Review Article · Übersichtsarbeit

ONKOLOGIE

Onkologie 1998;21:474–484

F. B. Zimmermann
M. Molls

Klinik und Poliklinik für Strahlentherapie und Radiologische Onkologie,
Klinikum rechts der Isar, Technische Universität München

Three-Dimensional Radiation Treatment Planning: Principles and Practice[1]

Key Words
3-D radiation treatment planning · Conformal radiation therapy

Summary
The clinical outcome in radiooncological treatment of malignant tumors such as glioblastomas and non-small-cell lung cancer is disappointing. In order to obtain a better local tumor control and survival rates, dose escalation seems to be an appropriate way. Especially in those anatomical sites where radiosensitive tissues surround the tumor a further increase of the total radiation dose with conventional radiotherapy is critical. In numerous studies 3-D treatment planning and its clinical realization as conformal radiotherapy demonstrated an improvement in dose distribution for the target volume as well as the surrounding radiosensitive tissues compared with 2-D conventional treatment planning. The high-dose region was very well conformed to the tumor. Outside the tumor the radiation dose decreased steeply. For prostate cancer it has been shown that an increase of the total dose is tolerable. The number of normal tissue complications remained low. We expect that 3-D treatment planning and conformal radiotherapy may substantially improve the therapeutic ratio. There is no doubt that oncology in general, and especially radiooncology, may profit from this new technology in the near future. Continued clinical research, however, is necessary to take full advantage of this promising method.

Schlüsselwörter
3-D-Bestrahlungsplanung · Konformale Strahlentherapie

Zusammenfassung
Das klinische Ergebnis der radioonkologischen Behandlung bösartiger Tumoren wie Hirntumoren und nichtkleinzellige Bronchialkarzinome ist enttäuschend. Um die lokale Tumorkontrolle und das Überleben zu verbessern, scheint die Erhöhung der Strahlendosis eine geeignete Methode zu sein. Eine Erhöhung der Gesamtdosis mit der konventionellen Strahlentherapie ist besonders in den Gebieten problematisch, in denen strahlensensibles Gewebe den Tumor umgibt. In zahlreichen Studien zur 3-D-Bestrahlungsplanung und ihrer klinischen Verwirklichung in der konformalen Strahlentherapie zeigte sich eine Verbesserung der Dosisverteilung im Tumor wie in den umgebenden strahlensensiblen Strukturen im Vergleich mit der konventionellen 2-D-Bestrahlungsplanung. Der Bereich hoher Strahlendosis paßte sich in seiner Form der des Tumors sehr gut an. Außerhalb des Tumors fiel die Dosis steil ab. Für das Prostatakarzinom konnte gezeigt werden, daß eine Dosiseskalation möglich ist. Die Häufigkeit von Nebenwirkungen in den Normalgeweben blieb gering. Wir erwarten, daß die 3-D-Bestrahlungsplanung und die konformale Strahlentherapie die therapeutische Breite verbessern könnten. Es besteht kein Zweifel, daß die Onkologie und besonders die Radioonkologie von der neuen Technologie profitieren werden. Eine Fortsetzung der klinischen Forschung ist jedoch unabdingbar, um die Vorteile dieser vielversprechenden Technik vollständig auszunutzen.

Introduction

Conformal radiotherapy (CRT) aims at an optimal dose distribution, this means to maximize the dose to the tumor and to minimize the dose to the surrounding normal tissue [1, 2]. The most important requirement to obtain such an ideal dose distribution is sophisticated planning of radiation treatment. Over the past 10 years there have been substantial developments and impressing improvements in the production of commercially available new planning devices. The application of this modern technology has led to a number of publications which compared traditional treatment planning with the new 3-D treatment planning (3-DTP) [3, 4]. With regard to the reduction of the radiation dose in normal tissues an advantage of 3-DTP could be shown for various anatomical sites. Further-

[1] Supported in part by a grant from the Deutsche Krebshilfe.

Dr. F. B. Zimmermann
Klinik und Poliklinik für
Strahlentherapie und Radiologische Onkologie
Klinikum rechts der Isar, TU München
Ismaninger Straße 22, D-81675 München

more, there are clinical trials which attempt to escalate the radiation dose to the tumor in curative treatments with the intention to improve local tumor control [5, 6].
However, some thoughtful critics about the aims of CRT have been brought forth:
Can CRT with high doses be performed in a safe and reproducible way?
Will it be reasonable and efficient with regard to economic aspects in modern medical care?
It is the aim of this publication to briefly answer these questions and to demonstrate the clinical advantage of CRT. Special attention is paid to the procedure of 3-DTP. CRT has been introduced in various tumor sites in which malignant tissue is close to radiosensitive structures. As the potential of 3-DTP and CRT has been investigated mainly in prostate cancer, lung cancer and brain tumors, we concentrate on these entities, although CRT has been evaluated also in other sites (i. e. nasopharyngeal carcinoma, esophageal malignancies).

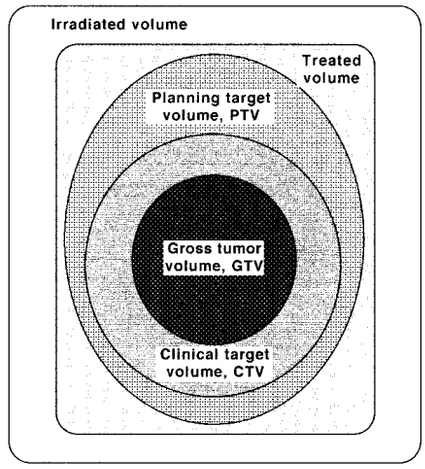


Fig. 1. Target volumes according to ICRU 50. Gross tumor volume (GTV): Visible tumor. Clinical target volume (CTV): Clinically evident tumor (or tumor bed) with a margin of suspected microscopic tumor spread. The CTV has to obtain 100% of the radiation dose. Planning target volume (PTV): CTV with a safety margin for suspected organ and patient movements [7].

Basic Aspects

In order to maximize the dose to the tumor and to minimize the dose to the surrounding normal tissue, the clinical target volume (CTV) and the normal tissue must be defined with very high accuracy by the radiotherapist.
Anatomically the CTV contains the clinically evident tumor (gross tumor volume, GTV) or the tumor bed (after resection of the tumor) and a margin of suspected microscopic tumor spread, in some cases including the lymphatics. The CTV has to obtain 100% of the radiation dose with a dose distribution of highest homogeneity (100% –5% +7% (ICRU-report 50) (fig. 1) [7]. Outside the target volume the dose has to decrease very steeply. The tools used for the definition of the target volume are modern diagnostic procedures such as computed tomography (CT), magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT), positron emission tomography (PET), and others [1, 8, 9]. Furthermore, the detailled reports of the surgeon and the pathologist influence the definition of the tumor bed.

Diagnostic Procedures

The modern imaging modalities can detect macroscopic tumor masses by contrast enhancement (CT, MRI), or they can demonstrate the biological activity of the tumor (SPECT, PET) [10–13] and can thereby help to define the GTV. Modern 3-D planning systems allow integrating and correlating scanning imaging procedures with each other (fusion of CT and MRI images) [8, 11]. The operator can modify scaling, rotation, and translation of one image type so that it fits on another. External computer systems support the correlation of CT or MR images with PET or SPECT images.
The combined use of different imaging techniques may lead to a better definition of the tumor extension in relation to the normal tissue environment [71]. However, the new technologies of imaging do not allow to detect microscopic involvement around the GTV. With regard to this problem, the knowledge of the radiooncologist concerning the kinetics of tumor growth and spread is mandatory for definition of the CTV.

General Considerations about Immobilization

In order to ensure an optimum of precision and reproducibility in dose delivery and dose distribution, the positioning of the patient has to be identical during the diagnostic procedures, the process of treatment simulation, and the whole radiation treatment [14]. This secures that the mode of dose distribution does not differ between the steps of treatment planning and radiation treatment itself. Discrepancies in field placement could result in underdosage of the target volume [15, 16]. Even small changes in the total dose (about 10%) can influence local tumor control as well as the frequency and severity of side effects in normal tissue [17]. Especially in modern 3-D-planned CRT with high geometric accuracy it is obligatory to secure the sophisticated application of high doses in any single treatment. Dependent on the treatment site, various devices are used for immobilization. All of them are tolerable for the patient and show in small inaccuracies of different size. These inaccuracies are taken into account when defining the planning target volume (PTV) that will be irradiated.
The immobilization devices are created under X-ray control during the first planning phase called localization (e. g. head holders with masks (fig. 2), foam molds, evacuated bags) so that the movement of almost any anatomical region of a cooperative patient can be reduced to less than 5 mm. Therefore, the PTV can be defined with very close margins around the CTV [16]. Special techniques used for the irradiation of intracranial lesions can yield positioning accuracies of ≥1 mm (stereotactical frames). They are used for stereotactic radiation therapy [18, 19]. A laser system present in every planning and treatment room produces a 3-D system of laser beams and coordinates. External markers are placed on the immobilization device or/and the patient to delineate this coordinate

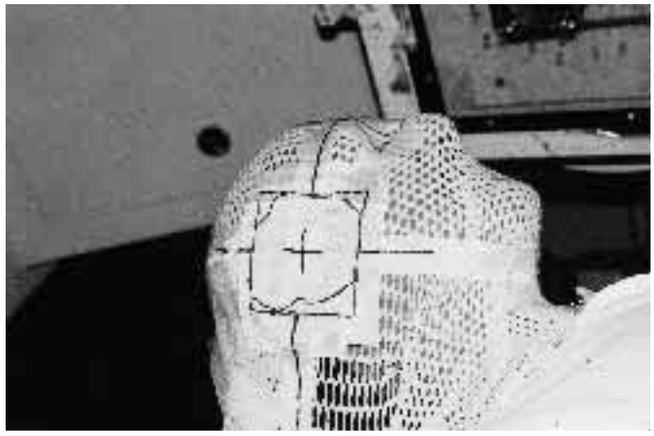


Fig. 2. Mask fixation system for patients treated for brain or head and neck malignancies. Accuracy of mask fixation differs between the different existing fixation systems and ranges from 2 to 5 mm. The accuracy is taken into account when defining PTV by adding a margin arround the CTV.

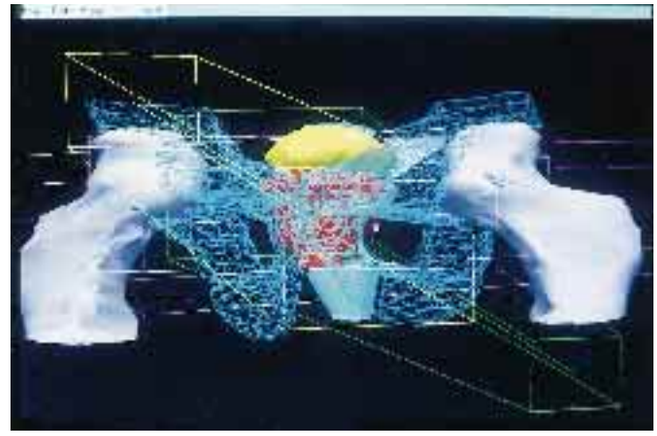


Fig. 3. Observer's eye view. The observer can examine the marked target volume, the surrounding organs and the beams (prostate red, bladder yellow, rectum light blue, femoral heads grey). One can rotate the images on the screen so that a observation from all directions is possible. According to a central axis of a beam this observation is called beam's eye view.

system. With these markers it is feasible to compare different imaging datasets with each other and to achieve a reproducible positioning of the patient during the whole planning and treatment procedure.

Identical Positioning of the Target Volume

The safety margins around the CTV which should be considered in the planning process also depend on the movement of the target inside the patient, e.g. in response to filling of the rectum and the bladder (in prostate cancer) or in response to breathing (in lung cancer) [15, 16, 20]. There are essentially two approaches to solve this problem: One is to reduce the movements, the second is to take them into account in the treatment plan. There are studies which investigate the tool of respiratory gating in lung cancer treatment or a definite filling of the rectum and the urinary bladder just before the irradiation of the prostate to assure a definite position of the target volume during treatment. Other studies have evaluated the movement of different organs in response to their physiological behavior. They have described the safety margins that should be respected in percutaneous radiotherapy. The values quantify the organ movements (in cm or mm) and can be used for the definition of the PTV [15] (fig. 1). Considering these data and the observations of target movements of every individual patient during the process of treatment simulation (e.g. using contrast medium in rectum (fig. 6a) and bladder), PTV can be precisely and reproducably defined.

Beam Modelling, Calculation of Dose Distribution, Dose-Volume Histograms, and Normal Tissue Complication Probability

After positioning and fixation, the patient pass the planning CT and/or other imaging modalities. Using the fixation devices and laser system, it is ensured that every point of the coordinates in the X-ray, CT or MRI device will be at the same coordinates in each scan of the patient. MRI imaging distortion is considered. Images of CRT and MRI can be superimposed [11]. A highly precise definition of the extension of the tumor can be secured.

Stepwise in every single scan, the target volume as well as the surrounding critical, radiosensitive organs are delineated by the physician. This is one of the essential differences in comparison to conventional planning in which the tumor was delineated only in one or a few scans. After the contouring of the target volume (GTV, CTV, PTV) and the normal tissues, one can observe the marked tissues from all directions (3-D) (fig. 3). The first step in establishing a treatment plan with the computer is the creation of different beams which come from any chosen direction and enclose the PTV. It is possible to study the shape of the different beams in comparison to the contour of the tumor by looking along the central axis of the beam (beam's eye view). Using the beam's eye view, the contour of every beam can be designed very close to the tumor border [8, 21, 22].

Afterwards the dose calculation is performed [14]. The algorithms use the electron density (Hounsfield units) of the CT for the precise calculation of the dose distribution. Generally, for this purpose a MRI can not be used. The fast and flexible calculation in 3-DTP enables a close interactive work of the physisist or physician with the computer, comparing different treatment plans within a short time. The calculated dose distribution can be observed from all directions and in all plains (axially, coronally, sagittally) (fig. 4).

To compare different treatment plans on a numerical base, integrated dose-volume histograms (DVH) are used. They describe the 3-D dose distribution within tumor and normal tissue in a 2-D graphic. Every point on the diagramm indicates the volume amount of the considered structure that receives the defined or a lower dose (fig. 5) [23–26]. So far it is very difficult to compare treatment plans if the DVHs of alternative

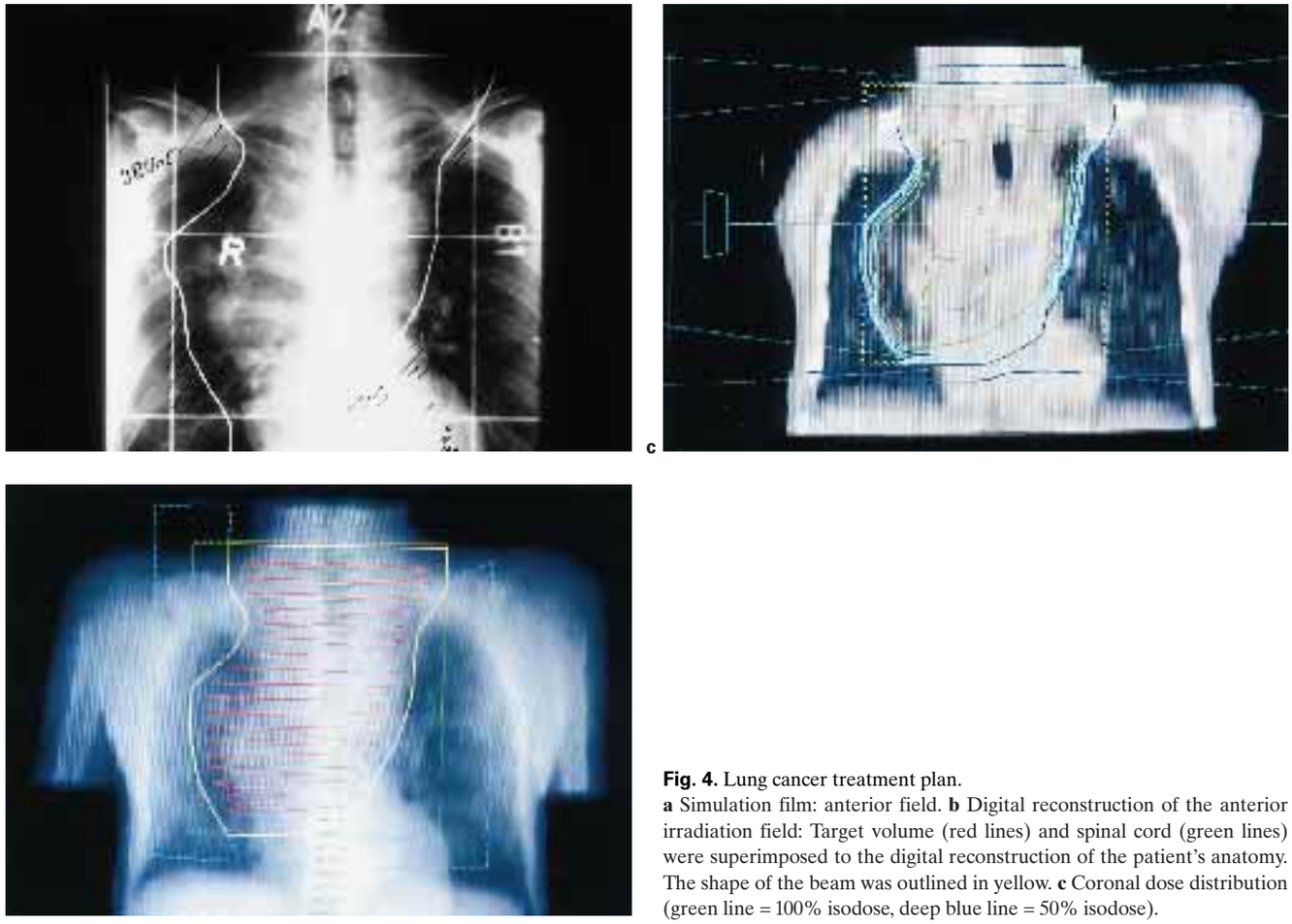


Fig. 4. Lung cancer treatment plan.
a Simulation film: anterior field. **b** Digital reconstruction of the anterior irradiation field: Target volume (red lines) and spinal cord (green lines) were superimposed to the digital reconstruction of the patient's anatomy. The shape of the beam was outlined in yellow. **c** Coronal dose distribution (green line = 100% isodose, deep blue line = 50% isodose).

plans cross each other. The reduction of volume within the high-dose region in one plan must then be compared with the effect of a decreased volume in the lower-dose region of an alternative plan. Because of the very complex structure of the DVH, there are different models to reduce them to one numeric value, the so-called normal tissue complication probability (NTCP) [27–29]. There are a number of unanswered questions in this scientific field, and the NTCP can not be used in routine for prediction of the treatment tolerance so far.

Simulation and Treatment Procedure

A very important step in the process of treatment planning is the verification of the calculated plan under X-ray control (simulation). Every single beam and field is controlled and documented by X-ray films. These simulation films are the basis for the control of the irradiation fields by using special films or a portal imaging system (special camera behind the patient) when performing radiation therapy at the linear accelerator [22, 30].
Portal imaging allows to actively intervene in treatments during each daily irradiation session. In case of misplacement, treatment may be interrupted, and correction of the beam or positioning of the patient can be done. Using special markers brought into the target volume a computerized control of the targets movement will be possible in future. The irradiation may be interrupted automatically if these markers leave the borders previously defined by the physician. Thus, a high precision of the dose application will be achieved.

Planning and Treatment Procedures and time consumption

The time needed for the different planning and treatment steps depends on the tumor site as well as on the complexity of the treatment plan (table 1). Establishing a standard plan for the treatment of breast cancer do not consume as much time as a very complex treatment plan for brain or lung cancer, for instance. On the other hand, the duration of time also depends on the physician's experience of 3-DTP and CRT. The given data are mean time values for providing a complex treatment plan of glioma by therapists of mean experience. In future the demand of time will be reduced by improvements of technology and knowledge: semiautomated delineating of target as well as organ volumes, inclusion of faster diagnostic procedures (spiral CT), further improvement in physicians' and physicists' knowledge, network with automated transport of data to the different planning and treatment devices.

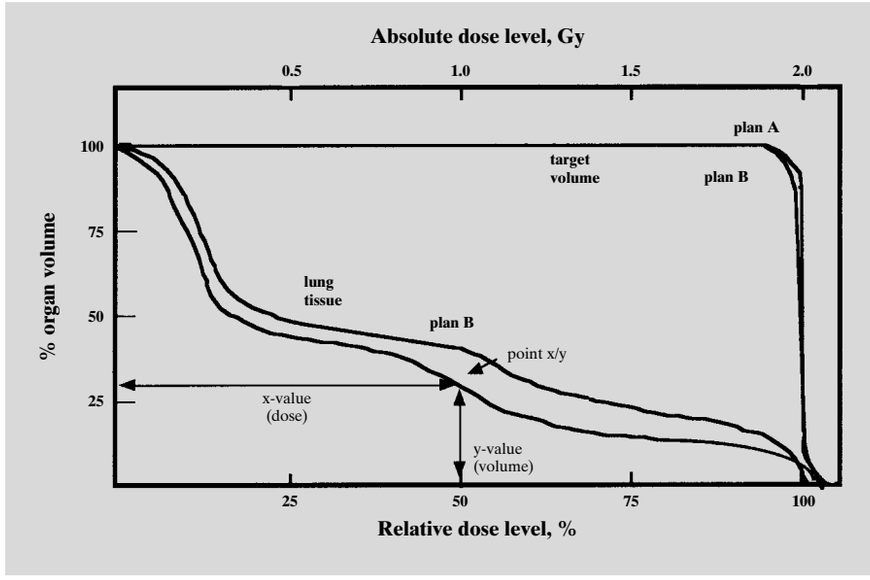


Fig. 5. The dose-volume histogram (also called cumulative dose-volume frequency distribution) describes the dose distribution in a defined volume (e.g. the lung or the target volume) in two dimensions. Every point on the curve is defined by an x- and an y-coordinate. The y-coordinate is the total dose (absolute or relative value). The x-coordinate defines the portion of the organ volume that receives this or a lower total dose. A lower curve indicates a lower radiation dose in the volume.
In figure 5 different treatment plans are compared: Plan A has a lower curve with a smaller volume of the lung treated with high doses resulting in a lower risk of pulmonal radiation side effects. The target volume was radiated with a high, fairly uniform dose in both plans. The steep drop is at the prescription dose (100%) and close to ideal. In the high-dose region it is closer to 100% in plan A. Therefore, plan A is the superior one for expected tumor control as well as for lower risk of side effects.

However, not only the planning procedures are more time consuming in 3-DTP than in conventional radiotherapy but also the realization of the plan at the linear accelerator, the production of individual formed blocks, and other treatment steps of CRT.

Clinical Results in 3-D Treatment Planning and Conformal Radiation Therapy

Brain Tumors

At the University of Michigan Thornton et al. [31] demonstrated a significant saving of normal brain tissue with conformal nonaxial techniques in 50 patients. When compared with conventional parallel opposed fields, uniform target volume coverage could be maintained while saving 30% of brain tissue treated with high dose (95% isodose) [31]. In our clinic, the quality of the 3-D treatment plans was compared to conventional treatment plans in 10 of 45 randomly selected patients with high-grade gliomas [32]. We used the reports of the neurosurgeon and the pathologist as well as CT, MRI, and PET and/or SPECT for CTV definition [13]. All plans were calculated in the 3-D planning device. DHV for critical cerebral structures and NTCP for the whole brain were calculated for both the conventional and the 3-D treatment plan using the calculation method of Lyman and Wolbarst [28] and Kutcher et al. [27], and the tolerance doses of Emami et al. [33]. We could demonstrate an advantage of 3-DTP over conventional treatment planning [32]. Especially within the high-dose regions the volume of irradiated normal brain tissue could be reduced up to 20% or more. The target volume was always enclosed by the 95% isodose. We also found a significant reduction of the NTCP ($p < 0.05$), indicating that the risk to develop a late side effect (brain necrosis, infarction, others) was potentially reduced.

Hess et al. [34] described the treatment outcome of 66 patients when applying CRT to a total dose of 60 Gy. Median survival time was 14 months. In 86% of the patients recurrences occurred within the CTV. Also in prior CT scan studies a high percentage of local in-field recurrences following radiotherapy could be demonstrated [35, 36]. Locally increasing the radiation dose would be a reasonable consequence. 3-D CRT seems to be the tool to enable this idea while maintaining the risk of side effects low. The first data from dose escalation studies have already been published but no clear survival benefits have been demonstrated. Nakagawa et al. [37] observed a local failure in 16 of 19 patients treated with 68.5 Gy median dose and only 4 of 13 patients treated with 90 Gy following surgical intervention (partial or subtotal resection in 89.5% of the patients). They found no difference in survival time due to increased distant brain and subependymal seeding in the high-dose group. In contrast, the first data from the Michigan group are very encouraging. Sandler [38] demonstrated an improvement of median survival time in patients with malignant glioblastoma treated with total doses of up to 80 Gy. He observed no notable radiation therapy toxicity to the brain.

Even in the radiotherapy of low-grade gliomas with total doses of up to 59.4 Gy, the failure within the radiographic abnormality (either T2 prolongation or CT hypodensity) was the leading cause of treatment failure [39]. The use of CRT did not result in increased marginal or out-of-field failures. The delivery of higher doses might be necessary even in this low progression tumor.

Also in the re-irradiation of primary brain malignancies, 3-D CRT is useful. Kim et al. [40] could demonstrate a neurologic improvement in 67% of 16 patients treated with CRT for local tumor recurrences. Even with cumulative doses of up to 119.4 Gy morbidity was acceptably low [40].

In addition to external beam irradiation, dose escalation through brachytherapy boosts as another form of CRT has been investigated. Selection criteria (size, shape, and location of tumor) permit the application of these modalities in only about 30% of patients with malignant glioma. In several single-institute studies [41–43] brachytherapy improved local tumor control

Table 1. Time consumption per staff and treatment step in a patient treated for malignant glioma

Treatment step	Time consumption in 3-D/2-D treatment, min			
	place of work	physicist	physician	RTA
Positioning of the patient	simulator		20/0[a]	30/0[a]
Planning scans (CT and/or MRI), transport of data into the planning system	CT/MRI		20/0[b]	60/0[b]
Definition of the volumes of interest, plan calculation	computer	45/30	45/15	240/60[c]
Calculation of DVH and NTCP	computer	120/0[d]		
Simulation	simulator		60/60	45/45
Discussion of treatment plans and simulation films		30/5	30/30	30/5
Starting treatment, daily and weekly controls	accelerator	120/60[e]	150/90[e]	480/240[e]
Posttreatment controls			180/120	
Data collection	computer	30/0[d]	90/0[d]	30/0[d]
Sum		345/90	595/315	925/345

RTA = Medical assistent in radiology
[a] Including the application of contrast medium, but not in glioma.
[b] Including the application of contrast medium.
[c] Plan calculation can be done by a special dosimetrist, a physicist, or a RTA (as in our clinic).
[d] Scientific work.
[e] Time consumption during the whole treatment of about 6 weeks.

and moderately prolonged survival time in selected patients in the initial treatment as well as in the treatment of recurrent tumor. Severe acute toxicity was seen in less than 10%, late toxicity requring surgical intervention for symptomatic radiation necrosis in up to 64% of patients [42]. However, fatal toxicity is rare, and brachytherapy resulted in good-quality survival of most patients [41]. Even after the application of extremely high radiation doses (up to 120 Gy cumulatively) by the combined modalities of external beam radiotherapy and interstitial boost, local in-field recurrence was the predominant failure [44]. This might be caused by an extremely high radioresistence of the tumor or by dose inhomogeneity typically achieved by interstitial implants.

Summarizing all published data (table 2), one can postulate that a dose escalation will be possible using CRT without increasing the risk of side effects compared with conventional planning. With higher radiation doses (>60 Gy) hopefully the local control of high-grade and low-grade gliomas might be improved. Dose escalation studies have been already started, but definitive results are lacking.

The definition of the appropriate target volume in locally effective treatments of malignant gliomas remains highly controversial. For a long time it has been defined as the tumor and edema visible in CT. During the last years, functional cerebral imaging (MRI, SPECT) has influenced the definition of the CTV [13, 29, 45]. Whether this will improve local tumor control and survival time or not is still an open question and subject of several studies.

Lung Cancer

Results of early dose escalation trials in non-small-cell lung cancer showed significantly improved dose-dependent local tumor control and overall survival increasing total dose in conventional fractionation from 40 Gy to 60 Gy [46]. For the following years, irradiation up to 60 Gy total dose was the standard radiotherapy in inoperable bronchial carcinoma. Unfortunately, local tumor control as well as cure rates remained low (5-year overall survival rate <10% in stage III and 5–20% in stage I–II). Therefore, altered fractionation, combination with chemotherapy, or further dose escalation have been evaluated with the intention to improve the patients' outcome without increasing secondary effects. In this connection CRT offers considerable promises by sparing normal tissue: Dose escalation to the tumor might improve local tumor control without increasing toxicity, and combined modality treatment might be less toxic.

In 1991, the first experiences in 3-DTP of lung cancer were published by Emami et al. [21]. For two patients the authors could show an advantage of the 3-DTP. The target volume was covered in a better way, and the surrounding normal tissue

Table 2. 3-DTP in radiation treatment of primary brain tumor

Authors	Result
Kim et al. [40]	3-D CRT in recurrent brain malignancies produces radiographic regression and neurologic improvement in 68% of previously irradiated patients (analysis of 20 patients)
Nakagawa et al. [37]	Reduced local tumor recurrence following high-dose 3-D CRT in 38 patients treated with 60–90 Gy total dose
Rosenman [66]	Tolerable toxicity with concurrent RCT and total radiation doses of 66.6–70.2 Gy, but no positive impact on overall survival in 40 patients with glioblastoma and high-grade astrocytoma
Sandler [38]	Dose escalation to 80 Gy with improved median survival time (16 months) without notable radiation therapy morbidity in 40 patients with 95% glioblastoma
Thornton et al. [31]	Nonaxial techniques allows uniform target coverage with reduction of 30% of brain tissue irradiated with high doses (95% of the target dose). Computer-based comparison of CRT and conventional radiotherapy techniques in 50 patients

could be spared. Other authors [23, 30, 47] described the possibility of dose escalation without increase of acute and late toxicity in normal tissue. Armstrong and colleagues [23] determined the dose distribution to the target and normal tissues with 3-DTP and conventional planning in 9 patients. They ensured that the same target volumes were used in both planning techniques and could demonstrate a better tumor coverage by 3-DTP. The mean percentage of GTV treated with a lower dose as prescribed was reduced by 60%, and the mean volume of the normal lung that received 25 Gy or more was reduced by 7% compared to conventional planning. Later, they described that the volume of ipsi- and contralateral lung irradiated with doses of more than 25 Gy was reduced by 11% and 51%, respectively. They suggested a potential for improvement in therapeutic ratio. A dose escalation study is in progress [22].

In 27 postoperative patients with lung cancer of different locations we could demonstrate an advantage of the 3-DTP, too. The volume of the heart within the high-dose region (>40 Gy total dose) was reduced by 8% on average (range 0–21%) compared with the conventional treatment plan. The volume of the lung within the high-dose region was reduced by 5% on average [48]. These results are comparable to those of Schraube et al. [49]. These authors described a reduction of the mean dose in the tumor-surrounding lung tissue in 75% of the treated patients.

Dose escalation studies have also been started in radiation therapy of lung cancer [50]. We would like to point out that in connection with 3-DTP and dose escalation the target volume concept in radiotherapy of non-small cell lung cancer is again under discussion. There seems to be a trend that in conformal radiation of lung cancer the volume of irradiated lymphatics should be reduced [2, 51].

Target delineation in the CT scans remains a challenging problem in CRT of lung cancer. While CT currently gives the most accurate delineation of gross disease, it is very limited in delineating tumor infiltration into the mediastinum and separating tumor tissue from postobstructive pneumonitis and partial lung collapse. New imaging modalities (MRI, PET) may assist in the definition of the GTV. The determination of the CTV remains a difficult task for the radiooncologist: The probability of nodal involvement depends on nodal size and location as well as on tumor size, location, and histology, and can only be estimated using lymph node mapping schemes and postoperative pathologic evaluation of former patients. On the other hand, lung tissue tolerance to irradiation has to be taken into consideration. That means that in 3-D CRT the radiooncologist has to find the best compromise regarding the chance of tumor control and the risk of producing sequelae.

Prostate Cancer

For radiation treatment of localized prostate cancer a dose-dependent tumor response is evident. In a review of 624 stage C prostate cancer patients, the actuarial 7-year local recurrence rate for patients receiving less than 64.9 Gy was 36%, for those receiving 65–69.9 Gy 32%, and for those receiving 70 Gy or higher doses 24% [52]. Therefore, a dose escalation seems reasonable. So far, the risk of urinary and rectal morbidity (according to the literature up to 20% proctitis WHO grade WHO II and 7% WHO grade III) has limited the ability to deliver total doses of 70 Gy or more using conventional techniques. Hanks et al. [53] could demonstrate treated volume to be an important factor influencing significant morbidity in patients with localized prostate cancer. Therefore, the introduction of CRT into radiation treatment of prostate cancer, which reduced the irradiated volume of radiosensitive structures, was the logical consequence [53].

A number of authors reported improved dose distribution with conformal radiation when compared with conventional techniques [3, 54–56] (see also table 3). Lower volumes of bladder and rectum received high doses.

Soffen et al. [57] compared 20 patients treated with conventionally planned radiotherapy with 26 consecutive patients treated immediately afterwards with CRT. Only 31% of the conformally treated group versus 60% of the conventionally

Table 3. Advantage of 3-DTP in radiation treatment of prostate and lung cancer

Authors	Advantage
Prostate cancer	
Corn et al. [3]	better covering of target volume by 3-D radiotherapy (retrospective analysis of 260 consecutively treated patients)
Forman et al. [6]	hyperfractionated dose escalation without increasing severe side effects (dose escalation study of 24 patients with 11% dose escalation for early effects compared to conventional fractionation, with $\alpha/\beta = 10$)
Hanks et al. [54]	reduction of acute grade II toxicities of the rectum (retrospective analysis of 247 consecutively treated patients)
Hanks et al. [58]	dose escalation to 79 Gy results in improved biochemical freedom of disease in patients with PSA > 10 ng/ml ($p = 0.002$) (retrospective analysis of 233 consecutively treated patients)
Kagawa et al. [8]	image fusion of CT and MRI supports definition of CTV in CRT (tested in 1 phantom and 22 patients)
Leibel et al. [22]	dose escalation to 81.0 Gy (rectal dose restricted to 75.6 Gy) in 324 patients with 0.6% grade III–IV RTOG late effects
Pollack et al. [4]	reduction of bladder volume in the high-dose volume using conformal technique for the dose boost ($p < 0.05$). No increase of side effects despite increased dose from 70 Gy (conventional radiotherapy) to 78 Gy (CRT) (phase-III randomized study of 60 patients)
Sandler [55]	low risk of chronic rectal morbidity (3% RTOG) in 721 patients using CRT (retrospective analysis)
Wachter et al. [67]	reduction of high-dose volume of organs at risk by CRT using beam's eye view (retrospective analysis of DVH in 115 patients)
Zelefsky et al. [68]	minimal treatment-related morbidity with postoperative CRT of prostate cancer (retrospective analysis of 42 patients, no grade III toxicity)
Zierhut et al. [56]	incidence and severity of toxicity is low using CRT (prospective toxicity evaluation, phase-II study in 32 patients)
Lung cancer	
Derycke et al. [69]	3-D CRT with non-coplanar techniques allows dose escalation in lung cancer treatment (comparison of treatment plans in a 3-D planning system in 10 nonselected patients with NSCLC)
Graham et al. [47]	reduced toxicity allows combined modality therapy of increased intensity (radiochemotherapy) (description of clinical experience with 3-D CRT in 82 patients with NSCLC)
Leibel et al. [20]	reduction of volume of ipsi- and contralateral lung receiving ≥ 25 Gy (11% and 51%, respectively) (prospective comparison in 9 patients)
Oetzel et al. [9]	realistic prediction of radiation-induced pneumonitis by DVH (retrospective analysis of 46 patients with lung cancer)
Robertson et al. [50]	successful dose escalation study, new information about the tolerance dose of the lung
Sibley et al. [70]	high-dose CRT with improved local control without increased side effects (retrospective review of 37 patients with NSCLC)
Zimmermann et al. [48]	reduction of radiation dose to normal tissue (comparison of 2-D vs. 3-D CRT in 27 patients)

treated group experienced symptoms which required medical intervention (treatment interuption and/or medication) ($p < 0.05$). Hanks et al. [53] evaluated the factors influencing the incidence of acute grade II morbidity. In 409 patients receiving either conventionally or conformally planned irradiation the conformal treatment group had significantly fewer complications than the standard treatment group. In a multivariate analysis the variables of conformal technique ($p < 0.001$) and treatment volume ($p < 0.001$) were independently significant indicators of the incidence of grade II morbidities. The authors started a dose escalation using conformal radiotherapy with total doses up to 79 Gy to improve local tumor control. Patients with pretreatment PSA levels higher than 10 ng/ml showed biochemical levels being closer to normal values

(PSA < 1.5 ng/ml) when treated with doses above 71.5 Gy ($p = 0.002$). Unfortunately, the risk of side effects increased, too. The slopes of the morbidity responses were even steeper than the tumor response slopes [58]. Therefore, dose escalation trials should be carried out very carefully not to increase late sequelae. Further computer support in the broad field of 3-DTP may help to overcome this problem. In 1995, Oldham and colleagues [45] presented a comparison of conventional plan optimization of a human planner with inverse treatment planning in 12 patients. Using inverse optimization, a slightly better treatment planning (better tumor and lower normal tissue coverage) and a planning time reduced by a factor of up to 20 compared with the human planner was observed [45].

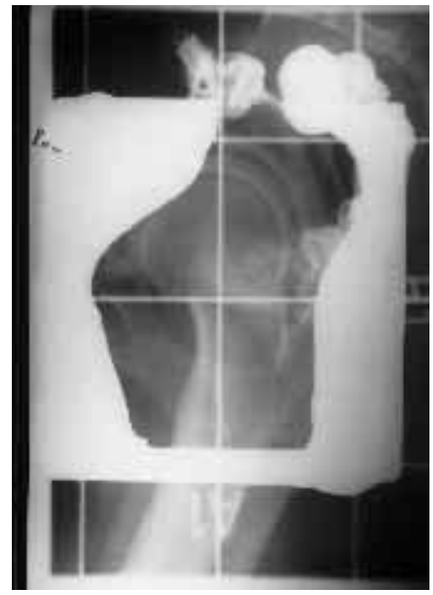
In early stages (T1–2) conformal prostate brachytherapy can be an alternative treatment in hand of an experienced radiotherapist. Various techniques of interstitial irradiation are available (iodine-125 or gold-198 permanent implants, iridium-192 removable implants). Modern planning and treatment devices are required in any case (endorectal ultrasound, CT planning). In combination with external beam irradiation (30–50 Gy in conventional fractionation) a sufficient local tumor control comparable with high-dose external beam irradiation alone can be achieved [59]. Genitourinary complications requiring transurethal radical prostectomy (TURP) might increase [60]. The optimal treatment schedule is not yet known. Therefore, brachytherapy of prostate cancer is under investigation in selected cancer centers.

Since 1993 we use 3-DTP system in radiotherapy of localized prostate cancer. 163 patients with primary or recurrent localized prostate cancer (cT1–3 cN0 cM0) underwent 3-D-planned CRT using total doses of 60–70 Gy (5×1.8–2.0 Gy per week) (fig. 6).

In 9 of 113 patients with a follow-up of more than 1 year a proctitis WHO grade II with occasional or longer lasting mild hemorrhagia was found. No severe side effects occurred (WHO grade III–IV). This outcome is better than historical ones in radiation treatment of prostate cancer. In 6 of 9 patients with hemorrhagia the seminal vesicles were irradiated with doses up to 60 Gy, increasing the risk of proctitis by augmentation of the treatment volume.

An important aspect are vascular risk factors such as diabetes mellitus or long-persisting hypertension. Five of the patients with late side effects had vascular alterations due to such diseases. Such problems should be taken into account when giving high total doses or performing dose escalation studies.

Summarizing essential publications and our own results, 3-DTP demonstrated an advantage over conventional planning in prostate cancer with respect to normal tissue toxicity and tumor coverage. For selected cases dose escalation might be reasonable to improve local tumor control but should only be conducted in clinical trials.



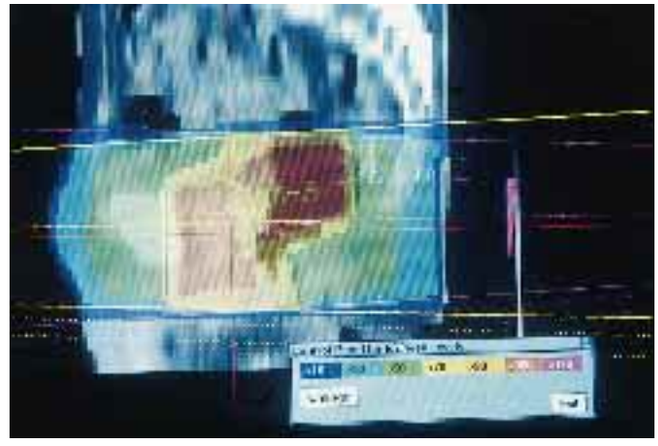


Fig. 6. Prostate cancer treatment. **a** Simulation film of a lateral, individual shaped beam of a conformal prostate plan: Prostate and seminal vesicles were treated. The rectum was filled with contrast medium. The posterior part of the rectum was not included by the lateral field. **b** Sagittal dose distribution (red high-dose region, blue low-dose region).

Cost-Benefit Aspects of Conformal Radiotherapy

The costs for modern treatment and planning devices are high. Nevertheless, modern technology aims at the reduction of side effects and hypothetically can facilitate improved local tumor control because of better coverage of the target volume with a specific dose. Therefore, an improvement of the therapeutic ratio might be achieved, especially in combined radiochemotherapy. Furthermore, these techniques allow carrying out dose escalation studies, if acceptable levels of morbidity are maintained.

The cost benefit of 3-D CRT has been evaluated by several authors [61, 62]. In these studies a careful integration of CRT into the clinical routine was demanded, because its clinical benefit – influence on tumor control and effect on normal tissue complication – can only be estimated. Therefore, CRT should be further evaluated compared with standard techniques in a larger, multiinstitutional protocol in order to justify its somewhat higher initial cost. Moreover, in and beyond such studies quality assurance guidelines for CRT should be followed to secure a high treatment quality [63]. Within the European

Society for Therapeutic Radiology and Oncology a commission has been founded in order to precisely define the planned and systematic actions to povide satisfying requirements for quality in 3-D CRT [64]. A high standard of quality assurance can be secured, if those prescriptions are followed.

Considering economic aspects of oncological therapy, one should remind that an overall cost reduction is possible due to higher curation rates. The cost of treating a patient with local tumor being controlled and no distant metastases is about one third of that for a patient who suffers a treatment failure. Moreover, regarding the economic aspects of reduced side effects (lower costs for managing treatment sequelae, better reintegration in the workaday life), radiation therapy is probably the cheapest oncological treatment when compared with surgical intervention or chemotherapy.

Conclusion and Future Prospects

3-DTP and its realization as CRT are used for different tumor sites such as brain tumors, lung cancer, and prostate cancer in a number of radiooncological centers. It could be demonstrated that the new techniques help to reduce the radiation dose in normal tissues [1, 4, 29, 30, 32, 53, 65, 72]. This is of high importance for patients who are treated with curative intention and good prognosis, because late sequelae might be reduced. Furthermore, improvement of normal tissue sparing allows dose escalation studies with the aim to improve the local tumor control [3, 20, 27, 29, 50]. However, at present it is unclear whether dose escalation will improve the therapeutic ratio in terms of increased tumor control and survival rate while maintaining a low incidence of acute side effects and long-lasting normal tissue complications. Only a few pilot studies [3, 6, 49, 51, 58] were performed as mentioned above. Prior to starting such dose escalation studies it is essential to precisely describe and define the target volume. Especially with view on the treatment of brain tumors and non-small cell lung cancer, the ideal definition of target volume has still to be established. To a certain extent this holds true also for prostate cancer. Under the auspices of the German Society of Radiation Oncology a working group has been established to discuss and work out basic rules which can be recommended for practical clinical use of 3-DTP.

For 3-DTP different devices are essential: diagnostic devices with high spatial resolution, immobilization devices as well as precise treatment devices with multi-leaf collimators (MLC) and high-performance computers. However, a completely computer-controlled treatment delivery is still in its infancy. The main problem is the lack of a good network and of programs which fit all devices to one single unit (linear accelerator, MLC, portal imaging, patient data acquisition) [14]. In future it should be possible to direct all treatment devices by one computer which should be linked to the computer used for treatment planning. After the interactive preparation of a treatment plan and the simulation procedure, this plan should be copied on the treatment computer. All other devices supporting the treatment apparatus should be controlled by this computer. In the next few years such a computer-controlled treatment delivery will help to reduce treatment and planning time, and the treatment quality will be further improved.

References

1 Sailer SL, Tepper JE: Clinical implications of new innovations in radiation treatment delivery. Semin Radiat Oncol 1995;5:166–171.

2 Vijayakumar S, Chen GT: Implementation of three-dimensional conformal radiation therapy: Prospects, opportunities, and challenges. Int J Radiat Oncol Biol Phys 1995;33:979–983.

3 Corn BW, Hanks GE, Schultheiss TE, Hunt MA, Lee WR, Coia LR: Conformal treatment of prostate cancer with improved targeting: Superior prostate-specific antigen response compared to standard treatment. Int J Radiat Oncol Biol Phys 1995;32:325–330.

4 Pollack A, Zagars GK, Starkschall G, Childress CH, Kopplin S, Boyer AL, Rosen II: Conventional vs. conformal radiotherapy for prostate cancer: Preliminary results of dosimetry and acute toxicity. Int J Radiat Oncol Biol Phys 1996;34:555–564.

5 Byhardt RW: The evaluation of radiation therapy oncology group (RTOG) protocols for non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1995;32: 1513–1525.

6 Forman JD, Duclos M, Shamsa F, Porter AT, Orton C: Hyperfractionated conformal radiotherapy in locally advanced prostate cancer: Results of a dose escalation study. Int J Radiat Oncol Biol Phys 1996;34:655–662.

7 Purdy JA: Defining our goals: Volume and dose specification for 3-D conformal radiation therapy. Front Radiat Ther Oncol 1996;29:24–30.

8 Kagawa K, Lee WR, Schultheiss TE, Hunt MA, Shaer AH, Hanks GE: Initial clinical assessment of CT-MRI image fusion software in localization of the prostate for 3D conformal radiation therapy. Int J Radiat Oncol Biol Phys 1997;38:319–325.

9 Oetzel D, Schraube P, Hensley F, Sroka-Perez G, Menke M, Flentje M: Estimation of pneumonitis risk in three-dimensional treatment planning using dose-volume histogram analysis. Int J Radiat Oncol Biol Phys 1995;33:455–460.

10 Pardo FS, Aronen HJ, Kennedy D, Moulton G, Paiva K, Okunieff P, Schmidt EV, Hochberg FH, Harsh GR, Fischman AJ: Functional cerebral imaging in the evaluation and radiotherapeutic treatment planning of patients with malignant glioma. Int J Radiat Oncol Biol Phys 1994;30:663–669.

11 Schad LR, Boesecke R, Schlegel W, Hartmann GH, Sturm V, Strauss LG, Lorenz WJ: Three-dimensional image correlation of CT, MR, and PET studies in radiotherapy treatment planning of brain tumors. J Comput Assist Tomogr 1987;11:948–954.

12 Seither RB, Jose B, Paris KJ, Lindberg RD, Spanos WJ: Results of irradiation in patients with high-grade gliomas evaluated by magnetic resonance imaging. Am J Clin Oncol 1995;18:297–299.

13 Weber W, Bartenstein P, Gross MW, Kinzel D, Daschner H, Feldmann HJ, Reidel G, Ziegler SI, Lumenta C, Molls M, Schwaiger M: Fluorine-18-FDG-PET and iodine-123-IMT SPECT in the evaluation of brain tumors. J Nucl Med 1997;38: 802–808.

14 Fraass BA, McShan DL, Kessler ML: Computer-controlled treatment delivery. Semin Radiat Oncol 1995;5:77–85.

15 Beard CJ, Kijewski P, Bussiere M, Gelman R, Gladstone D, Shaffer K, Plunkett M, Castello P, Coleman CN: Analysis of prostate and seminal vesicle motion: Implications for treatment planning. Int J Radiat Oncol Biol Phys 1996;34:451–458.

16 Verhey LJ: Immobilizing and positioning patients for radiotherapy. Semin Radiat Oncol 1995;5: 100–114.

17 Fischer JJ, Moulder JE: The steepness of the dose-response curve in radiation therapy. Radiology 1975;117:179–184.

18 Grosu AL, Stärk S, Feldmann HJ, Kneschaurek P, Leonardi M, Lumenta C, Molls M: Stereotaktische Konvergenzbestrahlung am Linearbeschleuniger – Bildgebung, Technik und klinische Indikationen. Röntgenpraxis 1998;51:9–15.

19 Rosenthal SJ, Gall KP, Jackson M, Thornton AF Jr: A precision cranial immobilization system for conformal stereotactic fractionated radiation therapy. Int J Radiat Oncol Biol Phys 1995;33:1239–1245.

20 Leibel SA, Armstrong JG, Kutcher GJ, Zelefsky MJ, Burman CM, Mohan R, Ling CC, Fuks Z: 3-D conformal radiation therapy for non-small cell lung cancer. Front Radiat Ther Oncol 1996;29:199–206.

21 Emami B, Purdy JA, Manolis J, Barest G, Cheng E, Coia L, Doppke K, Galvin J, LoSasso T, Matthews J, Munzenrider J, Shank B: Three-dimensional treatment planning for lung cancer. Int J Radiat Oncol Biol Phys 1991;21:217–227.

22 Leibel SA, Kutcher GJ, Zelefsky MJ, Burman CM, Mohan R, Ling CC, Fuks Z: 3-D conformal radiotherapy for carcinoma of the prostate. Front Radiat Ther Oncol 1996;29:229–237.
23 Armstrong JG, Zelefsky MJ, Leibel SA, Burman C, Han C, Harrison LB, Kutcher GJ, Fuks ZY: Strategy for dose escalation using 3-dimensional conformal radiation therapy for lung cancer. Ann Oncol 1995;6:693–697.
24 Drzymala RE, Mohan R, Brewster MS, Chu J, Goitein M, Harms W, Urie M: Dose-volume histograms. Int J Radiat Oncol Biol Phys 1991;21:71–78.
25 Kessler ML, Ten Haken RK, Fraass BA, McShan DL: Expanding the use and effectiveness of dose-volume histograms for 3-D treatment planning I: Integration of 3-D dose display. Int J Radiat Oncol Biol Phys 1994;29:1125–1131.
26 Martel MK, Ten Haken RK, Hazuka MB, Turrisi AT, Fraass BA, Lichter AS: Dose-volume histogram and 3-D treatment planning evaluation of patients with pneumonitis. Int J Radiat Oncol Biol Phys 1994;28:575–581.
27 Kutcher GJ, Burman C, Brewster L, Goitein M, Mohan R: Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. Int J Radiat Oncol Biol Phys 1991;21:137–146.
28 Lyman JT, Wolbarst AB: Optimization of radiation therapy, III: A method of assessing complication probabilities from dose-volume histograms. Int J Radiat Oncol Biol Phys 1987;13:103–109.
29 Ten Haken RK, Martel MK, Kessler ML, Hazuka MB, Lawrence TS, Robertson JM, Turrisi AT, Lichter AS: Use of V_{eff} and iso-NTCP in the implementation of dose escalation protocols. Int J Radiat Oncol Biol Phys 1993;27:689–695.
30 Lee WR, Hanks GE, Hanlon AL, Schultheiss TE, Hunt MA: Lateral rectal shielding reduces late rectal morbidity following high dose three-dimensional conformal radiation therapy for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1996;35:251–257.
31 Thornton AF, Hegarty TJ, Ten Haken RK, Yanke BR, LaVigne ML, Fraass BA, McShan DL, Greenberg HS: Three-dimensional treatment planning of astrocytomas: A dosimetric study of cerebral irradiation. Int J Radiat Oncol Biol Phys 1991; 1309–1315.
32 Grosu AL, Feldmann HJ, Albrecht C, Kneschaurek P, Wehrmann R, Groß MW, Zimmermann FB, Molls M: 3-dimensional radiation treatment planning in brain tumors: Advantages and clinical results. Strahlenther Onkol 1998;174:7–13.
33 Emami B, Lyman J, Brown A, Coia L, Goiten M, Munzenrider J, Shank B, Solin LJ, Wesson M: Tolerance of normal tissue to therapeutic radiation. Int J Radiat Oncol Biol Phys 1991;21:109–122.
34 Hess CF, Schaaf JC, Kortmann RD, Schabet M, Bamberg M: Malignant glioma: Patterns of failure following individually tailored limited volume irradiation. Radiother Oncol 1994;30:146–149.
35 Hochberg FH, Pruitt A: Assumptions in the radiotherapy of glioblastoma. Neurology 1980;30: 907–911.
36 Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG: Patterns of failure following treatment of glioblastoma multiforme and anaplastic astrocytoma. Int J Radiat Oncol Biol Phys 1989;16:1405–1409.
37 Nakagawa K, Aoki Y, Fujimaki T, Tago M, Terahara A, Karasawa K, Sakata K, Sasaki Y, Matsutani M, Akanuma A: High-dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiforme. Int J Radiat Oncol Biol Phys 1998;40:1141–1149.
38 Sandler HM: 3-D conformal radiotherapy for brain tumors. The University of Michigan Experience. Front Radiat Ther Oncol 1996;29:250–254.
39 Pu AT, Sandler HM, Radany EH, Blaivas M, Page MA, Greenberg HS, Junck L, Ross DA: Low grade gliomas' preliminary analysis of failure patterns among patients treated using 3D conformal external beam irradiation. Int J Radiat Oncol Biol Phys 1995;31:461–466.
40 Kim HK, Thornton AF, Greenberg HS, Page MA, Junck L, Sandler HM: Results of re-irradiation of primary intracranial neoplasms with three-dimensional conformal therapy. Am J Clin Oncol 1997; 20:358–363.
41 Kolotas C, Birn G, Baltas D, Rogge B, Ulrich P, Zamboglou N: CT based interstitial high dose rate brachytherapy for recurrent malignant gliomas. Br J Radiol 1998 (accepted for publication).
42 Prados MD, Gutin PH, Phillips TL, Wara WM, Sneed PK, Larson DA, Lamb SA, Ham B, Malec MK, Wilson CB: Interstitial brachytherapy for newly diagnosed patients with malignant gliomas: The UCSF experience. Int J Radiat Oncol Biol Phys 1992;24:593–597.
43 Wen PY, Alexander E III, Black PM, Fine HA, Riese N, Levin JM, Coleman CN, Loeffler JS: Long-term results of stereotactic brachytherapy used in the initial treatment of patients with glioblastomas. Cancer 1994;73:3029–3036.
44 Sneed PK, Gutin PH, Larson DA, Malec MK, Phillips TL, Prados MD, Scharfen CO, Weaver KA, Wara WM: Patterns of recurrence of glioblastoma multiforme after external irradiation followed by implant boost. Int J Radiat Oncol Biol Phys 1994; 29:719–727.
45 Oldham M, Neal A, Webb S: A comparison of conventional 'forward planning' with inverse planning for 3D conformal radiotherapy of the prostate. Radiother Oncol 1995;35:248–262.
46 Perez CA, Stanley K, Rubin P, Kramer S, Brady L, Perez-Tamayo R, Brown GS, Concannon J, Rotman M, Seydel HG: A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat-cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 1980;45:2744–2753.
47 Graham MV, Purdy JA, Emami B, Harms W, Matthews J: 3-D conformal radiotherapy for lung cancer. Front Radiat Ther Oncol 1996;29:188–198.
48 Zimmermann FB, Molls M, Kneschaurek P, Pietzsch C: 3-D-Planung bei der Radiotherapie des Bronchialkarzinoms. Onkologe 1995;5:467–474.
49 Schraube P, von Kampen M, Oetzel D, Sroka G, Wannenmacher M: The impact of 3-D radiotherapy planning after a pneumonectomy compared to a conventional treatment set-up. Radiother Oncol 1995;37:65–70.
50 Robertson JM, Ten Haken RK, Hazuka MB, Turrisi AT, Martel MK, Pu AT, Littles JF, Martinez FJ, Francis IR, Quint LE, Lichter AS: Dose escalation for non-small cell lung cancer using conformal radiation therapy. Int J Radiat Oncol Biol Phys 1997;37:1079–1085.
51 Hazuka MB, Turrisi AT, Lutz ST, Martel MK, Ten Haken RK, Strawderman M, Borema PL, Lichter AS: Results of high-dose thoracic irradiation incorporating beam's eye view display in non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1993; 27:273–284.
52 Hanks GE, Martz KL, Diamond JJ: The effect of dose on local control of prostate cancer. Int J Radiat Oncol Biol Phys 1988:15:1299–1305.
53 Hanks GE, Schultheiss TE, Hunt MA, Epstein B: Factors influencing incidence of acute grade 2 morbidity in conformal and standard radiation treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1994;31:25–29.
54 Hanks GE, Lee WR, Hanlon AL, Hunt M, Kaplan E, Epstein BE, Movsas B, Schultheiss TE: Conformal technique dose escalation for prostate cancer. Int J Radiat Oncol Biol Phys 1996;35:861–868.
55 Sandler HM: 3-D conformal radiotherapy for prostate cancer. The University of Michigan experience. Front Radiat Ther Oncol 1996;29:238–243.
56 Zierhut D, Flentje M, Sroka-Perez G, Rudat V, Engenhart-Cabillic R, Wannenmacher M: The conformal radiotherapy of localized prostatic carcinoma: Acute tolerance and early efficacy. Strahlenther Onkol 1997;173:98–105.
57 Soffen EM, Hanks GE, Hunt MA, Epstein BE: Conformal static field radiation therapy treatment of early prostate cancer versus non-conformal techniques: A reduction in acute morbidity. Int J Radiat Oncol Biol Phys 1992;24:485–488.
58 Hanks GE, Schultheiss TE, Hanlon AL, Hunt M, Lee WR, Epstein BE, Coia LR: Optimization of conformal radiation treatment of prostate cancer: Report of a dose escalation study. Int J Radiat Oncol Biol Phys 1997;37:543–550.
59 D'Amico AV, Coleman CN: Role of interstitial radiotherapy in the management of clinically organ-confined prostate cancer: The jury is still out. J Clin Oncol 1996;14:304–315.
60 Wallner K, Roy J, Harrison L: Tumor control and morbidity following transperineal iodine-125 implementation for stage T1/T2 prostatic carcinoma. J Clin Oncol 1996;14:449–453.
61 Levitt SH, Khan FM, Higgins PD, Nierengarten MB: Cost-benefit analysis of 3 D conformal radiation therapy. Strahlenther Onkol 1997;173:441–443.
62 Perez CA, Michalski J, Ballard S, Drzymala R, Kobeissi BJ, Lockett MA, Wasserman TH: Cost benefit of emerging technology in localized carcinoma of the prostate. Int J Radiat Oncol Biol Phys 1997;39:875–883.
63 Kolitsi Z, Dahl O, Van Loon R, Drouard J, Van Dijk J, Ruden BI, Chierego G, Rosenwald JC: Quality assurance in conformal radiotherapy: DYNARAD consensus report on practice guidelines. Radiother Oncol 1997;45:217–223.
64 Thwaites D, Scalliet P, Leer JW, Overgaard J: Quality assurance in radiotherapy. Radiother Oncol 1995;35: 61–73.
65 Armstrong JG: Three-dimensional conformal radiotherapy. Precision treatment of lung cancer. Chest Surg Clin N Am 1994;4:29–43.
66 Rosenman J: 3-D treatment planning for brain tumors. Front Radiat Ther Oncol 1996;29:244–249.
67 Wachter S, Gerstner N, Dieckmann K, Stampfer M, Hawliczek R, Poetter R: Planned 3-dimensional low-volume conformal irradiation of a local prostatic carcinoma. Strahlenther Onkol 1997;173:253–260.
68 Zelefsky MJ, Aschkenasy E, Kelsen S, Leibel SA: Tolerance and early outcome results of postprostatectomy three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 1997:39:327–333.
69 Derycke S, Van Duyse B, De Gersem W, De Wagter C, De Neve W: Non-coplanar beam intensity modulation allows large dose escalation in stage III lung cancer. Radiother Oncol 1997;45:253–261.
70 Sibley GS, Jamieson TA, Marks LB, Anscher MS, Prosnitz LR: Dose escalation without elective nodal irradiation is indicated in stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 1996;36 (suppl):348.
71 Gross MW, Weber WA, Feldmann HJ, Bartenstein P, Schwaiger M, Molls M: The value of F-18 fluorodeoxyglucose PET for the 3-D radiation treatment planning of malignant gliomas. Int J Radiat Oncol Biol Phys 1998;41:(in press).
72 Ling CC, Burman C, Chui CS, Kutcher GJ, Leibel SA, LoSasso T, Mohan R, Bortfeld T, Reinstein L, Spiron S, Wang XH, Wu Q, Zelefsky M, Fuks Z: Conformal radiation treatment of prostate cancer using inversely-planned intensity-modulated photon beams produced with dynamic multileaf collimation. Int J Radiat Oncol Biol Phys 1996;35:721–730.