcinoma within the DHANCA (Danish Head and Neck Cancer Study) group. Since 1979 several randomized trials have been performed, applying a nationwide treatment policy for these cancers. Various hypoxic radiosensitizers have been studied and the modestly toxic drug, nimorazole has proved beneficial and is now an essential part of the standard treatment strategy (3).

The significance of overall treatment time has also been investigated in these clinical trials. J. Overgaard stated that radiobiological optimization, by shortening the overall treatment time from 9.5 weeks to 5.5 weeks in addition to the use of hypoxic modification by drugs, yielded a two-fold increase in both local control, disease-free and overall survival.

The rationale design for dose-escalation trials in radiation oncology was discussed by S. M. Bentzen, Aarhus, now with the Gray Laboratory in London. He critically reviewed the many prerequisites for testing hypotheses, such as the role of dose escalation with 3D conformal radiotherapy, the need for large and optimally designed

studies to detect improvements in the range of 10–15% as well as systematic prospective follow-up to disclose late sequelae of the treatment. One specific concern is the loss of statistical power associated with the selection of severe complications as the normal-tissue endpoint resulting from the low incidence of these severe adverse events. Another concern is the long latent period for late radiation sequelae, which makes standard designs for Phase I/II dose escalation studies less suitable. In particular, S. Bentzen underlined, the number of implicit assumptions in setting up clinical trials to evaluate the clinical benefits of conformal radiotherapy: locoregional control must be correlated to the survival or quality of life; irradiated normal-tissue volumes must be reduced, thereby decreasing late toxicity; and the design of the trial must ensure statistical resolution.

J.-E. Frödin, Stockholm, reported on the use and role of radiotherapy in Sweden. A study has been conducted to investigate the current use and clinical importance of radiotherapy, compared with what is known from the literature (4). The investigation also addressed the economic aspects and future trends in radiotherapy. This study was initiated by the Swedish Council on Technology Assessment in Health Care in 1991–1996 and has been published as supplements to *Acta Oncologica* (4). Frødin illustrates the expected future trends in incidence and prevalence as well as mortality from various cancers. He emphasized that a 10% increase in overall survival could be achieved if the current knowledge from radiobiology, dosimetry and clinical radiotherapy is implemented in the daily routine practice. An important challenge is to save as many of the 18% of the total cancer patient population currently dying from and/or with lack of locoregional tumour control.

S. Kvinnsland, Oslo, presented important data relating to the long-term treatment of 1496 patients with breast cancers stages I, II and III treated between 1975 and 1986. These patients had been given hypofractionated radiotherapy either as part of the primary treatment or for locoregional recurrence. The treatment schedule was 4.3 Gy × 10 (2 fractions/wk for 5 weeks). Of the 289 patients still alive at the time of the investigation (median follow-up time 17 years), 260 had no sign of disease and 84% were reinvestigated to assess disease status and radiation side effects. The evaluation was performed by an oncologist, a physiotherapist, and by patients answering a pain inventory questionnaire. The study also included an x-ray examination with special emphasis on osteoradionecrosis of the ribs. Fractures of the ribs were found in 30% of the patients, impaired shoulder movements in 22% and oedema in 20%, higher than reported with standard fractionation. Professor Kvinnsland stressed the inherent problems in dissecting out the role of radiotherapy in a retrospective study where the patients had also undergone surgery. Furthermore, the mean follow-up time in most studies investigating late toxicity is normally 5 to 6 years, compared with 17 years in this study. Is it true that most side effects accumulate within 5 years? Could late effects of radiation increase the normal biological process of ageing? This investigation is in process of publication and a new clinical re-examination of a cohort of patients treated with 2.5 Gy × 20 is underway.

Breast cancer was also the subject of the contribution by P. Pheiffer, Aarhus, who presented an investigation on radiation-induced brachial plexopathy. This was based on a thorough neurological follow-up examination in 240 recurrence-free patients treated in accordance with the Danish breast cancer cooperative group 77 and 82 protocols. In the first case, 36.0 Gy was given in 12 fractions, twice a week, in the latter case 50 Gy was given in 25 fractions 5 times weekly. Median follow-up was 60 and 50 months, respectively. Plexopathy was found in 16% in the first treatment group compared with 9% of those treated with 2 Gy fractions. It was also demonstrated that brachial plexopathy was more common in younger patients and in those patients receiving chemotherapy.

Important results regarding the value of adjuvant radiotherapy in the management of breast cancer were released in a presentation by M. Overgaard, Aarhus. The study, comprising a detailed evaluation of the effect of locoregional radiotherapy in high-risk breast cancer patients was carried out by the Danish Breast Cancer Cooperative Group; the results have later been published (5). The conclusion was that primary locoregional tumour control is of significant importance for survival in this group of breast cancer patients. Postmastectomy radiation is required with our current surgical and systemic treatment approach. Further studies are necessary to reach the optimal balance between treatment modalities in order to reduce early and late morbidity without compromising the survival. With a median follow-up of 10 years the frequency of locoregional failure was 8% in those patients receiving radiotherapy combined with adjuvant chemotherapy compared with 33% of those receiving only the latter modality. The corresponding overall survival figures showed a 9% improvement in survival for those receiving adjuvant radiotherapy.

The need for and consequences of radiotherapy among paediatric patients is constantly being discussed. Professor J. Dunst presented data on behalf of the German Cooperative Ewing's Sarcoma Study Group. A centralized, prospective quality assurance programme has been used in this organization since 1985 for all radiotherapy patients, virtually eliminating any protocol deviation. Cure of Ewing's sarcoma requires chemotherapy as well as surgery and/or radiotherapy to achieve local tumour control. This treatment strategy is an excellent example of the need for cooperation and the synergism between treatment modalities. On the basis of their data, surgery and radiotherapy seem to be almost equally as effective in terms of long-

term survival. Although local control is better after surgery than after radiotherapy (local failure 0% vs. 14%) for patients with poor prognostic factors (such as large tumour volumes, critical site with non-radical resection), surgery combined with postoperative radiotherapy has produced very favourable results in terms of local control rate (95%), with survival at 66% after 5 years. Timing of radiotherapy seems to be important for local control. An increased risk of local failure has been observed following long periods of induction chemotherapy prior to the start of radiotherapy, and this should therefore be avoided. Additional fractional lung irradiation of 15–18 Gy after complete regression following chemotherapy increases long-term survival in patients with initial lung metastases (6).

THERAPEUTIC NUCLEAR ONCOLOGY

Reviewing the field of therapeutic nuclear oncology, K. Britton, London, stressed the fundamental radiobiological differences of internal targeted radiotherapy from that of external beam radiotherapy. J. E. Westlin, Uppsala, presented impressive results from studies where ^{32}P-macro aggregated albumin was injected intratumorally in 33 patients, most of them with inoperable pancreatic adenocarcinomas. Stable retention at tumour site was demonstrated. Gamma camera-based dosimetry revealed very high, localized radiation doses in the 1000 Gy range! Ten complete remissions lasting up to 137 weeks and 6 partial remissions were registered. In one patient an episode of severe bleeding from the pancreas occurred, and in a few cases thrombocytopenia grade II/III was demonstrated.

Many interesting presentations on different aspects of targeted internal radionuclide therapy were presented. Of particular interest were the results from clinical trials in patients with non-Hodgkin's lymphoma, applying 131-iodine anti CD-20 monoclonal antibodies, presented by O. Press, Seattle (7, 8). Impressive response rates of long duration in patients with non-Hodgkin's lymphoma who had failed conventional chemotherapy, were demonstrated. Results from phase I/II trials and from an ongoing phase II trial using bone marrow ablative doses of radioimmunoconjugate in combination with high-dose cyclophosphamide and etoposide with subsequent stem-cell transplantation were reviewed. In the latter series, only 1 of 29 patients died of progressive lymphoma, whereas 25% have remained free of progression 1–27 months after treatment.

In general, the clinical therapeutic use of radiolabelled antibodies has been disappointing among patients with solid cancers (9). P. Abrams, Seattle, presented preclinical and clinical data on a pre-targeting/multistep approach using streptavidin-conjugated antibody followed by a clearing step using biotinylated human serum albumin. The complex is eliminated by the liver. Following i.v. injection of the effector arm, 90-yttrium-biotin, the pre-targeted tumour rapidly accumulated the radiopharmaceutical, and non-bound radioactivity was quickly eliminated via the urine. A more than tenfold improvement in tumour radiation dose has been achieved with this strategy and clinical responses are observed in ongoing clinical trials.

Lastly, different applications using bone-seeking radiopharmaceuticals were presented. First, S. Srivastava, New York, presented the use of 117 mSn-DTPA for the palliation of bone pain in patients with skeletal metastases. Owing to the radiophysical properties of this radionuclide, a very low bone marrow toxicity was observed, allowing repeated injections and effective pain relief. Ø. S. Bruland and co-workers presented the first clinical use of 153-Sm-EDTMP in patients with relapsing osteosarcoma. Substantial growth delay and estimated tumour doses in the range of 20–60 Gy were achieved (10, 11).

CONFORMAL RADIOTHERAPY

The overall aim of conformal radiotherapy is to confine the high-dose volume as closely to the target volume as possible, reducing the dose to surrounding normal tissue. Restricting the high-dose region to the target volume is hardly a new idea in radiotherapy, the novel interest in conformal radiotherapy is due to advances in computed tomography and the possibilities for 3D treatment planning. Furthermore, the tools for shaping the beams using multi-leaf collimators and the possibility of modulating the beam profiles are now available. The development of conformal radiotherapy was addressed by four different contributors during the meeting: O. Dahl, K.-H. Höver, A. Nahum and B. H. Knutsen. A. Nahum, Royal Marsden, described conformal radiotherapy and its development as a journey from religion to science (12). Whereas the technology required for performing conformal radiotherapy is fairly well developed, the volume effect of normal tissue—the major underlying radiobiological rational for conformal radiotherapy—is still not fully understood. If a decrease in irradiated volume reduces the normal tissue toxicity, conformal radiotherapy should provide an opportunity for delivering higher doses to the target volume without increasing the late toxicity in patients. On the other hand, if the development of late toxicity in an organ is dependent only on dose rather than the irradiated volume, then conformal radiotherapy is not an approach that allows dose escalation in radiotherapy. It was pointed out that to bring conformal radiotherapy forward on its 'journey from religion to science', we have to understand much more about the nature of the volume effect, not only mechanistically but also quantitatively. Lyman was among the first authors to present an empirical model accounting for the volume effect on the probability of late complications in normal tissue, also known as NTCP (13). Since

then, a number of biophysical-founded models have been suggested, among these is the relative seriality model published by Brahme & Källman (14).

As pointed out by Dahl et al. (15), the term 'conformal radiotherapy' is not very well defined. A number of papers appearing under the title of conformal radiotherapy have used completely different treatment techniques. In order to compare the clinical gains of conformal radiotherapy, with respect to late toxicity and tumour control, it is important to have a common understanding of what is meant by a conformal radiotherapy technique. Dahl et al. (15) have therefore suggested a classification of conformal radiotherapy according to the methodology and tools associated with each step of the entire procedure. As the conformity of the treatment technique increases, the margin between the target volume outline and the field borders decreases. Reduced margins require an enhanced accuracy in beam set-up. As pointed out by K.-H. Höver, to get the full advantage of conformal radiotherapy, a highly sophisticated quality assurance program is mandatory (16).

The technology for implementing conformal radiotherapy in the clinical routine is in place. The underlying radiobiological rationale has been established. However, the clinical gain from using conformal radiotherapy has so far not been thoroughly evaluated. Long-term results on tumour control and late toxicity are not yet available. In prostatic cancer, dose escalation protocols have been running for some time. Conformal radiotherapy of small adenocarcinomas of the prostate is given in doses of more than 80 Gy, with an acceptable level of acute side effects. Whether the long-term tumour effect is enhanced remains to be seen. One of the main concerns about dose escalation in radiotherapy of the prostate is the late toxicity in the rectum. Dale et al. report on the correlation between late toxicity of the rectum, assessed by questionnaires and calculated NTCP values after conformal radiotherapy of prostatic cancer (17). Unlike most studies in the literature, this study addresses less severe late sequelae. Apparently, there is a lack of correlation between calculated NTCPs and the actual late effects. However, when the rectum was regarded as a serially organized organ rather than constituted by a parallel functional architecture, a statistically significant correlation between observed late toxicity and calculated NTCPs was found. This indicates that the functional architecture of the rectum may depend on the endpoint assessed. The study also revealed that the clinical gain of conformal radiotherapy may not be large when less critical endpoints of late toxicity are addressed (17).

DOSIMETRY

High precision dosimetry is a prerequisite for quality assurance in radiotherapy when comparing clinical data between institutions. Modern radiation detectors provide accurate dosimetric information, but from one single point at a time only. As the focus in radiation oncology moves towards the 3D dose planning in patients, new features such as visualizing spatial dose distribution, are required. A new approach was introduced by Gore et al. in 1984 (18), where they utilize the well-known Frick and Hart principle of converting ferric into ferrous ions by radiation. The unequal paramagnetic properties of ferrous and ferric ions will also alter the T_1 relaxation time of the nuclear spin of hydrogen, linearly with absorbed radiation dose. By trapping the ions in the biopolymer lattice, spatial distribution of ferric and ferrous ions is achieved. Information about the 3D dose distribution can then be recorded by conventional MR imaging. Applications and limitations of the novel dosimetry concept were discussed by A. Skreeting and B. H. Knutsen, as well as in the current paper by Bäck et al. in this issue of *Acta Oncologica*. Attractive features of gel dosimetry is the independence of dose rate and radiation quality. This is important in brachytherapy, as the energy as well as dose rate changes significantly with increasing distance from the source. Being an integrating detector, gel dosimetry is applicable in measurements of radiation dose distributions from non-static fields. This is crucial in brachytherapy where stepping sources are applied or in intensity modulated beams where the multi-leaf collimator positions are constantly changing during irradiation. One of the inherent problems with gel dosimetry is the rather low sensitivity of the detector. Normally, doses between 5 and 60 Gy are required to achieve a good signal to noise ratio of the MR image and thereby an adequate low uncertainty in dose. The sensitivity of the gel dosimetry system does not merely depend on the gel and the concentration of the components, but also on the characteristics of the MR scanner and the pulse sequence applied. Accurate information about the 3D dose distribution requires maximum spatial resolution. Spatial resolution is determined by the pixel size and the slice thickness of the MR scan. Hence, by increasing the spatial resolution, the sensitivity decreases. The inherent, low sensitivity of gel dosimetry is especially problematic when high spatial resolution dose distributions of low dose-rate sources are measured. One way of compensating for low sensitivity is to prolong the irradiation time. Unfortunately, this may ruin spatial resolution, as the diffusion of ferric and ferrous ions will obscure the initial dose distribution. Skretting et al., Oslo, reported on how the diffusion coefficient can be determined by image processing of MRIs of the evolution of a radiation-induced edge in a gel phantom. They have also shown that the diffusion coefficient can be lowered by almost a factor of 2 by adding xylenol orange to the gel solution (19).

An important application of gel dosimetry is the verification of dose calculations performed by treatment planning systems, for both external beam radiation and brachytherapy applications. Knutsen et al., Oslo, have compared the 3D dose distribution from an intracavitary

brachytherapy applicator with calculated dose distributions. Measurements using thermoluminescence dosimetry (TLD) were also performed. They found that the accuracy of the gel dosimeter was of the same order as the TLD measurements, and that dose distributions obtained by MR images of gel phantoms were in good agreement with computed distributions (20). In this issue, Beck et al., Malmö, report on the comparison between the dose distribution measured by ferrous sulphate gel dosimetry and calculated doses using a treatment planning system for a single, external beam. They found a difference between measured and calculated doses of less than 2% for photons. For electrons, calculated and measured doses also agreed well, while the treatment planning system underestimated the lateral scattering dose outside the primary beam. These authors all conclude that gel dosimetry is a suitable tool for verification of dose calculations in both brachytherapy and external beam radiotherapy.

HYPOXIA

For many years radiobiological research has recognized the main factors controlling tumour and normal tissue radiosensitivity, such as the intrinsic radiosensitivity, repair of DNA damage, hypoxia, and proliferation. The recent development in modern molecular biology has significantly contributed to the understanding of the nature of each of these mechanisms. Hypoxia is known to be present in a number of solid human cancers. A recent meta-analysis of a number of clinical trials conducted by J. Overgaard, addressing the modification of tumour hypoxia, provides indirect evidence for tumour hypoxia being a limiting factor for locoregional control following radiotherapy (21). Pretreatment hypoxia may therefore be a prognostic factor.

Because the range of oxygen diffusion in tissue is limited, inadequate vascular architecture of tumours may give rise to hypoxic regions at distances beyond the oxygen diffusion range. This is often referred to as chronic hypoxia. In contrast, acute hypoxia occurs when small tumour vessels transiently close. Cells may then be subjected to hypoxia for several minutes until blood flow is resumed. As pointed out by J. Denekamp, Umeå, chronically hypoxic cells bordering necrotic regions are so starved that they become energy depleted, and are therefore unable to adapt to radiation stress by induction of new proteins for DNA synthesis. These cells may have significantly reduced repair capacity, and their radiosensitivity may thus be enhanced by a factor of 20. These cells will constitute an extremely thin layer close to the border of the necrotic regions. The Eppendorf micro-electrode, commonly used in measuring pO_2 in tumours, does not have the spatial resolution required to detect these cells. Since the radiosensitivity of chronic and acute hypoxic cells differs significantly, as suggested by J. Denekamp, measurements of hypoxic fractions using micro-electrode probes may be inadequate for prediction of the radiosensitivity of tumours.

The classical oxygen effect is a modification of the cellular radiosensitivity. However, hypoxia may also alter gene expression and cause malignant progression, causing more aggressive locoregional and distant metastases, as pointed out by R. Sutherland, Palo Alto. Hypoxia may cause disruption of signalling within cells associated with the molecular pathways regulating activation of genes, such as oncogenes and tumour suppressor genes. In this issue, R. Sutherland reviews the complicated signal transduction pathways relevant for hypoxia. The tumour suppressor gene P53, known to be essential in the regulation of apoptosis, increases its expression in response to hypoxia. Thus, hypoxia could not only modify the cellular radiosensitivity of tumour cells, but also induce apoptosis in tumours.

APOPTOSIS

Hypoxia and ionizing radiation are only two of many potential triggers of apoptosis. The ongoing research provides increasing knowledge about the different stress factors causing apoptosis and the basic mechanisms involved. R. Verheij et al., Amsterdam, demonstrated how apoptotic cell death is triggered by membrane-derived signals, independent of the DNA damage, and stressed the importance of the sphingomyelin pathway in radiation-induced apoptosis. This membrane-associated pathway generates a second messenger, Ceramide-induced radiation stress, subsequently leading to apoptosis (22). In this issue, R. Verheij underlines that the identification of the signal transduction pathways also enables the modulation of the apoptotic response, and may thus be of clinical relevance in future radiation therapy strategies.

A number of clinical studies have also been carried out in order to correlate the pretreatment apoptotic fraction with treatment outcome. Experimental data have indicated that there is a correlation between the pretreatment apoptotic fraction and the sensitivity for radiation-induced apoptosis. The clinical data, however, show conflicting results. Whereas some data indicate that a high baseline apoptotic fraction correlates with a favourable prognosis, a number of papers indicate the opposite trend. It is essential to realize that apoptosis may be triggered by multiple factors. In tumours possessing no or low fractions of pretreatment hypoxic cells, no hypoxic-induced apoptosis is though to be present. In contrast, tumours with substantial hypoxia may also have a larger fraction of pretreatment apoptotic cells due to the hypoxic stress. In these tumours pretreatment apoptosis may not predict the outcome of radiotherapy, since the presence of hypoxia inevitably will reduce the radiocurability of tumours.

MATHEMATICAL MODELLING IN RADIOBIOLOGY

With modelling, we have the intriguing task of providing quantitative estimates of the biological effects of radiation. This topic was challenged by J. Fowler, Leuven. Probably the first attempt at mathematical modelling in radiation biology was fitting a straight line to the data of Strandquist, investigating the effect of time and number of fractions. Later, time and fraction number was separated into two different parameters in the NSD concept. Today the linear quadratic model is generally used for calculating the effect of fractionated radiotherapy. The effect of time has been separated into the repair component, often described by the incomplete repair model or the promising hyperbolic repair model recently developed by J. Fowler, and a repopulation term including both the onset of tumour cell repopulation and the proliferation rate. The linear quadratic model has gained more recognition in recent years and is now dominating calculations performed for predicting tumour control in new fractionated radiotherapy schedules. As shown by A. Brahme, an early version of the LQ-model was actually proposed by Rolf Wideröe as early as the mid-60s but the interpretation of the parameters of the model was somewhat different from the current interpretation. The LQ-model has many shortcomings, as stressed by J. Fowler: there are limitations in the prediction of late complications when these are related to unhealed acute reactions. Furthermore, if the interfraction interval is less than 6 h, an additional term taking into account non-repaired damage is required in order to make an adequate prediction of late effects. Lastly, the volume effects of normal tissue are not included in the model. The use of mathematical models in clinical radiobiology has been criticized for being over-simplistic and because the limitations of the models tend to be ignored. It is therefore worth stressing that models can never be used to draw general conclusions, irrespective of the assumptions made. The use of the LQ formalism in predicting clinical effects of fractionated radiotherapy has definitely been successful. The hyperfractionated EORTC trials and the accelerated hyperfractionation trials such as the CHART trial are examples of the successful use of this formalism. Furthermore, the LQ formalism combined with the incomplete repair model has been successfully used in calculating altered dose rates and fractionation schedules in brachytherapy. The cautious use of mathematical models in radiobiology should therefore stimulate a discussion about the possible implications of new treatment strategies.

RADIOTHERAPY AS A TREATMENT MODALITY: THE PAST AND THE FUTURE

In his introductory lecture, H. Suit underlined that modern radiotherapy has gained much from the technological development: primarily related to improvements in accelerator technology, but also in computer technology and medical imaging principles. One of the pioneers in the field of accelerator technology who helped to make modern radiotherapy feasible was the Norwegian scientist Rolf Wideröe. His achievements in this field are milestones in the development of high-energy radiation treatment. He was the inventor of the betatron and developed the principles on which modern linear accelerators are based. In addition, he was actively involved in radiobiological modelling. In this issue of *Acta Oncologica* T. Brustad, Oslo, and B. Wiik, Hamburg, pay their tribute to an outstanding scientist.

One of our contemporary scientists, following the lead of Rolf Wideröe in his interest for technological developments as well as the implementation of current radiobiological knowledge in the application of radiation to cancer, is A. Brahme, Stockholm. For his achievements, he was presented with the Rolf Wideröe Award by the Norwegian Minister of Health, G. Hernes during the symposium in Rosendal. A. Brahme's award lecture is published in this issue of *Acta Oncologica*.

In conclusion, it may be relevant to quote from Ø. S. Bruland's keynote address at the opening of the symposium:

> It may seem as a paradox that we are currently facing a revitalization of radiotherapy, an old and established treatment modality. This is due to several circumstances. Improved diagnostic imaging makes it easier to delineate the extension of the malignant tumour. We are experiencing a significant increase in the incidence and prevalence of cancer forms where radiotherapy plays a major part as both a curative and a palliative treatment modality. Increased focus and new methods for early diagnosis, including screening programmes, make it possible to detect disease earlier, leading to a stage migration, making optimal treatment of truly local and locoregional disease important. All these factors increase the need for radiotherapy.
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> Today we know more about the nature of cancer than ever before, but there is still a distance to go before this translates into improved cure rates. We who work in clinical medicine today are overwhelmed by bio-technological advances. Radiation oncology is indeed a treatment modality based on and made possible by advances in physics and driven by computer-based technology. However, technology is a tool, not an end in itself. The Danish poet and mathematician Piet Hein reminds us: 'When technology becomes master, we will reach disaster faster'. The art of clinical medicine is still an important element and probably will remain so in the future.

We believe that this symposium has served as a strong stimulus to the young oncologists and scientists present, that many scientific contacts have been made, and that opportunities for useful research collaboration will emerge.

REFERENCES

1. Radiotherapy in Cancer Management. A practical manual. World Health Organization, WHO Working Group on Radiation Therapy in Cancer. London: Chapman & Hall Medical, 1997.
2. Suit H. Assessment of the impact of local control on clinical outcome. Front Radiat Ther Oncol 1996; 29: 17–23.
3. Overgaard J, Hansen HS, Overgaard M, et al. A randomized double-blind phase III study of nimorazole as a hypoxic radiosensitizer of primary radiotherapy in supraglottic larynx and pharynx carcinoma. Results of the Danish Head and Neck Cancer Study (DHANCA) Protocol 5–85. Radiother Oncol 1998; 46: 135–46.
4. Einhorn J, et al., editors. Radiotherapy for cancer. The Swedish Council on Technology Assessments in Health Care. Acta Oncol 1996; (Suppls 6 and 7).
5. Overgaard M, Hansen PS, Overgaard J, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. N Engl J Med 1997; 337: 949–55.
6. Dunst J, Jurgens H, Sauer R, et al. Radiotherapy in Ewing's sarcoma: an update of the CESS 86 trial. Int J Radiat Oncol Biol Phys 1995; 32: 919–30.
7. Press OW, Appelbaum FR, Eary JF, Bernstein ID. Radiolabelled antibody therapy of lymphomas. Important Advances in Oncology 1995; 157–71.
8. Press OW, Earl JF, Appelbaum FR, et al. Phase II trial of 131-I-B1 (anti CD-20) antibody therapy with autologous stem cell transplantation for relapsed B cell lymphomas. Lancet 1995; 346: 336–40.
9. Bruland OS. Cancer therapy with radiolabeled antibodies. An overview. Acta Oncol 1995; 34: 1085–94.
10. Bruland OS, Skretting A, Solheim OP, Aas M. Targeted radiotherapy of osteosarcomas using ^{153}Sm-EDTMP. Acta Oncol 1996; 35: 381–4.
11. Bruland OS, Skretting A, Sæter G, Solheim OP, Aas M. Targeted internal radiotherapy in osteosarcoma patients using ^{153}Sm-EDTMP. Med Ped Oncol 1996; 27: 215.
12. Huddart RA, Nahum A, Neal A, et al. Accuracy of pelvic radiotherapy: prospective analysis of 90 patients in a randomised trial of block versus standard radiotherapy. Radiother Oncol 1996; 39: 19–29.
13. Lyman JT. Complication probabilities as assessed from dose-volume histograms. Radiat Res 1985; 104: 13–9.
14. Källman P, Ågren A, Brahme A. Tumor and normal tissue responses to fractionated non-uniform dose delivery. Int J Radiat Oncol Biol Phys 1992; 62: 249–62.
15. Dahl O, Kardamakis D, Lind B, Rosenwald JC. Current status of conformal radiotherapy. Acta Oncol 1996; 35: 41–57.
16. Gademann G, Schlegel W, Debus J, et al. Fractionated stereotactically guided radiotherapy of head and neck tumors: a report on clinical use of a system in 195 cases. Radiother Oncol 1993; 29: 205–13.
17. Dale E, Olsen DR. Normal tissue complication probabilities correlated with late effects in the rectum after prostate conformal radiotherapy. Int J Radiat Oncol Biol Phys 1998 (in press).
18. Gore JC, Kang YS, Schultz RJ. Measurement of radiation dose distributions by nuclear magnetic resonance (NMR) imaging. Phys Med Biol 1984; 29: 1189–97.
19. Pedersen TV, Olsen DR, Skretting A. Measurement of the ferric diffusion coefficient in agarose and gelatine gels by utilization of the evolution of a radiation induced edge as reflected in relaxation rate images. Phys Med Biol 1997; 42: 1575–858.
20. Knutsen BH, Skretting A, Hellebust TP, Olsen DR. Determination of 3D dose distribution from intracavitary brachytherapy of cervical cancer by MRI of irradiated ferrous sulphate gel. Radiother Oncol 1997; 43: 219–27.
21. Overgaard J. Sensitization of hypoxic tumour cells—clinical experience. Int J Radiat Oncol Biol Phys 1989; 56: 801–11.
22. Verheij M, Bose R, Lin XH, et al. Requirement for ceramide-initiated SAPK/JNK signalling in stress-induced apoptosis. Nature 1996; 380: 75–9.