Three-Dimensional Radiation Treatment
Frontiers of Radiation Therapy and Oncology

Vol. 34

Series Editors  

W. Hinkelbein, Berlin
Frontiers of Radiation Therapy and Oncology


Prof. Dr. H.J. Feldmann, Fulda
Klinik für Radioonkologie-Strahlentherapie, Klinikum Fulda, Fulda

Prof. Dr. P. Kneschaurek, Munich
Prof. Dr. M. Molls, Munich
Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie der Technischen Universität München, Klinikum rechts der Isar, München

Library of Congress Cataloging-in-Publication Data

Bibliographic Indices. This publication is listed in bibliographic services, including Current Contents® and Index Medicus.

Drug Dosage. The authors and the publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently employed drug.

All rights reserved. No part of this publication may be translated into other languages, reproduced or utilized in any form or by any means electronic or mechanical, including photocopying, recording, microcopying, or by any information storage and retrieval system, without permission in writing from the publisher.

© Copyright 2000 by S. Karger AG, P.O. Box, CH-4009 Basel (Switzerland)
www.karger.com
Printed in Switzerland on acid-free paper by Reinhardt Druck, Basel
ISSN 0071-9676
ISBN 3-8055-6947-5
Contents

IX Preface
   Feldmann, H.J. (Fulda); Kneschaurek, P.; Molls, M. (Munich)

Essentials of Conformal Radiotherapy

1 Significance of Local Tumor Control
   Gérard, J.P.; Roy, P. (Pierre-Bénite); Cucherat, M.; Leizerowicz, A. (Lyon)

8 Mechanisms in the Development of Normal Tissue Damage – Fiction and Facts
   Trott, K.R. (London)

17 Epidermal Growth Factor and Its Receptor in Tumor Response to Radiation
   Milas, L. (Houston, Tex.)

26 New Technologies in Conformal Radiation Therapy
   Schlegel, W. (Heidelberg)

Principles of Conformal Radiotherapy

40 Intensity-Modulated Stereotactic Radiosurgery
   Mohan, R.; Cardinale, R.M.; Wu, Q.; Benedict, S. (Richmond, Va.)

49 Three-Dimensional Endovascular Brachytherapy
   Quast, U.; Flühs, D.; Bambynak, M.; Baumgart, D.; von Birgelen, C. (Essen)

59 New Tools of Brachytherapy Based on Three-Dimensional Imaging
   Baltas, D.; Milickovic, N.; Giannouli, S. (Offenbach, Athens); Lahanas, M.; Kolotias, C. (Offenbach); Zamboglou, N. (Offenbach, Athens)
Three-Dimensional Lung – State of the Art and Future Perspectives

71 Lung Cancer – Radiotherapy in Combined-Modality Schedules
Stuschke, M. (Berlin); Pöttgen, C. (Essen)

80 Modified Fractionation in the Radical Treatment of Non-Small-Cell Lung Cancer
Baumann, M.; Appold, S.; Zips, D. (Dresden); Nestle, U. (Homburg/Saar);
Petersen, C.; Herrmann, T. (Dresden)

89 Target Volume Definition and Locoregional Failure in Non-Small-Cell Lung Cancer
Rübe, C.; Nestle, U. (Homburg/Saar)

Three-Dimensional Brain – State of the Art and Future Perspectives

97 PET and SPECT in Three-Dimensional Treatment Planning of Brain Gliomas

106 Radiation Dose Escalation for the Treatment of Gliomas: Recent Experience
Fitzek, M.M. (Berlin)

116 Three-Dimensional Brachytherapy in Malignant Gliomas
Baltas, D.; Zamboglou, N. (Offenbach)

123 Fractionated Radiotherapy of Inoperable Meningiomas without Histological Verification: Long-Term Results in 59 Patients
Engenhart-Cabillic, R.; Wannenmacher, M. (Heidelberg)

130 Modern Management of Brain Metastases: Prognostic Factors in Radiosurgery

Conformal Radiation Therapy of Prostate Cancer – Techniques, Outcomes, Pitfalls

145 Adjuvant Radiotherapy following Radical Prostatectomy
Wiegel, T. (Berlin)

152 Morbidity following Radiation Therapy
Three-Dimensional versus Two-Dimensional Radiation Therapy, Treatment Planning and Treatment Delivery to the Prostate, Seminal Vesicles, and Pelvic Lymph Nodes
Lahaniatis, J.E.; Brady, L.W.; Brutus, R.A. (Philadelphia, Pa.)

158 Dose Escalation with External-Beam Radiotherapy for Prostate Cancer
Sandler, H.W. (Ann Arbor, Mich.)
165 Prostate Cancer – Combination of Hormonal Ablation and Conformal Therapy
Feldmann, H.J. (Fulda); Stoll, P.; Geinitz, H.; Zimmermann, F.B. (Munich)

177 Value of Dose-Volume Histograms in Estimating Rectal Bleeding after Conformal Radiotherapy for Prostate Cancer
Geinitz, H.; Zimmermann, F.B.; Stoll, P. (Munich); Narkwong, L. (Munich/Bangkok); Kneschaurek, P.; Busch, R.; Kuzmany, A.; Molls, M. (Munich)

186 Author Index

187 Subject Index
Major advances have been accomplished in recent years in conformal and stereotactic techniques, dosimetry as well as in target volume concepts, and clinical studies have been performed. This peer-reviewed volume of *Frontiers of Radiation Therapy and Oncology* includes a selection of the important topics discussed at the meeting on '3-D Radiation Treatment: Technological Innovations and Clinical Results' which was organized by the Department of Radiation-Oncology of the Technical University of Munich and focused on conformal and stereotactic radiotherapy in the treatment of tumors.

The papers published in this volume emphasize the significance of local tumor control, mechanisms of normal tissue damage, report new technologies in conformal radiation therapy, dynamic intensity modulation and three-dimensional endovascular brachytherapy. They also describe new tools of three-dimensional brachytherapy and analyze clinical results in the treatment of lung cancer, brain tumors and prostate cancer.

This book aims at making this new information available to biologists, physicists, radiation oncologists and clinicians. It updates currently available information, provides a comprehensive overview of the field and suggests future directions.

*H.J. Feldmann, Fulda*

*P. Kneschaurek, M. Molls, Munich*
Significance of Local Tumor Control

J.P. Gérard a, P. Roy b, M. Cucherat c, A. Leizerowicz c

a Service de Radiothérapie-Oncologie, and
b Service de Biostatistique, Centre Hospitalier Lyon-Sud, Pierre-Bénite, and
c Service de Pharmacologie Clinique, UFR Laennec, Lyon, France

The Natural History of Cancer Is Still Based on a Cellular Concept

Modern biology techniques have brought new understandings into the field of gene functioning and subcellular pathways. Cancer is now considered as a multifactorial and multistep process leading to alteration of oncogenes and antioncogenes resulting in a malignant genotype. Conversely, in clinical practice, cancer is still seen as a cellular process, usually of monoclonal origin. Starting from one or a few malignant cells, the cellular clone progressively grows into a primary gross tumor. One of the key points of cancer disease is the ability of cancer cells to migrate and generate distant metastases which are often fatal: the UICC TNM classification clearly reflects this double aspect of cancer with a primary tumor ‘T’ and lymphatic or organ metastases ‘N’ or ‘M’. Local control of cancer consists primarily in the eradication of all cancer cells in the primary tumor ‘T’ (and neighboring lymph nodes).

From the first cancer cells, which are usually undetectable, the natural history of cancer can be divided into two steps. The subclinical phase, when there are less than $10^9$ cells, is clinically silent. The second phase starts when clinical symptoms or a gross tumor are apparent. It is usually shorter than the subclinical phase. If not treated, the cancer will lead to death in a few months or years when the tumor mass is close to $10^{12}$ cells [1, 2].

The Cure of Cancer Is a Reality: It Makes Sense to Give Treatment with a Curative Intent

When, after radical treatment and complete disappearance of all cancerous lesions, a patient remains free of disease for 20 or 30 years, the clinician
has the ‘feeling’ that cure has been reached. In fact, as residual subclinical disease is difficult to demonstrate, the definitive proof of cancer cure is often difficult to provide. From the epidemiological point of view a patient or a group of patients are cured when their posttreatment survival probability is the same as the survival of a population of same age and characteristics without cancer. This definition leads to the concept of relative survival [3]. Eurocare is a compilation of the data of all the cancer registries in the world. It provides relative survival at 10 years, which ranges between 30 and 40% in Europe. These figures are close to the cure rate at the end of the 20th century for all cancers when small basal cell cancers of the skin are excluded. Though the improvement in cure rate is slow [4], it can be seen from the US cancer registries that the overall survival of cancer patients has recently been increasing [5].

The cure of cancer is difficult to demonstrate in an individual person; to cure cancer, all the cancer cells of a malignant tumor must be eradicated including the last one. A complete response and, of course, a partial response are not synonymous of cure. It is necessary to totally control (or eradicate or sterilize) the subclinical disease. The detection of minimal residual disease in children with acute lymphoblastic leukemia (ALL) is a good demonstration of the need for total eradication of all cancer cells to achieve cure. After complete remission following radical treatment of ALL, it is possible to detect 1 leukemic cell among 10,000 normal cells in a bone marrow aspirate using multiparametric flow cytometry. If no cell can be seen in the bone marrow aspirate at week 32 after the end of chemotherapy, there is only 7% of relapse (93% of cure). If 1 or 1,000 leukemic cells are found, the relapse rate is 75% [6].

A treatment can have a curative aim if, considering the patient’s condition, tumor size and location as well as the available treatment, it is possible to eradicate 100% of the malignant cells. If this goal cannot be achieved, only a palliative treatment can be proposed [7].

**Local Tumor or Distant Metastases Can Be Responsible for Death**

If the primary tumor grows in an organ with a vital function, it can be directly responsible for death (glioblastoma, hepatocarcinoma). If the primary develops in the patient’s periphery (skin melanoma, breast cancer, sarcoma of the extremities), it will not kill the patient unless distant metastases to vital organs (brain, liver, lung) appear. In many situations, the risk of dying of cancer is related either to uncontrolled primary or distant metastases (cancer of the head and neck, thorax, abdomen or pelvis).
The Cure of Cancer Is Impossible without Definitive Local Control

Local control of a tumor can be defined as the total disappearance of the primary tumor and neighboring lymph node metastases without any local recurrence on long-term follow-up. From a methodological point of view, local control is not always easy to measure objectively. Quantification is not simple. Actuarial methods are not well adapted to estimate local control. Local failure and distant metastases fall into the category of competing risks.

Actuarial methods can be used only if the endpoints are statistically independent [8]. Crude rate of local failure or time to first local failure could be more appropriate. Clear and simple recommendations to analyze and report local control should be given by biostatisticians.

It is commonsense to admit that cure cannot be achieved without local control of tumor in the brain, head and neck, lung or pelvis, for example. It is still a matter of debate how local control (or local relapse) affects overall survival in peripheral tumors, such as melanoma or sarcoma of the extremities. Breast cancer is a paradigm of this controversy [9]. Two recent randomized trials after mastectomy and adjuvant chemotherapy show that radiotherapy by improving local control can improve overall survival [10, 11]. These results are still a source of controversy because in some countries surgery and adjuvant chemotherapy are more intensive. In a retrospective analysis of 4,144 patients treated with radical surgery without chemotherapy for breast cancer at the Gustave Roussy Institute, the authors concluded that local relapse is a nidus for metastatic dissemination which might not have appeared without such a local relapse [12]. As usual, the demonstration of a causal relationship is difficult without a prospective randomized trial [13]. Experiments in C3H/sed mice presenting with spontaneous fibrosarcoma or squamous cell carcinoma have shown that the frequency of distant metastasis increased steeply with local relapse and increasing size of the recurrent tumor at the time of salvage amputation. For a primary of 6 mm in diameter, the rate of distant metastasis was 5%, for local recurrences of 6 mm and 12 mm it was 30% and 60%, respectively [11].

Radiotherapy Aims at Local Control, Which Significantly Depends on the Dose of Irradiation

The main goal of radiotherapy is to control the primary tumor either alone (head and neck, prostate, anus) or in association with surgery (breast, rectum, uterus) or chemotherapy (Hodgkin's disease). The dose delivered to the tumor (and the pathological type of the tumor) is the key point for local

Significance of Local Tumor Control
control. The history of one century of radiotherapy can be schematically summarized as a continuous escalation of dose to the tumor enabled by improved radiation devices.

With 200 kV, it was possible to deliver 40 Gy to a deep-seated tumor in 1930; in 1960, with the use of cobalt, the dose could be increased to 60 Gy and, in 1980, with the linear accelerator that provided an x-ray beam of 10 or more megavolts, doses of 70 Gy were achieved. With conformal therapy, it seems possible to deliver 75 or 80 Gy with acceptable toxicity. In all situations, this dose escalation has provided better local control and has improved survival, though to a lesser extent.

**Normal Tissue Tolerance Is the Limiting Factor of Dose Escalation**

The aim of any radiation technique is to keep severe late radiation toxicity to 3–5% at the most. It would be inappropriate to increase the dose in such a way that severe side effects exceeded those limits. This is particularly true when other curative treatments, such as surgery, may be applied [14].

**Subclinical Disease Can Be Controlled with Doses between 45 and 60 Gy**

It has been well demonstrated by MacComb and Fletcher [15] that doses of 45–60 Gy were able to control subclinical disease either alone or following surgery. This has been the foundation of the association of surgery and radiotherapy. Surgery removes gross disease, and irradiation sterilizes residual subclinical disease. At present, most solid tumors are treated with such a strategy, often associated to some medical adjuvant treatment. It is probable that neoadjuvant radiotherapy is superior to adjuvant use if it does not disturb the surgical technique. Treatment of rectal cancer is a typical example of this conception [16].

**Immediate Primary Local Control Appears to Be Important**

The importance of the timing of irradiation has been illustrated by a trial conducted by the National Cancer Institute of Canada in small-cell lung cancer. Thoracic irradiation was given either along with the first cycle of chemotherapy or 4 months later, after completion of chemotherapy. Overall survival was significantly better in the group with early irradiation. It was
concluded that early irradiation was able to eradicate chemotherapy-resistant cells before they spread outside the mediastinum. In this trial, brain metastases were significantly reduced in the early irradiation group (18 vs. 28%; p = 0.04) [17].

Local Recurrence in Organ-Saving Treatments: Some Limits Should Not Be Exceeded

One of the main improvements in cancer treatment during the past 20 years has been the increasing development of organ-saving treatments as in cancer of the eyes, larynx, bladder, limbs, breast and rectum. Radiotherapy plays a major role in this conservative approach. Nevertheless, it seems necessary to keep the rate of local relapse inferior to 10–15% in such treatments. Local relapse is always a severe psychological trauma, and though local control is often possible with salvage surgery, it is likely that such a local recurrence may increase the risk of distant metastases and death. The patient must be aware of such a dilemma and the choice is often difficult in medium-sized tumor between a conservative approach with a high risk of local failure and a radical amputation which can be safer from the point of view of survival [18].

Conformal Radiotherapy is the Best Option to Improve Local Control and Cure through New Advances in Radiation Treatment

Telecobalt and radium were the basis of radiotherapy in the 1960s but have nearly disappeared. Radiotherapy is a field of cancer treatment where the improvements in procedures and techniques have been really dramatic during the past 30 years. Improving the differential effect using the time factor or chemical sensitizers is an exciting way of research. Quality assurance aiming at a daily reproducible ideal treatment should certainly improve our results. Technological improvement for a better dose distribution is a very promising area for future research. It has been clearly demonstrated during the past 50 years that increasing the dose without increasing the toxicity leads to better local control and survival. The computer revolution with three-dimensional virtual simulation and accurate conformal radiotherapy is already in clinical practice. There are examples in the USA that in lung carcinoma and prostate cancer doses of 75–80 Gy can be given safely. Preliminary results show improved local control and disease-free survival. In France, a recent dose escalation program was conducted in prostate cancer by Bey [19] using conformal
Radiotherapy. The probability of achieving a posttreatment PSA nadir ≤ 1.0 ng/ml was increased by 20% (p = 0.04) in a group of 109 patients when comparing doses of 66–70 Gy to doses of 74–80 Gy. In the coming years, this technique will be used routinely in most radiotherapy departments and should give a clear benefit at public health level in the field of cancer cure.

Radiotherapy: Still a Major Treatment for the Cure of Cancer in the Coming Years

At the beginning of the 20th century after the first Halsted, Wertheim or Bilroth operations, the 3-year overall survival of operable patients was less than 5%. Nearly no patient with cancer was cured.

A century later, close to 40% of those patients can be cured in industrialized countries. Nevertheless, cancer is still the leading cause of death of 40- to 65-year-old individuals. In France, 210,000 new cases of cancer are seen every year (small skin cancers excluded). It can be estimated that only 60,000 will be cured. One third of those who will die of cancer will have a component of local failure. Insufficient local control remains a major cause of cancer death. If modern radiotherapy generally used conformal three-dimensional treatment, up to 10% of the 50,000 deaths due to insufficient local control might be avoided. The goal of radiotherapy research is to further improve local control. This is the challenge of the early 21st century.

In France, it is estimated that the cost of cancer is close to 7 billion euros. The cost of radiotherapy all included is only 350 millions euros (5%). The cost effectiveness of radiotherapy is among the best in cancer treatment. Of 100 patients cured, 30–40% were treated with irradiation. The best quality of life is reached by patients who undergo conservative treatment in which radiotherapy plays a major role.

References


Prof. J.P. Gérard, Service de Radiothérapie-Oncologie, Centre Hospitalier Lyon-Sud, Chemin du Grand-Revoyet, F-69495 Pierre-Bénite (France)
Tel. +33 4 78 86 11 57, Fax +33 4 78 86 33 30, E-Mail Gerard@radiotherapy.univ-lyon1.fr

Significance of Local Tumor Control
Mechanisms in the Development of Normal Tissue Damage – Fiction and Facts

Klaus Rüdiger Trott

St. Bartholomew’s and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, University of London, London, UK

It is a common radiotherapeutic perception that the severity of acute and chronic side effects increases as the volume of normal tissue irradiated is increased. However, problems arise when this general statement has to be quantified so that it might be used in the optimisation process during treatment planning which is the topic of this conference.

Although the severity of normal tissue injury may depend on volume, dose and time, information on the spectrum of lesions and their severity is rarely published. Rather, data are usually quantified and expressed as a frequency of patients who exceed an arbitrary threshold of an acceptable severity of injury (e.g. EORTC grade 2). This process involves a considerable loss of information, but yields well-defined sigmoid dose-response curves that can be readily analysed using established mathematical procedures. The clinical perception that reactions were generally milder if irradiated volumes were smaller was further complicated by stating that tolerance increases as the volume of normal tissue irradiated is decreased. The assertion that tolerance increases as irradiated normal tissue volume decreases was finally translated into equations that quantify how tolerated radiation dose increases as irradiated normal volume decreases. Obviously, there is a chaotic mix-up of words and concepts which only superficially describe the same facts.
The Role of Stem Cell Inactivation in the Pathogenesis of Normal Tissue Damage

In order to quantify the clinically observed dependence of damage severity on the irradiated proportion of an organ, in order to extrapolate them to new clinical situations and develop new treatment options in radiotherapy, a framework of hypothetical mechanisms of action of radiotherapy on normal tissues has to be chosen. In the commonly used algorithms, this framework of hypothetical mechanisms is based on radiobiological data of clonogenic survival of cells with unlimited proliferative potential, i.e. stem cells. The inactivation of clonogenic cells by radiation has been shown to occur at random [1]. This hypothetical mechanism has very successfully been used to explain the action of radiotherapy on tumours [2]. The number of tumour stem cells is exponentially reduced by a course of fractionated radiotherapy until, following Poisson statistics, the probability that no tumour stem cell survived the irradiation – i.e. local tumour control – increases with further increasing radiation dose following a sigmoid dose-response curve. Tumour cure or tumour recurrence, treatment success or treatment failure are a matter of probabilities of none or one cell surviving a randomly damaging event.

The extraordinary success of this concept in describing tumour responses to radiotherapy has prompted radiobiologists to use the same concept for explaining the mechanisms of radiation damage, acute and chronic, in irradiated normal tissues and organs. Radiobiological methods were developed to investigate the response of normal tissue stem cells to irradiation, studying the dose dependence of their clonogenic survival. Typical examples are the stem cells of the bone marrow [3], of the gut [4] or of the skin [5]. Normal tissue damage is assumed to occur if the density of surviving stem cells decreases below a critical threshold. This threshold would be 1% for the bone marrow, 0.1% for the gut and 0.01% for the skin.

Whereas for tumour responses, the relationship between clonogenic survival of stem cells is very close, this relationship is less clear for the clinical signs and symptoms of acute normal tissue damage and probably totally inadequate for the signs and symptoms of chronic normal tissue damage.

The radiosensitivity of tissues is measured as loss of function, or as change of structure or by subjective criteria such as pain. Cellular damage is measured as loss of clonogenic ability and associated effects such as DNA damage induction or DNA damage repair. The popular kinetic models of pathogenesis of normal tissue damage after radiotherapy are based on the assumptions that there is a definite, quantitative relationship between stem cell survival and clinical, functional tissue damage.
Tissues may be classified into hierarchical and flexible tissues [6]. Hierarchical tissues are defined as those with a defined stem cell compartment with unlimited proliferative potential, committed transit cell compartments which lose proliferative potential as they commit themselves to differentiation and, finally, post-mitotic functional cells with a limited life span. The different subcompartments are characterized by different markers of cell differentiation; transition between compartments is a one-way road. The prime example for this hierarchical tissue is the bone marrow. On the other hand, flexible tissues lack the distinction between stem cell, transit cell and functional cell compartments, each parenchymal cell has the capacity to perform all functions switching from one compartment to another depending on demand. Typical examples are liver and kidney.

These models have been designed in order to describe their radiation response mathematically. The unquestioned basic hypothesis has been that tissue injury is a numerical problem and is quantitatively related to the degree of loss of functional cells. This relationship is well documented for the radiation response of the bone marrow. The clinical signs and symptoms of bone marrow radiation damage are primarily related to the severity of granulocytopenia and thrombopenia. The pathogenesis of radiation damage to the bone marrow has then been generalized to other tissues without ever questioning the basic assumption that there was a close relationship between (functional) cell number and clinical signs and symptoms. Yet, the only tissue where such a close relationship does exist is in fact the bone marrow. In all other tissues with determined clinical radiation tolerance there is little or no relationship between decrease of cell numbers, called hypoplasia, and tissue function or structure. If, however, this relationship does not exist, predictive models, e.g. of the volume effect, which are based on the proliferative capacity of stem cells become meaningless.

Using data on the radiosensitivity of regenerating stem cells and the shape of the dose-response curve of structural or functional tissue injury, the concept of the ‘tissue rescuing unit’ has been developed [7]. The number of surviving tissue rescuing units would determine the severity of the clinical tissue response after irradiation. This has been modelled for those tissues which show acute responses such as skin and bowel mucosa. This mathematical model, too, is based on the assumption that hypoplasia determines the severity of acute normal tissue injury.

The Role of Functional Radiation Effects in the Pathogenesis of Acute Normal Tissue Damage

In all tissues which cover external or internal surfaces, the clinical signs of acute radiation damage are very similar: erythema after moderate doses
and denudation after high doses. Erythema is an unspecific inflammatory response of the vascular connective tissue to all sorts of damage. It is the most important and commonest of all acute radiation effects. In skin and oral mucosa, erythema occurs after minor degrees of cellular hypoplasia, usually if cell density decreases to about 50% of normal values [8]. It appears to be a regulated stress response and not directly induced by radiation. In skin, it is not related to a loss of function of the parenchymal epidermis [9]. On the other hand, acute radiation injury of the bladder it is not related to any degree of cell number loss but to loss of function of the covering cells [10].

Thus, the most characteristic acute side effect of radiotherapy, erythema, is not directly related to a markedly decreased number of functional cells. Rather, there is evidence of radiation-induced changes in cell function of functional or other cells, which appears to be more important than changes in cell numbers. Even denudation might be more related to local inflammatory responses than to stem cell killing. This is suggested by results of some experiments on the modification of exudative radiation dermatitis by anti-inflammatory treatment.

In mouse skin, even before any radiation effect becomes visible in the epidermal keratinocytes, pro-inflammatory cytokines such as TNF-α, IL-1 and nitric oxide synthase are induced in dermal cells, particularly endothelial cells and myofibroblasts of small vessels [11]. Erythema is not just a milder reaction compared to denudation on the same scale, as suggested by the skin scores used in radiobiology and the EORTC/RTOG scores, nor is the reaction of the dermis to impaired epidermal function caused by pronounced epidermal hypoplasia. Inflammation in the dermis is a separate response chain to radiation injury which initially is not closely related to the proliferative damage in the epidermal hierarchical cell structure, yet which interacts with it in many ways. Progressive epidermal hypoplasia may increase dermal inflammation, no doubt, but there is evidence that the influence goes the other way, as well.

Figure 1 shows the progression of acute skin reactions in mice after a single dose of 23 Gy [12]. Confluent moist desquamation (score 2.5) is reached in 6/8 fields in the third week. Quite naturally, this was associated with massive inflammatory reactions. Yet the non-steroidal anti-inflammatory drug indomethacin given after the initial signs of erythema had developed did not alter the signs of moist desquamation: the curves looked identical. If, however, anti-inflammatory treatment was started immediately after irradiation during the early induction of the inflammatory cytokines, moist desquamation could be prevented in all skin fields and the dry desquamation response was delayed. This means that post-irradiation modulation of inflammation suppresses denudation which also proves that denudation is not just a radiation-induced epidermal hypoplasia but the response of the tissue as a whole to various interacting pathological processes. Radiation effects in all tissue compartments
Fig. 1. The time course of the acute radiation injury in mouse skin after a single dose of 23 Gy. The scoring system used gives scores of <1.5 to different grades of erythema and dry desquamation. Score 1.5 denotes a small area of moist desquamation whereas any score ≥ 2.5 denotes moist desquamation of the entire field and ulceration. Mean scores of 8 skin fields per group are plotted. Group 1 was given daily indomethacin for 2 weeks starting 7 days after irradiation just before erythema started (●); group 2 was given daily indomethacin for 2 weeks starting a few days before irradiation (■). There was no difference in response of irradiated animals not given indomethacin and irradiated animals given indomethacin after 7 days. Data from Heasman [12].

Table 1 summarizes the evidence for pathogenetic mechanisms of acute radiation injury in different organs.

**Pathogenesis of Chronic Radiation Damage**

The pathogenesis of chronic radiation damage is even more complex than that of acute radiation damage and it involves even more interactions between the various structural compartments of an organ. The most frequent chronic outcomes are atrophy and fibrosis both of which may progress to necrosis if secondary damage such as trauma or infection exceeds the capacity of the irradiated (atrophic or fibrotic) tissue to cope with the additional stress (table 2).

Atrophy is a reduction in the number of functional cells; however, it is not due to a decrease in the proliferative capacity of these parenchymal cells
Table 1. Mechanisms of acute radiation injury in different organs

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Effect</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow</td>
<td>infection, haemorrhage</td>
<td>hypoplasia of functional cells: granulocytopenia, thrombopenia</td>
</tr>
<tr>
<td>Skin, oral mucosa</td>
<td>erythema</td>
<td>dermal inflammation caused by change of communication (?) between epidermal cells</td>
</tr>
<tr>
<td></td>
<td>denudation</td>
<td>patchy or confluent loss of surface cells related to severe hypoplasia and inflammation (?)</td>
</tr>
<tr>
<td>Gut</td>
<td>diarrhoea</td>
<td>not related to denudation but (?) to changes in neuropeptides which control motility and secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>decreased absorption due to functional changes in brush border enzymes</td>
</tr>
<tr>
<td>Bladder</td>
<td>decreased compliance</td>
<td>no evidence for hypoplasia but change in urothelial cell function (uroplakin expression)</td>
</tr>
<tr>
<td>Salivary gland</td>
<td>xerostomia</td>
<td>no evidence of hypoplasia, change in function of glandular cells</td>
</tr>
</tbody>
</table>

Table 2. Mechanisms of different manifestations of chronic radiation damage in normal tissues

<table>
<thead>
<tr>
<th>Damage</th>
<th>Critical cell</th>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrophy</td>
<td>endothelial cell</td>
<td>destruction of capillaries caused by focal dysfunction of endothelial cells; also damage to myofibroblast differentiation/ function in structured vessels</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>fibroblasts</td>
<td>differentiation, directly induced and modulated by radiation-induced expression of TGF-β and other fibrogenic messengers</td>
</tr>
<tr>
<td>Necrosis</td>
<td></td>
<td>tissue breakdown caused by secondary trauma or infection which exceeds the compensatory capacity of the atrophic/ fibrotic irradiated tissue</td>
</tr>
</tbody>
</table>

and, in most cases, is actually associated with hyperproliferation. Atrophy is due to a reduction in the life span of functional cells due to an impaired microenvironment, usually ischaemia caused by the rarefaction of the capillary network. Loss of capillaries is not related to proliferative damage of endothelial cells. It occurs earlier than post-irradiation mitosis and cell death. Moreover, it is focal, and these foci are closely related to focal changes in endothelial cells.
cell function after irradiation [13]. The focal nature of most if not all chronic radiation damage in different normal tissues such as the spinal cord [14] or the heart [13] is a particularly strong argument against the basic hypothesis that normal tissue damage is due to random killing of stem cells as this would not be compatible with focal development of damage.

Fibrosis has been related to radiation damage in fibroblasts; however, a smaller number of fibroblasts is unlikely to produce more collagen unless radiation induced premature differentiation of undifferentiated fibroblasts pushing them into increased collagen production [15]. This is a very attractive theory, which, however, would not be consistent with the cell number theory of normal tissue damage pathogenesis. Yet, in addition to the modulation of the inherent cellular differentiation programme by irradiation, the development of radiation fibrosis is also regulated by radiation-induced messenger molecules such as transforming growth factor-β [16].

The simple dichotomy of acute and chronic normal tissue damage is a gross oversimplification of reality, suitable for a radiobiology textbook but not a valid description of the complexity of radiopathology. Organs and normal tissues consist of different cell types arranged in well-defined structures. Direct intercellular communication and intercellular signalling molecules maintain their structural and functional integrity and guarantee a large degree of flexibility of response to any damaging interference. Damage to any one of the constituent cells or signalling pathways leads to co-reaction of other structures of the respective organ. Even if the pathogenetic process is started in, or is dominated by, one defined subpopulation of constituent cells, the organ or tissue responds as a whole according to its tissue-specific reaction patterns.

Progressive, chronic radiation damage to the microvasculature leads to atrophy of the dependent parenchyma. Atrophy, fibrosis and necrosis are by no means separate and well-defined pathogenetic mechanisms. All three pathological features of chronic radiation damage are end stages which are more characteristic of the involved tissues and organs than of the damaging agent. Moreover, late fibrosis or necrosis may be the end stages of very different processes, indistinguishable in their clinical and pathological features, but involving very different processes during their development. These interactions between different cellular compartments in all organs and tissues make the target cell concept for chronic normal tissue radiation damage obsolete.

**Pathogenesis of Consequential Late Radiation Damage**

The complexity of tissue responses to any damage becomes even more important if specific or unspecific secondary injury adds to primary radiation
effects in a process which has been termed ‘consequential late radiation damage’ [17]. It occurs under the surfaces of tissues which are covered by epidermis or by a mucosal lining, in particular in the mucosae of the upper aerodigestive tract or of the bowels. Consequential late radiation damage occurs if healing is prevented or delayed for months by additional toxic influences, e.g. chemotherapy or by excessive radiation doses. Tissue breakdown and scarring develop as the persistent mucosal denudation permits infection and invasion of external toxic substances into the severely inflamed connective tissue which gradually, together with its capillary network, loses its reserve capacity. The morphological and clinical features of genuine late radiation damage and of consequential late radiation damage are very similar. They depend on the characteristic response patterns of the respective organs, but not on the pathogenetic pathway. Pathological signs include chronic inflammation, reactive fibrosis and tissue necrosis.

**Conclusion**

There is no evidence to support the hypothesis that chronic radiation damage is causally or quantitatively related to the reduction in the number of certain parenchymal cells due to their impaired proliferative capacity or of that of their progenitor cells.

Both acute and chronic (i.e. genuine chronic and consequential late) side effects of radiotherapy are more related to functional radiation effects in critical cell populations than to numerical radiation effects in presumed target cell populations. These functional changes may be induced directly by irradiation or may be secondary to changes induced in the cytokine network or in the intercellular communication pathways. This has profound consequences for any attempt to quantitatively relate the risk of normal tissue complications of critical organs or tissues to the anatomical distribution of radiation doses within the respective organ or tissue. The probability of normal tissue complication is more related to the anatomy and physiology of the respective organ than to cellular radiobiology.

**References**

11 Favaretto S. Changes in the expression of TNF-α, IL-1α, integrin-α, EGF-receptor and iNOS after X-irradiation of mouse skin; MSc thesis, London, 1996.

Prof. K.R. Trott, Department of Radiation Biology, St. Bartholomew’s and the Royal London School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ (UK)
Tel. +44 20 7982 6106, Fax +44 20 7982 6107, E-Mail k.r.trott@mds.qmw.ac.uk
Epidermal Growth Factor and Its Receptor in Tumor Response to Radiation

Luka Milas
University of Texas M.D. Anderson Cancer Center, Houston, Tex., USA

Growth factors and cytokines are substances that regulate cell growth and proliferation, and maintain architectural and functional tissue homeostasis. By binding to specific cell membrane receptors, these substances set in motion a highly regulated network of cellular events: signal transduction, gene activation, transcription. These in turn regulate cell cycle checkpoints. Growth factors can act locally by autocrine or paracrine actions or on distant tissues (endocrine activity). More than a hundred different growth factors are known, many of which interact with each other exerting complementary or opposing effects on cell growth. For example, while in general transforming growth factor-α (TGF-α) promotes cell growth, TGF-β inhibits it.

Growth factors and cytokines play a critical role in the pathogenesis of radiation injury, both in normal tissues and tumors [1, 2]. They act by affecting molecular and cellular determinants of cytotoxicity, and tumor pathophysiology. These include cellular repair mechanisms, cell cycle redistribution, cell repopulation and tissue microenvironment, such as tumor hypoxia and acidity. Although our knowledge on the biology of growth factors and cytokines has greatly increased recently, research on the interaction of these factors with radiation has been limited. Hence, this interaction is still poorly understood, and is likely complex. This paper will overview our current understanding only of the effects of epidermal growth factor (EGF) and its receptor (EGFR) in cell and tumor response to radiation and their implications for tumor radiotherapy.

EGFR Signal Transduction

EGF, TGF-α, heparin-binding EGF-like growth factor (HB-EGF) and heregulin are major members of the EGF family of growth factors. They bind
to EGFR, a 170-kD transmembrane protein with intrinsic tyrosine kinase activity. There are four known members of the EGFR gene family: EGFR, ERBB2 (also designated neu and her), ERBB3 and ERBB4. The EGF family members share sequence similarities as well as high binding affinity for EGFR and mitogenic effects on EGF-responsive cells.

EGF, like the majority of growth factors that act through tyrosine kinase, regulate cell cycle (and cell proliferation) through mechanisms that act on G1 phase progression. On ligand binding, EGFR dimerizes with neighboring receptors and becomes autophosphorylated, a process in which the activity of tyrosine kinase is essential. The receptor phosphorylation triggers the biochemical cascade of events, involving a number of proteins including growth factor receptor protein 2 (Grb2) and mitogen-activated protein kinase (MAPK) that constitutes signal transduction pathways (fig. 1). Cyclins and cyclin-dependent kinases (cdks) are essential in this cascade, and mediate progression through each phase of the cell cycle. The D-type cyclins (D1, D2, and D3) bind to cdk4 or its homolog cdk6 and mediate cell progression through G1.

Fig. 1. EGFR signaling pathway.
Fig. 2. Cyclin D involvement in G\textsubscript{1} phase progression.

Cyclin E binds to cdk2 and also mediates G\textsubscript{1} phase cell cycle progression. The cyclin D/cdk4 (or cdk6) complex phosphorylates Rb protein which in unphosphorylated state is bound to the E2F family of transcription factors. This Rb/E2F complex represses transcription, but when Rb is removed from it by phosphorylation the ‘free’ E2F induces E2F-dependent gene transcription allowing cell progression into S phase. The action of cyclin D/cdk4 on Rb phosphorylation can be inhibited by a number of genes including p27, p21, and INK (inhibiting kinases) that include p15, p16, p18, and p19. Radiation can mimic the activity of EGF and induce EGFR phosphorylation and thus initiate transduction signals [3].

EGFR Expression in Tumors

In contrast to normal tissues, the complex cascade of growth factor signaling is commonly dysregulated in tumors. Often, there is an overexpression of growth factor receptors or growth factor production. EGFR is frequently expressed at high levels in many human tumors, including breast, cervix, lung, and head and neck carcinomas [4]. The high expression of EGFR is associated
with more aggressive tumors, poor prognosis, and resistance to treatment with cytotoxic agents. Recently, high levels of EGFR and TGF-\(\alpha\) in primary head and neck squamous cell carcinomas were reported to be significantly associated with both decreased disease-free and cause-specific overall survival [5]. In vitro experimental studies have yielded solid evidence linking EGFR status with resistance to cytotoxic drugs [6-9]. Transfection of EGFR into human breast cancer cells, for example, was reported to increase cellular resistance to drugs [7]. On the other hand, blockage of the EGFR-mediated signaling pathway with antibodies to EGFR enhanced the sensitivity of tumor cells to a number of chemotherapeutic agents [6, 8]. More recent studies have shown that anti-EGFR antibodies are effective in the treatment of human tumor xenografts, particularly when combined with chemotherapeutic drugs [9].

**EGFR Expression and Tumor Radioresponse**

Although many reports imply the existence of a positive association between overexpression of EGFR and poor response to therapy [4, 6], information on the relevance of EGFR expression in cell or tumor response to radiation is scarce. We have recently initiated a study to explore the possible association between EGFR and radioreponse of mouse carcinomas. These tumors exhibit a broad range of radioreponse measured by TCD\(_{50}\) (radiation dose yielding 50% local tumor control) and of radiation-induced apoptosis [10]. The two endpoints positively correlated with each other, implying that radiation-induced apoptosis is a major mechanism by which radiation kills tumor cells in these carcinomas [10].

EGFR protein levels, analyzed by Western blotting in 9 carcinomas of different histological types, showed more than 20-fold variability among tumors. This technique repeatedly provided consistent values within individual tumors of the same type, and EGFR expression was not influenced by tumor size (the investigated range was from 8 to 12 mm). As a rule, higher EGFR protein levels were found in tumors less responsive to radiation. There was a highly significant positive correlation between the level of EGFR and TCD\(_{50}\) value [11]. The existence of this inverse relationship between the magnitude of EGFR expression and tumor radiocurability may have important clinical implications in that pretreatment assessment of EGFR expression could predict radiotherapy outcome and assist in selecting an effective radiotherapeutic approach to radioreistant tumors.

The association between EGFR and tumor radiocurability does not establish a causative relationship, as other factors, both genetic and epigenetic, are likely involved as well. However, ongoing studies in our laboratory have shown that radiation can induce EGFR phosphorylation, and thus initiate down-
stream molecular processes, the same or similar to those initiated when EGF is bound to its receptor. That the level of EGFR expression influences tumor cell radiosensitivity was recently shown by Sheridan et al. [12]. These investigators determined sensitivity to 2-Gy single-dose radiation of primary cultures derived from 14 head and neck carcinoma patients, and found that cell cultures expressing high levels of EGFR were more radioresistant than those expressing low levels of EGFR. Resistance was measured by the extent of radiation-induced cell growth inhibition.

**Modification of Tumor Cell Radiosensitivity by EGF**

Recently, there have been a number of studies investigating the influence of EGF and TGF-α on in vitro sensitivity of tumor cells to ionizing radiation. They provided evidence that these molecules can exert either radiosensitizing [13–15] or radioprotective [16, 17] effects. Addition of EGF to cultures of squamous cell carcinoma cell lines having high-affinity cell surface receptors to EGF showed variable response to radiation [13, 14]. While the radiation sensitivity of the CsSki, HN5, and A431 cell lines increased, no effect on sensitivity of the SiHa cells or of a mouse 3T3 cell line was observed. The enhancement of sensitivity was most significant in G1 phase cells and was primarily associated with a reduction of the shoulder region of the dose-survival curve. The effect of EGF was receptor density dependent as the degree of EGF radiosensitization was inversely related to the number of high-affinity EGFRs [13]. Another study showed that the radiosensitizing effect of EGF was more pronounced if the cells were intrinsically more radiosensitive [15]. Addition of TGF-α, another member of EGF family, enhanced radiosensitivity of MCF-7 cells by downregulation of estrogen receptors [18].

EGF was also reported to protect cells against radiation killing [16, 17]. The addition of EGF to cultures of hormone-deprived MCF-7 breast carcinoma cells before radiation increased the radioresistance of these cells, affecting primarily the exponential portion of the radiation survival curve. The observed resistance was associated with increase of cells in the radioresistant S phase of the cell cycle, and in elevation of the intracellular glutathione content that acts radioprotectively. The effect of EGF was abrogated by adding to the medium a specific antibody to EGFR [16]. In another study [17], EGF decreased radiosensitivity of A431 squamous cell carcinoma cells when present during and after irradiation. The major effect was an increase in size of the shoulder of the radiation survival curve. In contrast to the radioprotective effect of EGF, treatment of A431 cells with monoclonal antibodies to EGFR sensitized them to radiation by enhancing radiation-induced apoptosis. The
authors concluded that radiation activated EGFR, which initiated downstream signaling pathways that led to cell radioresistance, and therefore blocking such activation resulted in increased cell killing. In a more recent study, exposure of SCC-13Y head and neck squamous cell carcinoma cells to C225-anti-EGFR monoclonal antibody either for 3 days prior to, or during and after irradiation enhanced cell radiosensitivity [19]. The major mechanism for enhanced radiosresponse was attributed to the ability of the antibody to enhance susceptibility of these cells to radiation-induced apoptosis.

**Radiation and EGFR Signaling**

There is growing evidence that ionizing radiation can mimic the action of ligand-receptor binding, which triggers downstream signaling [3, 17, 20, 21]. Balaban et al. [17] showed that radiation affects multiple signaling pathways, but induction of radioresistance is predominantly associated with activation of EGFR. Goldkorn et al. [21] demonstrated that tyrosine autophosphorylation of EGFR in A431 cells occurred spontaneously after radiation, but that the binding of EGF to the receptor and receptor stability remained unaffected. Also, radiation caused a decrease in protein kinase C activity, which may underly the sensitizing effect of EGF on irradiated cells in this system. Thus, results suggest that the level of protein kinase C activation or suppression may determine the ability of growth factors to regulate radiation sensitivity in mammalian cells. Using human mammary and squamous carcinoma cells, Schmidt-Ullrich et al. [20] and Carter et al. [22] demonstrated that radiation induced EGFR autophosphorylation, which was followed by activation of transduction-signaling pathways including Raf-1 and MAPK. However, the transduction signals were not activated when EGFR autophosphorylation was blocked by the specific inhibitor tyrphostin AG148 [22]. These investigators postulated that activation of these signals stimulates cell proliferation that could be a major mechanism underlying accelerated repopulation of tumor cell clonogens during fractionated radiotherapy.

Our own investigations [1, 11] demonstrated that radiation can induce EGFR autophosphorylation in tumors growing in vivo. However, induction depended on the basal level of EGFR expression, occurring only in high EGFR-expressing tumors. This suggests that a certain basal level of EGFR must be present to respond to radiation in order to activate downstream processes leading to cell protection. We further observed [unpubl. data] that radiation affected the expression of cyclin D1, which also depended on the basal level of expression of this protein. The basal level of cyclin D1 expression differed more than 40-fold among the 9 carcinomas studied, it paralleled that
of EGFR, and like EGFR, positively correlated with tumor resistance to radiation. Radiation had no influence on constitutive expression of cyclin D1 in radioresistant tumors, but it reduced the expression of cyclin D1 in radiosensitive tumors. To establish whether EGFR or cyclin D1 levels influenced cell proliferation or cell loss after radiation, tumors were analyzed for the percentage of proliferative cells, assessed by proliferating cell nuclear antigen (PCNA) staining, and for apoptosis within 2 days following irradiation. While no significant apoptosis or change in the percentage of PCNA-positive cells was observed in tumors with high EGFR (or cyclin D1) levels, radiation-induced significant apoptosis and a decrease in the percentage of proliferating cells in tumors with low EGFR expression. Thus, these findings imply that EGFR and its sensor cyclin D1 play an active role in tumor response to radiation. When highly expressed, these proteins act protectively either through inhibition of apoptotic cell death, increasing cell proliferation, or both.

**Therapeutic Implications**

There are two major clinical implications of dysregulation of EGF and its receptors: prognostic tool and target for therapy. Elevated EGFR is associated with more aggressive tumors, poor response to standard treatment modalities, and poor patient survival. Our own studies with murine tumors provided clear evidence of an inverse correlation between EGFR expression and tumor radiocurability. Therefore, quantitation of EGF and its receptors may be a useful tool for identifying subgroups of patients with high-risk adverse treatment outcome, and thus enable the use of the most rational individualized therapeutic strategy.

EGFR and its signaling pathways may serve as a therapeutic target that could be used to improve efficacy of cytotoxic treatments, including radiotherapy. One could interfere with EGFR binding or with individual steps in downstream processes. For that purpose, a number of protein kinase inhibitors are currently under investigation [23]. Antibodies are being developed to block EGFR, and one of them, C225, was shown to be highly effective when combined with chemotherapeutic agents [6] or radiotherapy [unpubl. data]. Therapeutic efficacy of C225 is currently undergoing clinical trials when combined with radiotherapy. Preliminary results show that this combination can significantly increase the percentage of local head and neck tumors controlled by radiotherapy [24]. Thus, interference with EGFR binding has a high potential to improve tumor radiotherapy. As mechanisms involved in growth factor radiation interactions become better understood, the ability to interfere with adverse actions of EGFR on tumor control is likely to improve.
References


Luka Milas, MD, PhD, Department of Experimental Radiation Oncology, UT M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030-4095 (USA) Tel. +1 713 792 3263, Fax +1 713 794 5369, E-Mail lmilas@mdanderson.org

EGF and EGFR in Tumor Radiosensitivity
New Technologies in Conformal Radiation Therapy

W. Schlegel

Department of Medical Physics Research Program Radiological Diagnostics and Therapy, Deutsches Krebsforschungszentrum, Heidelberg, Germany

Radiation therapy is in the process of a continuous change. This movement has mainly been driven by rapid and exciting achievements in computer technology which led to the development of three-dimensional (3D) treatment planning and to completely new treatment delivery systems. However, besides computer science, a couple of other disciplines, like neurosurgery, radiological diagnostics, physics, mathematics as well as mechanical and electronic engineering, also had a strong impact on radiotherapy. As a result, real 3D conformal therapy, as proposed by Takahashi [1] as early as 1965, is now more and more becoming reality in clinical practice. In this contribution, some relevant physical and technical developments in the different fields of radiotherapy will be described.

Patient Fixation, Target Localisation and Positioning

The field of patient fixation and patient positioning profited especially from stereotactic neurosurgery. Today, two different strategies exist for stereotactically guided radiotherapy procedures: those for single-dose irradiation (‘radiosurgery’ [2, 3]) and those for fractionated treatments (often called ‘precision radiotherapy’ [4, 5]).

Fixation Systems for Single-Dose Irradiation

For single-dose irradiation (the main indications of which are arteriovenous malformations and metastases), different stereotactic systems, modified for use in computed tomography (CT), positron emission tomography (PET) and di-
digital subtraction angiography, are being applied. Recently, we have also developed a stereotactic frame completely compatible with magnetic resonance (MR), made of a special ceramic material. This frame allows to obtain MR images which are absolutely free of artefacts. Using this system in CT and MR imaging (MRI), a stereotactic image of utmost precision can be registered [6].

**Fixation Systems for Fractionated Treatments**

For fractionated treatments of lesions in the brain and head and neck, special mask systems have been developed. The one used in our department is made from Scotch cast bandages. This relocatable mask system results in a standard deviation of 1–2 mm in fixation and repositioning accuracy (fig. 1) [4, 5, 7].

For conformal stereotactic treatment of lesions in the body, relocatable stereotactic whole-body fixation systems are being introduced. The system which we developed together with the University of Tucson can also be used in connection with a rigid fixation to the spinal column for radiosurgical treatment of lesions close to or within the spine (fig. 2a, b).
**Fig. 2.** Extracranial stereotactic fixation and positioning system. **a** System attached to the patient’s couch at the linac and equipped with target localiser. **b** System attached to the CT couch and equipped with stereotactic CT target localisers.

**Target Localisation**

Various stereotactic localisation techniques of target points have been developed by different groups. We use the localisation procedure as developed for linear accelerator (linac) radiosurgery by Pastyr [8]. The same target-localiser consisting of 4 Plexiglas squares with imbedded V-shaped fiducial wires is now also used for single-dose or fractionated treatments. A similar system was developed by our group to enable stereotactic localisation of lesions in the body (fig. 3a–c).

**Stereotactic Patient Positioning**

Stereotactic positioning principles are used for radiosurgery and precision radiotherapy, both for brain and head and neck lesions as well as for treatments
Fig. 3. a Extracranial stereotactic fixation and positioning system in use in connection with a Scotch cast fixation torso and CT target localisers for a patient with a paraspinal tumour. b Extracranial system in use in connection with a vacuum cushion, stereotactic CT target localisers and an abdominal compression plate for the treatment of liver metastases. c CT image for the patient shown in b.

with the whole-body fixation system (fig. 1). The stereotactic coordinates of the target point, calculated during 3D treatment planning, are transferred to the x-, y- and z-callipers of the stereotactic target positioner. The patient’s couch is then adjusted in x-, y- and z-directions, until the laser crosses match the fiducials on the callipers.
Tracking Systems for Automated Patient Set-Up, and Movement Detection and Correction

To improve and facilitate patient set-up during positioning at the linac, tracking devices quite similar to those used in neuronavigation are being developed. The device which was developed at the Deutsches Krebsforschungszentrum in Heidelberg (DKFZ) allows automated positioning of patients with head and neck lesions with an accuracy below 1 mm. The system is also able to detect target movement by measuring the patient’s position up to 25 times per second. With a computer-controlled table top, significant position deviations which occur due to patient movements can be automatically and instantly corrected [7, 9].

Three-Dimensional Treatment Planning for Conformal Therapy

The most spectacular developments in radiotherapy in this decade were those initiated by the availability of small and powerful computers known as ‘workstations’ and ‘PCs’. On the basis of the new 3D imaging techniques, CT and MRI, a complete change from the 2D consideration of the radiotherapy problem towards 3D planning took place. In a modern 3D treatment-planning program, a set of ‘3D options’ allows a comprehensive and precise 3D simulation of the radiotherapy procedure.

Definition of Target Volume and Organs at Risk

The basic module of a 3D treatment-planning program is a tool to define target volumes and organs at risk in a stack of CT or MRI images. Besides basic drawing and editing tools, such a module has to provide an interface for image registration, either on the basis of stereotactic coordinates or with the help of anatomical landmarks or surfaces [10]. 3D computer graphic features support the understanding of the therapy-relevant anatomical structures (fig. 4).

Designing a Treatment Plan in Three Dimensions

3D treatment planning is not restricted to the spatial definition of anatomical structures: a major advantage is that the 3D orientation and shape of the beams can now also be interactively altered and optimised. In this respect, modern 3D treatment-planning systems show much similarity to computer-aided design techniques used in engineering sciences, e.g. the software model VIRTUOS, which is implemented in our 3D treatment-planning program VOXELPLAN, is a 3D computer graphics interface to define treatment techniques for conformal therapy [11]. The program provides all options which
characterise current 3D treatment-planning programs: Beam’s Eye View, 3D Observer’s View, multiplanar reconstructed sections and the implementation of irregular-shaped fields and also more advanced tools as the linac view and the spherical view have recently been implemented (fig. 5).

Three-Dimensional Dose Calculation

Probably the most important features of modern 3D treatment planning are the new dose calculation algorithms which have the ability to consider irregular field shapes and 3D tissue inhomogeneities and to quantify their influence on the 3D distribution of beam scatter. The new models for 3D dose calculation are known as superpositioning or convolution algorithms and significantly improve the accuracy of 3D dose calculations in the majority of
clinical situations [12–15]. It can be foreseen that the problems that arise in complicated cases can be overcome by fast and highly precise Monte Carlo calculations in the near future [16–18].

Visualisation and Evaluation of Three-Dimensional Treatment Plans

A further important characteristic of 3D planning is the new computer graphics software enabling 3D visualisation of treatment plans. Besides multiplanar reconstruction sections with dose distributions in the transverse, coronal and sagittal planes, voxel-based as well as 3D-shaded surface representations can be used [19]. The calculation of dose volume histograms and of tumour control probabilities and normal tissue complication probabilities according to different biological models are very helpful tools for the comparison of treatment plans during the process of treatment plan optimisation.

Fig. 5. User interface of the 3D virtual therapy simulation module VIRTUOS within the VOXELPLAN program. Implement and shown are the following tools: linac view (upper right image), Beam’s Eye view (upper middle), Multiplanar reconstructions (right column) and Observer’s view (lower middle).
Fig. 6. User interface of the result display module of the VOXELPLAN 3D treatment-planning system. Shown are the dose volume histogram display section (upper left), 3D dose surface display (upper middle), colour wash dose distributions in multiplanar reconstructions (right column) and 3D-shaded surface display of the patient’s contour, target volume, organs at risk and the 3D isodose distribution of the 80% isodose.

Inverse Planning of Conformal Therapy

A completely new approach to the solution of the treatment-planning problems, so-called ‘inverse planning’, was proposed at the end of the last decade [20]. The principal idea of inverse planning is to allow intensity variation within the different beams of a cross-fire or moving beam treatment technique. Interactive trial-and-error optimisation is abandoned. Instead of this, a special computer program iteratively optimises fluence distribution in the different beams until a prescribed conformal dose in the target volume is reached, on the condition that tolerance doses in critical organs are not exceeded [21].
Different optimisation criteria and different strategies were developed in order to solve the inverse-planning problem: the group at the Karolinska Institute in Stockholm proposed to use optimisation criteria based on biological models, while our group at the DKFZ favours purely physical criteria [20–22]. The group at the Royal Marsden Hospital in London implemented an optimisation algorithm which is known from crystallography and called ‘simulated annealing’ [23], while our group implemented a gradient-driven optimisation procedure. Both approaches are now implemented in commercial inverse-planning tools. However, clinical evaluation is still needed.

From the theoretical point of view, the concept of inverse planning soon improved to be very powerful, especially for treatment planning of concave-shaped lesions. An example of an inverse treatment plan is shown in figure 7. This plan was computed with our inverse-planning program KONRAD.

KONRAD uses the target volumes and organs at risk, defined with the conventional 3D treatment planning (in our case the TOMAS target delineation program within VOXEPLAN), but then has its own strategy to determine the treatment technique by using an iterative algorithm which was described by Bortfeld et al. [21]. Dose volume histogram calculation and display are implemented as well as some basic viewing tools for 3D dose distributions. For a more elaborate evaluation of the dose distributions generated with KONRAD, the VIRTUOS module can be used. The program is described in detail in Preiser et al. [24].

The practical problem with inverse planning is the fact that intensity-modulated beams have to be produced in order to deliver the inversely planned treatment techniques. The techniques which have been recently developed in this context are called intensity-modulated radiotherapy (IMRT) (see below).

**Modern Conformal Treatment Techniques**

As already mentioned, the need for conformal dose distributions has always been obvious and was formulated many decades ago. Conformal therapy became a reality with the advent of 3D treatment planning, but still suffered from problems connected with practical aspects: until recently, irregular-shaped beams could only be produced by the time-consuming procedure of cerrobend blocking. This situation has completely changed during the last 4–5 years with the development and implementation of beam-shaping devices, the so-called multi-leaf collimators (MLCs). Two kinds of MLCs are available today: those for medium-sized and large fields, which are implemented in the gantry of linacs, and added on MLCs for small field sizes (often called mini- or micro-MLCs) which can be used in conjunction with stereotactic radiotherapy.
Fig. 7. User interface of the inverse-planning program KONRAD. Shown are the transverse section (left) and multiplanar reconstructions (middle and right) with target volume and organs at risk and isodose distribution for an inverse planned prostate case. The lower row shows the dose volume histogram and the organ parameter specification fields.

Linac-Implemented Multi-Leaf Collimators

In the early 90s, the companies involved in the development of linacs came up with computer-controlled MLCs integrated into the irradiation head of the accelerator. At the very beginning, a couple of problems had to be overcome before these devices could be safely and routinely applied: e.g. dosimetry of MLCs, verification of leaf positioning, interfacing with the treatment-planning program, and quality assurance turned out to be non-trivial difficulties. Today, most of these problems have been solved and the MLCs are being used in clinical practice, mainly with the purpose of replacing blocks for the creation of irregular-shaped fields. Though the modern MLCs have
dynamic properties, they are still applied in static treatment techniques practically everywhere. The real potential of MLCs will be in the future, when dynamic treatment techniques with MLCs will be implemented to perform dynamic field shaping and generate intensity-modulated beams (as discussed below).

Micro-Multi-Leaf Collimators for Stereotactic Radiotherapy

The need for conformal, homogeneous dose distributions was the reason to start with the development of highly resolving MLCs for small field sizes (5–50 mm diameter), which are attachable to the accessory holder of a stereotactic linac. Today a variety of mini- and micro-MLCs are available, which can be attached to the accessory holder of a linac and used within the context of radiosurgery or precision radiotherapy.

Intensity-Modulated Radiotherapy

As mentioned above, inverse planning requires the generation of intensity-modulated beams. For radiotherapy with charged particles, the most elegant method would be the scanning of pencil beams. For photons, however, the scanning beam idea cannot be applied: there is no physical way to directly deflect a photon beam. The most obvious way for the generation of an intensity-modulated photon beam therefore is to use X-ray compensators, or, as recently suggested by several groups, to apply computer-controlled MLCs. Two different techniques are currently being used: the first method, known as the step-and-shoot technique (or after those who devised it, the Bortfeld-Boyer method [25]), generates an intensity-modulated beam for a fixed gantry angle by superposition of several static irregular-shaped fields. The beam has to be turned on and off for each subfield. The second is a dynamic method which produces intensity modulation by dynamic movement of the leaves while the beam for a static gantry angle is turned on all the time [26, 27].

Tomotherapy is another development in the context of intensity modulation. The idea here is to apply intensity-modulated beams by using a dynamic slit MLC in a rotation-translation treatment technique.

Today, about 20 centres worldwide already apply IMRT clinically, either using compensators, static or dynamic MLC or tomotherapy. In our institute, we decided to start clinical studies first of all with the use of our inverse-planning program KONRAD in connection with the generation of intensity-modulated beams by compensators. Using compensators has the advantage that dosimetry, verification and quality assurance of the new technique can be done off-line and under conventional conditions. The plan for one of our first patients treated with ML-IMRT using the fast MLC control unit (SIMTEC) is shown in figure 8.
Fig. 8. Inverse-planned treatment plan for a patient with a meningioma. The plan shows the directions of the seven IMRT beams, which were produced with a Siemens-MLC using the fast ML-sequencer SIMTEC. The delivery time was in the range of 15 min.

Conclusions

Modern radiotherapy is characterised by new technological developments. It is very much influenced by developments in computer science and medical imaging. The whole chain of radiotherapy is benefitting by these developments. First of all, concerning the aiming problem in radiotherapy, the introduction of stereotactic patient fixation, target localisation and positioning techniques lead to a higher degree of precision. The development of CT- and MRI-based 3D treatment planning is the basis of conformal therapy, which has the potential of improved sparing of organs at risk and dose escalation in the
target volume. The same holds for the implementation of computer-controlled MLCs in modern linacs. The development of inverse treatment planning and the initiation of IMRT are further milestones in the development of 3D conformal radiotherapy, especially of concave-shaped lesions. All these innovations and developments are contributing to improved precision, efficiency and safety of radiotherapy. It seems that with these developments, we are now close to the physical and technical frontiers of high-energy photons. Future research in radiotherapy will have to clarify whether further physical improvement in 3D dose distribution, especially by minimising volume and integral doses in healthy tissues with the use of charged particle beams will result in additional benefit for the patient.

Acknowledgments

I am indebted to Otto Pastyr, Thomas Bortfeld, Karl-Heinz Grosser and Rolf Bendl from the Medical Physics Department, and to Jürgen Debus, Klaus Herfarth and Andrea Pirzkal from the Radiotherapy Department of the DKFZ for their contributions to this paper.

References


Prof. Dr. Wolfgang Schlegel, Deutsches Krebsforschungszentrum (DKFZ),
Im Neuenheimer Feld 280, D-69120 Heidelberg (Germany)
Tel. +49 6221 422 551, Fax +49 6221 422 561 E-Mail w.schlegel@dkfz-heidelberg.de

New Technologies
Intensity-Modulated Stereotactic Radiosurgery

Radhe Mohan, Robert M. Cardinale, Qiuwen Wu, Stanley Benedict

Department of Radiation Oncology, Medical College of Virginia Hospitals, Richmond, Va., USA

Intensity-modulated radiotherapy (IMRT) is being widely embraced by the radiotherapy community as a means of producing dose distributions that are considerably superior to those using standard methods. In this chapter, we present examples based on some preliminary work to determine the effectiveness of IMRT for stereotactic radiosurgery (SRS) of tumors of the brain. Specifically, we would like to answer the following questions: Can IMRT, using a set of fixed fields and delivered with a dynamic multileaf collimator (DMLC) lead to improved dose distributions compared to SRS using multiple arcs or fixed uniform-field radiotherapy using multileaf collimators (MLCs)? Secondly, does IMRT have advantages in terms of superior dose distributions and efficiency when multiple small tumors are encountered? We assume that superiority of IMRT for large, complex shapes has already been demonstrated for other sites.

A goal of SRS is to reduce the dose immediately outside of the planning target volume (PTV) to levels below those considered injurious to normal brain. Therefore, a margin of zero is often used when treating brain tumors with fixed conformal fields to produce high gradients at the target boundaries while accepting higher dose inhomogeneity within [1]. Our aim was to exploit the property of IMRT to sharpen beam boundaries and produce more homogeneous dose distributions by depositing the needed extra photon fluence inside and near the target boundaries [2]. While this feature of IMRT has been demonstrated for larger tumors, its efficacy is not guaranteed for small tumors due to the lateral transport of radiation.
Fig. 1. Transverse dose distributions on an image section through the PTV for example 1 comparing a five-arc plan (a), a plan with 11 fixed-gantry uniform fields chosen along arcs (b) and an intensity-modulated plan with the same 11 fixed-gantry fields (c). All plans were normalized to deliver 15 Gy to 95% of the PTV.

Intensity-Modulated Radiosurgery Methods

In our investigations, we employed a Brainlab mini-micro MLC (m3). The main distinguishing feature of m3 is that it has narrower and variable leaf widths as compared to the industry standard, i.e. 14 pairs of 3-mm, 6 pairs of 4.5-mm and 6 pairs of 5.5-mm leaves. It would seem logical to assume that thinner leaves are important for improving IMRT dose distributions, more so than when MLCs are used to deliver uniform field treatments, but we have not demonstrated this conclusively so far. For the latter, the MLCs are used to define only the boundary of the target volume, whereas for the former the leaf width affects dose distributions within the slabs of target volume and tissues.

The formalisms, algorithms and software comprising the IMRT system for optimization of intensity distributions, for conversion of optimized intensity distributions into leaf trajectories of the Brainlab m3, and for dosimetric
verification of IMRT and other quality assurance, steps specific to IMRT were developed at our institution. The IMRT system was coupled to the ADAC Pinnacle\textsuperscript{3} three-dimensional radiation treatment planning (3-DRTP) system, whose dose calculation engine was used by the IMRT system for optimization. The 3-DRTP system was also used to provide the contours of target volumes and normal critical structures and beam directions for the IMRT system and for the final evaluation of treatment plans. For treatment delivery, the leaf trajectories, consisting of leaf positions as a function of monitor units obtained from optimized intensities, are transferred to the DMLC controller. This DMLC controller utilizes the driver software, developed by the vendor of the treatment machine (Varian), to move the leaves to their designated positions while the beam is on.

The objective function for optimizing intensity distributions, i.e. the optimization criteria, was specified in terms of dose-volume limits. An example of such criteria may be that at least 95\% of the target volume should receive higher than the prescription dose and that no more than 5\% of the target volume should receive higher than prescription dose $\pm 10\%$. Similarly, the normal tissue dose may be constrained so that no more than the specified volume receives higher than the specified dose. Such constraints are expressed mathematically as variance of dose (sum of squares of actual and desired dose values at all points of interest) from desired dose ranges and only the values lying outside the dose ranges are penalized by factors specified by the user. Of course, the specified constraints are rarely met and the values ultimately achieved are compromises between competing constraints. Often a trial-and-error process is needed to adjust constraints and penalties to achieve optimum results. We present two illustrative examples of the application of these methods in the next section.

\begin{table}[h]
\centering
\begin{tabular}{|l|c|c|c|}
\hline
 & SRS & 11 uniform & IMRT \\
 & 5 arcs & beams & 11 beams \\
\hline
Normal brain & & & \\
volume in 1,500 cGy isosurface & 4.81 & 2.98 & 2.69 \\
volume in 1,350 cGy isosurface & 6.42 & 3.7 & 3.45 \\
volume in 1,200 cGy isosurface & 7.64 & 4.86 & 4.69 \\
volume in 750 cGy isosurface & 14.31 & 10.21 & 10.4 \\
irradiated vol./tumor vol. & 2.52 & 1.56 & 1.41 \\
volume in 1,500 cGy isosurface & 0.09 & 0.09 & 0.04 \\
volume in 1,200 cGy isosurface & 0.2 & 0.24 & 0.18 \\
volume in 750 cGy isosurface & 0.39 & 0.55 & 0.42 \\
\hline
Brainstem & & & \\
\hline
\end{tabular}
\caption{Normal brain and brainstem dose-volume data for example 1}
\end{table}
Fig. 2. Intensity distributions for 5 of 11 beams of example 1 of IMRT.
Examples

The first example is a case of a 6-year-old girl with an ependymoma of the posterior fossa, diagnosed first at the age of 3, resected and treated with chemotherapy and external-beam radiotherapy. She had three local recurrences prior to the current recurrences, all resected. In the current recurrence, a small tumor was found in the tumor bed near the brainstem. In fact, the delineated PTV and the brainstem overlapped slightly. The tumor was resected and a radiation dose of 15 Gy in one fraction was prescribed to the tumor bed. To minimize the dose to the brainstem and normal brain, coverage of 95% of
the PTV by the prescription dose of 15 Gy was considered acceptable. The dose to the brainstem was to be limited to 12 Gy. The patient was treated with 5 arcs: 2 lateral, 2 superior obliques and 1 through the vertex. We compared this plan to a plan with fixed-gantry-angle conformal uniform fields as well as fixed-gantry-angle intensity-modulated fields. For both of the fixed field plans, 3 fields were chosen along each of the 2 lateral arcs, two fields along each of the superior oblique arcs and 1 field through the vertex, for a total of 11 fields. Gantry angles were chosen to be maximally avoiding each other. As discussed
above, the block (or MLC) margin around the PTV for the fixed-field plans was set to zero to minimize the volume of normal brain receiving high doses, but accepting higher target dose inhomogeneity. Figure 1 compares these 3 plans. It is evident that the uniform-field plan is far more conformal as compared to the 5-arc plan. However, the IMRT plan is only modestly more conformal than the uniform-field plan. Dose-volume histograms indicate that the target dose is most homogeneous for the arcs plan and least homogeneous for the uniform fields. As expected, IMRT improves target dose homogeneity over uniform fields.

Table 1 shows dose-volume data for normal tissues for all 3 plans. The main point to be noted is that the volumes of normal brain and brainstem exposed to higher doses are somewhat smaller for the IMRT plan than for the uniform-field plan, and both are significantly smaller than for the arc plan.

The index of conformity defined by the ratio irradiated volume/tumor volume is the smallest for the IMRT plan.

Considering dose homogeneity and normal tissue sparing, the IMRT plan was judged to be the best overall. However, for this case involving a small convex tumor, IMRT offered only a modest gain as compared to uniform fields. It would seem logical that for small convex tumors, conformal arcs (arcs in which the field shape is continuously changed to conform to the target shape as the gantry rotates) may perform even better due to the inherent capacity of beams incident from all directions to geometrically produce higher gradient at the border of objects being irradiated. Similarly, IMRT arcs or a large number of IMRT beams may further improve dose distributions provided one can conceive of an efficient way of delivering them.

Figure 2 shows intensity distributions of 5 of the 11 beams (all except those along the lateral arcs). It is interesting to observe that intensities at the outer edges of the beams are generally higher than for regions in the middle, possibly due to an attempt by the IMRT optimization process to produce sharp dose gradients at the boundaries.

The IMRT plan shown here is one of many plans produced. Other plans generated were for different beam configurations, including coplanar ones, different margins and for a range of parameters of the objective functions. Further trial-and-error may yield further improvement.

The second example is that of recurrent metastasis to the brain from mixed adenosquamous carcinoma of the lung. There were 2 tumor nodules 5 cm apart, one located medially and the other laterally, each about 1 cm³. Each tumor was treated with 2 sets of 5 and 4 arcs on a protocol for enhancing recurrent tumors with fractionated stereotactic radiotherapy of 9 Gy/fraction × 3. As in example 1, a margin of zero was assigned for IMRT to minimize the volume of normal brain exposed to high doses, accepting higher
Fig. 4. Dose-volume histograms for the two tumor nodules.

Table 2. Dose-volume data for the normal brain for example 2

<table>
<thead>
<tr>
<th></th>
<th>Arcs</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume in 600 cGy isosurface</td>
<td>12.57</td>
<td>10.31</td>
</tr>
<tr>
<td>Volume in 700 cGy isosurface</td>
<td>9.22</td>
<td>5.99</td>
</tr>
<tr>
<td>Volume in 800 cGy isosurface</td>
<td>6.83</td>
<td>3.17</td>
</tr>
<tr>
<td>Volume in 900 cGy isosurface</td>
<td>3.56</td>
<td>1.32</td>
</tr>
<tr>
<td>Volume in 1,000 cGy isosurface</td>
<td>0.41</td>
<td>0.45</td>
</tr>
<tr>
<td>Irradiated vol./tumor vol.</td>
<td>2.57</td>
<td>1.58</td>
</tr>
</tbody>
</table>

target dose inhomogeneity. The IMRT plan was designed with 9 equispaced coplanar beams (every 40°) centered around the mid point between the centers of the two tumors and were intended to treat both tumors simultaneously.

Figure 3 a–d show the dose distributions on selected transverse sections comparing the 9-arc plan with the 9 coplanar beam IMRT plan. Plans were normalized so as to deliver the prescription dose of 9 Gy/fraction to 95% of the target volume.

Figure 4 shows dose-volume histograms for the two tumor nodules. Table 2 shows the dose-volume data for the normal brain and indicates that the volume of normal brain exposed to high doses is substantially reduced. From these data it appears that the IMRT dose distributions are more conformal than arcs. Part of the difficulty of obtaining adequate dose distributions when more than one set of arcs is employed is that each arc contributes dose to the region
treated by other arcs. For this reason conformal arcs may not be able to produce as good dose distributions for multiple foci as they do for a single tumor.

Conclusions

Two examples are presented to examine the potential of IMRT for SRS. The first example of a small convex tumor is too simple a case to fully take advantage of IMRT. The second case of 2 foci is better able to take advantage of the ability of IMRT to plan and treat both tumors simultaneously. The IMRT dose distributions are better than arcs and the delivery would be easier and require less time. Although not shown here, IMRT should do better for complex tumor shapes as well, especially those requiring multiple isocenters.

Acknowledgment

This work is supported by grant CA74043 from the National Cancer Institute.

References


Three-Dimensional Endovascular Brachytherapy

Ulrich Quast a, Dirk Flühs a, Markus Bambynek a, Dietrich Baumgart b, Clemens von Birgelen b

a Clinical Radiation Physics, Department of Radiotherapy, and
b Department of Cardiology, University Hospital, Essen, Germany

Intravascular Brachytherapy to Inhibit Restenosis

Stenoses of coronary arteries are the main cause of mortality in the western world. Dilation of stenotic vessels was enabled by percutaneous transluminal coronary angioplasty (PTCA) developed by Dotter and Judkins [1] and introduced into clinical practice by Grüntzig et al. [2] as a minimal invasive treatment modality (fig. 1). Recurrent stenosis, however, was observed in about half of the cases a few months after the intervention. Since then, inhibition of restenosis has been the focus of research in numerous experimental studies and clinical trials. Alternative or additional treatment modalities, such as stenting, directional, rotational and laser atherectomy were developed and successfully applied. However, all these attempts, even when combined with a large variety of pharmacological agents, could not inhibit recurrent stenosis.

Vascular radiotherapy [3–9] with low doses applied immediately after the intervention has recently proven to be the first method to significantly reduce the risk of restenosis. The success of endovascular brachytherapy, first achieved in the treatment of large peripheral vessels [10], was also verified in the treatment of coronary arteries in numerous animal studies [11, 12] and in more than 30 clinical trials [9]. Although a wide variety of therapeutic photon and beta radiation sources (table 1) and dose delivery techniques have been applied [13], decisions about the optimal method of vascular radiotherapy and radiation source are not yet possible. The reliability and practicability of the technique must be taken into consideration.

Three processes contribute to restenosis as a response to arterial wall injury: elastic recoil effects immediately after PTCA (requiring stenting in
Fig. 1. Angiogram and IVUS tomogram of a stenotic coronary artery prior to (a) and after PTCA (b).

about half of the cases) [14], *neointima hyperplasia* developing a few weeks after the intervention, and *negative* remodeling [15], a serious shrinkage of the vessel wall after several months of wall thickening. Intravascular brachytherapy can inhibit both neointima hyperplasia and arterial remodeling.

**Intravascular-Ultrasound and Plastic-Scintillator Dosimetry**

Accurate vascular radiotherapy demands high-resolution localization and precise dosimetry, careful treatment planning, documentation, reporting and evaluation [16].
**Target Volume**

Neither the biology of stenosis and restenosis nor the radiobiology of radiation inhibition of stenosis are sufficiently understood. But there is evidence that the whole arterial wall of the injured vessel section, including intima, media and adventitia, has to be considered as the target volume [16]. Suitable safety margins have to be applied to avoid edge restenoses at the ends of the vessel section injured by the intervention.

**Structures at Risk**

Irradiation-related complications have not been observed so far in vascular radiotherapy [17], but there is experimental and clinical evidence [18] that the vasa vasorum supplying the arterial wall have to be regarded as the structures at risk. The risk, however, seems to be low, as the doses delivered in vascular radiotherapy are much smaller than the tolerance of the microvasculature. Radiation-induced stenosis has been observed only for high doses exceeding 40 Gy of mediastinal irradiation in the treatment of Hodgkin's disease or breast cancer, and only in patients with a high stenotic risk, such as smokers, diabetics, or overweight patients [19]. In addition, the latency period of 5–20 years is very long compared to a few months after the intervention.

**High-Resolution Localization**

X-ray angiography provides projectional views of the stenotic vessel section in relation to its environment (fig. 1), but does not enable quantification of the stenotic situation nor does it provide the data required for treatment planning. Intravascular ultrasound (IVUS) [20, 21] is the solution for localization for vascular brachytherapy planning (fig. 1). IVUS allows to quantify and characterize the vessel wall architecture [14, 15, 22, 23]. Derived from a series of IVUS tomograms, two-dimensional ultrasound views of the artery wall in vivo can be reconstructed [24, 25] (fig. 2). The high ultrasound frequency (40 MHz) and the potential of phased-array focusing and echo acquisition allow for high-resolution localization. In addition, Fourier transform analysis of the frequency spectrum of the sound signal enables quantification of the blood flow situation prior to, during and after the intervention.

**High-Precision Dosimetry**

Dosimetry of intravascular brachytherapy with low-energy photon radiation or therapeutic beta radiation (table 1), both with very high dose rates (up to 50 Gy/min) and an extremely steep dose decrease (e.g. for beta radiation more than 4 orders of magnitude of dose within 10 mm) mean a great challenge for medical physicists [16, 26]. The requirements for the direct measurement of the absorbed dose to water cannot be satisfactorily performed by common
methods of brachytherapy dosimetry, such as thermoluminescence dosimetry or radiochromic film dosimetry [26–30]. Also, dose calculations or Monte Carlo simulations [31] cannot replace direct measurement, as they require knowledge of the physical situation in advance. Thus, high precision, high resolution and fast measurement of the absolute and relative distributions of the absorbed dose to water are basically required for endovascular brachytherapy.

Plastic scintillators, which have been known for years to be ideal for eye plaque dosimetry [32–34], are optimal for endovascular source dosimetry as well [16]. The tissue-substituting detector probe enables energy-independent dosimetry (≤ ±2%) for all beta radiation sources and for photons with energies above 200 keV. Due to its high sensitivity, very tiny detectors (e.g. 1 mm in diameter and 0.4 mm in length) can be used, providing the high spatial resolution required in vascular brachytherapy. The scintillation light guided by thin tissue-substituting fibers, converted by highly sensitive photo-multipliers into electrical current and integrated by a PC within fractions of a second, is proportional to the absorbed dose to water. The large and linear dynamic range of the dosimeter system (over up to 6 orders of magnitude of dose) enables high-precision dose measurements around all sources for endovascular brachytherapy, e.g. from the surface of the high-activity source down to the background of bremsstrahlung (fig. 3).

Detector and dosimeter system (including a precision 90Sr check source) are calibrated in terms of absolute absorbed dose (rate) to water for beta radiation at the National Institute of Standards and Technology, Gaithersburg, Md., USA and for photon radiation at the Physikalisch Technische Bundesan-
<table>
<thead>
<tr>
<th>Source</th>
<th>$E_{\text{max}}$/MeV</th>
<th>$E_{\text{max}}$/MeV</th>
<th>$T_{1/2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta emitter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{186}$Re</td>
<td>0.35</td>
<td>1.1</td>
<td>90.6 h</td>
</tr>
<tr>
<td>$^{32}$P</td>
<td>0.69</td>
<td>1.71</td>
<td>14.26 days</td>
</tr>
<tr>
<td>$^{90}$Sr/$^{90}$Y</td>
<td>$^{90}$Sr: 0.2</td>
<td>0.54</td>
<td>28.8 years</td>
</tr>
<tr>
<td></td>
<td>$^{90}$Y: 0.93</td>
<td>2.28</td>
<td>64.1 h</td>
</tr>
<tr>
<td>$^{106}$Ru/$^{106}$Rh</td>
<td>$^{106}$Ru: 0.01</td>
<td>0.039</td>
<td>371 days</td>
</tr>
<tr>
<td></td>
<td>$^{106}$Rh: 1.42</td>
<td>3.54</td>
<td>30 s</td>
</tr>
<tr>
<td><strong>Beta, gamma emitter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{133}$Xe</td>
<td>$\beta$: 0.1</td>
<td>$\beta$: 0.35</td>
<td>5.24 days</td>
</tr>
<tr>
<td></td>
<td>$\gamma$: 0.05</td>
<td>$\gamma$: 0.08</td>
<td></td>
</tr>
<tr>
<td>$^{198}$Au</td>
<td>$\beta$: 0.3</td>
<td>$\beta$: 0.96</td>
<td>2.7 days</td>
</tr>
<tr>
<td></td>
<td>$\gamma$: 0.4</td>
<td>$\gamma$: 0.4</td>
<td></td>
</tr>
<tr>
<td>$^{188}$W/$^{188}$Re</td>
<td>$^{188}$W: 0.1</td>
<td>0.35</td>
<td>69 days</td>
</tr>
<tr>
<td></td>
<td>$^{188}$Re: $\beta$: 0.77</td>
<td>$\beta$: 2.12</td>
<td>17 h</td>
</tr>
<tr>
<td></td>
<td>$\gamma$: 0.16</td>
<td>$\gamma$: 0.93</td>
<td></td>
</tr>
<tr>
<td>$^{53, 55, 58}$Co, $^{58}$Fe; radioactive</td>
<td>$\epsilon$, $\beta^+$</td>
<td>–</td>
<td>18 h– &lt;2.7 years</td>
</tr>
<tr>
<td>Palmaz-Schatz® stent</td>
<td>$\gamma$, X</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>$^{48}$V; radioactive</td>
<td>$\beta^+$: 0.3</td>
<td>0.7</td>
<td>16 days</td>
</tr>
<tr>
<td>Nitinol® stent</td>
<td>$\gamma$: 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gamma emitter</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{193}$Pd/$^{193m}$Rh</td>
<td>0.020</td>
<td>0.021</td>
<td>17.0 days</td>
</tr>
<tr>
<td>$^{121}$I</td>
<td>0.028</td>
<td>0.035</td>
<td>59.4 days</td>
</tr>
<tr>
<td>$^{99m}$Tc</td>
<td>0.14</td>
<td>0.14</td>
<td>6.0 h</td>
</tr>
<tr>
<td>$^{192}$Ir</td>
<td>0.37</td>
<td>1.06</td>
<td>73.8 days</td>
</tr>
<tr>
<td><strong>X-radiator</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endovascular X-ray tube</td>
<td>0.015</td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

stalt, Braunschweig, Germany. A high-precision, computer-controlled three-dimensional (3D) positioning device allows determination of the spatial distribution of dose in water with high resolution and a reproducibility of 1–2%. Due to its high sensitivity, the computer-controlled system enables fast dose acquisition: a beta radiation depth dose distribution measured at 50 measuring points requires less than 10 min.
Thus, plastic-scintillator dosimetry allows endovascular source calibration in terms of absorbed dose to water, for all beta and most photon sources applied. All dosimetric data required by the AAPM TG 60 recommendations for basic dosimetry and for source characterization as well as those for treatment planning and evaluation can be determined precisely and quickly.

**Intravascular-Ultrasound-Guided and Dosimetry-Based Vascular Brachytherapy Planning**

Commercial treatment planning systems for endovascular brachytherapy are not yet available. But combined, 3D IVUS localization and 3D plastic-scintillator dosimetry provide a powerful tool for high-precision treatment planning of endovascular brachytherapy (fig. 4).

Several influences on the spatial distribution of dose have to be considered. Atherosclerotic arteries show irregular, noncylindrical shapes. The lumen di-
Fig. 4. IVUS localization for treatment planning combined with isodoses of a $^{90}$Y-line source, normalized to 100% at a radial distance of $z = 2$ mm from the source center.

Parameters and vessel wall dimensions vary rapidly (fig. 2). In addition, the living coronary artery changes its tortuous shape and position with each heart beat and blood pulse. Thus, for practical treatment planning and evaluation of dose distribution, a typical average situation has to be considered.

In intravascular brachytherapy, the spatial distribution of dose is primarily influenced by the strong dependence on distance (fig. 2–4). Further, the spatial distribution of dose is characteristically shaped by the type and energy of radiation and source geometry. The dose distribution delivered to the coronary artery also depends strongly on the position of the (line) source relative to the vessel wall layers. Centering devices, e.g. segmented or spiral-shaped balloon catheters can center up the source relative to the vessel lumen, but not to all vessel wall layers. Although the resulting distributions of dose delivered to the target structures are very broad, the clinical results are good – as long as the dose delivered is sufficiently high and as sufficiently long safety margins are applied to fully cover the injured section of the vessel.
Conclusion

Dosimetry is not yet performed routinely for all endovascular brachytherapy sources, ultrasound localization is not commonly used (not even in all clinical trials), and true 3D IVUS-based localization is still in a developmental stage (Fig. 5). But this will change soon. Individual IVUS-based localization and plastic-scintillator-based 3D dosimetry enable precise and fast treatment planning as well as evaluation of dose distribution and complete reporting, which are needed to understand and optimize 3D endovascular brachytherapy.

Acknowledgment

The authors would like to express their thanks to R. Erbel, M. Heintz, F. Indenkämpen, H. Sack, and K.C. Willborn. The work presented was partially supported by DFG grants (Qu 39/7-1,2, Qu 39/10-1, and Qu 39/16-1) of the German Research Foundation.
References


27 Meigooni AS, Nath R: A comparison of radial dose function for $^{103}$Pd, $^{125}$I, $^{153}$Sm, $^{241}$Am, $^{192}$Ir, and $^{137}$Cs brachytherapy sources. Int J Radiat Oncol Biol Phys 1992;22:1125–1130.


Prof. Dr. rer. nat. Ulrich Quast, Klinische Strahlenphysik, Abteilung für Strahlentherapie, Universitätsklinikum Essen, D-45122 Essen (Germany)
Tel. +49 201 723 2090, Fax +49 201 723 5728, E-Mail ulrich.quast@uni-essen.de
New Tools of Brachytherapy Based on Three-Dimensional Imaging

Dimos Baltas\textsuperscript{a,c}, Natasa Milickovic\textsuperscript{a,b}, Stavroula Giannouli\textsuperscript{a,b}, Michael Lahanas\textsuperscript{a}, Christos Kolotas\textsuperscript{a}, Nikolaos Zamboglou\textsuperscript{a,c}

\textsuperscript{a} Department of Medical Physics and Engineering, Strahlenklinik, Städtische Kliniken Offenbach, Offenbach, Germany; \\
\textsuperscript{b} Department of Electrical and Computer Engineering, and \\
\textsuperscript{c} Institute of Communication and Computer Systems, National Technical University of Athens, Athens, Greece

Nowadays, brachytherapy planning is based on imaging modalities \cite{1-8}, among which computer tomography (CT) is the most frequently used. Magnetic resonance (MR) and ultrasound imaging have also been considered for brachytherapy planning. However, even if MR had some advantages with reference to tissue resolution and classification (brain and gynecological localizations), its use would be limited, mainly because of the long acquisition times (much longer than for CT). Current developments in three-dimensional (3D) ultrasound imaging open new horizons for the routine integration of this imaging modality into brachytherapy.

This chapter focuses on the CT imaging modality. The integration of imaging into brachytherapy planning enables clinicians to define the planning target volume (PTV) and the relevant critical structures similarly to external-beam radiotherapy. This information can then be used to adjust the dose distribution to fulfill the clinical aims.

The available implementations of CT-based brachytherapy planning systems enable the manual CT-based reconstruction of implanted catheters and the dose optimization with regard to the PTV. The accuracy of reconstruction mainly depends on CT imaging parameters such as slice thickness and interslice distance. In addition, the accuracy also depends on graphic resolution and the user’s expertise. The overall reconstruction accuracy of a CT-based treatment planning system can be as low as 1.0 mm \cite{1}. In clinical brachytherapy, catheter reconstruction is the most time-consuming and error-prone part of the treat-
Table 1. Imaging parameters for the 35 clinical implants analyzed

<table>
<thead>
<tr>
<th>Images¹</th>
<th>Matrix pixels × pixels</th>
<th>Slice thickness mm</th>
<th>Interslice distance mm</th>
<th>Catheters¹</th>
<th>Plastic</th>
<th>Metallic</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 ± 10</td>
<td>512 × 512</td>
<td>3.0</td>
<td>3.0–5.0</td>
<td>6 ± 3</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>15–57</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Means ± 1 SD and ranges (in parentheses).

...ment planning procedure. This is because the number of catheters can be very large, as in the case of interstitial brachytherapy, where more than 30 catheters may be necessary. Imaging-based treatment planning methods can significantly reduce the time required for treatment planning compared to the use of projectional reconstruction methods (PRM) using radiographs. Even so, a significant part of the treatment planning time is still spent on catheter reconstruction. For a large number of catheters or complex catheter geometries, manual catheter reconstruction can account for more than half of the total treatment planning time.

Furthermore, the result of the dose optimization procedure strongly depends on the correct selection of the source dwell positions within the catheters. Current optimization methods are based mainly on minimizing the dose variance values on the PTV surface. Even if dwell positions outside the PTV were selected, by mistake these will be considered in the optimization, and some of them (depending on the implant and PTV geometries) will have non-zero dwell times. PTV shapes are usually complex and adding in the catheters with the source dwell positions results in a confusing geometry even for very experienced planners. Manual selection of the source dwell positions, which is current practice even for modern systems based on 3D imaging, is a time-consuming procedure devoid of any guarantee of success.

From the analysis we made on 35 clinical implants (tables 1, 2) manual catheter reconstruction took up an average of 41% (range 21–71%) of the total treatment planning time. These times do not include those for image processing and contouring. Mean reconstruction time was 13.1 min (range 4.5–50.1 min). Mean reconstruction time per catheter was 142.4 s (range 42.9–312 s), and mean reconstruction time per catheter per CT image was 4.1 s (range 1.2–10.0 s). 17% of the treatment planning is spent on selecting the source dwell positions (range 6–33%). The mean time spent on this procedure is 5.1 min (range 1.5–15 min), which corresponds to a mean time of 56 s per implanted catheter (range 22.5–100.0 s).
Table 2. Time analysis for the different components of the treatment planning procedure for the 35 clinical implants

<table>
<thead>
<tr>
<th></th>
<th>Imaging and contouring min</th>
<th>Reconstruction min</th>
<th>Source dwell position selection min</th>
<th>Optimization min</th>
<th>Evaluation min</th>
<th>Total min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>16.3 ± 7.3</td>
<td>13.1 ± 10.5</td>
<td>5.1 ± 3.5</td>
<td>5.7 ± 4.8</td>
<td>5.8 ± 2.5</td>
<td>46.0 ± 19.1</td>
</tr>
<tr>
<td></td>
<td>(7.5–38.0)</td>
<td>(4.5–50.1)</td>
<td>(1.5–15.0)</td>
<td>(2.0–30.0)</td>
<td>(1.5–12.0)</td>
<td>(21.7–102.9)</td>
</tr>
<tr>
<td></td>
<td>36 ± 9%</td>
<td>26 ± 11%</td>
<td>11 ± 5%</td>
<td>20 ± 10%</td>
<td>14 ± 7%</td>
<td>29.6 ± 14.5</td>
</tr>
<tr>
<td></td>
<td>–</td>
<td>41 ± 14%</td>
<td>17 ± 7%</td>
<td>26 ± 11%</td>
<td>22 ± 11%</td>
<td>(12.7–76.1)</td>
</tr>
</tbody>
</table>

Means ± 1 SD and ranges (in parentheses).

1 Values exceeding the duration of the imaging and contouring procedure.

These results demonstrate that there is an obvious need for methods of automatic catheter reconstruction and selection of the correct source dwell positions that significantly decrease the duration of treatment planning and increase its safety and reliability. In the following we are presenting our solutions.

**Computer-Tomography-Based Catheter Autoreconstruction**

Algorithms have been developed [9] for the automatic reconstruction and recognition of plastic and metallic implanted catheters (fig. 1, 2). The process is based on postimplantation-acquired CT images with the catheters in situ in their final positions. This includes the relevant patient anatomy, target volume(s), organs at risk, and the catheters. Catheter searching is made on a sequence of CT slices and is based on the Hounsfield number of the catheter material, catheter outer diameter, interslice distance, slice thickness and catheter geometry on the CT slices. If there is no patient motion during CT data acquisition, there is virtually no error in the autoreconstruction process.

Our algorithms overcome a number of difficulties which arise when a large number of catheters are present. These include situations with intersecting catheters and with loop techniques. The time required for the catheter reconstruction using our autoreconstruction method is significantly reduced. The accuracy of our autoreconstruction is at least as high as that of the classical manual slice-by-slice method.
Fig. 1. Cervix implant with nine metallic trocar point needles. a Representative CT image showing the catheter areas. b 3D view of the autoreconstructed catheters and the PTV volume.

Fig. 2. Clinical implant in the head with five plastic flexible catheters. a Representative CT image showing the catheter areas. b 3D view of the autoreconstructed catheters and the PTV volume.
The accuracy of our autoreconstruction method has been tested in routine clinical practice. Twenty-two implants were selected to cover a representative spectrum of anatomical sites and implant geometries as well as different catheter types and materials. The accuracy of our automatic catheter reconstruction method was analyzed for the catheter-describing points and for the reconstructed source dwell positions within the catheters produced every 2.5 mm starting from the given catheter tip [1]. The mean errors over all catheters or source dwell positions for each catheter are stated where the manual catheter reconstruction was used as reference. The error analysis based on catheter-describing points showed mean geometrical errors varying from $0.34 \pm 0.23$ to $1.1 \pm 3.33$ mm with a mean value of $0.65 \pm 0.34$ mm for all 22 implants. Analysis based on source dwell position gave mean geometrical errors varying from $0.36 \pm 0.16$ to $1.31 \pm 0.42$ mm with a mean value of $0.84 \pm 0.34$ mm.

A time analysis was further performed for another group of 30 clinical implants. For this purpose, the autoreconstruction was compared to manual reconstruction as performed in the clinical routine. In 27 of the 30 cases (90%), no manual intervention by the user was needed during the autoreconstruction-based process. For these 27 cases, automatic catheter reconstruction was 25.7 times (mean value) faster than the manual reconstruction as applied in the clinical routine. The mean time needed for our autoreconstruction method was 21.4 s compared to 9.12 min for the corresponding manual procedure. For the 3 cases where manual intervention was required, the catheter reconstruction based on our autoreconstruction algorithm was 8.2 times faster (mean value) than the corresponding manual reconstruction. The mean reconstruction time with our method, including the intermediate manual intervention, was 81.7 s compared to 12.33 min for the manual procedure.

**Catheter Reconstruction Based on Digitally Reconstructed Radiographs**

We have developed efficient tools for catheter reconstruction based on CT-reconstructed radiographs calculated from the 3D volume constructed from CT slices. Until now, and for projectional reconstruction methods, catheter reconstruction was done from true X-ray radiographs [10–13]. This can cause errors because of patient motion between two radiograph acquisitions and because of geometrical inaccuracies of the X-ray system. Additionally, catheters or parts of these can be covered by bones.

Two different methods have been developed for radiograph-based reconstruction from a CT volumetric data set. One method is the real simulation of the physical process (X-rays passing through inhomogeneous human tissue)
Fig. 3. Four DRRs calculated from the same volumetric data set. DRRs were produced with different anatomical filters included. 

- **a** Bone filter.
- **b** Soft tissue filter.
- **c** Fat tissue filter.
- **d** Original data set projected.

and the second is a real-time volume-rendering method (splatting algorithm). The user can choose 1 of 12 simulation energies, volumetric resolution parameters, source and isocenter position, FAD and FFD, geometrical region to be projected and anatomical and/or catheter filters (fig. 3). Projecting only the wanted kind of catheters, there is no loss of information in the regions covered by bones or soft tissue.

The user can work with one or two digitally reconstructed radiographs (DRRs). Target and contours of organ of interest, markers, already reconstructed catheters and region of influence of the current slice can be projected on DRR. One can obtain information for the active DRR, save it or load any previously saved DRR. There is a ruler which helps the user to get the true geometrical distance in millimeters between any two points on the DRR plane.

Six image-processing filters are included. These are different sharpening and smoothing filters, and edge detection filters. Navigation tools from one to the other reconstructed radiograph, from radiographs to CT volume and from the volume to radiograph are provided. Two different methods have been
developed for catheter reconstruction: (a) matching of corresponding points supported by navigation tools (fig. 4) and (b) automatic matching of corresponding points and catheters on the CT-reconstructed radiographs (polynomial method without need for defining the correspondence).

As we use two CT-reconstructed radiographs for catheter reconstruction, we do not have the problem of reconstruction errors resulting from patient motion, as occurs when making two real radiographs. Navigation tools help the user during the whole process, and real-time 3D visualization offers the opportunity of an effective control of the reconstruction result, looking at it in the 3D view window or at any CT slice (fig. 4b).

In the case of classical gynecological brachytherapy applications the newly developed reconstruction methods based on CT-reconstructed radiographs can further help identify bony structures and reference points as proposed by ICRU 38 [14].

Autoactivation of Source Dwell Positions

A new technique has been developed [15], the autoactivation procedure, which automatically recognizes those source dwell positions within reconstructed catheters that satisfy specified geometrically defined constraints relative to the PTV and critical structures.

Our method is based on postimplantation CT images which include the implanted catheters and the relevant patient anatomy with target volume(s) and critical organs. We consider the following geometrical constraint criteria for the autoactivation procedure. (a) The dwell position is inside the PTV with or without an isotropic 3D margin around it. (b) The dwell position retains a specified minimum distance from one or more critical structures. The isotropic 3D margin around the PTV [16–19] is defined as a negative or positive distance value in millimeters and takes into account the cases where the source dwell positions either must be inside the PTV, keeping a minimum distance from its surface (negative margin value) or they can also be outside the PTV, keeping a maximum distance from its surface (positive margin value).

If the requirement is to activate (select) only source dwell positions that retain a minimum distance (offset) from the surface of a given contoured structure, this is methodologically equivalent to setting an isotropic margin equal to the offset around the 3D surface of the object and then searching for those source dwell positions which are inside or outside the new 3D surface consisting of the original 3D surface to which the margin is added. Generally, this can result in an increase (positive offset and margin) or a decrease (negative offset and margin) in the volume considered. For our purposes, we suggest
Fig. 4. Prostate implant with four metallic needles. a Two DRRs calculated from the same volumetric data set and with the same isocenter coordinate. Navigation tool from one to the other DRR is presented. b After catheter reconstruction, the results can be seen in 3D and 2D (on CT slice) view.
that the 3D surface of any anatomical structure (PTV, critical structures) is described by an adequate triangulation based on the contours of that structure.

Our autoactivation tool offers four different methods for calculating distances. Three of them are based on the provision of an isotropic 3D margin (positive or negative value) around the triangulated surface of a contoured structure: (a) center of gravity method, (b) normal vector based method and (c) distance-mapping method. The fourth method is based on directly calculating the distance of a point from a triangulated 3D surface. Analysis of the accuracy of all four options has shown [15] that the autoactivation procedure based on the normal-vector method to provide isotropic 3D margins is the most adequate for the clinical routine regarding speed and achievable accuracy.

To demonstrate the benefits of the autoactivation algorithm, 27 different clinical implants were investigated and the results obtained with our method were compared to those obtained using the manual source dwell position selection procedure. The PTVs ranged between 19 and 265 cm³ and the number of catheters ranged between 3 and 13. The mean number of catheters per implant was $5 \pm 3$. The mean number of CT transaxial images per implant was $39 \pm 10$ (range 15–57 images).
Fig. 6. Brain implant with 10 plastic catheters and a PTV of 87.3 cm³. 

Representative CT transaxial images and the corresponding 3D views of the PTV and the reconstructed source dwell positions within the catheters for two selected clinical cases are shown in figures 5 and 6.

After clinical treatment planning was completed, these implants were input into our software [1] and the autoactivation procedure was utilized based on the margins (offset values) previously used for clinical treatment planning. The time needed for the autoactivation was electronically recorded. During the clinical planning procedure, the time needed for the manual selection of the appropriate source dwell positions was measured and recorded. The mean time needed for the autoactivation procedure was 15.2 s compared with 306.6 s for the manual procedure (speed-up factor of 20.2). This corresponds to a mean autoactivation time per source dwell position of 0.071 s compared with 1.32 s for the manual selection procedure.

Discussion

The new tools developed and described here simplify the treatment planning procedure of brachytherapy. Not only the achieved speed-up but
also the accuracy and reliability of the solutions we presented open new horizons in modern brachytherapy. Treatment planning can be done by clinicians, physicists and dosimetrist and is not any more limited to highly experienced ‘experts’. The running developments in the field of anatomy-based dose optimization will enable a real inverse planning and conformation in brachytherapy. The future of imaging-based treatment planning and imaging-based brachytherapy in general will be definitely influenced by these efforts.

Acknowledgments

This work was partly supported by a grant (GRI-154-97) from the Federal Ministry for Education, Science, Research and Technology, International Bureau, German Aerospace Center Department (DLR), Bonn, Germany and by Nucletron BV, Veendendaal, The Netherlands.

References


Dimos Baltas, PhD, Department of Medical Physics and Engineering, Strahlenklinik, Städtische Kliniken Offenbach, Starkenburgring 66, D–63069 Offenbach (Germany)
Tel. + 49 69 8405 4480 or 3335, Fax. + 49 69 8405 4481 or 864480, E-Mail dbaltas@compuserve.com
Lung Cancer – Radiotherapy in Combined-Modality Schedules

M. Stuschke\textsuperscript{a}, C. Pöttgen\textsuperscript{b}

\textsuperscript{a} Department of Radiotherapy, University Hospital Charité, Berlin, and
\textsuperscript{b} Department of Radiotherapy, University Hospital Essen, Essen, Germany

About 30\% of patients with non-small-cell lung cancer (NSCLC) have locally advanced tumors with involvement of mediastinal lymph nodes (stage IIIA/B). In this situation, radiotherapy is the mainstay of treatment, either alone or in combined-modality schedules [1]. At the time of diagnosis, patients often present with bulky primary tumors and extensive mediastinal involvement so that the initial planning target volume amounts to 30–40\% of the volume of both lungs. For example, according to a restrictive definition, the initial planning target volume has to include the clinical target volume and a margin of 0.7 cm in all directions, which considers setup errors and organ movements. The clinical target volume then contains the gross primary tumor volume and lymph node stations with nodes >1 cm in their shortest diameter as well as all lymph node sites known to be involved by mediastinoscopy with a margin of 0.5–1.0 cm but not beyond uninvolved anatomical borders (such as periost of noninvolved vertebral bodies or mediastinal pleura). In addition, most combined-modality protocols include the ipsilateral mediastinal lymph nodes except the paraesophageal and pulmonary ligament nodes below the carina as well as the contralateral paratracheal nodes in the clinical target volume up to a cumulative dose of 45–50 Gy. The corresponding large target volumes preclude the application of total doses larger than 60–70 Gy in many patients without exceeding the tolerances of the surrounding normal tissues, especially in the lung and spinal cord. After conventionally fractionated radiotherapy up to 60–70 Gy, however, local control rates of less than 20\% were observed [2, 3].
Combined Radiochemotherapy

One of the most effective strategies to improve locoregional control of locally advanced NSCLC is the combination of chemotherapy and simultaneous radiotherapy. This has been first demonstrated by an EORTC study combining daily or weekly cisplatin and simultaneous split-course radiotherapy [3]. The locoregional control rates at 3 years increased from 5% after radiotherapy alone to 28% after radiochemotherapy (p < 0.01). However, this result was not unequivocally reproduced in another moderate-sized phase III study with more than 100 patients per arm comparing radiotherapy alone with radiotherapy and cisplatin every 3 weeks [4]. More recently, Furuse et al. [5] compared conventionally fractionated radiotherapy to 56 Gy with a 10-day break after 28 Gy and simultaneous chemotherapy with mitomycin C, vindesine, and cisplatin versus the same chemotherapy regimen and continuous-course radiotherapy to the same total dose given sequentially. They found the simultaneous schedule with a shorter total treatment time to be significantly more active, with a surviving fraction of 16% at 5 years in comparison to 9% after sequential therapy. This important study demonstrates that the total treatment time of both radiotherapy and chemotherapy critically determines the therapeutic effect. Furthermore, the dose intensity of radiotherapy during concurrent radiochemotherapy is an important factor for the locoregional treatment effectiveness. A randomized trial strictly testing this hypothesis is only available for small-cell lung cancer (SCLC) patients [6]. In this trial, conventionally fractionated thoracic radiotherapy to 45 Gy in 5 weeks was compared with accelerated hyperfractionated radiotherapy to 45 Gy in 3 weeks with 2 × 1.5 Gy per day both starting simultaneously with the first course of etoposide/cisplatin. SCLC is more chemoresponsive than NSCLC and therefore repopulation should be more effectively hindered by chemotherapy in SCLC. Nevertheless, survival was significantly better after accelerated hyperfractionated radiochemotherapy, reaching the very good mark of 26% at 5 years compared to 16% after conventionally fractionated radiotherapy. Locoregional recurrences were observed in 52% of patients after conventionally fractionated radiotherapy and 36% of patients treated with accelerated hyperfractionated radiotherapy.

Cisplatin-containing chemotherapy regimens given in full dose have the potential to decrease the risk of distant metastases in patients with locally advanced NSCLC. This has been demonstrated in a moderate-sized French trial analyzing the concurrent risks after radiotherapy alone and sequential radiotherapy and chemotherapy with vindesine, cisplatin, lomustine, and cyclophosphamide [2]. The two other randomized trials with more than 100 patients per treatment arm comparing conventionally fractionated radiotherapy alone
with sequential cisplatin-containing chemotherapy and conventionally fractionated radiotherapy also showed a trend toward better survival and less distant metastases in the combination arm [7, 8]. However, the risk of cerebral metastasis is not substantially reduced by current cisplatin-containing chemotherapy regimens according to a retrospective analysis of the Radiation Oncology Therapy Group (RTOG) database [9]. Meta-analyses giving overviews of all past randomized trials comparing radiotherapy in combination with cisplatin-containing chemotherapy and radiotherapy alone for patients with locally advanced unresectable NSCLC, showed that the radiochemotherapy trials are associated with better survival. This holds for both sequential and simultaneous cisplatin-based radiochemotherapy schedules [10, 11]. However, the average 13–17% reduction of mortality by the combined-modality schedules translates only to a modest absolute increase in survival at 5 years. The latter exceeds 10% only in very few studies. Therefore, it is important to select patients for combination programs who may profit most from the intensified treatment. Selection criteria chosen by the RTOG, the Eastern Cooperative Oncology Group (ECOG) and the Cancer and Leukemia Group B (CALGB) are the following: Karnofsky performance status \( \geq 70 \), weight loss \(< 5\%\) in the last 3 months, and no pleural effusion.

Based on these data, radiochemotherapy according to well-evaluated schedules that have shown their efficacy in large randomized studies [3, 8] is suggested for selected patients with a good performance status outside clinical trials [12, 13]. However, the gain in life expectancy is only modest and generalization of the results of the randomized studies towards the various different subsets of patients with inoperable locally advanced NSCLC is difficult. Thus, there is up to now no general agreement on the routine use of radiochemotherapy as standard treatment in inoperable locally advanced carcinomas [14, 15]. According to the current guidelines of the Deutsche Krebsgesellschaft, radiochemotherapy should be applied solely in the frame of clinical trials [15]. It is awaited that these guidelines will be rediscussed in the near future.

Further improvements of the results of definitive radiochemotherapy in locally advanced NSCLC are awaited from the introduction of new drugs, i.e. the taxanes. Randomized studies, which compare traditional cisplatin-containing regimens with regimens containing new drugs given concurrently or sequentially with radiotherapy are not available at this time in LAD-NSCLC. Up to now, phase I/II studies have been performed that define the toxicity profile of taxane-radiotherapy combinations. Acute mucosal toxicity to the esophagus is intensified and can become dose-limiting, even in combinations with conventionally fractionated radiotherapy [16]. The latter causes grade 3 esophagitis in less than 5% of the patients as a single modality. In addition, the risk of acute lung reactions also appears to be also slightly raised.
in simultaneous radiotherapy-taxane schedules [17]. A retrospective analysis reported by Yamada et al. [18] reveals that the risk of pneumonitis is also increased in radiotherapy and simultaneous administration of the topoisomerase-I inhibitor CPT11. However, all published phase I/II studies lack sufficient data characterizing the radiation dose distributions to the lungs. Therefore, a quantitative analysis of the lung-tolerance-modifying effects of the new drugs cannot be made.

Quantitative data have been reported recently allowing the estimation of the pneumonitis risk after radiotherapy alone from the inhomogeneous dose distributions to the lungs. Kwa et al. [19] analyzed the association between the mean physical lung ($D_{\text{mean}}$) as a simple descriptive parameter of the dose distributions and the risk of pneumonitis grade ≥ 2 in a retrospective series of 399 lung cancer patients. $D_{\text{mean}}$ above 22 Gy led to a marked increase in the pneumonitis risk. $D_{\text{mean}}$ associated with a pneumonitis risk of 50% ($D_{\text{mean}50}$) was about 34 Gy. We also retrospectively evaluated 64 patients with NSCLC who received either cisplatin/etoposide sequentially and/or simultaneous thoracic irradiation and found a slightly smaller value for $D_{\text{mean}50}$ of 29 Gy. The accuracy of those estimates is limited by the number of patients as well as treatment- and patient-related confounding factors. Experimental and clinical data indicate that the radioresponsiveness of the lungs is not isotropic: the basal parts which show enhanced perfusion may have an increased number of functional units per unit volume and are therefore more radioresponsive [20, 21]. Furthermore, low pretreatment lung function and preexisting lung disease as well as older age have been identified as important negative modifiers raising the pneumonitis risk [22–25]. It is well known from retrospective studies that the pneumonitis risk is not only affected by total radiation dose but also by fraction size. Roach et al. [26] analyzed 1,911 patients and found an increased pneumonitis risk at doses ≥ 2.7 Gy per fraction. Twice-daily irradiation with reduced doses per fraction lead to a reduction in pneumonitis risk.

**Neoadjuvant Radiochemotherapy and Resection**

Neoadjuvant radiochemotherapy schedules aim at optimizing local tumor control using radiochemotherapy followed by resection. Combined schedules with full-dose chemotherapy either preoperatively alone [27–29] or pre- and postoperatively [30, 31] take advantage of the systemic efficacy of this treatment modality. Comparison of the results from the different phase II studies reveals that the rate of pathologic complete remissions (PCR) in the mediastinum (ypN0-1) rises with increasing biological effective doses of preoperative radiotherapy component in patients with initial mediastinal involvement (table 1).

Stuschke/Pöttgen
Table 1. Mediastinal remission as a prognostic factor after preoperative radiochemotherapy for stage IIIA/IIIB NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Preoperative schedule (total radiation dose and chemotherapy)</th>
<th>N2/N3 patients evaluable for mediastinal remission</th>
<th>ypN0-1 Survival %</th>
<th>ypN0-1 Survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleveland [32]</td>
<td>27 Gy (b.i.d.)</td>
<td></td>
<td>FEP</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>27 (2 y)</td>
</tr>
<tr>
<td>Boston [31]</td>
<td>42 Gy (b.i.d. (12-day break))</td>
<td></td>
<td>2 × FVP</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>18 (3 y)</td>
</tr>
<tr>
<td>Essen [27]</td>
<td>3 × EP → 45 Gy (b.i.d.)</td>
<td></td>
<td>EP</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 (3 y)</td>
</tr>
</tbody>
</table>

E = Etoposide; P = cisplatin; F = 5-fluorouracil; V = vinblastine; → = followed by; || = simultaneous with; b.i.d. = 2 × 1.5 Gy/day; q.d. = 1 × 1.8 Gy/day.

Preoperative radiochemotherapy was highly effective in the mediastinum. A PCR in mediastinal lymph nodes was achieved in 37–77% of the patients evaluable for response in the mediastinum. PCR is an important prognostic factor for long-term survival after neoadjuvant combined-modality treatment (table 1). Survival rates of > 40% were found for patients with initial mediastinal involvement who had a PCR in the mediastinum. Patients with persisting tumor in mediastinal nodes at the end of the neoadjuvant radiochemotherapy had a markedly less favorable prognosis. The Essen Group pointed out the prognostic value of downstaging in the mediastinum after neoadjuvant radiochemotherapy a while ago and as a consequence introduced repeat mediastinoscopy as an obligatory reevaluation procedure at the end of neoadjuvant radiochemotherapy. Only patients with either PCR in the mediastinum or persisting tumor in only one single lymph node site were operated on [27]. Compared with PCR in the mediastinum, several series demonstrated that the frequencies of PCR in both the mediastinal lymph nodes and the primary tumor, i.e. a ypT0pN0 stage, were significantly lower, i.e. 15 (5–26%) in intent-to-treat analyses of all recruited patients in the different trials [27–33].

The preoperative radiation dose can only be increased within certain limits in combination with cisplatin-containing chemotherapy in order to achieve a PCR. In two studies, an increased postoperative death rate of about 20% was observed after total radiation doses of 60 Gy given preoperatively with conventional fractionation. The rate of severe complications increased especially after pneumonectomy [34, 35]. Only one neoadjuvant radiochemotherapy study demonstrated no postoperative mortality with total radiation doses.
above 50 Gy [36]. A concurrent boost schedule was used giving 45 Gy with 1.8 Gy per daily fraction to the larger initial treatment volume. The second daily fraction was given with 1.5 Gy to the small boost volume for 6–10 days. Only 4 pneumonectomies were performed in this study. On the other hand, neoadjuvant radiochemotherapy schedules up to total doses of <50 Gy given either with conventional fractionation or with accelerated hyperfractionation (2 × 1.5 Gy per day) led to a postoperative mortality <10% in almost all of the reported trials.

The large studies using neoadjuvant radiochemotherapy showed satisfactory locoregional control rates [27–33]. Only 15% of all recruited patients showed isolated locoregional relapses, 32% had one or multiple distant metastases, 11% had both locoregional recurrence and distant relapses on average. These incidences of local recurrences compare favorably with those achieved with radiotherapy alone or curative radiochemotherapy up to total doses of 60–70 Gy [2, 9]. Brain metastases as one component of failure were found on average in 27% of patients with relapses across the different trials. Studies, which offered prophylactic cranial irradiation demonstrated a substantial decrease in the incidence of brain metastases. Especially in patients with a high chance of locoregional tumor control (ypN0-1 stage, complete tumor resection), prophylactic cranial irradiation is a valuable treatment option within clinical trials [37].

At 3 years, the surviving fractions of patients with locally advanced disease ranged from 18 to 37% (mean 29%) [27–33]. These are favorable results in locally advanced NSCLC. Unfortunately, randomized studies directly comparing neoadjuvant radiochemotherapy followed by surgery with curative radiochemotherapy schedules are yet lacking. Therefore, preoperative radiochemotherapy has to be given within clinical trials.

**Future Perspectives**

Various active neoadjuvant as well as definitive radiochemotherapy regimens have been evaluated in patients with locally advanced NSCLC in patients with a good performance status. Escalation of total radiation dose and the introduction of new drugs such as taxanes in definitive as well as neoadjuvant radiochemotherapy schedules are important developments. The evaluation and validation of prognostic factors constitute a major task to improve treatment selection. Apart from performance status and weight loss, other factors, such as tumor volume, tumor localization, pretherapeutic lung function, response to induction chemotherapy or radiochemotherapy, as well as the molecular characteristics and micromilieu of the tumor may gain strong significance for individual treatment selection and optimization.
References


Martin Stuschke, MD, Department of Radiotherapy, University Hospital Charité, Schumannstrasse 20/21, D–10117 Berlin (Germany)
Tel. +49 30 2802 2073, Fax +49 30 2802 8306, E-Mail martin.stuschke@charite.de
Conventional fractionation (CF), that is the application of 1.8–2.0 Gy per fraction and five fractions per week, to total doses of about 60 Gy has been used over the last decades with only modest success as standard treatment for patients with locally advanced or medically inoperable non-small-cell lung cancer (NSCLC) [1]. The randomized Radiation Therapy Oncology Group (RTOG) trial 73-01 was the scientific basis of this schedule [2]. In this trial, different total doses given either as continuous treatment or as a split course were compared in 400 patients. Overall survival after 60 Gy was better than after 40 Gy continuous radiation therapy, 40 Gy split course, and 50 Gy continuous irradiation; however, these differences did not reach significance. Doses higher than 60 Gy using CF were not tested in this or other randomized trials published to date. Even if no formal statistical proof is available to support the choice of 60 Gy in 2-Gy fractions, this schedule became the gold standard in clinical practice and in most prospective clinical trials testing novel treatment approaches, such as combined radiochemotherapy [3, 4]. Originally, it was thought that local tumor control after CF to 60 Gy is in the order of 40–50% and that distant metastasis is by far the most important cause of treatment failure [5]. However, more recent studies with rigorous follow-up using CT and/or bronchoscopy revealed that local tumor control after conventionally fractionated radiation therapy to 60 Gy is only in the order of 10–20% [6] and that local failure is the leading cause of death after
Radiotherapy at the present time [7]. Survival rates at 2 years are usually 10–20% and at 5 years about 5%. This grim prognosis of locally advanced NSCLC after standard radiation therapy calls for novel therapeutic approaches. Among other strategies, such as combined radiochemotherapy or radiation dose escalation, modified fractionation schedules have been explored in recent years.

**Radiobiological Basis of Modified Fractionation**

A host of experimental and clinical studies performed in the last two decades clearly demonstrate that the radiobiological parameters of a given fractionation schedule, that is dose per fraction, time interval between fractions and overall treatment time, importantly influence the probability of local tumor control as well as of early and late normal tissue damage. High doses per fraction increase the probability of radiation pneumonitis and fibrosis, radiation myelopathy, and chronic damage to heart and pericardium [8, 9, 11–13, 21]. In contrast, little or even no impact of dose per fraction has been shown for the majority of experimental tumors [14]. Overall treatment time is of major importance for local tumor control [10, 15–20], but has only little impact on classical late radiation damage, such as lung fibrosis and spinal cord damage [12, 13, 21]. Short overall treatment times increase acute normal tissue damage, such as esophagitis [13, 22, 23], but also radiation pneumonitis [24]. With current treatment techniques, the lung usually is the critical, i.e. dose-limiting organ in radiation therapy of lung cancer. Therefore, the therapeutic ratio of modified fractionation schedules depends mainly on the probability of achieving locoregional tumor control versus the risk of radiation-induced intermediate-late and late lung damage.

Two prototypes of modified fractionation, i.e. hyperfractionation (HF) and accelerated fractionation (AF) have been developed to take advantage of the differential effects of dose per fraction and overall treatment time on tumor control versus late normal tissue damage, e.g. to the lung [25, 26]. HF is the application of a dose per fraction lower than the 1.8–2.0 Gy used in CF, whereas AF is the application of more than 10 Gy per week [27]. The biological basis of HF is to exploit the postulated different capacity of target cells in tumor tissue and late responding normal tissue to recover from sublethal radiation damage between fractions, provided that the time interval between two fractions is sufficiently long. The biological basis of AF is to counteract the so-called time factor of fractionated radiotherapy, i.e. the loss of local tumor control with increasing overall treatment time. This time factor is generally explained by rapid repopulation of clonogenic tumor cells [15], however,
alternative mechanisms, such as increasing hypoxia, increasing cellular radiore-
sistance, or selection of highly malignant tumor cells might also play a role
[10, 28, 29]. A significant time factor has been demonstrated for squamous
cell carcinoma, but this phenomenon may also be important in other tumors.
In clinical practice, HF and AF are rarely used in their pure form, i.e. HF
schedules often have a minor acceleration component (e.g. $10 \times 1.2 \text{ Gy per}
\text{ week}$) and AF schedules often apply decreased doses per fraction (e.g. 15
fractions of 1.5 Gy per week). Such hybrid schedules are best categorized
according to their major difference compared to CF.

**Hyperfractionated Radiation Therapy**

A randomized phase I/II dose escalation trial using HF in 884 patients
was performed by the RTOG (trial 83-11) using two fractions of 1.2 Gy
per day and interfraction time intervals of at least 4 h [30]. No CF arm
was included in this trial. Patients were allocated to total doses of 60.0,
64.8, 69.6, 74.4 and 79.2 Gy. At no time were all of the five dose levels
open for accrual in this trial. The authors conclude that the results improved
when the dose was increased to 69.6 Gy, but that the outcome remained
constant or even became worse at higher doses. The differences between
the treatment arms were not significant in primary analysis. Retrospective sub-
group analysis among 350 patients with favorable prognostic parameters
suggested a significantly better survival with 69.6 Gy compared to lower
doses. However, this post-hoc analysis appears questionable from a statistical
point of view [31]. The incidence of severe radiation-induced pneumopathy
(grade 3+ ) increased from 2.6% after 60.0–64.8 Gy to 5.7% after 69.6–74.4
Gy and 8.1% after 79.2 Gy ($p=0.09$). Thus, increased morbidity might have
contributed to the lack of a positive dose-effect relationship at doses higher
than 69.6 Gy. HF to 69.6 Gy was used in the randomized phase III RTOG
88–08/Eastern Cooperative Oncology Group (ECOG) 4588 trial and com-
pared with CF to 60 Gy [4, 32]. A total of 306 patients were included in
these arms, a third arm tested combined radiochemotherapy. Median survival
time and overall survival after 1, 2 and 4 years were higher after HF than
after CF, but the differences were not significant (table 1). The relatively
low number of patients included in this trial and undetected imbalances
between the patient groups may possibly have contributed to these disap-
pointing results. In addition, from today’s point of view, the interfraction
time interval of 4 h used in the RTOG-HF trials might not have been
sufficient to allow for complete recovery from sublethal radiation damage
between fractions.
Table 1. Results of the randomized RTOG 88-08/ECOG 4588 phase III trial comparing CF with HF radiation therapy

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Total dose Gy</th>
<th>Dose per fraction Gy</th>
<th>n</th>
<th>MST months</th>
<th>Survival rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>60.0</td>
<td>2.0</td>
<td>152</td>
<td>11.4</td>
<td>46 20 4</td>
</tr>
<tr>
<td>HF</td>
<td>69.6</td>
<td>1.2 b.i.d.</td>
<td>154</td>
<td>12.3</td>
<td>51 24 9</td>
</tr>
</tbody>
</table>

MST = Median survival time.

1 Two fractions per day, time interval at least 4 h.

No significant differences were observed. Note: A third arm of the trial tested induction chemotherapy followed by radiotherapy [4, 32].

Table 2. Results of the randomized CHART-Bronchus trial comparing CF radiotherapy to 60 Gy with CHART to 54 Gy [7, 22]

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Total dose Gy</th>
<th>Dose per fraction Gy</th>
<th>n</th>
<th>MST months</th>
<th>Survival rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CF</td>
<td>60.0</td>
<td>2.0</td>
<td>225</td>
<td>13.0</td>
<td>21 13</td>
</tr>
<tr>
<td>CHART</td>
<td>54.0</td>
<td>1.5 (^1)</td>
<td>338</td>
<td>16.5</td>
<td>30 20</td>
</tr>
</tbody>
</table>

MST = Median survival time.

1 Three fractions per day, time interval at least 6 h.

Accelerated and Accelerated Hyperfractionated Radiation Therapy

The most important trial on AF in NSCLC is the Continuous Hyperfractionated Accelerated Radiotherapy (CHART)-Bronchus trial of the MRC [7, 22]. A total of 563 patients were randomized to CF to 60 Gy or to CHART. In the CHART arm, three daily fractions of 1.5 Gy each were given with a minimum interfraction interval of 6 h without interruptions at weekends to a total dose of 54 Gy in 12 days. Despite the lower total dose, survival was significantly increased by about 9% after 2 years in the CHART arm compared to the CF arm (table 2). Post-hoc analysis revealed that this effect was most pronounced in squamous cell carcinoma. This hypothesis needs to be addressed in further investigations. As expected, early side effects, especially esophagitis, occurred earlier and reached higher scores in CHART patients. However, symptoms also settled earlier than after CF and were of no major concern.
Radiation-induced pneumopathy in the CHART-Bronchus trial comparing CF radiotherapy to 60 Gy with CHART to 54 Gy [7, 22]

<table>
<thead>
<tr>
<th>Time after treatment</th>
<th>Endpoint</th>
<th>CF, %</th>
<th>CHART, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis</td>
<td>3 months chest x-ray</td>
<td>65</td>
<td>56</td>
</tr>
<tr>
<td></td>
<td>3 months clinical symptoms</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>2 years chest x-ray</td>
<td>48</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>2 years clinical symptoms</td>
<td>4</td>
<td>16</td>
</tr>
</tbody>
</table>

on longer follow-up. Radiation pneumopathy was not decreased after CHART treatment. This was unexpected from a radiobiological point of view since CHART applied lower total doses with lower doses per fraction than CF (table 3). Possible explanations include an undetected imbalance in the distribution of risk factors for pneumopathy (e.g. treatment volume, pretreatment lung function), longer than expected repair half times in lung tissue, or consequential late effects.

Ball et al. [33] published the final report of the results of an Australian multicenter trial. Two-hundred and four patients with medically or technically inoperable NSCLC were randomized into one of four arms using a $2 \times 2$ factorial design. Radiation therapy was applied either with 30 fractions of 2 Gy in 6 weeks, or with 30 fractions of 2 Gy in 3 weeks, applying two fractions per day with a minimum time interval of 6 h. Half the patients in each group were treated additionally with 1 or 2 courses of carboplatin (70 mg/m²/day for 5 days). The median survival time of all patients was 16 months with a survival rate of 31% at 2 years. There were no significant differences between the different treatment arms or treatment factors. While application of carboplatin led to a highly significant greater hematological toxicity, AF resulted in a severer and more protracted esophageal toxicity than CF. The authors concluded, that halving of overall treatment time resulted in significantly greater esophageal toxicity with no trend to survival advantage.

Comparison of the Australian trial with the CHART trial reveals no obvious medical or radiobiological reasons that explain the different results [34]. However, with 200 patients, the Australian trial was rather small compared to the CHART trial, and, because of the factorial design, this trial was more prone to undetected biases from interaction. Differences in survival rates in the order of 10% or less would only very unlikely be detected by a trial of such size. Therefore, at the present time, evidence for a therapeutic gain from CHART in inoperable NSCLC clearly overweighs the evidence for equivocal results from the Australian trial.
Need for Conformal Radiation Techniques in Combination with Intensified Modified Fractionation

Radiobiological studies indicate that, while local structural damage is independent of the volume of lung irradiated, there is a clear volume effect for total functional lung injury [35, 36]. This is supported by clinical data [37, 38]. Furthermore, recent investigations show that irradiation of a small lung volume with high fibrogenic doses does not affect the dose-response relationship for development of fibrosis in distant parts of the lung [39]. Taken together, these findings support the concept that restriction of the volume of irradiated lung allows escalation of the dose to the tumor with acceptable risk of clinically important pneumopathy [40–42].

Clinically relevant radiation-induced lung injury was observed to occur dose-dependently in the RTOG 83-11 HF-trial [30], and, with a higher incidence than anticipated from radiobiological considerations, in the CHART trial [7, 22] (table 3). It therefore appears unlikely that substantial further improvements of the therapeutic ratio can be achieved solely based on dose escalation of modified fractionation schedules or on combination of modified fractionation with chemotherapy. To reduce the volume of lung irradiated with high doses as much as possible, state-of-the-art conformal three-dimensional radiation techniques need to be integrated into such intensified treatment strategies.

Conclusions

Presently, local recurrence is the major cause of failure after radiation therapy of locally advanced NSCLC. This observation calls for escalation of the biological dose to the tumor. In theory, HF should allow to increase the dose to the tumor without a simultaneous increase in late complications, however, so far randomized trials have not shown an advantage of HF in NSCLC. The highly accelerated CHART regimen significantly improved survival by 10% compared to CF. This result is among the most promising recent improvements in the management of NSCLC. Nevertheless, even when treated with CHART, about 80% of the patients will eventually develop local recurrence and 60% distant metastases. These figures are disappointing and call for further improvement of both local and systemic treatment. Among other approaches, radiation dose escalation using a CHART-like regimen, e.g. CHARTWEL (CHART weekend less), appears to be a promising option [43, 44]. Since long-term lung toxicity after CHART is possibly greater than anticipated, state-of-the-art conformal radiation techniques should be integrated into clinical trials testing such strategies.
Acknowledgment

This work was supported in part by a grant awarded by the Deutsche Krebshilfe.

References


———

86

18 Horiot JC, Bontemps P, Van den Bossart W, Le Fur R, Van den Weijngaert D, Bolla M, Bernier J, Lusinchii A, Stuschke M, Lopez-Torrecolia J, Begg AC, Pierart M, Collette L: Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: Results of the EORTC 22581 randomized trial. Radiother Oncol 1999;44:111–112.


Prof. Dr. Michael Baumann, Klinik und Poliklinik für Strahlentherapie und Radioonkologie, Medizinische Fakultät Carl-Gustav-Carus, Technische Universität Dresden, Fetscherstrasse 74 D-01307 Dresden (Germany)
Tel. +49 351 2095, Fax +49 351 5716, E-Mail michael.baumann@mailbox.tu-dresden.de
Target Volume Definition and Locoregional Failure in Non-Small-Cell Lung Cancer

Christian Rübe, Ursula Nestle

Abteilung für Strahlentherapie, Radiologische Klinik, Universitätskliniken des Saarlandes, Homburg/Saar, Deutschland

In the treatment of localized advanced non-small-cell lung cancer (NSCLC), local failure is the leading cause of death after radical radiotherapy and/or radiochemotherapy.

According to the literature, the local relapse rate after definitive radiotherapy was initially estimated to range between 50 and 60%, and distant metastases were thought to be the main cause of death [1]. However, more recent studies with rigorous follow-up including bronchoscopy showed that only 9–13% of patients were free of primary tumor at the time of death, while distant metastases were present in only about 50% of patients [2].

In many studies, local control clearly correlates with the incidence of distant metastases and survival [2]. In a retrospective analysis by Dosoretz et al. [3], the incidence of distant metastases correlated with the size of the primary tumor, but this correlation disappeared in patients with locally uncontrollable disease.

In NSCLC, a response to intensified dose fractionation regimens has been shown. In the randomized Radiation Therapy Oncology Group (RTOG) trial 73–01 [4], different total doses in conventional fractionation – partly given as a split course – were compared in about 400 patients. Overall survival after 60 Gy was better than after all other regimens tested, but no statistically significant difference could be shown. However, the 60-Gy schedule became the gold standard in clinical practice and in most prospective clinical trials testing novel treatment approaches, such as combined radiochemotherapy [5, 6]. The joint administration of platinum-based chemotherapy and radiotherapy significantly improved local control and survival in at least three randomized trials [7–9].
the MRC Continuous Hyperfractionated Accelerated Radiotherapy (CHART) Bronchus trial [2, 10], patients were randomized to 60 Gy in conventional fractionation or CHART. After CHART, local control and survival were significantly increased compared to 60 Gy in conventional fractionation.

Therefore, in radiotherapy of locally advanced NSCLC, there is a need for the application of higher doses in biologically more intensive fractionation to the site of the tumor. This intensification of treatment can only be achieved if the doses to the surrounding normal tissues are simultaneously reduced.

With three-dimensional conformal radiotherapy planning (3-DCRT) a tool has been developed that allows to conform a treatment volume covered by a prescribed dose to anatomopathological structures in their three-dimensional configuration. The required dose can thus be escalated to the clinical target volume (CTV) with a reduction of dose to normal tissues. Combined with modified fractionation and multimodal treatment approaches, 3-DCRT may result in better local tumor control and possibly in better survival of patients with locally advanced NSCLC.

**Conventional Target Volumes**

According to the definitions of the Internal Commission on Radiation Units and Measurements (ICRU) [11], the CTV includes the gross demonstrable extent of malignant growth (= gross tumor volume) and/or subclinical microscopic malignant disease that has to be eliminated.

Assuming that bronchoscopy and computed tomography (CT) – with some limitations like atelectasis – can determine the size and shape of the primary tumor with sufficient accuracy for radiation therapy planning, and that in most cases the detection of a distant metastasis will result in a palliative concept, the main problem in the planning of radical radiotherapy for NSCLC is to identify the areas of lymphatic spread, which often represent the major part of the CTV.

In the current literature on irradiation techniques in NSCLC [12], the inclusion of large volumes of tissues ‘at risk’ in the CTV (elective nodal irradiation; ENI) is recommended for curative treatment. As the radiation tolerance of several normal tissues in the chest [13–15] is below the 50 Gy/2 Gy usually prescribed to these regions, and as radiation morbidity especially of the lung, increases with the volume irradiated [16, 17], these recommendations bear a substantial risk of damage to normal tissues and may compromise the achievable dose to the gross tumor.

This has been clearly demonstrated by McGibney et al. [18] comparing dose-volume histograms for irradiation of locally advanced NSCLC with and
without ENI. They showed a significant reduction in the lung volume irradiated with 25 Gy or more in the plans without ENI.

The evidence for the concept of ENI is mainly based on a retrospective analysis of several RTOG trials by Choi et al. [19]. In this analysis, patients with major protocol violations related to field size and treatment of uninvolved nodes had impaired local control and survival compared to patients without violations. However, to our knowledge no prospective analysis was ever published supporting these data. On the contrary, Hazuka et al. [20] found a relationship between dose and survival irrespective of the target volume in their patients.

How do other specialties deal with the problem of ‘prophylactic treatment’ of mediastinal nodes in NSCLC? In the surgical literature, there is agreement about the need for mediastinal lymph node dissection in curative surgery of lung cancer [21–25]. A distinct localization system for mediastinal lymph nodes [26] has been developed, and is widely used. The evidence for this policy is based on the comparison of anatomopathological results with preoperative CT staging showing high discrepancies with 25–30% each for up- or downstaging [27, 28]. However, the basic analyses date back to the late 80s, when recent major improvements in thoracic imaging, such as optimal contrast enhancement, spiral CT scanning, and multiplanar reconstructions were not available yet. Furthermore, these analyses suppose complete resection of the primary tumor, and treatment does not systematically include other modalities than surgery.

The poor local control rates after radiotherapy show a need for more intense treatment of gross disease. Considering the improved treatment of microscopic disease by additional chemotherapy, and the improvement of pretherapeutic staging by new imaging modalities, it may be appropriate to omit ENI in order to allow dose escalation to the gross tumor volume.

**Methods for Determination of the Clinical Target Volume**

As outlined above, in most cases the anatomopathological boundaries of primary locally advanced NSCLC are sufficiently defined by CT scans, especially in lung window settings [29] and/or bronchoscopy. Problems may arise from large atelectases; patients may then be ineligible for 3-DCRT. As outlined above, the main issue in target volume definition is the identification of the lymphatic spread within the mediastinum. For this difficult task, some methods are discussed in the following.

**Potential Lymphatic Drainage**

As for other oncologic fields – e.g. head and neck tumors – there also exist data derived from pathologic specimens of operated regional lymph...
nodes for NSCLC. Unfortunately, such analyses [23] have shown a rather unsystematic lymphatic spread within the mediastinum, allowing retrograde spread and skipping of lymph node areas. In addition, the frequently present concomitant lung diseases, such as silicosis, are also believed to affect lymph nodes and alter the function of the lymphatic drainage system [30]. Therefore, assumptions of potential lymphatic drainage in individual patients with inoperable tumors must remain rather vague. Furthermore, there is no evidence that data from operable cases may be used to predict the situation in patients with inoperable disease.

**Mediastinoscopy**

Mediastinoscopy has been considered the gold standard of lymph node staging in NSCLC. In a meta-analysis by Dales et al. [31], the sensitivity of mediastinoscopy in mediastinal lymph node staging was > 90%, the specificity 100% compared to CT with 79 and 78%, respectively. However, the value and validity of this method are still discussed. Firstly, there is wide interinvestigation variation concerning the performance of the examination. Secondly, there are lymph node stations that can technically never or rarely be reached by the mediastinoscope.

For the use of mediastinoscopic results for target volume definition, all these limitations must be taken into account, and a thorough correlation of the surgeon’s report with imaging is required. Secondly, the topographic information from imaging modalities before mediastinoscopy cannot be used in treatment planning anymore, while imaging after mediastinoscopy may bear surgical artefacts. Thirdly, due to its invasive nature and the limited surgical capacities, in inoperable patients undergoing radical radiotherapy, this method will only be performed in the setting of clinical studies.

**Computed Tomography and Magnetic Resonance Imaging**

Lymph node staging by CT uses node enlargement as the criterion for malignant growth. Compared with pathologic specimens, diagnostic accuracy is poor, and after surgical procedures a 2.7-fold higher incidence of mediastinal lymph node metastases was reported by Bollen et al. [24] in 1993. New techniques, such as spiral CT scanning and multiplanar reconstruction have improved the accuracy, however, morphology leads to clear limitations of the method.

In selected cases, MRI might help in the differentiation of nodes in the aortopulmonary window and the hila [32, 33]. However, as both methods are morphologically oriented and as a general superiority of MRI in the detection of mediastinal nodes has not been shown, its routine use in the staging of lung cancer is not justified.
18-Fluorodeoxyglucose-Positron Emission Tomography

This new rather expensive functional imaging method is not yet widely employed. However, it has demonstrated a unique capacity in the noninvasive detection of nodal metastases in the mediastinum with an accuracy of 80–100%, which is far better than that of CT and MRI [34–36]. The impact of positron emission tomography (PET) on radiotherapy planning in lung cancer has already been demonstrated by several preliminary studies [37–40]. Its impact on target volume definition may become important in the near future, especially by the method of image fusion [41] with CT, which adds functional information to anatomic structures. Furthermore, the distinction of malignant tissue from the collapsed lung by FDG-PET might be useful for radiation therapy planning in cases with tumor-related atelectases [40].

Factors Influencing the Planning Target Volume

According to the definition of ICRU 50, the planning target volume (PTV) is obtained by adding a margin accounting for variations in patient positioning and organ motion to the CTV. Several factors influence the required size of this margin in the treatment of lung cancer.

In 1998, Ekberg et al. [42] published a detailed analysis of organ motion and set-up accuracy in the treatment of lung cancer. They measured that the average CTV movement with quiet respiration was 2.4 mm in mediolateral and ventrodorsal directions, while it was 3.9 mm in cranio-caudal direction. The systematic set-up errors were on average 2.0 mm in the transverse plane and 3.0 mm in craniocaudal direction. They concluded that a margin of 11 mm in transversal plane and 15 mm cranially and caudally is appropriate for defining the PTV for lung cancer patients. Bentel et al. [43] showed the importance of using immobilization devices. Furthermore, the method of on-line correction using portal imaging has been proposed [44, 45] for other tumor locations, which might also be useful in the treatment of lung cancer. To minimize internal organ motion, routine measurements of respiratory movement prior to therapy planning, self-gated triggering and breath-holding techniques have been applied [46].

Conclusion: New Target Volume Concepts for Three-Dimensional Conformal Radiotherapy

In the radiotherapy of locally advanced NSCLC, 3-DCRT enables dose escalation to an anatomically defined volume with reduction of dose to normal...
tissues. Due to the poor local control rates of conventional radiation, this dose escalation should be mainly targeted on the macroscopic tumor itself. Therefore new target volume concepts have to be designed.

A proposal for the definition of the CTV of locally advanced lung cancer for 3-DCRT was made by Armstrong [47] 1998: Omitting ENI, the CTV consists of the primary tumor – as known from bronchoscopy and visible in the lung window of a contrast-enhanced spiral-CT-scan – and nodes visible in CT larger than 1 cm. Singular nodes smaller than 1 cm are included without the surrounding tissue, in case of multiple small nodes, the whole ATS-station is included into the target volume.

Factors influencing the PTV must then be taken into account, and new techniques, such as breath-holding or self-gated triggering, should be developed to further enable dose escalation and reduction of normal tissue damage.

Concepts like this have to be tested in prospective multicenter clinical trials potentially integrating dose escalation in the CTV with concurrent chemoradiotherapy including a thorough analysis of the pattern of failure. Possibly, new imaging modalities like FDG-PET should also be integrated and evaluated in such trials.

References


Prof. Dr. Christian Rübe, Direktor der Abteilung für Strahlentherapie, Radiologische Universitätsklinik, D-66421 Homburg/Saar (Germany)
Tel. +49 6841 164626, Fax +40 6841 164699, E-Mail ruebe@med-rz.uni-sb.de
PET and SPECT in Three-Dimensional Treatment Planning of Brain Gliomas

A.L. Grosu\textsuperscript{a}, W. Weber\textsuperscript{b}, H.J. Feldmann\textsuperscript{c}

\textsuperscript{a} Department of Radiation Oncology, and
\textsuperscript{b} Department of Nuclear Medicine, Klinikum rechts der Isar, Technische Universität München, Munich, and
\textsuperscript{c} Klinik für Radioonkologie-Strahlentherapie, Klinikum Fulda, Fulda, Germany

Radiotherapy is a well-established approach in the treatment of malignant brain gliomas. It is known that increased doses lead to increased tumor control. Unfortunately, increased doses also lead to increased toxicity in normal brain tissue, with important clinical consequences [1, 2].

Computed tomography (CT) and magnetic resonance tomography (MRT) both became standard investigations in the management of brain gliomas [3, 4]. However, when analyzing the relationship between CT, MRT and the results of stereotactic biopsy, it was demonstrated that contrast enhancement is not always a real measure of tumor extent or malignancy. Tumor cells can be located both in the surrounding edema and in the adjacent normal-appearing brain tissue [5–9]. After neurosurgery or radiotherapy, the blood-brain barrier (BBB) disturbance and edema can also be treatment related and thus cannot be differentiated from persistent tumor on CT or MRT.

The goals of modern radiotherapy are to define the tumor area exactly and to encompass it completely, and also to spare the normal brain tissue as far as possible. The side effects of irradiation of the central nervous system are widely described in the literature. The frequency of these effects is dependent on the delivered radiation dose and the extent of irradiated volume [10].

Considering all these problems, it is clearly necessary to search for new methods to define tumor volume more precisely. In this report, we will focus on recent advances in positron emission tomography (PET) and single-photon-emission tomography (SPECT) in defining tumor volume and discuss the value
of functional investigation for three-dimensional (3D) radiation treatment planning of brain gliomas.

**FDG-PET**

One of the most widely used functional investigations in the diagnosis of brain gliomas is 18-fluoro-deoxy-glucose (FDG)-PET. The rationale for the application of the glucose analogue FDG to the study of brain gliomas is the known increased glucose metabolism in malignant tumor tissue [11]. Almost 80 years ago, Otto Warburg postulated that the rate of anaerobic glycolysis is positively correlated to the degree of tumor cell malignancy [12]. Thus, a high glucose utilization rate and an increased utilization of the glucose-6-phosphate intermediate will be observed. FDG is transported across the BBB by the same carrier molecules as glucose, so that disturbance of the BBB is not necessary for FDG accumulation. Hexokinase transforms FDG into FDG-6P which then accumulates in tumor tissue.

Clinical studies have demonstrated that FDG uptake in tumor tissue correlates with histological grading and has prognostic implications [11, 13]. Goldman et al. [14] analyzed 160 biopsies taken from 20 patients with low- and high-grade gliomas and compared the results with FDG uptake in PET. They demonstrated that FDG uptake in gliomas is anatomically heterogeneous and regionally related to the presence of anaplasia.

An important finding in practice is that FDG-PET investigation can be successfully used in the diagnosis of necrosis after radiotherapy or local chemotherapy, and also in the differentiation of necrotic tissue from a recurrence [15].

Gross et al. [16] assessed the value of FDG-PET for 3D treatment planning in 18 patients with malignant brain gliomas. Using PET/MR fusion images, tumor volume in PET was compared with tumor volume in MRT. The study showed that the difference in contrast between viable tumor and normal brain tissue in FDG-PET is small. FDG uptake in the gray matter is high, and this makes the demarcation of the tumor borders from normal brain tissue difficult. Nevertheless, tumor areas with lower cellular differentiation showed higher FDG uptake. An interesting finding of this study was that tumor areas with higher FDG uptake were closely correlated to the Gd enhancement areas in MRT. Although FDG-PET offers no additional data concerning tumor extension compared to MRT, it could be used to define areas with higher anaplasia. This raises questions regarding the possible significance of this investigation in the definition of a target in target, which could be potentially useful in dose escalation studies.
**MET-PET**

The mechanism and biological significance of increased $^{11}$C-methionine (MET) uptake in gliomas is not yet completely understood. Planas et al. [17] showed that although $^{11}$C-MET is incorporated into proteins, its uptake is probably not a measure of protein synthesis. The increased uptake seems to be mainly due to an activation of carrier-mediated transport at the BBB [18].

It is important to mention that low-grade gliomas, especially oligodendrogliomas, show a high MET uptake compared to FDG-PET [18]. Nevertheless, several studies demonstrated a correlation between MET uptake and histological tumor grading [19, 20].

Comparing CT, MRT and MET-PET using stereotactic biopsies, Mosskin et al. [21] and Ogawa et al. [19] concluded that MET-PET has a greater capacity to correctly outline the true extent of brain gliomas, compared to CT and MRT. This observation has important consequences for therapy planning and monitoring of patients with brain gliomas. The first findings regarding the value of MET-PET and FDG-PET in the follow-up of irradiated patients with brain gliomas were reported by Würker et al. [22]. They analyzed 10 patients with brain gliomas, investigated with FDG-PET and MET-PET, before and after brachytherapy with $^{125}$I seeds. After 1 year, glucose metabolism was not significantly changed, whereas MET uptake showed a significant dose-dependent decrease. Data about the integration of MET-PET in conformal irradiation planning are not reported.

**IMT-SPECT**

$^{123}$I-$\alpha$-methyl-tyrosine (IMT) is a synthetic amino acid with an affinity for the neutral amino acid carrier at the BBB similar to $L$-tyrosine. However, it is not further metabolized nor is it incorporated into cell proteins [23, 24]. Biersack et al. [25] and Langen et al. [23] showed that $^{123}$I-IMT is accumulated intensively in brain tumors, while its uptake in normal brain tissue is low. Comparing 14 patients with cerebral gliomas, Langen et al. [26] demonstrated that tumor extent with IMT-SPECT is comparable to MET-PET. These results and the good correlation between tumor extension diagnosed by MET-PET and stereotactic biopsies [19, 21] have been the rationale for including IMT-SPECT in radiation treatment planning for brain gliomas.

We integrated the IMT-SPECT investigation into the 3D radiation planning of 121 patients with brain gliomas. The aim of the study was to quantify the value of IMT-SPECT in tumor volume definition compared to MRT.
Fig. 1. Thirty patients with nonresected gliomas. Mean tumor volume measured on T$_2$-weighted images, T$_1$-weighted images with Gd and IMT-SPECT.

used as the standard investigation. Furthermore, we examined the influence of this additional functional investigation on 3D conformal treatment planning.

IMT-SPECT and MRT images are coregistered using a special software program developed by Pietrzyk et al. [27]. The data sets were moved across all three dimensions, using the outer skin contours as landmarks for the reorientation. The precision of the fusion was analyzed in phantom studies as well as in patients.

The data analysis included:

(a) The evaluation of contrast enhancement volume on T$_1$-weighted images and of the tumor-induced hyperintensity area on T$_2$-weighted images. Both were then compared with the tumor volume of IMT uptake in SPECT. In cases where IMT uptake was situated outside the tumor volume defined on MRT, a composite volume was calculated using the fusion images.

(b) The assessment of planning target volume (PTV) and boost volume (BV), defined by MRT, compared to the PTV and BV drawn by the coregistered images.

(c) Comparison of the results of IMT-SPECT and MRT concerning the diagnosis of tumor persistence in resected patients.

In high-grade gliomas, PTV consisted of the hyperintensity area in the T$_2$-weighted images plus a uniform expansion of 2 cm. In addition, the PTV included the tumor region in IMT-SPECT plus a 5-mm margin. The prescribed dose was 40 Gy, the daily delivered dose, 2 Gy. Subsequently, the PTV was reduced to include only the hyperdense area of tumor and edema in T$_2$-weighted
Table 1. Extension of IMT uptake by the tumor in SPECT compared to the hyperintensity area shown on T2-weighted images in 30 patients with nonresected histologically proven brain gliomas

<table>
<thead>
<tr>
<th>Volume</th>
<th>Mean/cm³</th>
<th>Median/cm³</th>
<th>SD/cm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>TV-IMT</td>
<td>43/48</td>
<td>44/45</td>
<td>21/16</td>
</tr>
<tr>
<td>TV-T2</td>
<td>82/49</td>
<td>70/56</td>
<td>54/14</td>
</tr>
<tr>
<td>TV-IMT/T2</td>
<td>88/74</td>
<td>82/81</td>
<td>51/19</td>
</tr>
<tr>
<td>Increase TV-IMT/T2</td>
<td>6/24</td>
<td>0/29</td>
<td>11/7</td>
</tr>
<tr>
<td>TV-T1,Gd</td>
<td>16/13</td>
<td>17/17</td>
<td>13/8</td>
</tr>
<tr>
<td>TV-IMT/T1,Gd</td>
<td>48/53</td>
<td>49/51</td>
<td>23/17</td>
</tr>
<tr>
<td>Increase TV-IMT/T1,Gd</td>
<td>32/40</td>
<td>30/40</td>
<td>17/11</td>
</tr>
<tr>
<td>PTV-T2</td>
<td>264/212</td>
<td>255/209</td>
<td>109/59</td>
</tr>
<tr>
<td>PTV-IMT/T2</td>
<td>266/223</td>
<td>261/227</td>
<td>108/59</td>
</tr>
<tr>
<td>Increase PTV IMT/T2</td>
<td>2/10</td>
<td>0/5</td>
<td>7/13</td>
</tr>
<tr>
<td>BV-T2</td>
<td>142/91</td>
<td>122/83</td>
<td>75/23</td>
</tr>
<tr>
<td>BV-IMT/T2</td>
<td>149/124</td>
<td>144/129</td>
<td>71/26</td>
</tr>
<tr>
<td>Increase BV-IMT/T2</td>
<td>7/33</td>
<td>0/30</td>
<td>15/9</td>
</tr>
</tbody>
</table>

Tumor volume (TV), PTV and BV were defined using IMT-SPECT, MRT and fusion images IMT-SPECT/MRT. The second figure represents IMT uptake outside the tumor borders defined by MRT (7 patients). Modified from Grosu et al. [29].

Images plus the additional tumor region defined by IMT-SPECT, and a 5-mm margin (BV). The total dose prescribed was 60 Gy. In low-grade gliomas the PTV encompassed the hyperintensity area in the T2-weighted images with a 1-cm margin plus the tumor region in IMT-SPECT. The total dose prescribed was 54 Gy, in 1.8 Gy daily fractions.

In 30 nonresected patients with histologically proven brain gliomas, the extension of IMT tumor uptake in SPECT was compared to the hyperintensity area shown on T2-weighted images. The evaluation was performed using MR/IMT-SPECT fusion images (fig. 1). These results are presented in table 1. In most cases, the tumor mass delineated by the IMT-SPECT was incorporated into the hyperintensity area outlined on the T2-weighted images. The most striking finding, however, was that the IMT tumor uptake also extended outside the hyperintensity area shown on T2-weighted imaging, which happened in a significant number of cases: 7 patients, representing 23% [28, 29].
Fig. 2. Patient with glioblastoma 2 weeks after tumor resection. T₁-weighted images with Gd, overlay IMT-SPECT/T₁ and IMT-SPECT. Focal IMT uptake reaches from the resection cavity to the midline. The area of contrast enhancement is considerably smaller. The resection cavity contains blood and is hyperintense in T₁-weighted imaging.

T₁-weighted imaging with gadolinium (Gd) was compared to IMT tumor uptake in SPECT. IMT uptake was significantly greater in all patients than Gd enhancement. Therefore, IMT uptake seems to be a better method to correctly assess the true extent of a tumor than Gd enhancement (fig. 2).

The main goal of the study was to investigate whether IMT-SPECT provides additional information compared to MRT for 3D treatment planning. We demonstrated that IMT-SPECT had no significant consequences on the initial PTV definition. This was not surprising, as tumor changes on IMT-SPECT were, in all cases, located less than 2 cm from the hyperintensity area on T₂-weighted images, and PTV was defined with a 2-cm margin. For the definition of BV, however, IMT-SPECT provided important findings in 7 cases, the BV outlined by IMT-SPECT/MRT being 30% higher than by MR alone [28–30].

In operated patients, the postoperative BBB cannot be differentiated by MRT from tumor infiltration (fig. 2). The additional information provided by IMT-SPECT may, in these cases, be of great value. When comparing the area of the Gd enhancement on MRT performed 24 h after resection (in 75 patients) with the IMT uptake area on SPECT, we obtained identical results in 38 patients and different results in 37 patients. In 10 patients (13%), we observed persistent tumor in IMT and no Gd enhancement on MRT; in 27 patients,
the MRT was positive for persistent tumor and the IMT negative [29]. Future studies aim to correlate these findings with survival.

Conclusions

(a) FDG uptake in PET correlates with histological tumor grading and has prognostic implications. In the tumor area, FDG metabolism is heterogeneous and regionally related to the presence of anaplasia. Using FDG-PET, tumor recurrence can be differentiated from cerebral necrosis induced by radiotherapy or chemotherapy. Compared to MRT, FDG-PET provides no additional information concerning tumor progression.

(b) MET-PET has a higher capacity to correctly outline the true extent of a tumor than CT and MRT. Although the correlation between MET uptake and tumor grading has been described in several studies, high MET metabolism was also observed in low-grade gliomas, especially oligodendrogliomas.

(c) IMT-SPECT offers important information regarding tumor volume in addition to T2-weighted images and is extended much more significantly than the contrast enhancement on T1-weighted images. The IMT-SPECT results concerning persistent tumor vary from the results of MRT investigations performed 24 h after resection. Future studies should correlate these findings with survival. The integration of IMT-SPECT into 3D radiation treatment planning could provide additional information to the definition of BV, with important consequences in dose escalation studies.

References


Dr. Anca-Ligia Grosu, Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, D-81675 Munich (Germany)
Tel +49 89 41404501, Fax +49 89 41404880, E-Mail anca-ligia.grosu@lrz-tu-muenchen.de
Radiation Dose Escalation for the Treatment of Gliomas: Recent Experience

Markus M. Fitzek
Department of Radiation Oncology, Charité, Humbold University, Berlin, Germany

Rationale for Dose Escalation Studies in Gliomas

The outcome of patients treated for malignant gliomas is dismal. Cure in a worthwhile proportion of patients has not been achieved with any method known today. In glioblastoma, surgery and conventional radiotherapy at doses of 55–65 Gy with high-energy photons led to median survival times of 8–10 months in patients with relatively good prognosis eligible for study participation [1, 2].

The analysis of patterns of tumor recurrence by modern imaging techniques and autopsy has shown that 80–90% of tumors first recur within a 2-cm margin of the original tumor [3–6]. The reasoning that more intensive local therapy should lengthen survival or even lead to a higher cure rate was therefore well founded.

Retrospective analyses and prospective trials indicated a modest dose-response relationship of improved outcome with higher radiation dose [1, 7]. Early reports of escalation of central tumor dose by adding brachytherapy or radiosurgery to conventional radiotherapy appeared to confirm the expectation of lengthened survival in selected patients. The limitation of these treatments to patients with favorable prognostic features and very small tumors however erroneously attributed the improved outcome to treatment rather than to patient selection [8, 9]. Local tumor recurrence was nevertheless the rule [10, 11]. Some technical factors could have contributed to this failure. Those could have been cold spots within a brachytherapy volume, or a practical size limitation for the high-dose volume, shifting the balance in the
relationship of risk versus benefit towards the negative effects of radiation necrosis.

Several protocols of dose escalation with markedly improved methods of conformal radiation delivery with external beams were initiated in the early nineties, completed, and reported recently. Among them were two phase II studies from the Massachusetts General Hospital in collaboration with the Harvard Cyclotron Laboratory using proton irradiation in addition to megavoltage x-rays. One was concerned with grade 4/4 tumors (glioblastoma multiforme), the other with grade 2/4 and grade 3/4 gliomas.

Massachusetts General Hospital Proton/Photon Dose Escalation Studies

Grade 4/4 Gliomas

The superior dose localization of protons compared to photons allows an increase in the dose to the target region where tumor is most likely to recur, with an only minimal increase of the dose to nontarget tissue [12]. The reasoning was that the region of radiation necrosis expected to occur thus could be limited and easier to deal with. The biological effects of photons and protons are so similar that the experience obtained with fractionated megavoltage x-rays could be transferred to treatment with protons.

An institutional phase II study in patients with malignant gliomas was initiated in 1992 to test this hypothesis [13]. A dose of 90 cobalt gray equivalent (CGE) in accelerated fractionation (1.8 Gy twice a day, separated by at least 7 h) was prescribed. The accelerated fractionation scheme was chosen because glioblastoma is generally a very fast-growing tumor, progressing on occasion even during therapy. A shortening of overall treatment time to about 5 weeks was desirable. The dose was delivered with a mixture of protons and photons – the proton component comprising at least one third of the total dose.

Patient Selection. Patients were selected for radiotherapy following resection of a glioblastoma multiforme. Eligibility criteria were: (1) patient age between 18 and 70; (2) pathologically proven grade IV/IV astrocytoma, Daumas-Duport classification [14]; (3) Karnofsky performance score (KPS) prior to radiotherapy of 70 or higher; (4) previous attempted maximal surgical resection; (5) largest postoperative tumor volume less than 60 cm³ (approximately equal to the largest postoperative diameter of 5 cm); (6) supratentorial primary tumor without involvement of the thalamus, corpus callosum, or subependyma. Exclusion criteria were: (1) prior radiotherapy to the head and neck, except for skin carcinomas; (2) genetic syndrome linked to CNS malignancies; (3) known radiation hypersensitivity syndrome; (4) collagen vascular
disease; (5) diabetes mellitus; (6) serious concomitant disease precluding completion of the protocol.

Radiotherapy Protocol. For every patient, three-dimensional (3D), CT-based treatment planning was employed [15]. The treatment volumes were delineated on the CT planning scan with the aid of MRI, fMRI (cerebral blood volume mapping; CBV and 18-fluoro-deoxy-glucose PET scan data, drawing the largest abnormality seen in these studies. Three clinical target volumes were defined: (1) the gross tumor volume (V1) encompassing the signal-intense rim of the tumor or the remaining cavity plus any residual gadolinium-enhancing volume on T2-weighted MRI on the earliest postoperative scan; (2) a second volume at high risk of harboring dense microscopic disease (V2), comprising V1 plus a margin of 2 cm; (3) a third volume at risk of less dense microscopic disease (V3), enclosing the edema volume as seen on T2-weighted MRI scans plus a margin of 2 cm. Prescriptions for V2 and V3 were similar to those used in most conventional treatment plans, except for the accelerated fractionation pattern. All three volumes were defined, taking into account the presence of natural anatomical barriers, such as bony structures, falx, and tentorium. Graded doses were prescribed to these volumes: V1, 90 CGE (proton-gray multiplied by 1.1 to account for relative biological effectiveness of the 160-MeV proton beam compared to cobalt gamma rays plus dose delivered with x-rays), V2, 64.8 CGE, and V3, 50.4 CGE. The dose given with protons as a fraction of total dose was variable but not less than 33% of the total dose. (The median proton dose actually delivered was 52.4 Gy (57.6 CGE) with a range of 29.7 to 62.9 Gy (32.7–69.2 CGE). A dose calibration change at the Harvard Cyclotron Laboratory was instituted 1 year after the last patient had been treated according to this protocol. That change recognized that the dose determined with an ion chamber technique was 6.5% higher than that determined with the Faraday cup technique, which had traditionally been used at the Harvard Cyclotron Laboratory [16, 17]. This resulted in a daily fraction size of 1.8 Gy with x-rays and 1.92 CGE with protons, according to the ion chamber technique. With doses recalculated, the median total dose delivered was 93.5 CGE).

The median number of proton fields per patient was 4 (range 2–7). The photon component was given with 4 MV and 10 MV x-rays with usually 3 conformal fields (range 2–4). Median overall treatment time of radiotherapy was 37 days (range 31–45 days). The median size of the high-dose target volume was 36 ml, calculated by the 3D planning system.

Patient Follow-Up and Intervention at Imaging Change. Patients were evaluated 1 month after completion of treatment and then 3-monthly. Functional imaging in the form of 18-fluoro-deoxy-glucose PET scanning or dynamic
contrast-enhanced relative CBV MRI was used to evaluate changes on routine MRI. The appearance of new areas of gadolinium enhancement on posttreatment MRI scans prompted a recommendation for histologic examination by stereotactic biopsy or craniotomy. If a resectable, symptomatic mass was present, reoperation was encouraged [18].

**Patient Group.** Twenty-three patients entered the protocol, none was lost to follow-up. There were 7 women and 16 men. The median age was 51 years with a range of 21–68 years. Seven patients met Radiation Therapy Oncology Group (RTOG) prognostic class III criteria, 7 met prognostic class IV, and 9 met prognostic class V criteria. Median Medical Research Council (MRC) prognostic index (see Appendix in Bleehan and Stenning [1]) was 15 (range 5–30). Fourteen tumors were located in the dominant hemisphere. Comorbidity and past medical histories were within the range of a generally healthy population of comparable age.

**Surgery, Pathology.** Nine resections were classified by the surgeon as gross total and 13 as subtotal; 1 patient had a biopsy only. The median largest preoperative tumor diameter on axial MRI studies in anterior-posterior or right-left dimension was 4.5 cm (range 2–7.5 cm). The median interval from surgery to the start of radiotherapy was 36 days (range 21–85 days). All tumors met Daumas-Duport criteria for grade IV/IV astrocytoma.

**Treatment Tolerance.** During therapy, 1 patient developed worsening cerebral edema causing imminent herniation and required a break of 1 week from day 19 to day 26. He needed decompressive surgery at completion of radiotherapy. Pathology from this and two subsequent resections showed only radiation necrosis. Acute tolerance was otherwise remarkably good, with the same range of symptoms occurring with conventional treatment. No patient initially free of steroids required initiation of steroids during treatment. All surgical incisions healed well.

Later on, all but 1 patient became steroid dependent. Clinical deterioration occurred at a median time of 7.5 months after irradiation. Aggressive tapering of steroid dose consistently precipitated clinical deterioration. Of the 4 patients currently alive, the patient surviving 60 months is the only one who did not require steroids after the postoperative period. All patients had areas of permanent alopecia. All patients with pathological material for assessment showed extensive radiation necrosis.

**Overall Survival and Quality of Survival.** Median survival of the entire group of patients was 20 months after the first operation. Actuarial survival at 1, 2 and 3 years was 78, 34, and 18%, respectively. No patient died of intercurrent disease. Only 1 patient died within the first year. Median time of survival with a KPS of 70 or higher was 12 months. Four patients were alive after treatment at the time of analysis for the primary report [13].
Analysis of Prognostic Factors. An attempt was made to assess patient selection factors. Patients were grouped according to both RTOG and MRC prognostic criteria for malignant glioma [1, 8]. In the RTOG analysis, class I patients represent the group with the best prognosis (younger patients with anaplastic astrocytoma) and class VI those with the worst prognosis (elderly patients with glioblastoma and a low KPS). Seven of our patients were class III, 7 class IV, and 9 class V. The median survival of class III and IV patients combined was 20 months, that for class V patients was 14 months (p = 0.07). Every patient was also assigned a prognostic index of the English Medical Research Council (MRC) scheme, a lower index representing a more favorable prognosis. The MRC index of our patients ranged from 5 to 30 (median 15). The actuarial survival of patients with an MRC prognostic index below 15 was higher than that of those with an MRC index above 15 (24 and 16 months, respectively; p = 0.06). A consistent improvement of 5–11 months compared to RTOG and MRC data, respectively, was evident.

Analysis of Imaging Change. All patients demonstrated new gadolinium-enhancing areas on T1-weighted MRIs during follow-up. The median time to these changes was 8 months. They correlated well with clinical deterioration (r = 0.89) in all but 1 patient who stayed asymptomatic. There was a trend for patients who developed early imaging changes to have shorter survival: 8 out of 12 (67%) of those who showed changes within the first 8 months survived for less than 20 months. New gadolinium enhancement occurred first within the high-dose (90 CGE) target volume (18 patients of 23 or 78%). It was seen outside the target volume in only 3 cases (13%). In 11 out of 23 patients, the lowest isodose of the change was 60 CGE or less.

Pathology at Reoperation or Autopsy. Thirteen patients (57%) underwent at least one reoperation after completion of radiotherapy for a newly enhancing mass, with 8 patients undergoing a significant resection. Three patients underwent postmortem examinations of the brain. All 3 autopsies revealed recurrent tumor, and in all 3 this was located outside the high-dose target volume which showed only radiation necrosis. In only 1 case of 23, was recurrent tumor found within the 90-CGE volume (by positive biopsy; the patient was retreated with a stereotactic proton boost of 15 CGE). In summary, pathological material was thus available in 15 of 23 (65%) patients. Six of these patients never developed pathologic evidence of tumor recurrence. One patient without pathological material developed new T1 gadolinium-enhancing areas 31 months after the first radiation treatment. She is the only long-term survivor, and the clinical course thus suggested necrosis only. The remaining 16 patients had a mixture of radiation necrosis and recurrent tumor. The 7 patients with necrosis only had a median survival of 29 months compared to 16 months for those who had both recurrent tumors and necrosis (p = 0.01).
The latter observation is probably the most significant one of this study. It strongly suggests that radiation necrosis, if relatively limited, carries a considerably better prognosis than tumor recurrence.

**Grade 2 and 3 Gliomas**

In this study, 20 patients were treated between 1993 and 1996 [19]. Male to female ratio was 14:6, median age was 36 years. Eligibility criteria were similar to those for grade 4/4 tumors with the exception of grade in the Daumas-Duport classification. In mixed tumors, the astrocytic component was the determinant of grading.

**Treatment.** Five patients underwent biopsy only, 12 a subtotal resection and 3 a gross total resection. In grade 3/4 tumors, target volumes were defined in the same way as for grade 4/4 tumors. Graded doses were prescribed to these volumes: V1, 79.7 CGE; V2, 68.2 CGE, and V3, 56.7 CGE. In grade 2/4 tumors, two target volumes were defined: the gross tumor volume (V1) encompassing the signal intense rim on T1 Gd-enhancing MRI, a second volume at high risk of harboring dense microscopic disease (V2), seen as the signal abnormality on T2-weighted MRI, plus a margin of 2 cm. Fractionation pattern was one fraction per day, 1.8 Gy (photons) or 1.92 CGE (protons) per fraction, 5 days per week. The fraction of dose given with protons was 84%. Nine patients with oligodendroglial components received PCV (procarbacine, CCNU, vincristine) chemotherapy prior to irradiation.

**Survival and Failure Analysis.** Actuarial 5-year survival rate for grade 2 lesions is 71% as calculated from diagnosis (median survival not reached), actuarial 5-year survival for grade 3 lesions is 31% (median 29 months); that of the entire group is 45%. Median follow-up is 49 months and 47 months for patients alive with grade 2 and grade 3 lesions, respectively. Two patients with grade 2 lesions and 10 patients with grade 3 lesions died. Both patients with grade 2 lesions died from tumor recurrence. Of the other 5 alive in this group, 2 had resections for radiation necrosis and one has a recurrence after several operations for radiation necrosis. One of the patients with grade 3 lesions died from pulmonary embolism, the others from tumor recurrence (n = 8) or, presumably, radiation necrosis (n = 1). In 7 of 9 patients with grade 3 lesions who had surgical intervention for a new enhancing lesion after therapy, recurrent tumor was demonstrated. Overall, 16 of 20 patients developed new gadolinium-enhancing regions after radiotherapy on T1-weighted MRI. The first radiographic change occurred centrally in 5 of 5 patients with grade 2 lesions, and in 7 of 11 patients with grade 3 lesions.

In summary, tumor recurrence was neither prevented nor noticeably delayed in this study.
**Other Recently Published Experience**

A more comprehensive discussion on dose escalation effects in high-grade gliomas has been published recently [13]. We are reviewing the most pertinent experience reported since. Almost concurrently with the Massachusetts General Hospital study, the University of Michigan conducted a dose escalation phase II study for high-grade gliomas treated at doses of 70, 80 and 90 Gy in conventional once-per-day fractionation, using 3D, conformally planned photons. They have reported on the patterns of failure of 36 patients who had recurrences and were treated at doses of 70 Gy (n = 15) and 80 Gy (n = 21) [20]. Median survival in this group was 13 months. The recurrences were central in 26 patients, in-field in 6, marginal in 3, and outside the target volume in only 1 case. The failure pattern was assessed by imaging studies with correlation to dosimetry; 8 patients, however, underwent further surgery and all of them had histologic confirmation of tumor recurrence. The reported sample came from a study consisting of 71 patients treated between 1989 and 1995, of whom 47 had had recurrences. The distribution of target volumes is not presented in this report. A comparison with other 3D planned studies, using target volume size as a prognostic factor, is therefore difficult at this time. The experience with escalation to 90 Gy in conventional fractionation awaits reporting. Early results were dismal [21].

In contrast to this, the pattern of failure was apparently changed in the experience of the group at the University of Tokyo [22]. Thirty-eight patients with glioblastoma multiforme were treated between 1984 and 1995 at doses of 60–80 Gy (n = 21) and 90 Gy (n = 16) in conventional fractionation, using 3D treatment planning. Postoperative volumes after resection were 32 ml (mean) and 3.4 ml, respectively (median). Median survival of their patients was 17 months, with no difference between the 90-Gy group and the lower-dose group. Seventeen of the 19 recurrences in the latter group were local, whereas 6 of 13 recurrences were local (or had a local component) in the 90-Gy group. The report is difficult to interpret, however: the relationship of the postoperative volume to the target volume is not clarified. The number of patients within a dose group (n = 37) does not add up to the number of patients analyzed (n = 38), or to the number of patients with a defined gender (n = 35). Only 2 patients appeared to have had postradiotherapy surgical procedures in the 90-Gy group (both were found to have radiation necrosis). Treatments apparently have not been performed within a study context, and predefined selection criteria were unclear. Conclusions are difficult to draw.

The Joint Center of Radiation Therapy has reported long-term results of its experience with radiosurgical boost therapy as part of the initial management of patients with glioblastoma [23]. Between 1988 and 1995, 78 patients
were treated with 12 Gy (median, prescribed to the 85% line) stereotactic radiosurgery in addition to conventional external-beam radiotherapy. Median survival was 19.9 months. Median tumor volume was 9.4 ml. The failure pattern was central in 38% of cases, marginal in 40%, and outside in 10% (12% of patients had no evidence of failure at the last imaging follow-up prior to death). Patient stratification by RTOG prognostic class indicated a modest gain in survival compared to standard RTOG survival times.

The question of a dose-response relationship for lower-grade glioma has been answered rather negatively by the EORTC study 22844, which randomized patients between 45 and 59.4 Gy. Overall survival and progression-free survival were virtually identical in both arms (58 vs. 59% and 47 vs. 50%, at 5 years, respectively) [24]. The concomitant quality of life study showed a tendency towards a negative effect on the quality of life in the higher dose arm [25]. The conclusions from the small phase II proton therapy study for an even higher dose range are essentially the same. One should remember that this applies to conventional fractionation patterns; dose escalation with altered fractionation remains to be explored.

**Conclusions**

The most consistent interpretation of these studies is that dose escalation leads to an extended regrowth delay in high-grade gliomas, conferring a modest survival advantage. Where the target volume is relatively small, radiation necrosis does not become the life-limiting factor. The failure pattern can be shifted towards peripheral recurrence if an accelerated fractionation scheme is used or overall treatment time is kept relatively short with radiosurgical boost therapy. Total treatment time in conventional fractionation at 80 or 90 Gy approaches 3 months. The regrowth of tumor centrally in the University of Michigan experience, in contrast to the Massachusetts General Hospital experience, is most likely due to the difference in overall treatment time. The high-dose target volume in the proton therapy study for grade 4/4 tumors was much larger than for other studies showing median survival rates in the range of 20 months. Although a dose and fractionation pattern to control glioblastoma has been found, it cannot be applied to larger brain volumes because of the limiting effects of radiation necrosis. With focal therapies at hand, which can limit development of radionecrosis, a strategy which would decrease its incidence or modify its debilitating effects could produce a major gain in the treatment of gliomas. Since vascular effects appear to play a central role in the development of radiation necrosis [26, 27], the recently discovered vascular growth factors provide an interesting new area of research in this field.
Given the disappointing results for lower grade gliomas, the emphasis in the near future will most likely be placed upon combination therapies with drugs and long-term toxicity reduction through conformal radiotherapy.

References


Markus M. Fitzek, MD, Charite, Humboldt University, Department of Radiation Oncology, Schumannstrasse 20/21, D-10117 Berlin (Germany)
Tel. +49 30 2802 2075, Fax +49 30 2802 8306, E-Mail markus.fitzek@charite.de

Radiation Dose Escalation for the Treatment of Gliomas 115
Three-Dimensional Brachytherapy in Malignant Gliomas

C. Kolotas\textsuperscript{a}, G. Birn\textsuperscript{b}, S. Hey\textsuperscript{a}, G. Strässmann\textsuperscript{a}, T. Martin\textsuperscript{a}, H.-G. Vogt\textsuperscript{a}, D. Baltas\textsuperscript{a}, N. Zamboglou\textsuperscript{a}

\textsuperscript{a} Strahlenklinik und Neurochirurgische Klinik, Städtische Kliniken Offenbach, Offenbach, Deutschland

The prognosis for patients with malignant gliomas remains poor, with local recurrences and persistent tumours being the dominant causes of treatment failure [1]. The median survival of patients with glioblastoma multiforme (grade IV) following surgery alone is only 4–6 months. The beneficial effect of post-operative megavoltage radiotherapy using daily fractions of 1.8–2.0 Gy to a total dose of 60 Gy, delivered using partial brain fields, has been documented in randomised clinical trials [2, 3].

The best reported median survival for patients with anaplastic astrocytoma (grade III) treated with radiation alone is 2 years [4, 5], whereas median survival rates of 3 years have been reported for selected groups of patients treated by combined irradiation and systemic therapy [6, 7].

Conventional low dose rate (LDR) brachytherapy using \textsuperscript{125}I, \textsuperscript{192}Ir and \textsuperscript{198}Au has been used both for recurrent [8, 9] and residual primary glioma [10] and a prolongation of median survival with an acceptable morbidity has been demonstrated. To obtain an optimal dose distribution with conventional LDR, computerized preplanning is first made to determine source locations. Using head frames and stereotactic techniques, flexible catheters are then placed within the tumour. However, it is quite common to be unable to exactly position the sources or catheters according to the preplanning.

This paper describes a preliminary study on 53 patients, treated between 1994 and 1997, with a new interstitial high dose rate (HDR) implantation technique for the treatment of recurrent glioma. The method includes a CT-guided implantation technique which takes advantage of the ability to
individually shape the dose distribution by using HDR treatment planning software.

**Material and Methods**

**Patients**

Of our 53 patients, 31 had grade IV glioblastoma and 22 had grade III anaplastic astrocytoma. All patients had experienced disease progression after previous surgery and external-beam radiotherapy of 60 Gy, administered 6–60 months earlier. Patients’ ages were in the range 23–70 years, with a mean of 54.2 years. The mean tumour volume was 67 cm³ with a range of 12–114 cm³.

**Implantation Technique**

A Perspex template is used to guide the drill and the catheters so that the required geometry was obtained relative to the tumour volume and there is no requirement for a stereotactic frame. The entire procedure was performed using interactive CT scanning under local anaesthesia and sedation. Post-implantation contrast-enhanced CT scans are made in planes 5 mm apart. This corresponds to the geometry of the template rows for brachytherapy treatment planning. The mean number of catheters implanted was 8 with a range of 2–17.

The maximum insertion depth and the catheter direction and position are estimated using CT image information. This is displayed on a monitor in the CT room and, therefore, is immediately available to the physician. Positional control of the first catheter is achieved by taking CT images with the catheter in situ and this procedure is repeated for all catheters. We aim at a regular array of catheters with separations of 0.5–2.0 cm depending on the size and location of the tumour.

Catheter reconstruction is based on CT images described above, and uses a software system developed by our institution in cooperation with the National Technical University of Athens [11] (fig. 1).

The first 28 patients received two HDR daily fractions of 5 Gy to a total dose of 30 Gy over 3 days. The following group of 25 patients received 40 Gy in 4 days. Brachytherapy planning and dose prescription were performed according to the rules of the Offenbach CT-based brachytherapy system [12]. After the catheters were removed, follow-up MR, CT and thallium scans were made at 2-month intervals.

**Results**

Figures 2 and 3 show overall survival results of all patients, using Kaplan-Meier curves with the survival time in weeks calculated both from the date of initial treatment and from the date of brachytherapy for the recurrence. Median survivals are 97 and 35 weeks, respectively.
Fig. 1. Isodose distribution for an HDR interstitial implant of a patient with a recurrent glioma in the left frontal region of the brain. The magenta circles represent the source dwell positions for the microSelectron-HDR remote afterloading machine. The target volume is delineated in red. A total of 9 catheters were used for this patient.
Fig. 2. Kaplan-Meier survival curves for 31 recurrent glioblastoma grade IV cases. 

a Survival measured from initial treatment prior to recurrence. b Survival measured from HDR brachytherapy for a recurrence.

When our patient series is divided into two histological groups – 31 glioblastomas grade IV and 22 astrocytomas grade III – the median survival times for glioblastomas are 71 and 29 weeks (fig. 2) and 192 and 53 weeks for astrocytomas (fig. 3).

Only 3 patients developed complications: 2/53 a pulmonary embolus, and 1/53 meningitis. In the two groups (glioblastoma and astrocytoma), there were no significant differences in age, tumour volume, and Karnofsky performance status before brachytherapy.
Fig. 3. Kaplan-Meier survival curves for 22 recurrent astrocytoma grade III cases. 

a Survival measured from initial treatment prior to recurrence. b Survival measured from HDR brachytherapy for a recurrence.

Discussion

Our interstitial brachytherapy treatment method differs from classical brachytherapy in the method of implantation of the catheters, in the use of HDR sources, and in the use of CT-based treatment-planning software. Catheter implantation in the CT suite using interactive scanning allowed tumour localisation, surgical implantation, catheter placement confirmation, and treatment planning without the need to transport the patient to the operating room.

Treatment planning based on post-implantation CT scans without the use of radiographs was possible for all patients. The time needed for the
planning procedure, including contouring of the target volume and critical organs, catheter reconstruction, dose distribution optimisation, evaluation using dose-volume histograms, was in the range of 20–75 min (mean 45 min).

Conclusions

We have presented a new HDR brachytherapy technique for the treatment of patients with recurrent gliomas which shows promising results. Although the patient group is relatively small, 53, it is already apparent that survival is similar to that obtained with LDR brachytherapy. However, there are significant advantages in the use of HDR compared to LDR and we can probably expect this technique to become widely used if further results from our centre are similar to those of the first 53 patients.

References


Dr. Christos Kolotas, Strahlenklinik, Städtische Kliniken, Starkenburgring 66, D–63069 Offenbach (Germany)
Tel. +49 69 8405 3335, Fax +49 69 8405 3334, E-Mail ckolotas@aol.com
Fractionated Radiotherapy of Inoperable Meningiomas without Histological Verification: Long-Term Results in 59 Patients

Jürgen Debus\textsuperscript{a,b}, Martina Wündrich\textsuperscript{b}, Andrea Pirzkall\textsuperscript{a}, Angelika Hoess\textsuperscript{a}, Daniela Schulz-Ertner\textsuperscript{a}, Rita Engenhart-Cabillic\textsuperscript{a}, Michael Wannenmacher\textsuperscript{a}

\textsuperscript{a} Department of Radiation Oncology, University of Heidelberg, and
\textsuperscript{b} Research Program Radiological Diagnostics and Therapy, German Cancer Research Center, Heidelberg, Germany

Meningiomas originate predominantly in the skull base or spinal canal and arise from the encasing cells of the arachnoid. They are known for their moderate cell density and low proliferative activity. Infiltration of dura mater or osseous structures is possible but more frequent in malignant forms. Meningiomas often recur locally, especially after incomplete surgical resection, while metastatic disease is extremely rare [1, 2]. If the tumor is operable, surgical resection is the treatment of choice. After complete resection, long-term disease-free survival rates and local tumor control rates of 81 and 96\%, respectively, are reported [3, 4]. The results discussed in the literature show that subtotal resection combined with postoperative radiotherapy, performed with precise treatment techniques, can achieve clinical results comparable to those after total resection [5]. So far, the potential of single high-dose radiotherapy (radiosurgery) has only been studied in patients with small inoperable tumors [6–10]. However, the role of this form of radiotherapy as primary treatment in extended tumors needs further research. The literature provides only little information about the potential of fractionated stereotactic radiotherapy of large, inoperable meningiomas. Fractionated stereotactic radiotherapy combines the precision of stereotactic positioning with the radiobiological advantage of fractionation for the treatment of large tumors. Thus, it might be an...
effective treatment alternative for meningioma in patients in whom surgery is contraindicated due to unfavorable tumor localization or to the patient's bad medical condition.

**Materials and Methods**

*Patients' Characteristics*

We have treated 189 patients with benign base of skull meningiomas since 1987. The present analysis focuses on 55 patients (16 males and 39 females) who had undergone primary radiotherapy between 1989 and 1988. The patients' mean age was 66 years (range 37–88 years) at the beginning of radiotherapy. All 55 patients had inoperable meningiomas of the skull base without histological verification. They had been considered inoperable by the neurosurgeons due to bad medical conditions or due to an unacceptably high surgical risk. They all suffered from progressive neurological symptoms. The diagnosis was based on neuroradiological readings. No patient received cytotoxic chemotherapy. The median target volume was 38.3 cm³ (range 5.2–137.7 cm³).

*Three-Dimensional Treatment Planning*

Patients were immobilized in an individual tightly fitting head mask attached to a stereotactic frame [11]. All imaging studies were performed under stereotactic guidance with a stereotactic localization system. The accuracy of patient repositioning was better than 2 mm [1, 2]. All patients had computed tomography (CT) and in 92% additionally magnetic resonance imaging (MRI) for treatment planning. Target volume and surrounding critical normal tissues were defined on the image modality with the best visualization of the tumor and were then transferred onto CT by the stereotactic localization technique. Three-dimensional (3D) dose distributions were calculated by the 3D treatment planning system, VOXELPLAN, developed at the Deutsches Krebsforschungszentrum (German Cancer Research Center; DKFZ) [13]. Details of stereotactic image registration, computer systems and technical aspects have been published previously [14–16].

*Irradiation Technique*

Radiotherapy was delivered with a 15-MeV linear accelerator (Siemens Mevatron 77 and Siemens Primus since 1997). Patients were treated with a manually operated mid-size multileaf collimator with a leaf thickness of 5 mm at isocenter which was developed at the DKFZ. Maximal field size was 15 × 15 cm.

The clinical target volume consisted of visible tumor in CT and MRI and potential residual tumor taking into account preoperative MRI and intraoperative findings. The planning target volume consisted of the clinical target volume plus a 2-mm safety margin.

Patients who underwent primary fractionated radiotherapy were treated with 3–5 irregularly shaped multiple isocentric noncoplanar fields. Median prescribed total dose at isocenter was 56.6 Gy (± 3.8 Gy) with a median daily fraction size of 1.8 Gy 5 times a week. Target volume was encompassed by 90% of prescribed dose (fig. 1).

Debus et al. 124
The resulting conformal dose distribution in a clivus meningioma provides a steep dose fall-off to the surrounding normal tissues. The different isodoses are presented in different gray shades. Total dose at isocenter was 57.6 Gy.

Evaluation of Response

Local response was evaluated according to clinical examinations and MRI which were obtained 6 weeks and 3 months after therapy and at 6-month intervals thereafter.

Local relapse was defined as an increase of two orthogonal tumor diameters of more than 25% or any increase in tumor size on two subsequent imaging sessions. Survival and recurrence-free survival were calculated according to the Kaplan-Meier method.

The physical status of the patients was judged according to the Karnofsky score [17]. Neurological symptoms were classified according to a recently published grading system [14].

Prior to and after radiotherapy, patients underwent a detailed examination regarding any neurological or visual deficits.

We evaluated dose-volume histograms to register isodose, maximal dose, median dose, 95% coverage (=dose, applied to 95% of the tumor volume) as well as the maximal doses to optic chiasm, optic nerves, brainstem and pituitary gland and the tumor volume covered by less than 90% of the isodose.

Patient data were statistically evaluated using the SAS® software, version 12. Overall survival and local tumor control were calculated from the first day of radiotherapy using the Kaplan-Meier method.
Results

Survival
Median follow-up was 60 months (range 19 months to 11 years). One patient died during follow-up, but not due to obvious local tumor progression. However, no autopsy was performed. Overall actuarial survival is 97.5% while progression-free survival is 95% (Fig. 2).

One patient, a 60-year-old man who was considered inoperable due to bad medical condition at the time of radiotherapy developed lymph node metastases 14 months after radiotherapy and presented with retropharyngeal tumor progression. Biopsy of the lymph nodes revealed a poorly differentiated squamous cell carcinoma. The local tumor at the skull base was locally controlled. The patient was retreated with external beam radiotherapy to the lymph nodes. Reevaluation of the patient revealed that this patient suffered from an early invasive nasopharynx carcinoma. He was scored in an intent-to-treat analysis as a locoregional failure.

Late Toxicity
None of the patients developed radiation-induced late toxicity ≥ WHO grade III. There was especially no brainstem toxicity or optic neuropathy.
**Discussion**

We have clearly demonstrated in our study that fractionated stereotactic radiotherapy is safe, reliable and effective in the treatment of inoperable extended meningiomas. Clinical results are promising: local control rates and survival rates were high while morbidity and subacute and late side effects were low.

We treated patients with meningiomas for which no histological verification was available. The neuroradiological diagnosis was based on the typical radiological appearance of these tumors. In 1 patient this diagnosis had to be revised: 14 months after radiotherapy, intense extracranial tumor progression was observed which was then histopathologically diagnosed as squamous cell carcinoma. The literature mentions other misdiagnoses: Hagen et al. [18] wrongly classified an astrocytoma grade III and a sclerosing subependymoma as meningioma. Furthermore, brain metastases of prostate carcinomas were diagnosed as meningiomas due to their great clinical and radiological similarity [19].

These diagnostic errors give rise to the question whether radiotherapy without prior biopsy entails an unbearable risk for the patient. Hagen et al. [18] examined the rate of correct diagnoses after (a) neuroradiological imaging and (b) after stereotactic biopsy or resection. Using T-weighted magnetic resonance (MRT) and/or CT they found a specificity for meningiomas of 97% and a sensitivity of 94%. Thus, in contrast to neurinomas and pituitary adenomas, meningiomas can be diagnosed by neuroradiological imaging with very high accuracy. However, the role of the so-called ‘meningeal sign’ to distinguish meningiomas from other intracranial lesions remains a moot point.

This phenomenon appears on MRT and is described by Schörner et al. [20] as a linear accumulation of contrast media in the dura adjacent to the margins of the meningioma. It tapers off with growing distance to the meningioma margins and is most intense directly at the lesion. Schörner et al. found a sensitivity of 52% and a specificity of 92%, and placed particular emphasis on the high relevance of this meningeal sign to tumor diagnosis. Hutzelmann et al. [21], however, consider this phenomenon not to be specific enough to meningiomas as it can also be observed in other pathological processes close to the dura (e.g. cerebral metastases). They found a specificity of 70% and thus proposed that the meningeal sign might be an indication but not a characteristic feature of meningiomas. The results of this study confirm the high specificity of radiological diagnosis observed by Hagen et al. [18]. Only in 1 patient was a squamous cell carcinoma wrongly diagnosed as a meningioma. Further diagnostic errors cannot be excluded, but the extremely good tumor control rates and recurrence-free survival rates achieved in our study indicate a very high specificity of neuroradiological diagnosis. Unidentified neoplasms,
especially malignant forms, would have resulted in lower tumor control and survival rates.

This leads to the conclusion that stereotactic irradiation without prior histological verification bears a risk of less than 2%. Whether this risk of incorrect diagnosis is tolerable depends on the clinical situation. In each patient, this risk has to be weighed carefully against the risk of biopsy. Nevertheless, a biopsy should be performed whenever possible. Of course, consideration of all available anamnestic and clinical data (e.g. age, sex and neurological symptoms) is always important as these parameters are very helpful in tumor diagnostics as well.

With the advent of less invasive neurosurgical procedures and developments in anesthesia, the number of patients considered inoperable will decrease. Further improvement in neuroradiological diagnosis can possibly be achieved by nuclear medical modalities with somatostatin antibodies and by angiography.

References


Dr. Jürgen Debus, Department of Radiation Oncology, University of Heidelberg, INF 400, D-69120 Heidelberg (Germany)
Tel. +49 6221 56 8201, Fax +49 6221 56 5353, E-Mail juergen_debus@med.uni-heidelberg.de
Modern Management of Brain Metastases: Prognostic Factors in Radiosurgery

G. Becker, B. Jeremic, R.D. Kortmann, M. Bamberg

Abteilung für Strahlentherapie, Radiologische Universitätsklinik, Tübingen, Deutschland

Treatment of brain metastases represents one of the major challenges in neuro-oncology. The number of patients developing brain metastases and their incurability are major factors contributing to continual investigation into this disease in the last few decades. While diagnostic techniques have been considerably improved by the use of computed tomography (CT) and magnetic resonance imaging (MRI), the results achieved with different treatment modalities are still far from satisfactory.

With supportive care and steroids, the survival of patients with newly diagnosed brain metastases is approximately 4–8 weeks. The use of whole-brain radiation therapy (WBRT) has extended survival up to 18–24 weeks in cases of multiple brain metastases [1–3]. The addition of surgery, mostly in cases with one or few brain metastases, seems to offer a benefit, with survival ranging from 48 weeks in randomised studies [2, 4] to up to 80 weeks in retrospective studies [5–7]. It was also shown that combined-modality treatment is superior to surgery alone in local control [2–4]. In cases of recurrences, surgery can prolong survival to 50 weeks [8, 9], while WBRT appears somewhat inferior, prolonging survival to 20 weeks only [10–12]. However, there are new techniques that hold promise of improved treatment for patients with newly diagnosed as well as recurrent brain metastases.

Radiosurgery (RS) is increasingly used. This treatment technique was originally developed for the treatment of non-oncological disorders using a device known as the ‘gamma knife’ [13]. Its first subsequent application was in a non-oncological setting [14, 15]. However, the last two decades witnessed the introduction of linear accelerator (linac)-based RS that enabled its wider
Table 1. Results of RS in brain metastases using a gamma knife

<table>
<thead>
<tr>
<th>Centre</th>
<th>Author</th>
<th>Year</th>
<th>Patients/metastases</th>
<th>Local control</th>
<th>Median survival months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester</td>
<td>Coffey [16]</td>
<td>1993</td>
<td>22/26</td>
<td>68</td>
<td>11.3</td>
</tr>
<tr>
<td>Sapporo</td>
<td>Fukuoka et al. [19]</td>
<td>1996</td>
<td>160/160</td>
<td>95</td>
<td>6.4</td>
</tr>
<tr>
<td>San Francisco</td>
<td>Shiau et al. [20]</td>
<td>1997</td>
<td>119/261</td>
<td>47</td>
<td>10.2</td>
</tr>
<tr>
<td>München</td>
<td>Wowra et al. [21]</td>
<td>1997</td>
<td>126/165</td>
<td>89.5</td>
<td>9.2</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>Kim et al. [22]</td>
<td>1998</td>
<td>77/115</td>
<td>85</td>
<td>10</td>
</tr>
<tr>
<td>Pittsburgh</td>
<td>Mori et al. [23]</td>
<td>1998</td>
<td>60/118</td>
<td>90</td>
<td>7</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>Lavine et al. [24]</td>
<td>1999</td>
<td>45/59</td>
<td>97</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>885/1,255</td>
<td>81</td>
<td>7–11</td>
</tr>
</tbody>
</table>

application. It became widely possible to treat different intracranial malignan-
cies, such as brain metastases, recurrent malignant tumours, primary malignant
 tumours, low-grade tumours, and even benign tumours, such as acoustic neurinomas. This technique, however, remains investigational and confined to specialised centres, the number of which, however, is rapidly increasing.

Of all indications in neuro-oncology, brain metastases have been most fre-
quently treated with RS. The reason for this is that they are usually pseudospher-
ical and well circumscribed, and they mostly do not destroy surrounding healthy
brain tissue by infiltration. Therefore, they have been considered as ideal candi-
dates for RS [25]. On the other hand, progress in radio-therapy and chemother-
apy made cancers more amenable to treatment, and thus more patients with
this disease will live longer. Unfortunately, this will increase the risk of sub-
sequent development of brain metastases in some of them. Autopsy series seem
to confirm this since 50% of all autopsied cancer patients had brain metastases.

Nevertheless, RS demonstrated its effectiveness in the treatment of brain
metastases. The results achieved with this treatment technique in the last decade
with either the gamma knife (table 1) or linac-based RS (table 2) repeatedly
show good local control which, however, did not translate into improved overall
survival. From 1987 to 1999 more than 20 groups reported their results from RS
performed on 2,057 patients and 2,946 brain metastases. Local tumour control
over all groups was 86% and median survival ranged from 5.5 to 12.5 months,
whether RS was done with the gamma knife or linac-based systems (tables 1, 2).
Most of these series included a limited number of patients, and all were retrospec-
tive in nature. Since it is important to gain information regarding ‘optimal’ fac-
Table 2. Results of RS in brain metastases using a stereotactic modified linac

<table>
<thead>
<tr>
<th>Centre</th>
<th>Author</th>
<th>Year</th>
<th>Patients/ metastases n</th>
<th>Local control %</th>
<th>Median survival months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisconsin</td>
<td>Mehta et al. [26]</td>
<td>1992</td>
<td>40/58</td>
<td>82</td>
<td>6.5</td>
</tr>
<tr>
<td>LA + Umeå</td>
<td>De Salles et al. [27]</td>
<td>1993</td>
<td>19/34</td>
<td>92</td>
<td>n.a.</td>
</tr>
<tr>
<td>Boston</td>
<td>Alexander et al. [28]</td>
<td>1995</td>
<td>248/421</td>
<td>85</td>
<td>9.4</td>
</tr>
<tr>
<td>Gainesville</td>
<td>Buatti et al. [29]</td>
<td>1995</td>
<td>25/28</td>
<td>84</td>
<td>12</td>
</tr>
<tr>
<td>Houston</td>
<td>Bindal et al. [9]</td>
<td>1996</td>
<td>31/31</td>
<td>61</td>
<td>7.5</td>
</tr>
<tr>
<td>Stanford</td>
<td>Joseph et al. [31]</td>
<td>1996</td>
<td>120/189</td>
<td>95</td>
<td>8</td>
</tr>
<tr>
<td>Cincinatti</td>
<td>Breneman et al. [32]</td>
<td>1997</td>
<td>84/177</td>
<td>97.5</td>
<td>10</td>
</tr>
<tr>
<td>Sapporo</td>
<td>Shirato et al. [33]</td>
<td>1997</td>
<td>39/39</td>
<td>84</td>
<td>8.9</td>
</tr>
<tr>
<td>Baltimore</td>
<td>Williams et al. [34]</td>
<td>1998</td>
<td>30/45</td>
<td>50–100</td>
<td>7.9–8.4</td>
</tr>
<tr>
<td>Heidelberg</td>
<td>Pirzkall et al. [35]</td>
<td>1998</td>
<td>236/311</td>
<td>92</td>
<td>5.5</td>
</tr>
<tr>
<td>Köln</td>
<td>Kocher et al. [36]</td>
<td>1998</td>
<td>106/157</td>
<td>85</td>
<td>8</td>
</tr>
<tr>
<td>Tübingen</td>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>92</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td>1,172/1,691</td>
<td>89</td>
<td>5.5–12.5</td>
</tr>
</tbody>
</table>

Factors associated with RS, this paper analyses possible prognostic factors related to the patient, to the tumour, or to treatment that may help obtaining a better insight into this disease while we are embarking on prospective randomised trials evaluating the place and role of RS in the treatment of brain metastases. To do so, we searched the literature for reports containing information about the influence of potential prognostic factors on either overall survival or local tumour control. Several institutions published multiple reports, and in some instances, multi-institutional reports [25, 38–40] have included patients reported in other single-institution publications. Eliminating this duplication, only the largest published series of each institution were included in this investigation of prognostic factors for RS.

**Prognostic Factors**

*Number of Metastases*

Three of the more recent trials have consistently found that patients with 1 or 2 lesions fare equally well, but those with 3 or more metastases have a uniformly poor outcome in terms of survival [28, 31, 32]. Breneman et al. [32] reported on the Cincinnati experience (linac-based) with 84 patients, 79 of whom were treated for recurrence after previous WBRT. The total number of lesions was 177 and...
median minimum tumour dose was 16 Gy. The number of metastases (1 or 2 vs. >2) significantly influenced survival (log rank p = 0.02). Similar findings were made by Alexander et al. [28], who reported on a large single-institution experience with linac-based RS used to treat 421 brain metastases in 248 consecutive patients. The patients had a Karnofsky performance status (KPS) ≥ 70%, no evidence of acute neurological deterioration and tumours ≤ 4 cm. Seventy-six percent of the patients had recurrent disease, 69% had evidence of systemic disease and 69% had a single metastasis. The median RS dose was 15 Gy. When the number of metastases was ≥ 3, it adversely influenced survival (log rank p = 0.0024). Similar findings were reported by Joseph et al. [31] from Stanford. One-hundred and twenty consecutive patients with 189 lesions were treated with linac-based RS, 100 of them had also received WBRT at some time during treatment. The mean prescribed dose to 80–85% isodose contour was 26.6 Gy. Thirty patients had 2 metastases, and 20 had 3–4 metastases. Patients having 1 or 2 metastases had similar survival (p = 0.7), which was significantly better than that of patients with 3–4 metastases (p = 0.0003). Based on these data, it became worldwide current practice to treat only patients with up to 3 metastases by RS.

In contrast to these observations, Engenhart et al. [41], Buatti et al. [29], Shu et al. [42], Kocher et al. [36], Pirzkall et al. [35] and Becker et al. [37] did not find any influence of the number of metastases on survival using Kaplan-Meier analysis, nor did analyses performed at Pittsburgh University on patients with non-small-cell lung cancer (NSCLC) metastatic to the brain [22] or malignant melanoma [23] find any such influence. Interestingly, only half of the aforementioned studies used Cox’s proportional hazard regression (Cox PHR) in multivariate analysis to test an independent influence of this possible prognostic factor. Contrasting findings were made here as well: while Joseph et al. [31] and Mori et al. [23] found the number of metastases to be an independent prognostic factor, Alexander et al. [28], Shu et al. [42] and Kim et al. [22] did not (table 3).

The influence of the number of metastases on local control has apparently been neglected since only four studies evaluated it [20, 28, 36, 37]. An influence was only found by Shiau et al. [20], but only in a stratified univariate analysis [20]. However, when applying multivariate analysis, no study could identify it as an independent prognostic factor (table 3).

While it is reasonable to assume that the number of metastases may be important for survival – in contradistinction to local control – it seems that this factor may be interrelated with other factors, such as the use of WBRT, which remain to be investigated.

**Radiation Dose**

The influence of radiation dose on local control was investigated by Breneman et al. [32], who found that there was a significant improvement in local
Table 3. Review of the literature for 'number of metastases' as prognostic factor

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/ metastases, n</th>
<th>Local control</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td>Buatti et al. [29]</td>
<td>1995</td>
<td>25/28</td>
<td>–</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Alexander et al. [28]</td>
<td>1995</td>
<td>248/421</td>
<td>n.a.</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Joseph et al. [31]</td>
<td>1996</td>
<td>120/189</td>
<td>+</td>
<td>0.0003</td>
</tr>
<tr>
<td>Shu et al. [42]</td>
<td>1996</td>
<td>116/248</td>
<td>–</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Breneman et al. [32]</td>
<td>1997</td>
<td>87/177</td>
<td>+</td>
<td>0.02</td>
</tr>
<tr>
<td>Kim et al. [22]</td>
<td>1997</td>
<td>77/115</td>
<td>–</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Shiau et al. [20]</td>
<td>1997</td>
<td>119/261</td>
<td>+ 0.0009</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mori et al. [23]</td>
<td>1998</td>
<td>60/118</td>
<td>–</td>
<td>0.07</td>
</tr>
<tr>
<td>Pirzkall et al. [35]</td>
<td>1998</td>
<td>236/311</td>
<td>–</td>
<td>0.18</td>
</tr>
<tr>
<td>Kocher et al. [36]</td>
<td>1998</td>
<td>106/157</td>
<td>– &gt;0.05</td>
<td>n.a.</td>
</tr>
<tr>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>– 0.1885</td>
<td>&gt;0.05</td>
</tr>
</tbody>
</table>

control with a radiation dose of ≥18 Gy (p = 0.008). Similar findings were made by Shiau et al. [20], who reported a study in San Francisco, in which 219 lesions (100 patients) were treated with the gamma knife. The median prescribed dose was 18.5 Gy and the median tumour volume was 1.3 ml. One-hundred and nineteen metastases were retreated after previous WBRT with RS only. Of the remaining 100 metastases, 45 were treated with RS only, and 55 lesions used RS as a boost to WBRT. Both D99% and Dmax were found to influence survival. Alexander et al. [28], Kim et al. [22] and Becker et al. [37] did not find any such influence nor did a multi-institutional report by Flickinger et al. [18]. When multivariate analysis was performed in all these studies, only Shiau et al. [20] identified radiation dose as independently influencing local control in a stratified Cox PHR, all other studies disclosing the opposite (table 4).

Only four studies [18, 29, 33, 37] evaluated the influence of RS dose on survival. Univariate analysis showed no such influence, and no significance was found in the only multivariate study [37] (table 4).

Although this issue continues to be controversial, radiation dose may be an important prognostic factor, at least for local control, which may reconfirm some of the oldest radio-oncological principles. However, the true effect of the dose on local control (and dose-response relationship) is impossible to verify in the absence of prospective randomised trials. Furthermore, if there is such an effect, then additional effort should be made to investigate its possible influence on overall survival. Here, too, this variable may be interrelated with other variables, such as the activity of systemic disease, number of metastases.
Table 4. Review of the literature for ‘radiation dose’ as prognostic factor

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/ metastases, n</th>
<th>Local control</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td>Flickinger et al. [18]</td>
<td>1994</td>
<td>116/116</td>
<td>–</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Buatti et al. [29]</td>
<td>1994</td>
<td>25/28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alexander et al. [28]</td>
<td>1995</td>
<td>248/421</td>
<td>&lt;0.902</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Shiau et al. [20]</td>
<td>1997</td>
<td>119/261</td>
<td>&lt;0.0001</td>
<td>&gt;0.001</td>
</tr>
<tr>
<td>Shirato et al. [33]</td>
<td>1997</td>
<td>44/44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breneman et al. [32]</td>
<td>1997</td>
<td>84/177</td>
<td>+</td>
<td>0.008</td>
</tr>
<tr>
<td>Kim et al. [22]</td>
<td>1997</td>
<td>77/115</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>0.49</td>
<td>0.056</td>
</tr>
</tbody>
</table>

or previous (or concurrent) WBRT, which only stresses the necessity for performing prospective randomised trials designed to answer this as well as other questions.

Tumour Volume and Size

Four studies evaluated the influence of tumour volume or size on local control, and three of them found a survival advantage for smaller tumour volumes in univariate analysis. While the studies of Alexander et al. [28] and Shiau et al. [20] investigated this effect in patients with histologically mixed brain metastases, Kim et al. [22] found this effect in patients with NSCLC. However, when multivariate analyses were done, Becker et al. [37] confirmed the influence of volume and size as an independent prognostic factor in histologically mixed brain metastases and Kim et al. [22] in NSCLC (table 5).

On the other side, eight studies investigated the influence of tumour volume on survival. By univariate analysis, only San Francisco [42] and Tübingen [37] studies found it to be significant. While Flickinger et al. [18] did not enter this variable in their multivariate analysis, Mori et al. [23] did not identify it as an independent variable. All other studies dealing with volume as a prognostic factor in multivariate analysis could demonstrate the independent influence of metastatic tumour volume on survival [22, 35–37, 42]. Kim et al. [22] found it to be a significant factor in NSCLC patients. While Kim et al. [22], Pirzkall et al. [35] and Kocher et al. [36] found an influence only by multivariate analysis, the study by Becker et al. [37] demonstrated a high significance of tumour volume on survival both by univariate and in multivariate analysis (table 5).

Clearly, tumour volume plays an important role in local tumour control. However, this influence may be interrelated with other variables, such as radi-
Table 5. Review of the literature for 'tumour volume' as prognostic factor

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/metastases, n</th>
<th>Local control</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td>Flickinger et al.</td>
<td>1994</td>
<td>116/116</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Alexander et al.</td>
<td>1995</td>
<td>248/421</td>
<td>+ 0.018</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Shu et al.</td>
<td>1996</td>
<td>116/248</td>
<td>+ 0.0005</td>
<td>+ 0.0005</td>
</tr>
<tr>
<td>Shiu et al.</td>
<td>1997</td>
<td>119/261</td>
<td>+ &lt;0.0001</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>1997</td>
<td>77/115</td>
<td>+ 0.027</td>
<td>0.0411</td>
</tr>
<tr>
<td>Shirato et al.</td>
<td>1997</td>
<td>44/44</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mori et al.</td>
<td>1998</td>
<td>60/118</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Pirzkall et al.</td>
<td>1998</td>
<td>236/311</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kocher et al.</td>
<td>1998</td>
<td>106/157</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Becker et al.</td>
<td>2000</td>
<td>55/72</td>
<td>− 0.14</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

... continuation of the text

... (rest of the text)

Table 5. Review of the literature for 'tumour volume' as prognostic factor

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/metastases, n</th>
<th>Local control</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td>Flickinger et al.</td>
<td>1994</td>
<td>116/116</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Alexander et al.</td>
<td>1995</td>
<td>248/421</td>
<td>+ 0.018</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Shu et al.</td>
<td>1996</td>
<td>116/248</td>
<td>+ 0.0005</td>
<td>+ 0.0005</td>
</tr>
<tr>
<td>Shiu et al.</td>
<td>1997</td>
<td>119/261</td>
<td>+ &lt;0.0001</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>1997</td>
<td>77/115</td>
<td>+ 0.027</td>
<td>0.0411</td>
</tr>
<tr>
<td>Shirato et al.</td>
<td>1997</td>
<td>44/44</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mori et al.</td>
<td>1998</td>
<td>60/118</td>
<td></td>
<td>0.82</td>
</tr>
<tr>
<td>Pirzkall et al.</td>
<td>1998</td>
<td>236/311</td>
<td></td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Kocher et al.</td>
<td>1998</td>
<td>106/157</td>
<td></td>
<td>n.a.</td>
</tr>
<tr>
<td>Becker et al.</td>
<td>2000</td>
<td>55/72</td>
<td>− 0.14</td>
<td>0.0205</td>
</tr>
</tbody>
</table>

... continuation of the text
Table 6. Review of the literature for ‘KPS’ as prognostic factor for survival

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/metastases, n</th>
<th>Univariate p</th>
<th>Multivariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buatti et al. [29]</td>
<td>1995</td>
<td>25/28</td>
<td>−</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Joseph et al. [31]</td>
<td>1996</td>
<td>120/189</td>
<td>+</td>
<td>0.00002</td>
</tr>
<tr>
<td>Auchter et al. [39]</td>
<td>1996</td>
<td>122/122</td>
<td>+</td>
<td>0.0001</td>
</tr>
<tr>
<td>Shu et al. [42]</td>
<td>1996</td>
<td>116/248</td>
<td>+</td>
<td>0.02</td>
</tr>
<tr>
<td>Kim et al. [22]</td>
<td>1997</td>
<td>77/115</td>
<td>−</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Mori et al. [23]</td>
<td>1998</td>
<td>60/118</td>
<td>−</td>
<td>0.12</td>
</tr>
<tr>
<td>Pirzkall et al. [35]</td>
<td>1998</td>
<td>236/311</td>
<td>−</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>−</td>
<td>0.085</td>
</tr>
</tbody>
</table>

controlled primary tumour, or volume of metastases subsequently causing neurological deficits, which may all adversely influence survival. As stated above, this variable and its interrelation with other variables need to be fully explored in prospective randomised trials in order to avoid biases inherent in any retrospective analysis, even when multivariate analysis is done.

Activity of Systemic Disease

It seems that this factor is most likely to be universally accepted as one of the most important independent variables predicting survival. Nearly all studies that evaluated it found it to be significant in both univariate and multivariate analyses [22, 23, 28, 32, 33, 35, 36]. Only in the large study by Joseph et al. [31] did it show borderline non-significance (p > 0.058). But systemic disease activity may be interrelated with other variables, because in the first analysis by the Heidelberg group [41] with 102 metastases, in contrast to the last follow-up, it was non-significant; the same applies to the Tübingen results [37]. Nevertheless, it is safe to state that patients having no active systemic disease are those most likely to live long enough to benefit from RS, provided that RS is beneficial regarding local control. Only that way can improved local control translate into improved overall survival. Identification of such patients may be an important goal of future studies, before we embark on prospective randomised studies designed to investigate important questions in this disease and its treatment by RS.

Histology

The influence of histology on local tumour control was investigated in six studies. While Alexander et al. [28] and Williams et al. [34] did not find an influence of histology on local control, Flickinger et al. [18], Breneman et al. [32],
Table 7. Review of the literature for ‘histology’ as prognostic factor

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/metastases, n</th>
<th>Local control</th>
<th>Survival</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td>Engenhart et al.</td>
<td>1993</td>
<td>69/102</td>
<td>-</td>
<td>&gt; 0.05</td>
<td>n.a.</td>
<td></td>
</tr>
<tr>
<td>Flickinger et al.</td>
<td>1994</td>
<td>116/116</td>
<td>+ 0.0003</td>
<td>+ 0.0006</td>
<td>&lt; 0.05</td>
<td>0.0002</td>
</tr>
<tr>
<td>Buatti et al.</td>
<td>1995</td>
<td>25/28</td>
<td>- 0.273</td>
<td>&gt; 0.05</td>
<td>0.065</td>
<td>&gt; 0.05</td>
</tr>
<tr>
<td>Alexander et al.</td>
<td>1995</td>
<td>248/421</td>
<td>+ &lt; 0.0001</td>
<td>+ 0.0041</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Joseph et al.</td>
<td>1996</td>
<td>120/189</td>
<td>+ 0.002</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shiau et al.</td>
<td>1997</td>
<td>119/261</td>
<td>- 0.24</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breneman et al.</td>
<td>1997</td>
<td>84/177</td>
<td>+ 0.0165</td>
<td>0.0023</td>
<td>0.71</td>
<td>0.0499</td>
</tr>
<tr>
<td>Kim et al.</td>
<td>1997</td>
<td>77/115</td>
<td>- 0.24</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Williams et al.</td>
<td>1998</td>
<td>30/45</td>
<td>+ 0.0005</td>
<td>n.a.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Becker et al.</td>
<td>2000</td>
<td>55/72</td>
<td>+ 0.0165</td>
<td>0.0023</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Shiau et al. [20] and Becker et al. [37] did, although their findings are rather inconclusive. While Flickinger et al. [18] found that patients with melanoma and renal cell carcinoma fared better in univariate and multivariate analysis [18], as far as local control was concerned, Shiau et al. [20] reported a better local control only in renal cell carcinoma and no difference between melanoma and adenocarcinoma; however, using stratified multivariate analysis, the outcome of patients with melanoma was significantly worse than that of patients with adenocarcinoma. Breneman et al. [32] saw no local failure in melanoma, but they did not perform multivariate analysis. Using univariate analysis, the Tübingen group found only renal cell carcinoma to have an independent and adverse influence upon local control; by multivariate analysis, local control of renal cell carcinoma and melanoma was found to be significantly worse than for other cancer types [20] (table 7). The hypothesis was that the so-called radioresistant tumours may be better controlled by a single high dose [18, 20, 32], than by conventional fractionation, but except for Flickinger et al. [18], no study could confirm this by multivariate analysis. Shiau et al. [20] and Becker et al. [37], for their part, concluded that melanoma and renal cell carcinoma have a worse prognosis.

The influence of histology on survival was frequently investigated. Of eight studies published [18, 22, 28, 29, 31, 34, 37, 41], only the studies of Williams et al. [34] and Flickinger et al. [18] concluded that it was important based on univariate analysis; in the study of Alexander et al. [28] it reached borderline significance (p = 0.065). When the data were subjected to multivariate analysis, survival for breast cancer remained significantly improved in contrast to local control. Thus, in this multi-institutional study, the significantly better local control revealed by Kaplan-Meier analysis for renal cell carcinoma and melanoma did not translate
into better survival using multivariate analysis [18]. Among all comparable studies using multivariate analysis, only the Tübingen study identified radioresistant cancers to have a worse prognosis for local control resulting in a worse prognosis for survival [37] (table 7). Owing to the sharp contrasts among the published data for local control, no firm conclusions can be drawn concerning the role of large single-fraction radiotherapy, i.e. RS. While there are no data showing that RS improves survival in radioresistant cancers, the Tübingen multivariate analysis was the first to confirm their worse prognosis.

Necrosis or Pattern of Enhancement

The influence of this variable on local control was investigated in two studies [20, 22]. By univariate analysis, Shiau et al. [20], in contradistinction to Kim et al. [22], established its importance with homogeneous patterns of enhancement carrying a better prognosis than either heterogeneous or ring-shaped-enhancing patterns, the latter suggesting the presence of necrosis. The situation remained the same when multivariate analysis was done.

Kim et al. [22] and Kocher et al. [43] investigated the influence of necrosis on survival and showed that it does not influence survival in univariate analysis, but when multivariate analysis was done, necrosis was shown as an independent prognostic factor adversely influencing survival in NSCLC [22]. The simulation study by Kocher et al. [43] suggests that the therapeutic effect of single-dose RS in malignant brain tumours cannot be understood without considering vascular effects. Their computer model might serve as a basis for exploring new treatment modalities that modify both the cytotoxic and vascular effects of RS [43].

Primary or Recurrent Lesions

The influence of this variable was investigated by Flickinger et al. [18] and Alexander et al. [28]. While Flickinger et al. [18] did not confirm its influence on survival based on Kaplan-Meier analysis and did not include it in their multivariate analysis, Alexander et al. [28] used both univariate and multivariate analysis to confirm its importance, showing that RS instituted for newly diagnosed brain metastases achieves significantly better local control as RS instituted at the time of recurrence.

On the other side, the influence of the timing of RS on survival was uniformly shown not to be an important prognostic factor by either univariate or multivariate analysis.

Location

Three studies evaluated the effect of tumour location on local control. While Alexander et al. [28] found advantages for supratentorial tumours, Shiau et al. [20] were not able to demonstrate such an effect. The same applies to
multivariate analysis. Only the Tübingen study compared midline – brain stem up to basal ganglia – to all other locations of the metastases: The outcome of patients with midline locations was worse. Although the number of patients in the midline group was small, midline location was the strongest independent prognostic factor in their study [37] (table 8).

The possible influence of this variable on survival was investigated by Kim et al. [22] and Mori et al. [23] on two cohorts of patients with different histologies (namely, NSCLC, and malignant melanoma, respectively) from Pittsburgh. None found an influence of tumour location on survival. Nor did Becker et al. [37] find any influence on survival for mixed histologies (table 8).

**Whole-Brain Radiotherapy**

While prospective randomised studies showed that postsurgery WBRT was beneficial in cases with one or few brain metastases [2, 4], the role of WBRT after RS is unclear. Up to now, only 7 retrospective studies dealing with the impact of WBRT on local control and/or survival are available. By univariate analysis, Fuller et al. [44] and Flickinger et al. [18] found that its impact was significant, while Pirzkall et al. [35] and Becker et al. [37] did not. Alexander et al. [28] found that the use of WBRT improved local control, but the difference was borderline (p > 0.054). The non-randomised study by Flickinger et al. [18] included 51 patients treated with RS alone who were compared to 65 patients treated with RS plus WBRT. In their multivariate analysis, they found that actuarial local control at 24 months following RS alone was 50% compared to 80% for RS plus WBRT (p = 0.011). However, this did not translate into a survival advantage [18, 45] (table 9).

It may be surprising that this additional treatment intervention proved not to be of more benefit. However, other factors like activity of systemic disease may be interrelated with WBRT as well, and this emphasises the need for controlled studies. Thus, clarification of the role of WBRT after RS will have to await the results of randomised EORTC and RTOG studies.

**Table 8. Review of the literature for ‘location’ as prognostic factor**

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/metastases, n</th>
<th>Local control</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td>Alexander et al. [28]</td>
<td>1995</td>
<td>248/421</td>
<td>+ 0.003</td>
<td>+ 0.009</td>
</tr>
<tr>
<td>Kim et al. [22]</td>
<td>1997</td>
<td>77/115</td>
<td>– &gt;0.05</td>
<td>– &gt;0.05</td>
</tr>
<tr>
<td>Shiau et al. [20]</td>
<td>1997</td>
<td>119/261</td>
<td>– 0.0837</td>
<td>+ 0.0012</td>
</tr>
<tr>
<td>Mori et al. [23]</td>
<td>1998</td>
<td>60/118</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>
Table 9. Review of the literature for ‘WBRT’ as prognostic factor

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/ metastases, n</th>
<th>Local control</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>univariate p</td>
<td>multivariate p</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuller et al. [44]</td>
<td>1992</td>
<td>27/47</td>
<td>+ 0.0007</td>
<td>n.a.</td>
</tr>
<tr>
<td>Flickinger et al. [18]</td>
<td>1994</td>
<td>116/116</td>
<td>+ 0.004</td>
<td>+ 0.0111</td>
</tr>
<tr>
<td>Alexander et al. [28]</td>
<td>1995</td>
<td>248/421</td>
<td>− 0.054</td>
<td>n.a.</td>
</tr>
<tr>
<td>Joseph et al. [31]</td>
<td>1996</td>
<td>120/189</td>
<td></td>
<td>− 0.064</td>
</tr>
<tr>
<td>Mori et al. [23]</td>
<td>1998</td>
<td>60/118</td>
<td></td>
<td>− 0.26</td>
</tr>
<tr>
<td>Pirzkall et al. [35]</td>
<td>1998</td>
<td>236/311</td>
<td>− 0.13</td>
<td>n.a.</td>
</tr>
<tr>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>− 0.93</td>
<td>− 0.19</td>
</tr>
</tbody>
</table>

Table 10. Review of the literature for ‘time from diagnosis of primary tumour to the diagnosis of brain metastases’ as prognostic factor for survival

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Patients/ metastases, n</th>
<th>Univariate p</th>
<th>Multivariate p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Buatti et al. [29]</td>
<td>1995</td>
<td>25/28</td>
<td>+ 0.047</td>
<td>n.a.</td>
</tr>
<tr>
<td>Auchter et al. [39]</td>
<td>1996</td>
<td>122/122</td>
<td>− 0.11</td>
<td>n.a.</td>
</tr>
<tr>
<td>Becker et al. [37]</td>
<td>2000</td>
<td>55/72</td>
<td>+ 0.0369</td>
<td>+ 0.0004</td>
</tr>
</tbody>
</table>

Time from the Diagnosis of the Primary Tumour to the Diagnosis of Brain Metastases

This factor was only investigated by three groups: Auchter et al. [39], who reported on multi-institutional experience with RS in single brain metastases, found a trend to improved survival in patients with longer time intervals from diagnosis of primary tumour to the diagnosis of brain metastases, but it did not reach significance (p = 0.11) and prevented the authors from entering it in multivariate analysis. Buatti et al. [29] were the first to report a significantly higher survival (rate p = 0.0001) in patients with an interval of > 1 year to developing brain metastases and improved survival in this group after RS (p = 0.047). In addition, Shiau et al. [20] showed that the interval between diagnosis of brain metastasis and RS was a significant factor improving freedom from progression in univariate and multivariate analysis. Becker et al. [37] found this time interval to be significant in univariate analysis and identified it as an independent prognostic factor in multivariate analysis (p = 0.0004; table 10). It is somewhat surprising that this variable was not investigated more frequently, since it seems logical to expect favourable effects of the delayed appearance of brain metastases regardless of subsequent treatment. If this interval is shorter, it may, at least partially,
indicate more aggressive disease, with brain metastases appearing either alone or concurrently with other distant metastases.

**Conclusions**

According to the literature, the only factor unequivocally associated with improved survival appears to be the absence of active systemic disease. Therefore, it will be necessary to clearly identify these patients before RS, because they constitute part of a ‘favourable’ subgroup that may live long enough to experience improvements in local tumour translating into improved overall survival. Since systemic disease activity often correlates with KPS, it may be assumed that patients with a higher KPS would be likely to be free of systemic disease. This could also be extended to the number of brain metastases since it can also influence the remaining life of potential candidates for RS.

In summary, patients without active systemic disease, who probably have a KPS of at least 70%, and a limited number of brain metastases [1–3] would constitute this ‘favourable’ subgroup of patients most likely to live long enough to benefit most from RS. However, this impact is difficult to imagine without improved local tumour control. Therefore, factors such as radiation dose, tumour volume, histology, timing, pattern of enhancement/necrosis, and location should be thoroughly investigated in potential candidates for RS. Finally, the use of WBRT is of special importance. It may be a suitable method to increase the local control rate while enabling simultaneous treatment of microscopic disease in the brain outside the target volume which may additionally prolong survival.

All factors analysed were drawn from retrospective studies, sometimes with an extremely small number of patients. These facts, as well as the fact that some studies used only inconclusive Kaplan-Meier survival analysis while others included patients already reported in previous studies, make any firm conclusion impossible. Hopefully, ongoing studies [36, 40] will help to clear some of the issues regarding potential prognostic factors in RS of brain metastases.

**References**


Adjuvant Radiotherapy following Radical Prostatectomy

T. Wiegel

Department of Radiotherapy, University Hospital Benjamin Franklin, Freie Universität, Berlin, Germany

Prostate carcinoma is one of the most frequent malignant diseases affecting older men with increasing incidence. For clinical localized carcinomas without lymph node metastases, radiotherapy (RT) and radical prostatectomy (RP) represent two potentially curative, highly efficacious therapy options [1–4]. After RP, postoperative examination of clinical T1/2a carcinomas revealed a pathologic stage T3/4 in up to 25% of the cases; this probability increases to more than 40% in the case of a clinical T2b tumor [5]. If patients with clinical stage T3 carcinomas undergo RP, the probability of postoperative tumor growth beyond the organ capsule is 70–80% due to considerable preoperative staging uncertainties [6]. Prostate-specific antigen (PSA) screening in the follow-up period, routine since 1987, has shown that in pathologic stage pT3a-b (capsular penetration, infiltration of the periprostatic tissue and/or seminal vesicles) or pT4 (infiltration of adjacent organs) with or without positive margins, a PSA elevation exceeding the undetectable range can be expected within 3–5 years in 15–60% of the cases depending upon primary tumor extension [6–8]. In 35–54% of patients exhibiting PSA elevation after RP without clinical signs of tumor recurrence, vital tumor tissue was found using punch biopsy from the urethrovesical anastomosis [9, 10]. There is no uniform treatment recommendation for stage pT3/4 either with or without positive margins. Whereas some authors favor a wait-and-see strategy and possibly a delayed hormone therapy, others advocate immediate hormone therapy [5, 6, 11]. Adjuvant RT has been discussed in high-risk patients (pT3, positive margins, infiltration of the seminal vesicles) with an undetectable PSA. Others advocate radiotherapy when the PSA has increased to the detectable range, was persistent following RP [8, 12, 13] or for biopsy-proved local
recurrence without distant metastases [7, 14]. Technological developments over the past 10 years have led to significant improvements in radio-oncology, especially three-dimensional (3D) treatment planning, which has made adjuvant RT increasingly attractive to urologists. 3D treatment planning reduces acute as well as late side effects in rectum and bladder [11, 15].

The purpose of this paper is to discuss the value of early adjuvant RT in high-risk patients following radical prostatectomy.

**Results from Retrospective Series**

Historically, adjuvant RT has been used in pT3 patients with varying prognostic factors as positive margins, seminal vesicle involvement, Gleason score > 7 or large extracapsular extension [3, 4]. Several studies have noted significantly improved local control with adjuvant RT compared to without adjuvant RT (table 1). In most series with adjuvant RT, the 5-year local control rate was 95–100% compared with 79–83% (p = 0.05) [16, 18].

Additionally, significantly improved biochemical control rates (with undetectable PSA following RT) were shown in about 5–6 major retrospective series (table 2). In a recently published series, Valicenti et al. [22] demonstrated data of a matched-pair analysis of 72 patients with or without adjuvant RT after RP. In this analysis, patients were grouped using Gleason score (< 7 versus > 7), preoperative PSA value (< 10 ng/ml versus > 10 ng/ml), seminal vesicle infiltration (positive versus negative) and margin status (positive versus negative). All patients had an undetectable PSA following RP (< 0.2 ng/ml) and negative lymph nodes. Thirty-six patients had a median

---

**Table 1.** Series from the literature comparing patients with adjuvant RT and without adjuvant RT for pT3 tumors – clinical local control

<table>
<thead>
<tr>
<th>Reference</th>
<th>With RT patients</th>
<th>5-year local control rate, %</th>
<th>Without RT patients</th>
<th>5-year local control rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ansger et al. [7]</td>
<td>46</td>
<td>96</td>
<td>113</td>
<td>80</td>
</tr>
<tr>
<td>Wiegel and Bressel [16]</td>
<td>56</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schild et al. [17]</td>
<td>60</td>
<td>100</td>
<td>228</td>
<td>83</td>
</tr>
<tr>
<td>Syndicus et al. [18]</td>
<td>89</td>
<td>100</td>
<td>88</td>
<td>79</td>
</tr>
<tr>
<td>Petrovich et al. [19]</td>
<td>201</td>
<td>95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Series from the literature comparing patients with adjuvant RT and without adjuvant RT for pT3 tumors – biochemically disease free at 5 years

<table>
<thead>
<tr>
<th>Reference</th>
<th>With RT patients</th>
<th>With RT 5-year PSA ‘undetectable’ %</th>
<th>Without RT patients</th>
<th>Without RT 5-year PSA ‘undetectable’ %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Freeman et al. [20]</td>
<td>95</td>
<td>62</td>
<td>62</td>
<td>27</td>
</tr>
<tr>
<td>Zietman et al. [21]</td>
<td>84</td>
<td>73</td>
<td>228</td>
<td>40</td>
</tr>
<tr>
<td>Schild et al. [17]</td>
<td>60</td>
<td>57</td>
<td>88</td>
<td>74</td>
</tr>
<tr>
<td>Syndicus et al. [18]</td>
<td>89</td>
<td>93</td>
<td>67</td>
<td>74</td>
</tr>
<tr>
<td>Petrovich et al. [19]</td>
<td>201</td>
<td>67</td>
<td>36</td>
<td>55</td>
</tr>
<tr>
<td>Valcenti et al. [22]</td>
<td>36</td>
<td>89</td>
<td>36</td>
<td>55</td>
</tr>
</tbody>
</table>

dose of 64 Gy. The 5-year freedom from PSA relapse was 89% versus 55% (p<0.05).

However, in these series no prolongation of overall survival was seen [4]. Most of these series had relatively small numbers of patients. It was shown that the time from PSA increase until the development of metastases is between 5–8 years and a patient who undergoes RP has a life expectancy of more than 10 years [23]. Therefore, hundreds of patients are necessary to show a survival advantage of 5–10%. Additionally, for example, patients with infiltration of the seminal vesicles have a high rate of distant micrometastasis and possibly do not benefit from local RT [16].

Valcenti et al. [24] have shown that in case of RT for increasing PSA after RP, higher doses are necessary to achieve an undetectable PSA, again because the tumor burden may be higher. For their 52 patients with undetectable pre-RT PSA levels, the 3-year no-evidence-of-disease (NED) rate was 91% for patients irradiated to 61.5 Gy or more and 57% for those irradiated with lower doses (p<0.05). For patients with pre-RT PSA levels between 0.2 and 2 ng/ml, the 3-year NED rate was only 33% for those irradiated with doses lower than 64.8 Gy. Therefore a potential advantage of adjuvant RT is the lower risk of severe late side effects due to the lower doses needed.

Randomized Trials

Three major prospective phase III randomized trials have been completed or are accruing patients. In all of these studies, patients with pT3
tumors with or without positive margins were randomized between radiotherapy (about 60 Gy) and wait-and-see. One trial of the South Western Oncology Group (SWOG) including most patients before the start of routine PSA evaluation has been completed and the results are pending. The EORTC trial compares patients with pT3 tumors with PSA evaluation before the start of treatment and about 700 patients are randomized. The trial of the Arbeitsgemeinschaft Radiologische Onkologie der Deutschen Krebsgesellschaft (ARO) and Arbeitsgemeinschaft Urologische Onkologie der Deutschen Krebsgesellschaft (AUO), which additionally compares only patients with pT3 tumors who postoperatively achieved an undetectable PSA, has accrued 100 patients [4]. Therefore, within the next years results from these major trials will be available and might help for treatment decision in these patients.

**RT for Persistent PSA following Radical Prostatectomy**

The best treatment of patients with detectable PSA levels that postoperatively never decreased to the undetectable range remains controversial [2, 4, 12, 13, 25]. Link et al. [25] observed a complete remission in only 9% (n = 12) of patients with persisting PSA; similar results were reported by Coetzee et al. [26]: only 20% (n = 15) of these patients achieved an undetectable PSA value following RT. However, the data of Morris et al. [2] contrast with these studies. Among 67 patients with persisting PSA levels, 65% attained the undetectable range, precisely the same rate found among 59 patients with late elevation. In view of these data, RT for persistent PSA following RP opens the possibility of a curative treatment option in selected patients. Unfortunately, it is impossible to predict the outcome. The ASTRO consensus panel therefore was unable to exclude these patients from RT [27].

**Comparison between Adjuvant RT and RT for Increasing PSA**

There is only one comparison of both modalities available. Morris et al. [2] from the MGH reported about 88 patients: 48 were irradiated as a salvage measure for a PSA elevation and 40 had RT as an adjuvant treatment due to an estimated high risk of local failure. 88% of the patients receiving adjuvant treatment and only 68% of the patients treated for elevation of PSA were biochemically disease free 3 years after surgery. These data suggest that adjuvant irradiation of a smaller tumor burden has a higher chance of success.
**Acute and Late Side Effects**

A low rate of side effects is of particular importance for an adjuvant RT without histologic confirmation of persistent tumor. As demonstrated by data from the literature, doses of RT up to 63 Gy given with 3-day treatment planning are very rarely associated with serious long-term rectum and bladder side effects of grade III/IV (according to the RTOG-EORTC grading system), that is with a probability of less than 3%. Syndicus et al. [18] reported grade III/IV side effects in relation to bladder function; however, they did not distinguish between cystitis and incontinence, and patients who only underwent RP also had a high rate of grade III side effects. Although total doses of 50–56 Gy were moderate, the median single dose was 2.76 Gy. This was possibly the reason for the increased rate of serious bladder side effects [18, 28]. When the postoperative RT was performed in a 3D-planned, 3- or 4-field box technique with individual-shaped fields to spare the bladder and rectum, RTOG grade I/II side effects occurred in up to 15% of the patients. They did not have a significantly negative impact on quality of life [4]. Formenti et al. [29] investigated the rate and degree of incontinence and impotence after nerve-sparing RP with or without adjuvant RT. The follow-up examination comprised only a questionnaire. No difference was found between 72 patients who underwent both RP and RT and 138 patients who underwent only RP when the total dose was 45–54 Gy. In a randomized study of 100 patients, there was no difference in the number of completely continent patients between the group receiving 60 Gy and the group under observation after 24 months [10]. In a retrospective analysis from the Mayo Clinic, the side effects in 60 patients with adjuvant RT were not significantly different from those of 220 patients who did not receive adjuvant RT.

**Conclusions**

In conclusion, adjuvant RT offers a highly effective approach to reduce local recurrence rate, to improve the rate of biochemical freedom from relapse with low acute and late morbidity in patients with a high risk of local recurrence following RP. However, there is no survival advantage at the moment, perhaps due to the relatively small number of patients in these retrospective series. In patients with a high risk for local recurrence adjuvant RT seems to be superior compared to patients treated for elevation of PSA following RP. Three major prospective studies have been completed or are open for randomization, but data are not available yet. Until these data become available, clinicians have to treat these patients according to their own experience. In patients with high
risk for local recurrence, immediate adjuvant RT seems to improve clinical outcome compared to RT protracted until increased PSA values are found.

References


Dr. T. Wiegel, Freie Universität Berlin, Radiologische Klinik und Poliklinik, Abteilung für Strahlentherapie, Universitätsklinikum Benjamin Franklin, Hindenburgdamm 30, D–12200 Berlin (Germany)
Tel. +49 30 8554 30 51, Fax +49 30 8445 44 63, E-Mail wiegel@ukbf.fu-berlin.de

Adjuvant Radiotherapy following Radical Prostatectomy
Morbidity following Radiation Therapy

Three-Dimensional versus Two-Dimensional Radiation Therapy, Treatment Planning and Treatment Delivery to the Prostate, Seminal Vesicles, and Pelvic Lymph Nodes

John E. Lahaniatis, Luther W. Brady, Ralph A. Brutus

Department of Radiation Oncology, Medical College of Pennsylvania-Hahnemann University, Philadelphia, Pa., USA

According to the American Cancer Society, the number of new cases of cancer of the prostate in the United States has increased from 99,000 in 1988 to 122,000 new cases in 1991, to 244,000 cases in 1995, to 317,100 cases in 1996, and an anticipated 184,500 cases in 1999. This change in the absolute number of new cases diagnosed in the United States is related to better educational programs in cancer of the prostate for men, more regular physical examinations including digital rectal examination and prostatic specific antigen determinations. In 1999, cancers of the prostate, cancers of the lung, cancers of the breast, and cancers of the colon represent almost 60% of all new invasive cancers diagnosed in the United States.

However, many controversies remain in the management of patients with cancer of the prostate including the following:

- the importance of and impact of prostatic specific antigen screening
- the discussion relative to treatment versus no treatment
- the utilization of prophylactic or concomitant hormonal therapy
- the need for surgical exploration for lymph node involvement prior to the final decision for treatment management
- the pros and cons of prostatectomy versus radiation therapy
- the role for interstitial implantation brachytherapy technologies in the management of prostate cancer versus external beam radiation therapy
- the role for transurethral resection of the prostate
- the circumstances under which periaortic lymph node irradiation might be an advantage
- the timing for postradiation therapy biopsy and the impact of such biopsies
- the role for adjuvant chemotherapy
the role for cryosurgery
the role for hyperthermia
the role for combined-modality treatment
the impact of any treatment program on potency

Emerging in these points of controversy are the benefits that might accrue as a consequence of the utilization of three-dimensional (3D) conformal radiation therapy. Such treatment would allow high-dose volume tailored to the target volume while delivering a low dose to the nontarget tissues and non-involved tissues in the patient. A 3D conformal radiation therapy technology is based upon the evolution and appropriate utilization of patient immobilization devices, integration of imaging systems, simulators, 2D radiation therapy treatment systems for documentation of dose distribution, the development of linear accelerators and utilization of alloy-shaped fields or multileaf collimators, and ongoing continuing radiographs to document the volume being treated.

With the advent of better patient fixation devices, more precise specification of target volume and organs at risk, design of beam shapes and orientations for 3D treatment delivery, 3D dose calculations, multileaf collimators, set the stage for this new class of solutions in 3D radiation therapy treatment planning and treatment delivery. The utilization of computed tomography simulation for the 3D radiation therapy treatment systems allow for optimization of beam geometry and dose distribution. Online electronic portal imaging allows for confirmation of the treatment program during treatment. The development of 3D radiation therapy represents a new era in radiation oncology leading to anticipated substantially improved treatment-planning and dose delivery systems.

With this background in place, a program for assessment of 3D versus 2D radiation therapy treatment programs in cancer of the prostate was initiated. During the interval of this study, it was routine for this investigator to treat whole pelvis to 50.4 Gy. Our goal was to retrospectively determine any differences between the two planning modalities in treating whole pelvis with cone-downs to prostate and seminal vesicles as far a acute and chronic morbidities are concerned.

**Materials and Methods**

This study compares 3D versus 2D radiation therapy treatment planning. The charts of 56 patients were retrospectively reviewed from 1992 to 1997. Patients for this evaluation were all managed by a single investigator. All patients were seen regularly during the treatment program and all patients were carefully and continuously medically managed during their
### Table 1. Distribution of stage: number and percentage of patients in each planning modality

<table>
<thead>
<tr>
<th>Stage</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T1b</td>
<td>10 (27.8)</td>
<td>2 (10)</td>
</tr>
<tr>
<td>T1c</td>
<td>8 (22.2)</td>
<td>10 (50)</td>
</tr>
<tr>
<td>T2a</td>
<td>6 (16.7)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>T2b</td>
<td>7 (19.4)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T2c</td>
<td>2 (5.6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T3</td>
<td>3 (8.3)</td>
<td>3 (15)</td>
</tr>
</tbody>
</table>

Figures in parentheses are percentages.

### Table 2. Months of follow-up: number of patients in each planning modality

<table>
<thead>
<tr>
<th>Follow-up months</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average</td>
<td>60</td>
<td>24</td>
</tr>
<tr>
<td>Median</td>
<td>54</td>
<td>23</td>
</tr>
<tr>
<td>Range</td>
<td>20–110</td>
<td>12–38</td>
</tr>
</tbody>
</table>

### Table 3. Central axis dose (gray)

<table>
<thead>
<tr>
<th></th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average dose</td>
<td>68.3</td>
<td>69.9</td>
</tr>
<tr>
<td>Median dose</td>
<td>68.4</td>
<td>70.2</td>
</tr>
<tr>
<td>Range dose</td>
<td>64.8–70.4</td>
<td>66.6–73.8</td>
</tr>
</tbody>
</table>

The distribution of cases during this time period is shown in table 1. The data relative to follow-up are summarized in table 2.

All patients in both groups were simulated with contrast in the urethra to identify the apex of the prostate. They were simulated also with contrast in the small bowel, contrast in the rectum, and contrast in the bladder to more appropriately identify the true extent of the prostate, seminal vesicles and the surrounding normal tissues. Some patients in the 2D group were treated in the prone position with an abdominal wedge to maximally exclude small bowel from treatment. In both groups of patients, the initial treatment volume was defined as the prostate, seminal vesicles and the regional lymph nodes. Also in both groups, the patients were treated to 50 Gy at 1.8–2 Gy per fraction in 5–6 weeks with cone-down to the prostate and seminal vesicles to the dose distributions illustrated in table 3. The cone-down treatment program, seen on a regular basis throughout their entire treatment program and on a regular basis in follow-up.
Table 4. Radiation Therapy Oncology Group skin, acute genitourinary, gastrointestinal, proctitis and cystitis morbidity grade distributions

<table>
<thead>
<tr>
<th>Grade</th>
<th>2D</th>
<th>3D</th>
<th>Grade</th>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin morbidity</td>
<td></td>
<td></td>
<td>Acute genitourinary morbidity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>17 (47.2)</td>
<td>4 (20)</td>
<td>0</td>
<td>9 (25.0)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>I</td>
<td>13 (36.1)</td>
<td>13 (65)</td>
<td>I</td>
<td>14 (38.9)</td>
<td>11 (55)</td>
</tr>
<tr>
<td>II</td>
<td>5 (13.9)</td>
<td>3 (15)</td>
<td>II</td>
<td>12 (33.3)</td>
<td>5 (25)</td>
</tr>
<tr>
<td>III</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>III</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IV</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Gastrointestinal morbidity</td>
<td></td>
<td></td>
<td>Proctitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7 (19.4)</td>
<td>1 (5)</td>
<td>0</td>
<td>30 (83.3)</td>
<td>13 (65)</td>
</tr>
<tr>
<td>I</td>
<td>13 (36.1)</td>
<td>8 (40)</td>
<td>I</td>
<td>5 (13.9)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>II</td>
<td>15 (41.7)</td>
<td>11 (55)</td>
<td>II</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>III</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
<td>III</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Cystitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24 (66.7)</td>
<td>18 (90)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>6 (16.7)</td>
<td>2 (10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>1 (2.8)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number and percentage (in parentheses) of patients in each planning modality.

for the 2D group was designed by manually transposing the prostate-seminal vesicle anatomy from computed tomography images in the treatment position to simulation films and adding a margin of 1.8 cm which allows for day-to-day variation in positioning, organ movement, and beam penumbra. The dosage in both groups during this interval was calculated as tumor dose minimum.

Results

The patients were followed on a regular basis as noted in table 2 and toxicities were defined according to the scales set forth by the Radiation Therapy Oncology Group morbidity grading system. Table 4 defines the toxicities between the treatment regimens. No significant difference is noted between the two treatment regimens although there was a slightly greater incidence of toxicities of grade I and grade II in the 3D treatment group with regard to gastrointestinal morbidity.
All toxicities were assessed in toto as to acute, intermediate and long term. The follow-up on the patients shows that at 2 years, all patients continue to be alive without recurrence of their disease process.

**Discussion**

Technologic and computer developments have moved radiation oncology into the era of 3D conformal radiation therapy. Both computed tomography and magnetic resonance imaging provide a 3D model of the patient’s anatomy and tumor allowing the radiation oncologist to prescribe the radiation therapy dosage to the tumor more accurately while sparing neighboring critical normal organs. The potential to improve the therapeutic ratio by increasing efficacy and better therapeutic outcome needs to be confirmed in clinical trials.

The present study illustrates that this can be accomplished using both 2D and 3D treatment techniques without increasing normal tissue toxicities as a consequence of the treatment program and with results at 2 years being the same in the two groups with regard to survival without disease as well as toxicities from treatment. A larger cohort to assess statistical significance as well as a minimum follow-up of at least 4 years may be required to assess treatment-related toxicities more accurately [1].

It is well known that other patient factors such as a history of diabetes, androgen deprivation, prior transurethral resection of the prostate, history of urinary obstruction, and age have an impact on morbidity [2, 3]. Anterior rectal wall dose is an important factor. Smit et al. [4] reported an actuarial 2-year incidence of moderate to severe proctitis of 20% for anterior rectal doses between 70 and 75 Gy, with a sharply increased incidence to 60% when doses greater than 75 Gy were delivered to the anterior rectal wall. A combination of dose escalation, planning target volume restriction, innovative imaging and beam treatment setup studies with limited fields have been published reporting improved outcome as far as local control and morbidity are concerned [5–8]. Further studies also need to be carried out, assessing patient perspectives on quality of life and definitive radiation therapy for prostate carcinoma [9–11]. Maturation and analysis of the prostate trial data of the Radiation Therapy Oncology Group will provide greater insight into many yet fully unanswered questions.

**Conclusion**

The present trend in treating prostate involves conformal local fields to doses greater than 70 Gy. This study showed no significant difference between
2D and 3D radiation treatment planning and delivery when evaluating acute and long-term morbidity rates. The treatment of whole pelvis to 50 Gy as part of a 2D prostate radiation treatment course delivering 70 Gy to the prostate can safely be accomplished without sacrificing the benefits of a 3D treatment plan when proper patient positioning, anatomical delineations and clinical management are utilized.

References


Prof. L.W. Brady, Department of Radiation Oncology, Hahnemann University Hospital.
Broad & Vine Streets, Mail Stop 200, Philadelphia, PA 19102 (USA)
Tel. +1 215 762 8419, Fax +1 215 762 1155, E-Mail LWB23@Drexel.edu

Morbidity following Radiation Therapy 157
Over the past decade, there has been a revolution in treatment planning and dose delivery for external-beam radiotherapy. This revolution has resulted from the development of three-dimensional conformal radiotherapy techniques. Features of these techniques include the creation of three-dimensional dose distributions based on three-dimensional data sets, such as computed tomography (CT) scan data [1]. Requirements for successful three-dimensional treatment planning and dose delivery include tools for beam’s eye view aperture design, dose calculation algorithms that facilitate full-dose coverage of target structures, and the ability to perform treatment in axial and nonaxial planes [2]. In addition, dose-volume histogram analysis has become a crucial planning tool when comparing alternate treatment strategies and beam arrangements [3]. The ability of planning systems to calculate normal tissue complication probabilities using normal tissue histogram analysis tools is likely to further refine external beam treatment, but is beyond the scope of this chapter.

These features, and others, of modern external-beam dose delivery, have allowed a dramatic escalation in treatment doses without corresponding increases in morbidity. Naturally, it is of general interest to determine whether the application of higher doses of radiation therapy results in better long-term outcomes. The purpose of this chapter is to review current data with respect to the benefit of higher doses of radiation therapy on clinical outcome for prostate cancer treatment.

**Historical Data**

There are several important publications that set the stage for modern data. First, a patterns of care study of radiation therapy in the United States
[4, 5] revealed that when standard radiation therapy techniques were used and the potential benefit of higher-dose therapy was examined, no advantage was seen for doses greater than 70 Gy. In fact, when these nonconformal data were analyzed, an increase in complications was seen without any clinical benefit.

The University of Michigan published an external-beam photon study, the first published prostate dose escalation study, in 1992 [6]. These data revealed that it was feasible to deliver external-beam radiation therapy doses as high as 80 Gy using the, then developing, conformal radiation therapy techniques. These early data were obtained from a phase I study of patients with locally advanced disease. A 6-field axial technique with customized, beam’s-eye-view derived therapy apertures was used [7]. These results were reported as encouraging and served as an impetus to develop other high-dose, external-beam photon studies.

A landmark clinical trial was performed by Massachusetts General Hospital utilizing the dosimetric advantages of proton beams to assess the benefit of higher doses of radiation therapy [8]. After a phase I/II study was performed, a phase III study was initiated that compared a 75.6 cobalt-gray equivalent (CGE) dose arm, which used a conformal, perineal proton boost, to a photon-only treatment arm of 67.2 Gy. Approximately 100 patients were treated to each of the two doses. Although there were no significant differences in overall survival, disease-specific survival, or local control between the two arms, it is interesting to note that patients with a higher grade of prostate cancer, called ‘poorly differentiated’ in their study, were found to have a lower positive rebiopsy rate and an improvement in local control that was dramatically better: 64 vs. 19%, p = 0.0014.

**Current Data**

There is accumulating evidence that validates applying higher doses of external-beam therapy to patients with prostate cancer. The currently available data are primarily restricted to biochemical control as an endpoint. In addition, these reports indicate that higher doses can be delivered with acceptable morbidity.

MD Anderson Hospital performed a review of nearly 1,000 patients treated consecutively between 1987 and 1995 [9]. Patients received doses as low as 60 Gy and as high as 78 Gy. Patients were analyzed by dividing them into three dose groups, less than or equal to 67 Gy, 67–77 Gy, and greater than 77 Gy. Freedom from biochemical recurrence rates was dramatically different for the different doses employed. At 3 years, the actuarial freedom
from failure was 61% for the lowest doses, 74% for the intermediate dose, and 96% for the highest dose group. The benefit in dose escalation was most dramatic for the Gleason 8–10 patients.

Fox Chase Cancer Center in Philadelphia, Pa., has also reviewed their dose-response data for biochemical freedom from recurrence among patients treated with conformal radiation therapy. Hanks et al. [10] have analyzed their dose-response data and created sigmoid-shaped dose-response curves that indicate a reduction in biochemical relapse for patients treated with higher doses, although this effect was reduced for those with relatively low PSA [10]. The authors also noted an increased number of complications for higher doses; however, the complication rate was clearly acceptable in their hands. The authors’ statistical model indicated that for each 1-Gy increase in dose, the hazard of biochemical relapse decreased by 8%.

Memorial-Sloan Kettering Cancer Center has also performed a prospective dose-escalation study [11]. Zelefsky et al. examined doses up to 81 Gy. In their study, the authors reported several pieces of evidence that support the hypothesis that higher doses of radiation therapy result in improved outcome. First, they noted that the probability of achieving a posttherapeutic PSA nadir \(< 1\) was increased for those patients who received 75.6–81 Gy vs. 70.2 Gy or 64.8 Gy, \(p < 0.001\). Second, PSA relapse-free survival was statistically improved for the high-dose group vs. the lower-dose group for those patients who were at intermediate risk or unfavorable risk. Those with favorable disease were found to have no benefit from higher doses. Positive biopsies were observed in only 1 of 15 patients who received 81 Gy vs. 12 of 25 after 75.6 Gy, 19 of 42 after 70.2 Gy, and 13 of 23 after 64.8 Gy \( (p < 0.05)\). These data provide additional support for the beneficial effects of dose escalation. The prognostic scheme used in this study to divide patients into favorable, intermediate, and unfavorable risk groups was as follows: favorable patients had stage T1 or T2, and pretreatment PSA \(\leq 10\), and a Gleason score \(\leq 6\). Intermediate prognosis patients had one of those indicators with a higher value, and unfavorable prognosis patients had two or more of those indicators with higher values.

As mentioned previously, for example, in the MD Anderson report, and in the Massachusetts General Hospital proton study, there appeared to be an increased benefit of dose escalation for patients with high-grade disease. This hypothesis was further evaluated by a collaborative effort from the University of Michigan, Fox Chase Cancer Center, and the University of California-San Francisco [12]. One hundred eighty-six patients from these three institutions were combined into one data set. Putative prognostic factors were evaluated for their ability to predict freedom from biochemical relapse. Both radiation dose and PSA value were significant for predicting PSA failure in a multivariate
analysis. In a subset of patients with only high-grade disease, higher doses were statistically significant in multivariate analysis predicting PSA control.

In summary, current data indicate that higher doses of external beam radiotherapy are associated with an improvement in short-term endpoints such as biochemical freedom from relapse, especially in patients with high-grade neoplasms. In addition, it has been reported that these higher doses can be delivered tolerably.

**Future Directions**

The Radiation Therapy Oncology Group (RTOG) is currently completing a phase I dose escalation study using conformal therapy [13]. This study was initiated in 1994 and has accrued over 1,000 patients. The highest dose bin that has been completed is the 79.2 Gy, given in 1.8-Gy fractions. When this dose bin had been completed, the RTOG decided to increase the dose per fraction to 2 Gy per day, inorder to continue to escalate to higher dose but to avoid extremely protected courses of therapy, and opened a 74-Gy arm. This dose level is rapidly reaching its accrual goals, and it is expected that a 2-Gy per day, total dose 78 Gy, arm will open soon. The RTOG expects to initiate a large randomized study of different doses with overall survival as a primary endpoint, rather than biochemical endpoints only, once this phase I study is complete. It is expected that the two arms would be 70 and 78 Gy, but this depends upon the tolerance of the next open arm.

There are several other on-going or recently completed randomized studies evaluating the benefit of radiation dose on prostate cancer. These include a randomized study from the Netherlands Cancer Institute comparing 68 to 78 Gy, a recently completed study from MD Anderson comparing 70 to 78 Gy, and a proton study comparing 70 to 78 Gy, being performed at the Massachusetts General Hospital and Loma Linda University. These studies are designed to measure differences in biochemical freedom from relapse, not overall survival.

In summary, nonrandomized studies strongly suggest that a beneficial effect of higher doses of external-beam therapy can be observed using biochemical control as an endpoint. This may be most striking for high-grade disease. Based on reported data, morbidity is acceptable. Other benefits of external beam therapy include the lack of restrictions due to previous prostate surgery or prostate size and the fact that this therapy can be applied nearly universally to all patients with localized prostate cancer. These benefits are important to remember as other radiation modalities such as high dose rate brachytherapy or the combination of external-beam therapy and brachytherapy become available more widely.
Fig. 1. Preradiotherapy PSA of all patients undergoing conformal-beam radiotherapy for prostate cancer at the University of Michigan Medical Center from 1983 to 1998. Patients presenting with PSA over 40 have become markedly less frequent.

Fig. 2. External-beam radiotherapy dose of all patients undergoing conformal-beam radiotherapy for prostate cancer at the University of Michigan Medical Center from 1983 to 1998, demonstrating a gradual escalation in doses, especially from 1994 to 1998.

It is expected that future results of radiation for prostate cancer will be better than those currently being reported because of a wider application of androgen ablation, the gradual dispersion of conformal radiotherapy techniques, and the application of higher doses. In addition, as the earlier detection of prostate cancer due to the success of PSA screening results in patients...
presenting with less advanced disease that is more amenable to definitive local therapy, cure rates are likely to markedly improve. Clearly, at the University of Michigan there has been a decrease in the PSA, on average, of newly diagnosed patients undergoing external beam therapy. At the same time, there has been a gradual dose escalation that has resulted in the favorable combination of higher dose being applied to patients with earlier disease. Figures 1 and 2 show the preradiation PSA of all patients treated at the University of Michigan Medical Center and the total radiation dose used. All of these factors support an optimistic attitude towards future outcomes of patients undergoing external-beam therapy for prostate cancer.

Besides these factors, there are advances being made in dose delivery techniques. Those most notable involve various types of intensity modulation dose delivery techniques in combination with inverse-planning strategies [14–16]. Clearly, dose distributions can be improved with these approaches, however, ultimate validation still awaits additional follow-up. One concern is related to uncertainties in prostate location and prostate motion that might be more critical as dosimetric margins become closer.

References


Dr. Howard Sandler, University of Michigan, Department of Radiation Oncology, Ann Arbor, MI 48109 (USA)
Tel. +1 734 936 9338, Fax +1 734 763 7371, E-Mail hsandler@umich.edu
Prostate Cancer – Combination of Hormonal Ablation and Conformal Therapy

H.J. Feldmann a, P. Stoll b, H. Geinitz b, F.B. Zimmermann b

a Klinik für Radioonkologie-Strahlentherapie, Klinikum Fulda, Fulda und
b Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie der
Technischen Universität München, Klinikum rechts der Isar, München,
Deutschland

Radiation therapy has been the mainstay of treatment for locally advanced prostate cancer T3 and T4 stages [1, 2]. Treatment results, even the long-term results in the pre-PSA era were relatively poor. Patients with T3 and T4 stages had 10-year relapse rates of 56–65%. Fifteen years after irradiation, failure rates as high as 70 and 80% were reported [3–8]. In those reports, the classification of disease status was based on digital rectal findings and on clinical-radiographic evaluation. It is now established that posttreatment rising PSA profile, as an additional indicator of relapse, significantly influences the evaluation of treatment efficacy. When posttreatment PSA is included, and patients with rising values are scored as treatment failures, then outcome is significantly worse than that based on clinical-radiographic parameters alone.

A successful outcome now requires that the patient has no PSA-based evidence of relapse on long-term follow-up [9–11]. Long-term follow-up for patients treated with external beam radiation in the PSA era is limited to less than 10 years; thus, most single-institution series have only a small number of treated patients with follow-ups of more than 5 years.

A rising PSA level precedes clinical failure with a lead time of years and may never result in clinical metastases in men with a limited life span. It is, however, justified as an endpoint because it rigorously assesses the true ability of external radiation to cure the patient.

With regard to the results of radiotherapy, new treatment strategies were urgently pursued to improve treatment efficacy.
The first includes progressive dose escalation to reach a lethal tumor dose. This kind of therapy is the subject of the chapter by Sandler [12].

The second strategy includes peri-irradiation androgen deprivation which results in cytocidal effects, and a more favorable radiation dose-response curve.

The aim of this overview is to summarize the available studies exploring the use of androgen deprivation given in combination with radiotherapy for localized prostate cancer. The main question is whether any conclusions could be reached on the efficacy of this treatment approach and the patients most suitable for its application.

**Rationale for Combination of Hormonal Therapy with Definitive Treatment**

Whether unicellular or multicellular in origin, a clinically manifest prostate cancer (fig. 1) is to a variable degree composed of clones of both...
androgen-dependent and androgen-independent cancer cells. While in this heterogeneous tumor the androgen-independent cells have lost any responsiveness to androgens, in androgen-dependent cancer cells a modification or deletion of one or more of the mechanisms, such as initiation, negative feedback and autophagia, could lead to a continued and unlimited growth of these androgen-dependent clones in the presence of circulating androgens (fig. 1). If this growth is faster than the growth of the androgen-independent cells, a relative selection of androgen-dependent cell clones may occur in the growing tumor, that is, these clones will progressively dominate in prostate cancer. This indeed may explain why nearly all men with both local, recurrent or metastatic prostate cancer have an initial, often dramatic, beneficial response to an androgen withdrawal therapy [13–19]. This response is due to the death of the sole androgen-dependent cells. The androgen-independent cells, however, would continue to proliferate after androgen withdrawal. Their continuous growth eventually would lead not only to replacement of the initial tumor loss but to an enlargement of the tumor. This indeed may explain, that nearly all patients treated by androgen withdrawal, relapse to an androgen-insensitive state. Thus, if prostate cancer is heterogeneously composed of androgen-dependent and -independent cells, the ability to cure the patient with androgen ablation alone is lost. Therefore, it would be reasonable to combine androgen ablation therapy with a nonhormonal treatment of prostate cancer, such as radiation therapy, at an early time point, in order to kill tumor cells independent of their androgen status [20–28].

The Neoadjuvant Concept

In 1969, Scott and Boyd [29] reported about combined hormonal deprivation (orchiectomy or estrogen therapy) and radical prostatectomy in selected cases with advanced prostate cancer. However, an in-depth analysis of the neoadjuvant concept could only be performed in recent years because drugs (LHRH and nonsteroidal antiandrogens) became available that allowed a reversible androgen deprivation. Preoperative androgen suppression should reduce the gland volume and facilitate radical prostatectomy, i.e. reduced operating time and blood loss, and ultimately less operation-related morbidity. Neoadjuvant therapy before curative radiation of the prostate should reduce the target volume and therefore preserve the anterior rectal wall and the bladder, which in turn should result in less radiogenic side effects in these organs [30–34]. The most important advantage is expected in terms of a reduction in tumor volume. Several studies about radical prostatectomy uni-
formally showed that precise preoperative staging of local tumor extension is practically impossible. Up to 60% of prostate carcinomas that have been judged ‘locally confined’ with all diagnostic possibilities penetrate the prostate capsule or reach the surgical margins [35]. Patients with positive surgical margins are at a high risk of suffering disease progression, as shown by several authors [36]. The expectation with neoadjuvant hormonal ablation is to achieve tumor downstaging, resulting in a reduced number of positive surgical margins and improved survival time in the follow-up.

**Combination of Hormonal Therapy and Prostatectomy**

*Results of Nonrandomized Early Studies*

The aim of neoadjuvant androgen deprivation is to achieve a downstaging of a tumor that has already penetrated the prostatic capsule. Some nonrandomized studies with relatively low patient numbers consistently showed a reduction of prostate volume (‘downsizing’) and serum PSA levels after a 3-month preoperative hormonal deprivation. However, the main question is whether neoadjuvant therapy is able to decrease tumor volume and produce pathological downstaging. Several studies showed that the effect of hormonal downsizing is in the range of the well-known overstaging error [37–39]. Concerning the likelihood of positive surgical margins, Soloway et al. [40, 41] described a decreased incidence of positive surgical margins from 35.3% in 42 of 119 patients with all stages of prostate cancer undergoing radical prostatectomy alone to 11.5% in 18 of 156 patients undergoing neoadjuvant androgen deprivation. In 83 patients with stage cT2b cancer, the rates were 46.7 and 13.2%, respectively. Oesterling et al. [38] found higher rates of capsular penetration and positive margins in patients who had received preoperative hormonal deprivation therapy. Since most of the patients in their study suffered from cT3 cancers, no conclusions could be drawn for less extensive cancers.

*Randomized Studies of Neoadjuvant Therapy and Radical Prostatectomy*

First results of four large prospective randomized trials of neoadjuvant hormone deprivation before radical prostatectomy have been published [40, 42–44].

Patients with prostate cancer of clinical stage T2/T3 N0 M0 were treated in these studies using different methods and time periods of neoadjuvant therapy. In two trials, a combination of leuprolide acetate and flutamide was used for 3 months. In the study of Goldenberg et al. [42], the patients were pretreated with cyproterone acetate for 3 months. Van Poppel et al. [44] treated
their patients in the neoadjuvant group with estramustine phosphate for 6 weeks. Side effects of the neoadjuvant treatment were noted in all studies. Combined androgen blockade with leuprolide and flutamide resulted in reduced libido and decreased or absent erections, hot flashes, diarrhea, nausea with or without vomiting, and abnormal liver function tests [40, 44]. The adverse reactions of cyproterone acetate consisted mainly of fatigue, asthenia, depression and insomnia [42], whereas the side effects of estramustine phosphate consisted of temporary gynecomastia, and gastrointestinal problems in about 30% of the patients [44].

With regard to the pathological downstaging, it is interesting to note that in patients with clinical T3 tumors no difference between the two treatment regimens could be found with 40% pathological stage T3 in the pretreated and nonpretreated groups, whereas in patients with a clinical T2 tumor pathological upstaging occurred more rarely [44].

Concerning the rate of seminal vesicle infiltration, no conclusive data could be obtained for patients undergoing hormonal pretreatment [40, 42]. Concerning positive margins, all studies uniformly show a reduction in positive surgical margins after neoadjuvant therapy [42, 44].

The results must be interpreted with caution, because, firstly, the percentage of positive margins in the surgery-only group is unusually high, especially in the study of Goldenberg et al. [42] and, secondly, androgen deprivation causes tumor cells to undergo regressive changes that render the detection of tumor cells outside the prostate more difficult and might result in underestimation of extracapsular disease and positive surgical margins.

Long-term follow-up data from the randomized trials are necessary for defining the benefit of neoadjuvant therapy [45]. Five-year follow-up data are to be reported in about 3 years. However, preliminary data from two of the randomized studies did not show any difference in the rate of PSA progression after 2 years with and without neoadjuvant therapy [41, 46]. Recently, similar results have been reported in two other randomized studies with a follow-up of more than 3 years. In both studies, there was no difference in the rate of PSA progression and time to PSA progression with and without neoadjuvant therapy [47, 48]. Therefore, these data suggest that neoadjuvant therapy for 3 months does not reduce the biochemical failure rate after radical prostatectomy. A recent prospective nonrandomized trial with 135 patients showed that after 3 months of therapy the PSA nadir was reached in only 28% of the patients, but in 88% after 8 months [47]. The positive margin rate after prostatectomy was only 6% after a mean follow-up period of 2 years for the neoadjuvant groups. A phase III trial has been initiated recently to evaluate the possible benefit of longer neoadjuvant therapy.
Combination of Hormonal Therapy and Radiation Therapy

Results of Nonrandomized Studies

Within the last 5 years, a total of 7 retrospective studies have become available that reported treatment results combining various forms of hormonal manipulation with radiotherapy (table 1).

Anderson et al. [49] and Zagars et al. [50] retrospectively reviewed their experience with hormonal manipulation in patients with unfavourable disease (T2c/T3, Gleason score 7–10, PSA > 15 ng/ml or PSA > 20 ng/ml, PSA > 10 ≤ 20 ng/ml with Gleason score > 7 or positive pelvic lymph nodes). Biochemical failure was dramatically reduced at 5 years in patients receiving hormonal manipulation and radiotherapy vs. radiotherapy alone. Crook et al. [51] compared biopsy results following radiotherapy in 226 patients. 42% of patients had hormonal treatment before radiotherapy. Negative biopsy rates at 18 months were significantly lower for patients who did not receive hormones compared to those who received them for more than 4 months. In addition, Zelefsky et al. [52] recently published their experience with the use of complete androgen deprivation (CAD) in patients treated with three-dimensional conformal radiotherapy. The incidence of positive biopsies among patients pretreated with androgen ablation was significantly lower than for those who did not receive CAD. The 5-year PSA relapse-free survival, incidence of distant metastases, progression-free survival and overall survival were not significantly different between both treatment groups.

Pollack et al. [53] showed that in high-risk patients (PSA > 30 ng/ml, or poorly differentiated histology with PSA > 10 ng/ml) who underwent a variety of hormonal manipulations with radiotherapy experienced significantly improved local relapse- and disease-free survival and biochemical control rates. In addition, Duchesne et al. [54] showed that intermediate-risk patients (PSA > 25 ng/ml, Gleason score 2–4) had superior disease-free survival, if given initial hormonal therapy. In contrast, in the retrospective study of Arcangeliet al. [55], no difference in local or distant failure or disease-specific survival was evident. In this study, early androgen deprivation was given 0–9 months before radiotherapy and continued for 2 or more years. Surprisingly, a statistically significant difference in overall survival in favour of patients treated with radiation alone was noted.

Randomized Trials

A total of four prospective randomized trials was published that compared radiotherapy alone or in combination with androgen deprivation. Two of the studies compared the use of CAD prior to and during radiotherapy [56, 57]. In the RTOG 86-10 trial, patients treated with CAD and radiotherapy showed statistically significant improvements in local control and time to PSA failure compared with radiotherapy alone. No difference in survival was noted, how-
**Table 1.** Retrospective and prospective studies comparing radiotherapy with and without androgen deprivation

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Type</th>
<th>Stage</th>
<th>Patients</th>
<th>RT dose (Gy)</th>
<th>Hormones</th>
<th>Results (effect in comparison to radiation alone)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crook et al.</td>
<td>1995</td>
<td>retrospective</td>
<td>T1b-4</td>
<td>190</td>
<td>66</td>
<td>4 months before RT</td>
<td>significant lower biopsy rates at 18 months</td>
</tr>
<tr>
<td>Duchesne et al.</td>
<td>1996</td>
<td>retrospective</td>
<td>T1-3</td>
<td>85</td>
<td>64</td>
<td>cyproterone before and during RT</td>
<td>superior disease-free survival for intermediate-risk patients</td>
</tr>
<tr>
<td>Pollack et al.</td>
<td>1995</td>
<td>retrospective</td>
<td>T1-4</td>
<td>119</td>
<td>66</td>
<td>variable before, during and after RT</td>
<td>significant improved local relapse, biochemical failure and disease-free survival</td>
</tr>
<tr>
<td>Anderson et al.</td>
<td>1997</td>
<td>retrospective</td>
<td>T2c-3</td>
<td>112</td>
<td>62-79</td>
<td>LHRH ± antiandrogens</td>
<td>significant reduction of biochemical failure</td>
</tr>
<tr>
<td>Zagars et al.</td>
<td>1997</td>
<td>retrospective</td>
<td>T1-3, PSA &gt; 20 or PSA &gt; 10, GS 7-10</td>
<td>185</td>
<td>66-70</td>
<td>variable before, during and after RT</td>
<td>reduction of biochemical failure</td>
</tr>
<tr>
<td>Arcangeli et al.</td>
<td>1998</td>
<td>retrospective</td>
<td>T1-4</td>
<td>265</td>
<td>66-74</td>
<td>estrogen, LHRH ± antiandrogens</td>
<td>reduced overall survival for the combined treatment groups</td>
</tr>
<tr>
<td>Zelefsky et al.</td>
<td>1998</td>
<td>retrospective</td>
<td>T1c-3</td>
<td>137</td>
<td>75.6</td>
<td>complete androgen deprivation 3 months before and during RT</td>
<td>lower biopsy rates</td>
</tr>
<tr>
<td>Pilepich et al.</td>
<td>1995</td>
<td>prospective</td>
<td>T2c-4</td>
<td>456</td>
<td>65-70</td>
<td>complete androgen deprivation 2 months before and during RT</td>
<td>significant improvement of local control and PSA failure</td>
</tr>
<tr>
<td>Lavergière et al.</td>
<td>1997</td>
<td>prospective</td>
<td>B1-T3c</td>
<td>120</td>
<td>64</td>
<td>complete androgen deprivation 3 months before and during RT</td>
<td>significant lower positive biopsies at 12 and 24 months</td>
</tr>
<tr>
<td>Pilepich et al.</td>
<td>1997</td>
<td>prospective</td>
<td>T1-3</td>
<td>945</td>
<td>65-70</td>
<td>goserelin after RT until progression</td>
<td>significant improvement in local control, disease-free survival, PSA failure</td>
</tr>
<tr>
<td>Bolla et al.</td>
<td>1997</td>
<td>prospective</td>
<td>T1-4, GS ≥ 7</td>
<td>401</td>
<td>70</td>
<td>complete androgen deprivation during and 3 years after RT</td>
<td>significant improvement in local control, disease-free survival, freedom from relapse and overall survival</td>
</tr>
</tbody>
</table>

GS = Gleason score; LHRH = luteinizing hormone releasing hormone; RT = radiotherapy.
ever. In the Canadian trial, patients treated with radiotherapy alone showed significantly higher positive biopsies at 12 and 24 months compared to those treated with radiotherapy and CAD. Median PSA levels at 12 and 24 months also significantly favoured patients who received CAD. No survival analyses were presented.

Two additional studies compared radiotherapy alone versus the same therapy with androgen deprivation started during radiotherapy and continued for extended periods of time [58, 59]. In RTOG 85-31, patients receiving Zoladex until progression experienced statistically significant improvements in local control, disease-free survival, PSA failure, and distant metastases rates [59]. Only in a subset of patients with a Gleason score of 8–10 overall survival was improved. In the EORTC trial, patients received either CAD beginning during the first week of radiotherapy and continuing for 3 years or radiotherapy alone [58]. The overall survival at 5 years in the combined treatment group was 79% as compared with 62% in the radiotherapy group (p < 0.001). Among the patients who survived for 5 years, the disease-free rate was 85% in the combined treatment group and 48% in the radiotherapy group. 78 patients had disease progression in the radiotherapy group, as compared with 20 in the combined treatment group. The 5-year local control rate was 97% in the combined treatment group and 77% in the radiotherapy group. Actuarial data on cancer specific survival were not given, however.

**Discussion and Conclusions**

The published literature was reviewed to evaluate the impact of androgen withdrawal in combination with radiotherapy on the treatment of localized prostate cancer because cellular and molecular investigations indicate that there exist additive or supra-additive effects when combining androgen deprivation and radiotherapy.

Although there are major differences in study designs, pretreatment prognostic factors, type and duration of hormonal manipulation, total radiation doses and techniques, the addition of hormonal therapy resulted in significant improvements in various interim measures of local/biochemical control and disease-free survival. However, only two prospective studies showed a statistically significant improvement in overall survival.

In general, there are methodological problems in the reported studies. The first is associated with defining an appropriate endpoint that reflects treatment efficacy. Multiple time-dependent criteria were used to evaluate outcome. Horwitz et al. [60] showed that statistically significant differences in outcome can be observed when using such time-dependent criteria.

Furthermore, the impact of androgen withdrawal on outcome can be attributed to the imbalance of prognostic factors. Therefore, there is a need
Table 2. Ongoing phase II–III studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Stage</th>
<th>RT dose (Gy)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG 94-08</td>
<td>phase III</td>
<td>&lt; T2c and PSA &lt; 20</td>
<td>65–70</td>
<td>neoadjuvant hormonal therapy + RT vs. RT alone in early stage disease</td>
</tr>
<tr>
<td>RTOG 94-13</td>
<td>phase III</td>
<td>T2c-4</td>
<td>65–70</td>
<td>timing of hormonal therapy and the role of whole pelvic RT</td>
</tr>
<tr>
<td>RTO1 MRC</td>
<td>phase III</td>
<td>T1b–T3a</td>
<td>64 or 74</td>
<td>RT (64 Gy) vs. RT (74 Gy) + neoadjuvant hormonal therapy (4 months)</td>
</tr>
<tr>
<td>EORTC 22991</td>
<td>phase III</td>
<td>T1b–T2b</td>
<td>70–77.2</td>
<td>RT + adjuvant hormonal therapy (6 months) vs. RT alone</td>
</tr>
<tr>
<td>Munich, Tübingen, Vienna</td>
<td>phase II</td>
<td>T1b–T3b</td>
<td>70–74</td>
<td>neoadjuvant hormonal therapy (6 months) + RT</td>
</tr>
</tbody>
</table>

RT = Radiotherapy.

for prestratifying patients according to the two most important prognostic factors (PSA and Gleason score). Finally, the timing, duration and combination of androgen withdrawal with radiotherapy remains an unresolved topic.

In conclusion, a lot of time-dependent early responses using androgen deprivation in the treatment of locally advanced prostate cancer have been uniformly improved, which suggests a potential for improved cure rates in a longer follow-up. Therefore, it is justified to treat patients with locally advanced prostate cancer with hormonal deprivation and radiotherapy according to the schedules of the published trials (4–6 months before and during radiotherapy).

To evaluate the true impact of androgen withdrawal and radiotherapy on overall or cause-specific survival, patients should be treated in recently initiated and ongoing trials (table 2) that address this question [8, 61].

References


Combination of Hormonal Ablation and Conformal Therapy

Feldmann/Stoll/Geinitz/Zimmermann 174
48 Baert LV, Goethuys HJ, de Rudder DJ: Neoadjuvant treatment before radical prostatectomy decreases the number of positive margins in cT2-T3 but has no impact on PSA progression or survival in cT2-3. J Urol 1998;159:229A.

Prof. Dr. H.J. Feldmann, Klinik für Radioonkologie-Strahlentherapie, Radiologie Zentrum, Klinikum Fulda, Pacelliallee 4, D-36043 Fulda (Germany)
Tel. +49 661 84 6340/41, Fax +49 661 84 6342, E-Mail hjfeldmann.raz@klinikum-fulda.de
Value of Dose-Volume Histograms in Estimating Rectal Bleeding after Conformal Radiotherapy for Prostate Cancer

Hans Geinitz*, Frank Bodo Zimmermann*, Peter Stoll*, Ladawon Narkwong*,c, Peter Kneschaurek*, Raymonde Buschb, Alexander Kuzmany*, Michael Molls*

* Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie, 
† Institut für Medizinische Statistik, Klinikum rechts der Isar, Technische Universität München, Germany, and 
‡ Radiation Oncology Division, Vajira Hospital, Bangkok, Thailand

Radiation therapy is an effective treatment of prostate cancer. Since local control improves with increasing tumor dose [1], many centers are involved in dose escalation studies for prostate cancer [2–5]. With modern conformal radiation therapy, dose escalation seems to be feasible without a significant increase in toxicity [2, 3, 5, 6]. Nevertheless, the rectum remains the dose-limiting organ: a mostly moderate rectal bleeding occurs in 6–40% of the treated patients, and its frequency depends on the applied dose and the irradiated volume [2, 6–11]. Dose-volume histograms (DVHs) of the organs at risk, as an integral part of three-dimensional treatment planning, seem to be valuable in predicting the risk of late radiation side effects. They offer the chance of adapting the treatment concept before initiating radiation therapy and thus help avoid major late side effects. This becomes particularly important when the dose to target volume is further escalated.

The purpose of this paper is to discuss the value of rectal DVHs in predicting rectal bleeding after conformal radiotherapy of prostate cancer. Our own data on the influence of rectal contouring on the association of DVH parameters with rectal bleeding are presented.
Studies on the Value of Rectal Dose-Volume Histogram Parameters to Predict Rectal Bleeding

Hartford et al. [8] studied 41 patients who were treated with a combination of photons (50.4 Gy to the pelvis) and protons (25.2 Gy to the prostate and seminal vesicles) to a total dose of 75.6 cobalt gray equivalents (CGE). Follow-up was at least 4 years. The anterior rectal wall was contoured extending from the anus to 2 cm above the prostate. The significance of certain dose-volume combinations (e.g. 70 CGE to 60% of the anterior rectal wall) was tested to predict rectal bleeding. 10 of 128 tested dose-volume combinations proved to discriminate statistically significantly between 14 patients with and 27 patients without rectal bleeding.

Boersma et al. [2] subjected 130 patients with localized prostate carcinoma to conformal radiotherapy with photons according to the ‘simultaneous boost technique’. The pelvis was treated simultaneously with the planning target volume (PTV), but received only 64% of the dose through partial-transmission shielding blocks. Dose to the PTV was 70–78 Gy. DVHs of the whole rectal wall were generated, extending from 1.5 cm below the prostate to the start of the sigmoid colon. Minimum follow-up was 10 months. Four dose-volume combinations were identified that could distinguish statistically significantly between 4 patients with severe rectal bleeding (requiring laser treatment or blood transfusion) and 126 patients without severe rectal bleeding. If the data in this study were analyzed according to the methods used in the work of Hartford et al. [8], no significant dose-volume combinations could be found. Furthermore, there was no significant correlation between any of the dose-volume parameters and the incidence of actuarial late gastrointestinal complications ≥ grade II.

Dale et al. [12] applied the Lyman-Kutcher model to the DVHs of the whole rectum and the rectal wall (length 75–80 mm) of 52 patients treated conformally for prostate cancer. The estimated probabilities for normal tissue complications correlated significantly with the score of a 6-item questionnaire addressing late rectal toxicity including rectal bleeding. Mean dose to the PTV (prostate, seminal vesicles and a 2-cm safety margin) was 66 Gy applied by a four-field box technique.

Jackson et al. [9] presented an abstract with the data of 132 patients treated conformally for prostate cancer. Minimum target doses were 70.2 Gy (n = 46) or 75.6 Gy (n = 86) applied using a 6-field coplanar technique. The most significant variables associated with bleeding (35 of 132 patients) were the percent volume of the rectal wall that received more than 50% of the prescription dose and the total rectal wall volume. The exact definition of the cranio-caudal extension of the contoured rectal wall was not stated.
Factors Influencing the Predictive Value of Rectal Dose-Volume Histogram Parameters

The data published in the literature demonstrate that there is an association of rectal DVH parameters and rectal bleeding after conformal therapy of prostate cancer. Nevertheless, the fact that the cut-off values of one study population are not transposable to another population [2, 8] indicates that there are difficulties and uncertainties in generating and interpreting rectal DVHs. They are discussed in the following section.

Contouring

Before creating a DVH, the organ at risk has to be delineated. The organ contour may vary among different observers (interobserver variability) and even for the same observer if the same organ is redrawn after a certain time interval. For the prostate and seminal vesicles, Fiorino et al. [13] found an interobserver variability of up to 18% when the organs were contoured by 5 different physicians. Lebesque et al. [14] reported a drawing accuracy of 3% for the outer rectum contour (‘whole rectum’) and of 7% for the rectal wall when the structures were redrawn by the same physician. Moreover, the volume calculations differ substantially when various treatment planning systems are used: Fellner et al. [15] reported that the calculated volume of a cylindrical phantom could be 31% smaller or 15% larger than the true volume depending on what kind of planning system was used.

Organ Structures, Cranio-Caudal Borders

So far, there is no consensus in the literature on what rectal structures should be delineated when creating a rectal DVH: the whole rectum [12, 14, 16, 17], the rectal wall [2, 9, 12, 15], or the rectal surface [18] are mentioned. Besides, the cranio-caudal extension of the organ varies among work groups, predominantly because it is difficult to define the cranial border in CT scans. Hence, the caudal and especially the cranial rectal borders are chosen more or less arbitrarily. They are either set in relation to the anatomy of the intestine (i.e. anus to horizontal course of the rectum) and/or in relation to the extension of the prostate (i.e. anus to 2 cm above the upper border of the prostate) and/or in relation to the treatment portals [2, 8, 16, 19, 20]. In a first evaluation, we analyzed 12 of our patients who had definitive conformal irradiation, for prostate cancer. The rectum was outlined using four different cranio-caudal borders for each patient. Depending on how the rectal borders were defined, the percent rectal volume that received at least 90% of the prescribed dose varied by as much as 63% [21].
Organ Movement and Set-Up Deviations
Changes in the filling of the rectum and the bladder can lead to internal organ movement of the rectum [14, 19, 22]. Melian et al. [19] evaluated the organ shift in 6 patients with prostate cancer by performing 3 additional CT scans during radiation therapy [19]. They observed differences in the rectal wall dose of up to 32% as compared to the initial value from the first planning CT scan. Lebesque et al. [14] observed a trend to a declining rectal filling in 11 patients with prostate cancer during the course of therapy. The rectal volume in the planning CT scan that received at least 80% of the prescribed dose was on the average 14% higher than the values obtained from the CT scans on weeks 2, 4 and 6. If the rectal wall was contoured instead of the whole rectum, the difference was only 5%. In addition to organ movement, set-up deviations contribute to changes in rectum position in relation to the treatment portals.

Consequently, the DVH data on the basis of just one planning CT scan before therapy do not necessarily reflect the true dose distribution in the rectum during fractionated therapy that lasts up to more than 7 weeks.

Comorbidity
The dose to the rectum and the irradiated volume are possibly not the only factors responsible for late rectal toxicity. Concomitant diseases, such as cardiovascular disease or diabetes mellitus, are likely to influence the frequency and the onset of late radiation toxicity [23-27]. Furthermore, individual radiation sensitivity may play a more or less extensive role in the occurrence of late radiation side effects.

With regard to all these confounding factors, not all patients with a high risk of late rectal complications are likely to be detected on the basis of DVH parameters alone.

Dose-Volume Histogram Parameters and Rectal Bleeding: Munich Data
To obtain further insight into the influence of contouring on the association between DVH parameters and rectal bleeding, we analyzed 20 of our patients who were treated with definitive conformal radiotherapy for prostate cancer.

Patients
In patients who had definitive conformal irradiation for prostate cancer at our institution, the frequency of clinically apparent rectal bleeding was 19% (37 of 195 patients with

---

Geinitz et al.
a minimum follow-up of 12 months). In most cases, bleeding was minor, not requiring any major therapy and not disturbing the patients’ quality of daily life. Twenty patients who all had been prescribed the same dose to the prostate and seminal vesicles were retrospectively analyzed: 10 patients (group 1) with moderate (grade II) rectal bleeding and 10 patients (group 2) without rectal bleeding or any other kind of late rectal toxicity. Follow-up in the group without rectal bleeding was at least 30 months. Median follow-up of all 20 patients was 37 months (23–50 months). Eight patients in group 1 and 9 patients in group 2 received short-term neoadjuvant hormonal therapy. Age and concomitant disease were well balanced in both groups: median age was 74.5 years (67–78 years) in group 1 and 72 years (61–75 years) in group 2. The frequency of cardiovascular disease was 5/10 in group 1 and 6/10 in group 2. One patient in group 1 and no patient in group 2 suffered from diabetes mellitus.

In group 2, bleeding occurred 3–26 months (median 7 months) after the end of radiation therapy. Bleeding lasted between 1 and 40 months. Seven patients had persistent rectal bleeding on the day of their last follow-up. None of the patients required transfusions or laser coagulation. Rectoscopy or colonoscopy was performed in all of the patients in group 1 after rectal bleeding had started. It typically revealed contact-sensitive telangiectases in the distal rectum. Other reasons for rectal bleeding were excluded.

**Radiation Technique**

All the patients received a dose of 50 Gy to the prostate and seminal vesicles (plan 1), and an additional boost of 20 Gy to the prostate alone (plan 2). Fractionation was 2 Gy daily, 5 times per week. Median overall treatment time was 51 days (48–65 days). The dose was prescribed according to the ICRU 50 guidelines. The prostate and seminal vesicles were treated with a 4-field box technique (ap, pa, and lat-lat) in all patients. The boost was delivered either with the same box technique (6 patients, 3 in each group) or via 4 oblique noncoplanar fields (gantry angles of 70°, 100°, 260° and 290°; 9 patients). Five patients were treated with the latter boost technique, but with slightly modified gantry angles. The safety margins between the clinical target volume (e.g. the prostate) and the planning target volume were 1.2 cm in the dorsal and 1.5 cm in all other directions during the first 50 Gy, and they were 1 and 1.2 cm, respectively, during boost irradiation. Planning and dose calculation were done with a Helax planning system using the TMS software.

Plan 1 and plan 2 were combined to a single plan for each patient, the DVHs of the rectum were then calculated for the combined plan.

**Dose-Volume Histograms**

CT scans of the pelvis were taken in 5-mm slice thickness and 5-mm intervals. In each CT slice, the outer contour of the rectum (‘whole rectum’), the total rectal wall, the anterior rectal wall and the posterior rectal wall were delineated by one of the authors. Due to limitations of the TMS software, a little unmarked area was left when contouring the rectal wall [12]. We then generated 4 DVHs using 4 different sets of lower and upper rectal borders for each of the contoured organs at risk (i.e. for the whole rectum, the rectal wall, the anterior rectal wall, and the posterior rectal wall): border set 1 extended from the anus to the lower border of the sigmoid colon (the lower border of the sigmoid colon was defined as the point where the colon turned horizontally). Border set 2 extended from the anus to the plane between the upper border of both acetabula. Border set 3 extended from the anus to 2 cm above the upper prostate border, and border set 4 extended from 1.5 cm below the prostate apex to the sigmoid colon. The matrix for dose calculation was: 281 × 281 to 2,000 × 2,000
Fig. 1. Box plot graphs of absolute volume fractions of the anterior rectal wall, that received at least 80% of the reference dose (aV80), for bleeding and nonbleeding patients (border set 4). The median value (horizontal line within the ‘box’), the 50% confidence interval (the ‘box’), the 95% confidence intervals (the ‘whiskers’) and the range (circles or end of the ‘whiskers’) are demonstrated.

calculation points for the whole rectum, 97 to 400 calculation points for the total rectal wall, 47 to 228 calculation points for the anterior rectal wall and 55 calculation points for the posterior rectal wall.

Additionally, we analyzed rectal DVHs previously created by various radiation oncologists during the original planning of the patients. The physicians had contoured the whole rectum without a strictly defined caudal or cranial rectal border. Thus 340 DVHs were investigated in total (17 per patient). For each DVH, we compared the percent (V50, V80, V95) and the absolute (aV50, aV80, aV95) volume fractions that received more than 50, 80 and 95% of the reference dose, respectively.

Statistics
Variables were tested for differences in distribution between bleeding and nonbleeding patients applying the nonparametric Mann-Whitney test. Values below 5% were considered to be significant.

Results
Age, size of the PTV of plans 1 and 2, the prostate volume and the combined volume of the prostate and seminal vesicles revealed no differences in distribution between bleeding and nonbleeding patients.

Bleeding patients had significantly higher absolute volume fractions (aV50, aV80 and aV95) for all rectal border sets when the whole rectum or the anterior rectal wall were contoured (p between <0.001 and 0.035). The aV80 of the anterior rectal wall reached the lowest p value (p<0.001 for border set 2, border set 3 and border set 4, p=0.002 for border set 1, fig. 1).
There was also a good association with bleeding for the aV50 and the aV80 of the whole rectum for all rectal border sets (p between 0.002 and 0.009). Furthermore, the aV50 and aV80 of the whole rectum contoured by different physicians during the original planning procedure were highly significant (p = 0.007 and p = 0.005, respectively).

When the whole rectal wall was contoured, the aV50 and aV80 were significantly associated with bleeding for all rectal border sets (p between 0.002 and 0.035), whereas the aV95 showed significance only with border set 4. None of the volume fractions of the posterior rectal wall were associated with rectal bleeding.

The percent volume fractions V50, V80 and V95 showed no significant differences in distribution between bleeding and nonbleeding patients for all contoured parts of the rectum.

There was no cut-off value of any of the DVH parameters that could separate 100% between bleeding and nonbleeding patients. For each applied organ at risk and each border set there is considerable overlap between bleeding patients and nonbleeding patients.

When the whole rectum was contoured, a V80 values of more than 32 cm³ appeared exclusively in patients with rectal bleeding (6 of 10 patients), regardless of how the cranial and caudal rectal borders were defined.

**Discussion**

The data indicate that the association between rectal DVH parameters and rectal bleeding depends on how the rectum is contoured in the planning CT scans. Primarily, it seems to be of importance what structures are delineated in the scan: the whole rectum, the total rectal wall, the anterior rectal wall or the posterior rectal wall. In our group of patients, the association between DVH parameters and rectal bleeding is stronger when the anterior rectal wall or the whole rectum are contoured than when the total rectal wall or the posterior rectal wall are delineated. In fact, none of the DVH parameters of the posterior rectal wall correlated with rectal bleeding.

Secondly, the definition of the cranial and caudal borders influences the association with bleeding, although not as much as the delineation of different organ structures. In this study group, the association between DVH parameters of border sets 3 and 4 and rectal bleeding is little stronger than with the other border sets.

There was no cutoff value that could separate bleeding and nonbleeding patients with 100% certainty. A very good separation was achievable by applying a value of 10 cm³ for the aV80 of the anterior rectal wall: 10/10 patients with rectal bleeding had higher values whereas only 1 of 10 patients without rectal bleeding had an aV80 above 10 cm³ (border set 2–4).
Conclusions

Rectal DVHs seem to be a promising tool in predicting late rectal bleeding after conformal radiotherapy for prostate cancer. Nevertheless, there are some uncertainties in creating and interpreting rectal DVHs. Apart from organ movement, setup deviations and comorbidity, different modes of contouring appear to bias the association between DVH parameters and rectal bleeding.

Since almost all groups utilize different definitions of the cranial and caudal rectal borders and since it is not yet clear whether it is best to delineate the whole rectum, the total rectal wall or the anterior rectal wall, it appears to be important for every center to define its own cutoff values. A standard protocol in rectal contouring would facilitate the transposition of cutoff values from one study group to another.

Acknowledgment

This work was supported by a grant from Deutsche Krebshilfe.

References


Dr. Hans Geinitz, Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie, Klinikum rechts der Isar, Technische Universität München, Ismaninger Strasse 22, D-81675 München (Germany)

Tel. +49 89 41404501, Fax +49 89 41404882, E-Mail Hans.Geinitz@lrz.tu-muenchen.de

Dose-Volume Histograms and Rectal Bleeding
Author Index

Appold, S. 80
Baltas, D. 59, 116
Bamberg, M. 130
Bambynek, M. 49
Baumann, M. 80
Baumgart, D. 49
Becker, G. 130
Baumgard, D. 49
Benedict, S. 40
Beatty, L.W. 152
Bedn, G. 116
Birn, G. 116
Beck, R.W. 152
Busch, R. 177
Cardinale, R.M. 40
Cucherat, M. 1
Debus, J. 123
Engenhart-Cabillic, R. 123
Feldmann, H.J. 97, 165
Fitzek, M.M. 106
Flühls, D. 49
Gérard, J.P. 1
Geinitz, H. 165, 177
Giannouli, S. 59
Grosu, A.L. 97
Herrmann, T. 80
Hey, S. 116
Hoess, A. 123
Jeremic, B. 130
Knoshaurek, P. 177
Kolotas, C. 59, 116
Kortmann, R.D. 130
Kuzmany, A. 177
Lahanas, M. 59
Lahaniatis, J.E. 152
Leiherowicz, A. 1
Martin, T. 116
Milas, L. 17
Milickovic, N. 59
Mohan, R. 40
Molls, M. 177
Narkwong, L. 177
Nestle, U. 80, 89
Pottgen, C. 71
Petersen, C. 80
Pirkall, A. 123
Quast, U. 49
Rübe, C. 89
Roy, P. 1
Sander, H.W. 158
Schlegel, W. 26
Schulz-Ertner, D. 123
Stoll, P. 165, 177
Strässmann, G. 116
Stuschke, M. 71
Trott, K.R. 8
Vogt, H.-G. 116
von Birgelen, C. 49
Wannennacher, M. 123
Weber, W. 97
Wiegel, T. 145
Wu, Q. 40
Wündrich, M. 123
Zamboglou, N. 59, 116
Zimmermann, F.B. 165, 177
Zips, D. 80
Atrophy, chronic radiation injury 12–14

Brachytherapy, see also Intravascular brachytherapy
glioma

interstitial high dose rate brachytherapy
computed tomography-guided implantation 116, 117, 120
dosing 117
patient selection 117
survival 117, 119, 121
low dose rate brachytherapy 116
imaging modalities 59
treatment planning
autoactivation of source dwell positions 65, 67, 68
catheter reconstruction 59, 60
computed tomography-based catheter reconstruction
accuracy 59, 61, 63
algorithms 61, 63
digitally reconstructed radiographs for catheter reconstruction 63–65
dose optimization 60
time analysis for components of planning procedure 60, 61

Brain metastases
diagnostic imaging 130
prognosis 130
radiosurgery
gamma knife, overview of outcomes 130, 131
linac-based radiosurgery, overview of outcomes 131, 132
prognostic factors
dose 134, 135
histology 138, 139
location 140
necrosis 139
number of metastases 132, 133
performance status 136, 137
primary or recurrent lesions 139, 140
systemic disease activity 137, 142
time from diagnosis of primary tumor to metastasis diagnosis 141, 142
tumor volume and size 135, 136
whole-brain radiation combination therapy 140–142
rationale 131
whole-brain radiation therapy 130

Clinical phases, cancer 1

Computed tomography, see also Treatment planning
catheter reconstruction for brachytherapy
accuracy 59, 61, 63
algorithms 61, 63
glioma
guided implantation for interstitial high dose rate brachytherapy 116, 117, 120
treatment planning 97
non-small-cell lung cancer clinical target volume 91, 92, 94

Cost benefit, radiotherapy 6
Cure
definition in cancer 2
local control 3
trends in cancer 6

Denudation, radiation response 11
Dose-volume histogram, rectal bleeding estimation, see Prostate cancer

Epidermal growth factor receptor inhibitors for use with radiotherapy 23
radiation-induced phosphorylation 19, 22
radiosensitivity of tumors
effects of ligand 21, 22
effects of tumor expression 20, 21, 23
signal transduction
overview 17–19
radiation effects 22, 23
tumor expression 19, 20

Erythema, radiation response 10, 11

Fibrosis, chronic radiation injury 14
Fixation systems
fractionated treatments 27
single-dose irradiation 26, 27
Frame, see Fixation systems

Glioma
brachytherapy
interstitial high dose rate brachytherapy
computed tomography-guided
implantation 116, 117, 120
dosing 117
patient selection 117
survival 117, 119, 121
low dose rate brachytherapy 116
dose escalation studies
grade 2 and 3 gliomas
survival 111
treatment 111
grade 4/4 gliomas
accelerated fractionation
scheme 107, 108
follow-up 108, 109
imaging change analysis 110
necrosis outcomes 110, 111, 113

patient selection 107, 108
prognostic factor analysis 110
surgery and pathology 109, 110
survival 109
tolerance 109
treatment planning 108
Joint Center of Radiation Therapy Study 112, 113
lower-grade gliomas 113, 114
rationale 106, 107
University of Michigan Study 112, 113
University of Tokyo Study 112
prognosis 106, 110, 116
recurrence sites 106
treatment planning
computed tomography 97
magnetic resonance imaging 97
positron emission tomography
fluorodeoxyglucose tracer 98, 103
methionine tracer 99, 103
single-photon emission tomography
using 3-methyl-tyrosine
comparison with magnetic resonance imaging 99–103
metabolism of tracer 99

Hormonal ablation, see Prostate cancer

Intensity-modulated radiotherapy
advances 36, 37
beam boundary sharpening 40
brain tumor study
convex ependymoma of posterior fossa 44–46
intensity distribution optimization 42
recurrent metastasis from lung at two foci 46–48
treatment planning 41, 42
homogeneity of dose distributions 40
multi-leaf collimators 36, 37, 41

Intravascular brachytherapy
depth dose distribution 54, 55
positioning 53
radiation sources 51, 53
restenosis inhibition
processes contributing to restenosis 49, 50
rationale 49
treatment planning
intravascular ultrasound 51, 54, 56
plastic-scintillator dosimetry 51–54, 56
radiobiological basis 81, 82
structures at risk 51
target volume 51

Local tumor control
conformal radiotherapy 5, 6
definition 3
metastasis following recurrence 3
natural history of cancer 1
non-small-cell cancer 89
organ-saving treatments 5
radiation dose-dependence 3, 4
relative survival rates 2
timing of radiotherapy 4, 5

Lung cancer
clinical target volume
computed tomography 91, 92, 94
definition 90, 94
elective nodal irradiation 90, 91
magnetic resonance imaging 92
mediastinoscopy for lymph node staging 92
positron emission tomography with fluorodeoxyglucose 93, 94
potential lymphatic drainage 91, 92
three-dimensional conformal radiotherapy 93, 94
clinical target volume
conventional fractionated radiotherapy
efﬁcacy 71, 80, 81, 89
local failure rates and metastasis 89
lymph node involvement 90, 91
radiotherapy combined with chemotherapy
radiotherapy with cisplatin regimens 72, 73
dosing 72
local control 72
metastasis prevention 72, 73
neoadjuvant radiochemotherapy and resection
dosing 75, 76
local control 76
pathologic complete remissions 74, 75
pneumonitis risks 73, 74
survival 73
taxane regimens 73, 74
target volumes 71

Magnetic resonance imaging, see also
Treatment planning
glioma treatment planning 97
non-small-cell lung cancer clinical target volume 92
Meningioma
features 123
fractionated stereotactic radiotherapy
evaluation of response 125
histological diagnosis importance 127, 128
irradiation technique 124
late toxicity 126, 127
patient selection 124
treatment planning 124
surgical resectional 123

Mortality, local tumor vs metastasis 2
Multi-leaf collimator
field sizes and types 34
intensity-modulated radiotherapy 36, 37, 41
linac-implemented collimators 35, 36
micro-collimators 36
Natural history, cancer 1
Necrosis, chronic radiation injury 12, 14
Non-small-cell lung cancer, see Lung cancer

Patient positioning, advances 28, 29
Positron emission tomography
glioma treatment planning
fluorodeoxyglucose tracer 98, 103
methionine tracer 99, 103
non-small-cell lung cancer clinical target
volume determination with
fluorodeoxyglucose 93, 94
Prostate cancer
conformal radiotherapy in local control
5, 6
controversies in management 152, 153
dose escalation with external-beam
radiotherapy
Fox Chase Cancer Center Study
160
historical data 158, 159
MD Anderson Hospital Study
159, 160
Memorial Sloan Kettering Cancer Center Study
160
overview of benefits 161
prognostic factors 160, 161
prospects 161–163
Radiation Therapy Oncology Group
Study 161
rectal bleeding 176
treatment planning 158
University of Michigan Study 163
dose-volume histograms in rectal bleeding
estimation
confounding factors
comorbid conditions 180
contouring 179
organ movement and set-up
deviations 180
organ structures and cranio-caudal
borders 179
overview of studies 178
rationale 177, 184
study design
dose-volume histograms 181, 182
outcomes 182, 183

patients 180, 181
radiation technique 181
statistical analysis 182
epidemiology 152
hormonal ablation with adjuvant
therapies
conformal radiotherapy
nonrandomized studies 170, 171
ongoing phase II–III studies 173
randomized trials 170, 172, 173
rationale 164, 165
mechanism of action 166, 167, 172
neoadjuvant concept 167, 168
prostatectomy
follow-up 169
nonrandomized early studies
168
pathological downstaging 169
side effects 169
prostate-specific antigen screening
goals of treatment 165
radical prostatectomy follow-up
145
radical prostatectomy with adjuvant
radiotherapy
persistent prostate-specific antigen
management 148
phase III trials 147, 148
rationale 145, 146, 149
retrospective series 146, 147
side effects 149
three-dimensional vs two-dimensional
radiotherapy
dosing 154–157
patient characteristics in study
153, 154
prognostic factors 156
toxicity 155, 156
treatment planning 153, 154, 156

Radiation injury
consequential late radiation damage
14, 15
growth factors and cytokines in
pathogenesis 17
mechanisms in different organs
acute injury 12, 13
chronic injury 12–14
stem cell inactivation in normal tissues 9, 10
Restenosis, see Intravascular brachytherapy

Single-photon emission tomography, glioma treatment planning using α-methyl-tyrosine comparison with magnetic resonance imaging 99–103 metabolism of tracer 99 Stem cell, inactivation in normal tissue damage 9, 10

Target localization, advances 28 Tissue rescuing unit 10 Tolerance, irradiated tissue volume relationship 8 Tracking systems, advances 30

Treatment planning, see also Computed tomography, Magnetic resonance imaging, Positron emission tomography, Single-photon emission tomography advances dose calculation 31, 32 inverse planning 33, 34, 37 planning programs 30, 31 target volume definition 30 visualization and evaluation of plans 32 brachytherapy, see Brachytherapy, Intravascular brachytherapy

Whole-brain radiation therapy, brain metastasis combination therapy with radiosurgery 140–142 outcomes 130