Reduced Normal Tissue Doses Through Advanced Technology

Matthias Guckenberger, Reinhart A. Sweeney, Cedric Panje, and Stephanie Tanadini-Lang

Contents

Abstract

Re-irradiation is probably the most challenging situation in radiotherapy because the radiation tolerance of the normal tissue is significantly reduced compared with the first treatment series. Results with traditional radiotherapy techniques have been disappointing because of the poor conformality of the dose distributions: radiation doses were either insufficiently low resulting in poor rates of tumor control or substantial toxicity was the consequence of high-dose re-irradiation. This chapter will focus on modern techniques of radiation treatment planning and delivery, which make improved sparing of the normal tissue possible. All techniques will be discussed in the context of re-irradiation and theoretical and clinical data supporting the use of these technologies will be presented. Palliative reirradiation to moderate doses might be feasible without using advanced technology. However, under many circumstances 2D or 3D conformal approaches cannot fulfill the required normal tissue constraints. The present chapter discusses the advantages and challenges associated with more complex planning and delivery methods.

The original version of this chapter was revised. An erratum to this chapter can be found at 10.1007/978-3-319-41825-4_78.

M. Guckenberger (✉) • C. Panje • S. Tanadini-Lang
Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland
e-mail: guckenberger_m@klinik.uni-wuerzburg.de

R.A. Sweeney
Department of Radiation Oncology, Leopoldina Hospital Schweinfurt, Schweinfurt, Germany

Med Radiol Radiat Oncol (2016)
DOI 10.1007/174_2016_55, © Springer International Publishing Switzerland
Published Online: 13 Aug 2016

1 Introduction: Errors, Margins and Compensation Strategies in Radiotherapy

1.1 Rationale for Advanced Technologies in the Reirradiation Situation

Reirradiation is probably the most challenging treatment in the radiotherapy field. The radiation tolerance of the normal tissue is reduced compared to the first radiotherapy series unless complete repair of the radiation damage has occurred. Partial recovery has been suggested for some organs such as the spinal cord: Experiments on rhesus monkeys with two courses of radiotherapy (doses of >50 Gy in each course with intervals between 1 and 3 years) showed low rates of myelopathy (Ang et al. 2001), and preliminary clinical patient data support the hypothesis of recovery of the spinal cord (Nieder et al. 2006). However, this is unlikely for the majority of normal tissues after a first course of radiotherapy with a curative radiation dose, despite there being very limited data in the literature. Consequently, the need for effective sparing of critical normal tissue is even more important compared to primary radiotherapy.

Because of this reduced radiation tolerance of the normal tissue in the situation of a locoregional recurrence after primary radiotherapy, one could either reduce the maximum dose such that an acceptable risk of toxicity is met or reduce the exposure of the normal tissue best as possible by minimizing the irradiated volume and maximizing the conformity of the dose distributions.

New technologies in radiation oncology have always been utilized early after their clinical introduction for the purpose of reirradiation as a means to deliver clinically effective doses to the recurrent tumor with optimal dose reduction for the preirradiated normal tissue (Mantel et al. 2013; Chao et al. 2000; Loeffler et al. 1990). Although there is little literature available on the use of novel techniques specifically for reirradiation, this book chapter covers general aspects of target volume definition and radiation delivery in the reirradiation situation and demonstrates the potential improvement by advanced technologies.

1.2 Uncertainties in Radiotherapy and Compensation Strategies

The target volume concept in the reirradiation situation is in principle not different to primary radiotherapy and described in the ICRU reports 50 and 62 (ICRU 1993, 1999) (Fig. 1). The macroscopic tumor is defined as the gross tumor volume (GTV), and safety margins depending on histology and cancer site are applied for generation of the clinical target volume (CTV). Variations in shape, volume, and position of the CTV, for example, due to variable filling of hollow organs or due to breathing motion, are compensated via so-called internal margins, resulting in the internal target volume (ITV). Additional margins are then applied to ensure that the CTV is always exposed to the prescribed treatment dose, resulting in the planning target volume (PTV); setup uncertainties of patients contribute most significantly to these margins. If adequate dose coverage of the PTV is intended, all irradiating techniques deliver some dose outside the PTV, resulting in further increased irradiated volumes of normal tissue. Uncertainties are summarized in Table 1.

In recent years, multiple advanced technologies were introduced into radiotherapy treatment planning and delivery all owing the potential to

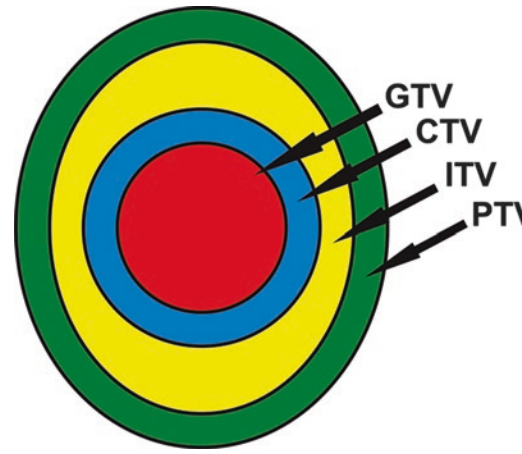

Fig. 1 Target volume concept according to ICRU 62: gross tumor volume (*GTV*); clinical target volume (*CTV*); internal target volume (*ITV*); planning target volume (*PTV*)

Table 1 Uncertainties in radiotherapy treatment planning and delivery

GTV stage	Inter- and intra-observer variability of target volume definition
	Sensitivity and specificity of imaging modality
PTV stage—intrafractional	Patient motion
	Target motion due to:
	Breathing
	Heartbeat
	Changes of the filling of hollow organs
PTV stage—interfractional	Patient setup:
	Rigid setup errors
	Nonrigid setup errors
	Shift of the target position due to:
	Changes of the filling of hollow organs
	Changes of the breathing pattern
	Complex changes of the patients' anatomy (e.g., atelectasis, effusions, etc.)
	GTV regression/progression
	Weight loss of the patient

reduce the margins described above resulting in reduced volumes of normal tissue exposed to mid- and high doses.

GTV Stage Reduction of the GTV is certainly not possible, but modern imaging for target definition using, for example, MRI, SPECT, or PEt allows for more precise and reproducible definition of the recurrent cancer with especially improved differentiation between postirradiation or postsurgical fibrosis and active tumor.

CTV Stage There are no data on the microscopic extension in the situation of loco-regional recurrences after a prior course of radiotherapy. However, it has been suggested, for example, for reirradiation of head-and-neck cancer, that the pattern of treatment failure after confining the target volume to the recurrent GTV with tight safety margins is in-field, which limits the potential benefit of elective nodal irradiation or irradiation of larger volumes where microscopic spread is assumed (Popovtzer et al. 2009). Additionally, the target volume concept needs to be adapted to the individual patient-specific situation: Different target volumes concepts can be considered in patients, where reirradiation intends short-term palliation or where a curative intend is followed.

PTV Stage, Intrafractional Uncertainties Changes of the target position during the treatment fraction may have several reasons: patient motion, breathing motion, cardiac motion, peristaltic motion, and changes of the filling of hollow organs. Depending on the target location and depending on patient individual factors, the above listed uncertainties reach different magnitudes and the contribution of each factor to the total intrafractional uncertainty varies significantly. For example, breathing motion is the dominant uncertainty in the thoracic region but may vary from few millimeters to 3 cm between patients. Management of intrafractional motion is highly challenging because of the short timescale of these uncertainties (e.g., cardiac motion with >1 Hz) as well as the random, unpredictable nature of motion (e.g., patient motion).

PTV Stage, Interfractional Uncertainties Uncertainties of the target position between treatment fractions influence safety margins significantly. The technique of stereotactic radiotherapy has been developed in the 1960s for high-precision radiotherapy of intracranial lesions (Leksell 1951, 1968), and this technique achieved an accuracy of patient setup with residual errors in the range of 1 mm. In the 1990s, the stereotactic principle of patient setup was transferred to the extracranial region, called stereotactic body radiotherapy (SBRT) (Lax et al. 1994). Recently, the need for external coordinates in stereotactic radiotherapy, both cranial and extracranial, has been questioned due to the availability of image guidance (IGRT) (Verellen et al. 2007), which allows verification of the target position prior to each treatment fraction. Besides changes of the target position, systematic changes of tumor volume and shape (regression or progression) and of the normal tissue (e.g., changes of pleural effusion and atelectasis; weight loss of the patient) have been observed during a fractionated course of radiotherapy. Adaptation of the

treatment plan to these systematic changes in an adaptive feedback loop is currently a focus of research.

Choice of Irradiation Technique It is important to adjust the irradiation technique to the individual patient case with location of the recurrent tumor, size and volume of the PTV, the type of normal tissue in relationship to the recurrence, and dose distribution of the previous treatment course being the most important factors. Kilovoltage X-rays or electrons may be considered for superficial recurrences and brachytherapy in cases, where implantation of the catheters in a suitable geometry or intraoperatively is reasonable. The standard delivery methods for photon reirradiation are currently intensity-modulated arc techniques such as volumetric modulated arc therapy (VMAT) or RapidArc, which can provide more conformal dose distributions than 3D-conformal techniques (Stieler et al. 2011). Protons and heavy ions offer distinct physical and biological advantages over photons which allow to reduce the dose to normal tissue. Although these properties are of particular interest in the reirradiation situation, there is only limited data on the use of particle therapy for reirradiation published (Plastaras et al. 2014).

1.3 Safety Margins in Radiotherapy

Despite all technological progress, the clinical application of radiotherapy will never be without errors or uncertainties at the planning and delivery stage. Consequently, margins always have to be added to the CTV or GTV if adequate coverage of this target volume is intended. Most important is the differentiation between systematic and random errors (Fig. 2). A systematic error affects all treatment fractions in an identical way and will result in a systematic difference between the intended and delivered dose distribution. An example is target delineation, where a certain part of the tumor is excluded from the target volume because of false-negative imaging for treatment planning. Random errors may affect all treatment fractions as well; however, all errors are centered around the planned position. It is the systematic error component which is most important and which should be minimized with highest effort in the primary and the reirradiation situation. The contribution of the random error component to the overall uncertainty and consequently to the overall safety margin is significantly smaller.

The most commonly used margin concept is a population-based probabilistic concept:

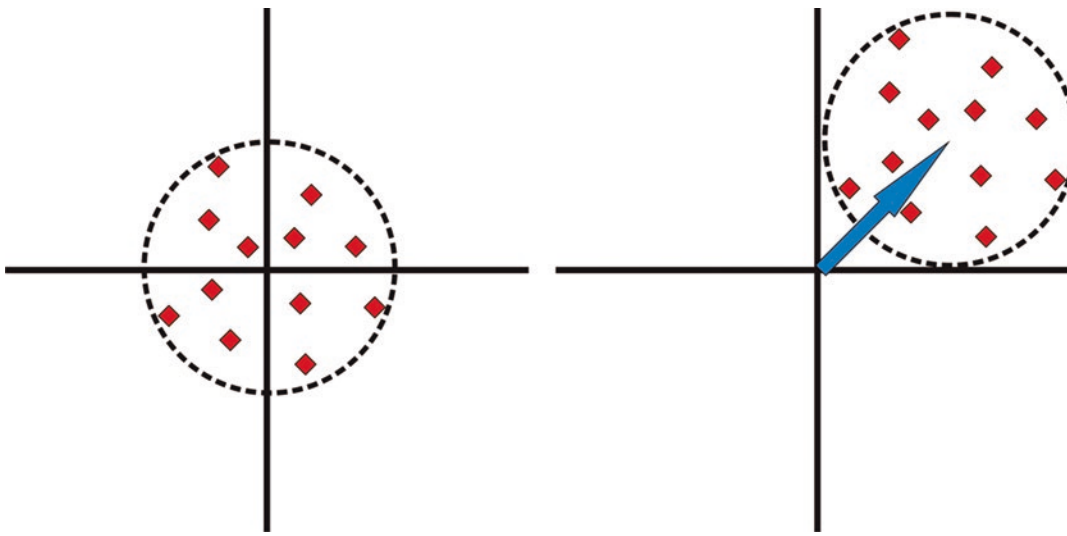

Fig. 2 Random (*left*) and systematic (*right*) uncertainties in radiotherapy treatment

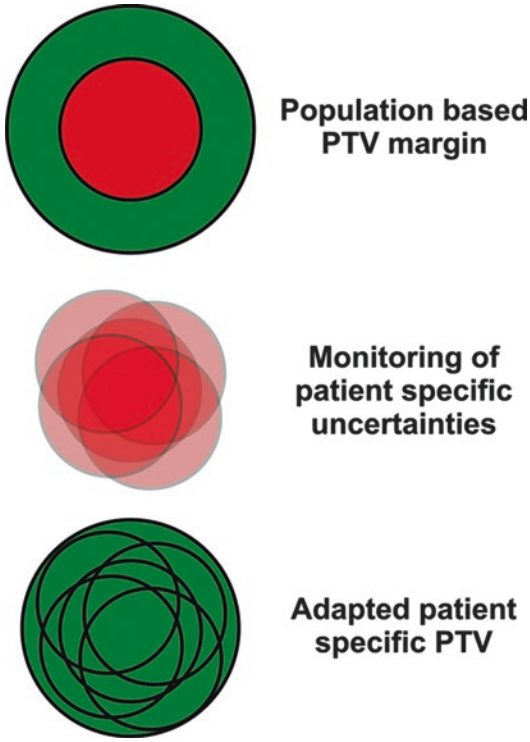

Fig. 3 Work flow of patient individual adaptation of safety margins: (1) Start of treatment with population-based margins; (2) assessment of patient individual uncertainties; and (3) adaptation of safety margins to the patient's individual errors

Application of a certain margin around the target volume ensures that the target volume is treated with at least 95 % of the prescribed dose in 90 % of the patient population (van Herk 2004). Systematic and random errors of all stages of radiotherapy need to be quantified for a patient population, and these data are used for calculation of population-specific safety margins. A different concept aims at adaptation of the safety margins to the individual, patient-specific uncertainties (Yan et al. 1997): Uncertainties are quantified at the beginning of the treatment course for each patient, and the safety margins and treatment plans are then adapted for the following treatment fractions based on the individual uncertainties (Fig. 3).

In the following of this chapter, we will focus in more detail on the distinct technological advances in external beam radiotherapy and discuss their potential role in the situation of reirradiation.

2 Imaging for Reirradiation

The integration of modern imaging modalities such as CT, MRI, and PET in the treatment planning process has become common practice; however, major advances in more specific imaging technologies have evolved in the last decade, requiring the radiation oncologist to have a detailed understanding of possibilities and limitations of these novel diagnostic modalities. Interdisciplinary discussion with radiologists or nuclear medicine specialists should lead to optimal integration of these modalities into the treatment planning process. Especially the development of image fusion software has significantly advanced in recent years, which was mainly driven by the radiooncological community; we are likely the specialty making greatest clinical use of image fusion, often more so than diagnostic radiologists themselves. Detailed discussion of imaging modalities for the different cancer sites is beyond the scope of this chapter and will be performed in the dedicated chapters of this book. Some important generalized points should be considered:

In the reirradiation situation, the radiation oncologist is frequently confronted with imaging results, which are significantly different to the situation of the primary irradiation (Meerwein et al. 2015): The normal anatomy is substantially altered after repeated surgical interventions and after prior radiotherapy. Especially differentiation between postsurgical/postradiotherapy scarring and recurrent tumor is difficult in many cancer sites: Our morphological imaging techniques of CT and standard MRI sequences are frequently limited in this situation. Additionally, we as radiation oncologists do not only need to differentiate between scarring tissue and recurrent tumor on a diagnostic level (yes or no) but must accurately delineate the recurrence in three dimensions for conformal treatment planning.

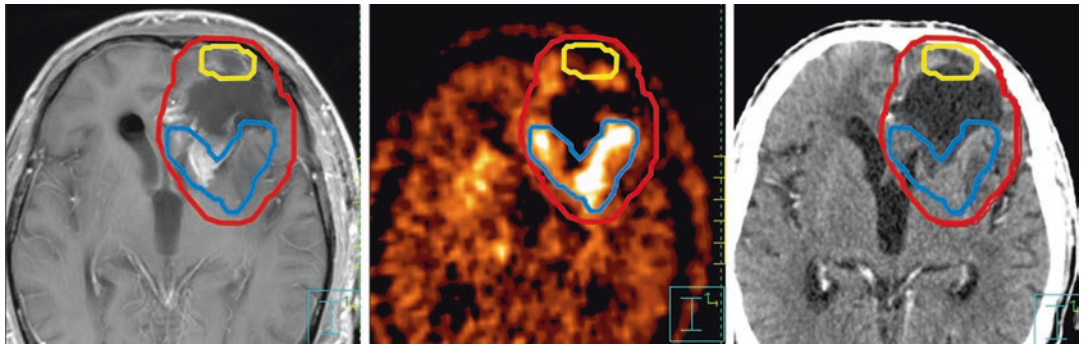

Fig. 4 A 79-year-old patient was treated with standard radiochemotherapy (60 Gy and Temozolomide) to a left frontal glioblastoma. Twelve months later a local recurrence was surgically removed. While the surgeons reported gross total resection, post-OP MRI (within 2 days) showed residual tumor at the very frontal pole (*left image*). The hyperintense region at the posterior of the tumor cavity was attributed to blood. FET-PET however showed marked activity in the dorsal region while the frontal region was inactive (*middle image*). The contrast-enhanced planning CT shows no residual disease (*right image*). *Yellow* GTV MRI, *Blue* GTV PET, *Red* PTV surrounding both regions

The potential advantage of advanced imaging modalities in this situation will be demonstrated exemplarily in two cancer sites.

Malignant gliomas most frequently recur locally within a distance of about 2 cm to the primary lesion, which makes differentiation of recurrent cancer and posttherapeutic changes, especially radiation necrosis, difficult. Amino acid PET imaging in addition to standard MRI imaging was shown to increase sensitivity and especially specificity in diagnosis, grading, and determination of tumor extension of malignant gliomas (Pauleit et al. 2005; Hatakeyama et al. 2008). In the situation of recurrent malignant gliomas, amino acid PET imaging improved the accuracy for differentiation between radiation necrosis and recurrent tumor (Terakawa et al. 2008). Early clinical results suggest that integration of this biological information into target definition in primary radiotherapy and reirradiation of malignant gliomas alters the target volume in a significant proportion of the patients (Rieken et al. 2013; Munck Af Rosenschold et al. 2015; Lee et al. 2009). Additionally, amino acid PET uptake kinetics before reirradiation have shown to be of prognostic value (Niyazi et al. 2012), and the use of PET-based "biological" target volumes may even improve clinical outcome (Grosu et al. 2005) (Fig. 4).

After anterior resection or abdominoperineal resection for rectal cancer, the differentiation between fibrotic masses in the presacral operative bed and a local tumor recurrence is extremely challenging with conventional CT imaging (Lee et al. 1981). This requires the use of further imaging modalities for accurate target volume delineation for reirradiation: Magnetic resonance imaging of recurrent rectal cancer may help to determine infiltration into pelvic structures (Dresen et al. 2010), and dynamic contrast-enhanced imaging may predict R0 resection (Gollub et al. 2013). FDG-PET imaging was reported to allow differentiation between benign scarring tissue and a locally recurrent rectal cancer with high sensitivity and specificity (Ito et al. 1992), and combined PET/CT imaging was shown to further improve the accuracy by avoiding the misinterpretation of displaced pelvic organs as recurrent tumor (Even-Sapir et al. 2004). Integration of this functional imaging into radiotherapy treatment planning with a focal dose escalation in volumes of increased FDG-PET activity has been reported recently (Jingu et al. 2010).

In principle, the requirements for imaging in preparation for reirradiation are comparable to those necessary for high-precision radiotherapy in the primary setting. Here also, there should be no compromise in utilizing possibilities of treatment volume definition as both marginal misses and sequelae due to unnecessarily large treatment volumes are of special issue in the reirradiation situation.

3 Photon External Beam Radiotherapy

3.1 Conventional Two-Dimensional Radiotherapy

Conventional two-dimensional (2D) radiotherapy planning was the standard for decades in photon radiotherapy. Few radiation beams were selected, frequently directly opposing fields, three- or four-field arrangements. Size and shape of the fields were adjusted in 2D simulation X-ray images, and unless the tumor was visible in these planar images, filed shaping was mainly based on bony surrogates instead of the patient individual position, shape, and size of the tumor. Also visualization of normal structures was limited. This makes conventional 2D planning inappropriate for the majority of patients, where reirradiation is intended.

3.2 Three-Dimensional Conformal Radiotherapy

Three-dimensional conformal radiation therapy (3DCRT) has been the standard for most indications in photon radiation therapy in the last years, although it is increasingly replaced by intensity-modulated techniques.

It offers distinct advantages compared to conventional 2D radiotherapy, which are especially important in the reirradiation situation. Target volume definition is based on CT images, and coregistration of further imaging modalities like MRI or PET images is supported by all current treatment planning systems. This allows for more precise definition of both the target and critical organs-at-risk (OAR). These structures are visualized in the beam's eye view for selection of the optimal beam directions and for field shaping aiming at best possible sparing of critical OARs. The benefit of 3D-CRT compared to 2D planning has been demonstrated in a randomized trial: In primary radiotherapy for prostate cancer conformal radiotherapy significantly reduced the incidence of proctitis and rectal bleeding compared to conventional radiotherapy; simultaneously local tumor control was not different between the two techniques (Dearnaley et al. 1999). This potential to reduced doses to the normal tissue with the consequence of reduced side effects is certainly of high clinical value in the reirradiation situation, where such large randomized trials are not possible (Fig. 5).

3.3 Intensity-Modulated Radiotherapy

The technique of intensity-modulated radiotherapy (IMRT) is an advancement of 3D-CRT. In 3D-CRT, homogeneous fluence profiles are delivered from each beam-angle. In contrast, IMRT is characterized by customized nonuniform fluence distributions to achieve certain dosimetric objectives (Fig. 6). 3D-CRT uses forward planning meaning that beams are specified, doses are calculated, and dose distributions in the relevant target volumes and OARs are evaluated at the end of the planning process. This is different to the inverse planning process in IMRT. Patient-specific dosimetric goals (objectives) are defined for all target volumes and OARs at the beginning of the treatment planning; the objectives are most frequently DVH parameters or since more recently biological parameters. These objectives are transferred into an IMRT optimization software, where the best possible beam parameters to achieve the desired dose distribution are calculated in an iterative fashion.

Several techniques are commercially available for delivery of intensity-modulated radiation therapy. For conventional linear accelerators equipped with multileaf collimators, the static (step-and-shoot), the dynamic (sliding window), and rotational (volumetric/intensity-modulated arc therapy) techniques can be distinguished. The static step-and-shoot approach segments each IMRT field into a number of shaped subfields, and the sliding window technique modulates the fluence by moving the multileaf collimators (MLCs) while the radiation is being delivered to the patient. Both approaches achieve the energy fluence modulation by the MLCs, and the radiation is given from different static gantry angles.

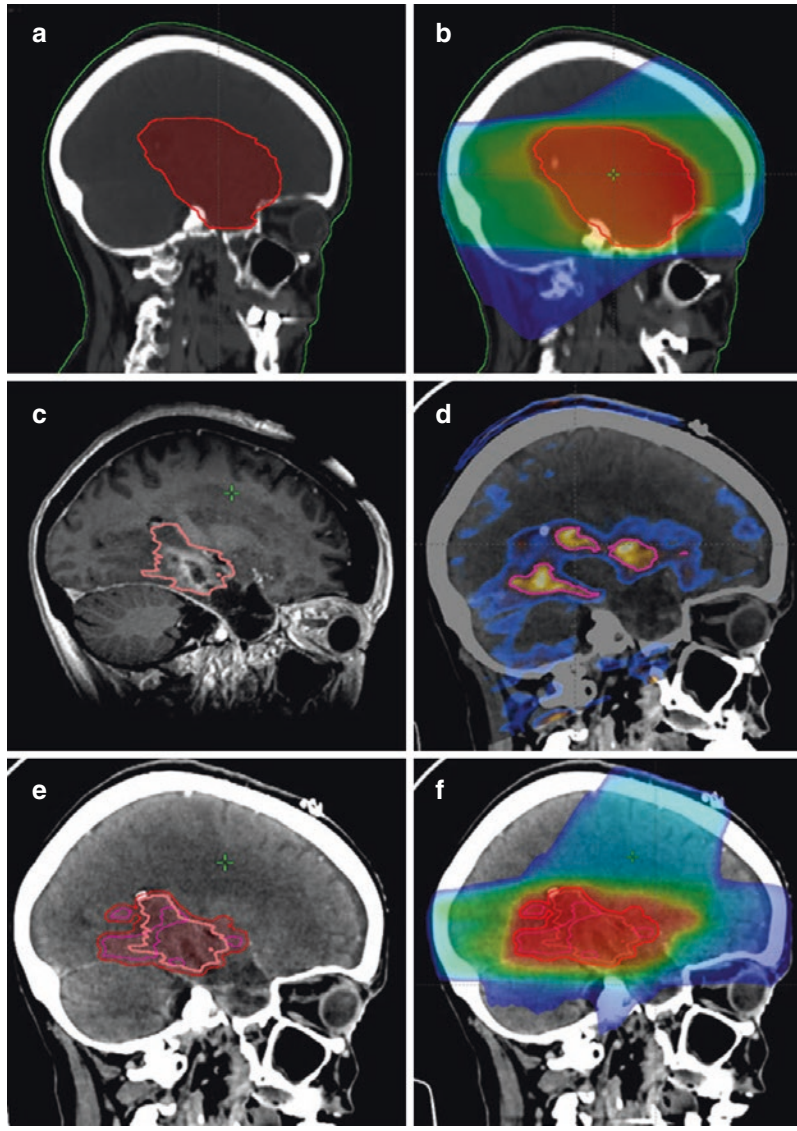

Fig. 5 Case example of reirradiation for a 58-year-old female patient with locally recurrent glioblastoma: Medical history: May 2013: primary diagnosis of glioblastoma; Macroscopically complete resection and adjuvant radiochemotherapy with 60 Gy and concurrent Temozolomide; No adjuvant chemotherapy due to grade III thrombopenia during radiochemotherapy November 2014: new contrast-enhancing nodule in the left temporal lobe; systemic therapy with bevacizumab May 2015: progressive recurrence in the left temporal lobe June 2015: repeat surgery, incomplete resection July 2015: stereotactic re-irradiation with 10 x 3.5 Gy using a PET/MRI-based target volume (**a**) Sagittal reconstruction of the primary volume definition; (**b**) Sagittal reconstruction of the primary irradition; (**c**) Target definition of the local recurrence in the MRI; (**d**)Target definition of the local recurrance in the FET-PET; (**e**) PET based GTV, MRI based GTV and PTV on the CT of the local recurrence; (**f**) Dose distribution for the local recurrent tumor

In contrast, volumetric/intensity-modulated arc therapy (IMAT/VMAT) rotates the linear accelerator around the patient while continuously delivering radiation, thereby applying hundreds of fields, by changing the position of the MLCs and the amount of radiation. A new promising approach still under investigation and not yet clinically available is the 4π- or dynamic-couch

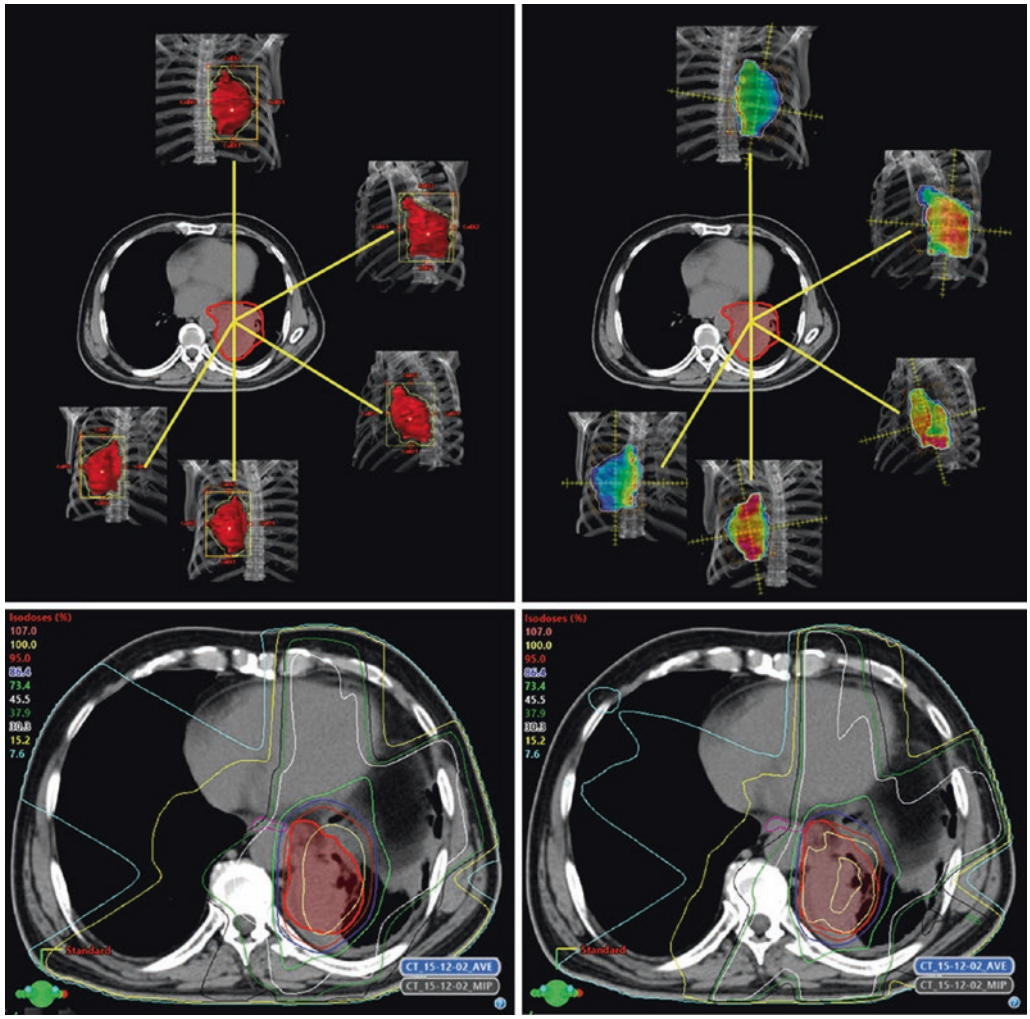

Fig. 6 3D-Conformal radiation therapy (*left*) and intensity-modulated radiotherapy (*right*) for a re-treatment of a lung metastasis. Non-uniform fluence distribution of the IMRT technique allows to more conformally irradiate the tumor and to better spare the organs at risk

rotation technique, which combines the VMAT techniques with continuous rotation of the treatment couch (Smyth et al. 2013; Liang et al. 2015). Major advantages of these rotational techniques are significantly reduced delivery times as well as increased monitor units efficiency. A different IMRT solution is the tomotherapy approach, where the linear accelerator constantly rotates around the patient. The fluence modulation is achieved with a binary collimator, and fan beams are delivered in a CT-like "sliced" fashion, either in spiral or more recently in helical mode (Mackie et al. 1993).

Numerous planning studies have shown the potential of IMRT to generate highly conformal dose distributions, especially for complex, concave-shaped target volumes in close distance to organs-at-risk. In such cases, the sparing of normal tissue is significantly improved compared to 3D-CRT (Nakamura et al. 2014). The superiority or inferiority of one of the above described IMRT delivery techniques has been the issue of countless planning studies and is still highly controversial (Fig. 7). An analytical model was used by Bortfeld and Webb for comparison of TomoTherapy, single-arc VMAT, and static

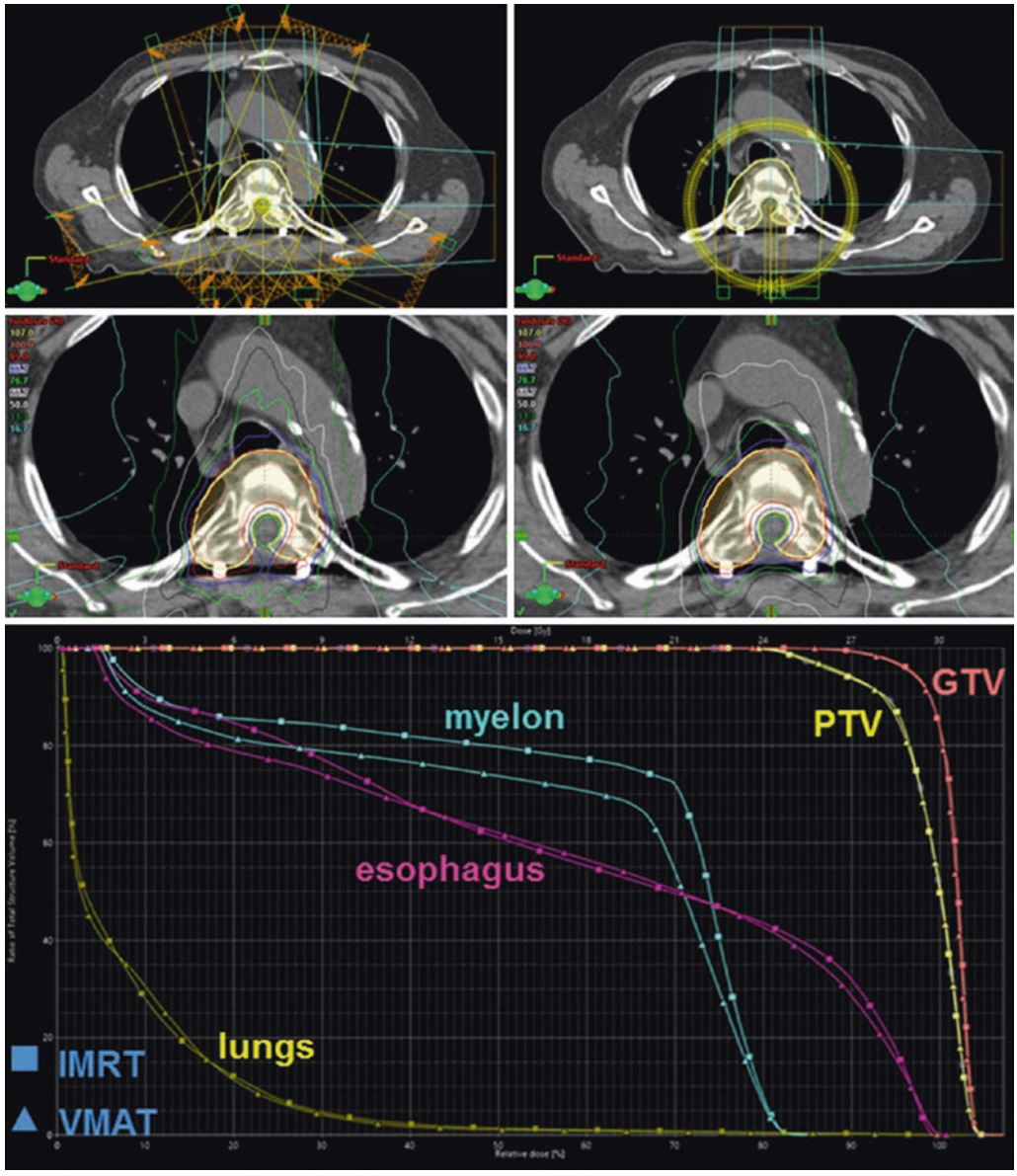

Fig. 7 Sliding window (*left*) and volumetric modulated arc therapy (*right*) treatment planning for re-treatment of a spinal metastasis. On the top the beam setups are shown, in the middle the dose distributions of the two techniques and on the bottom the dose volume histograms

IMRT (step-and-shoot and sliding window IMRT), and they concluded that the TomoTherapy system has the greatest dose shaping flexibility at cost of decreased efficiency of the treatment delivery (Bortfeld and Webb 2009). However, it needs to be considered that despite these theoretical calculations and other planning studies comparing different IMRT hard- and software, the results of IMRT planning are dependent on the experience of the IMRT team (both physician and physicist) in terms of selection of optimization objectives for the inverse planning (Marnitz et al. 2015).

IMRT treatment planning, delivery, and quality assurance are in principle not different between a primary course of radiotherapy and the

reirradiation course. However, some issues need to be considered more in detail in the reirradiation situation.

Unlike in 3D-CRT, IMRT planning distributes low doses over a larger volume of the patient. Additionally, volumes exposed to mid-doses or sometimes even high doses are frequently observed distant to the target volume. This may be of limited relevance in the primary course of treatment but could be deleterious in the reirradiation scenario, if these "hot spots" are located in volumes of normal tissue, where these additional doses exceed the radiation tolerance. Consequently, the physician should not only delineate the standard OARs as done in the primary treatment course; all volumes, where a significant prior irradiation dose had been delivered, should be defined as OARs and separate dose objectives should be defined for these volumes. Such normal structures could be the skin to avoid skin necrosis, joints and muscles to avoid contractures, and bones to avoid osteoradionecrosis.

In the reirradiation case, the radiation tolerance of normal structures is frequently significantly reduced. This is an extremely challenging situation for treatment planning, especially if this normal structure is located immediately next to recurrent cancer. A typical example is a spinal metastasis in the thoracic spine after primary radiotherapy for lung or esophageal cancer. In the situation of the OAR touching the PTV, the maximum dose of the OAR is the minimum dose to the PTV. The physician has now to decide where the dose gradient should be positioned: in the OAR aiming at a homogeneous dose in the PTV or in the PTV aiming at best possible sparing of the OAR at cost of an inhomogeneous dose in the target volume. The latter is certainly the most frequent situation in clinical practice. It is important that the IMRT planning objectives need to be adjusted to this desired dose distribution: Lower doses in the PTV immediately next to the OAR need to be allowed explicitly to the planning algorithm. The magnitude of this "underdosed" PTV depends on the steepness of the dose gradient between the target and the OAR. Mahan et al. reported a dose gradient of 10 %/mm using tomotherapy for retreatment of a spinal metastasis (Mahan et al. 2005). However, multiple variables influence the maximum achievable dose gradient: invariable factor like IMRT hard- and software and variable factors like geometry of target and OAR. For individual optimization of each plan, a ring-shaped help-volume around the OAR could be generated, where the dose gradient between OAR and PTV is to be located. Desired maximum and minimum doses of the OAR and the PTV excluding this help-volume are defined as hard constrains, and the size of the help-volume is step-wise decreased until these constrains can no longer be met by the planning system.

Clinical results of IMRT for reirradiation are promising. Loco-regional recurrent head-and-neck cancer is an example, where IMRT seems to improve outcome compared to conventional radiotherapy or 3D-CRT. Lee et al. reported about reirradiation in 105 patients with loco-regional recurrent head-and-neck cancer, and IMRT was used in 70 % of the patients (Lee et al. 2007). The median prior dose was 62 Gy and the median reirradiation dose was 59.4 Gy. Two-year loco-regional progression-free survival was 50 % and 20 % for patients treated with IMRT and non-IMRT, respectively. This benefit of IMRT remained statistically significant in multivariate analysis with a HR of 0.37. Other groups confirmed these favorable rates of ~50 % 2-year loco-regional control using IMRT (Biagioli et al. 2007; Duprez et al. 2009). Nevertheless, severe late toxicity was still considerable in these series.

Spinal metastases in previously irradiated areas are ideal IMRT indications for pain reduction or because of neurological symptoms (Fig. 8). Here, IMRT allows effective sparing of the spinal cord while treating the vertebral tumor, which is not possible with conventional radiotherapy or 3D-CRT. Milker-Zabel et al. reported the outcome in 19 patients with symptomatic spinal metastases, where a previous irradiation delivered a median dose of 28 Gy (Milker-Zabel et al. 2003). The median reirradiation dose was 39.6 Gy, while the dose to the spinal cord was limited to 20 Gy. With a median follow-up of about 1 year, only one patient developed a local recurrence. Pain relief and improvement of neurological deficits was

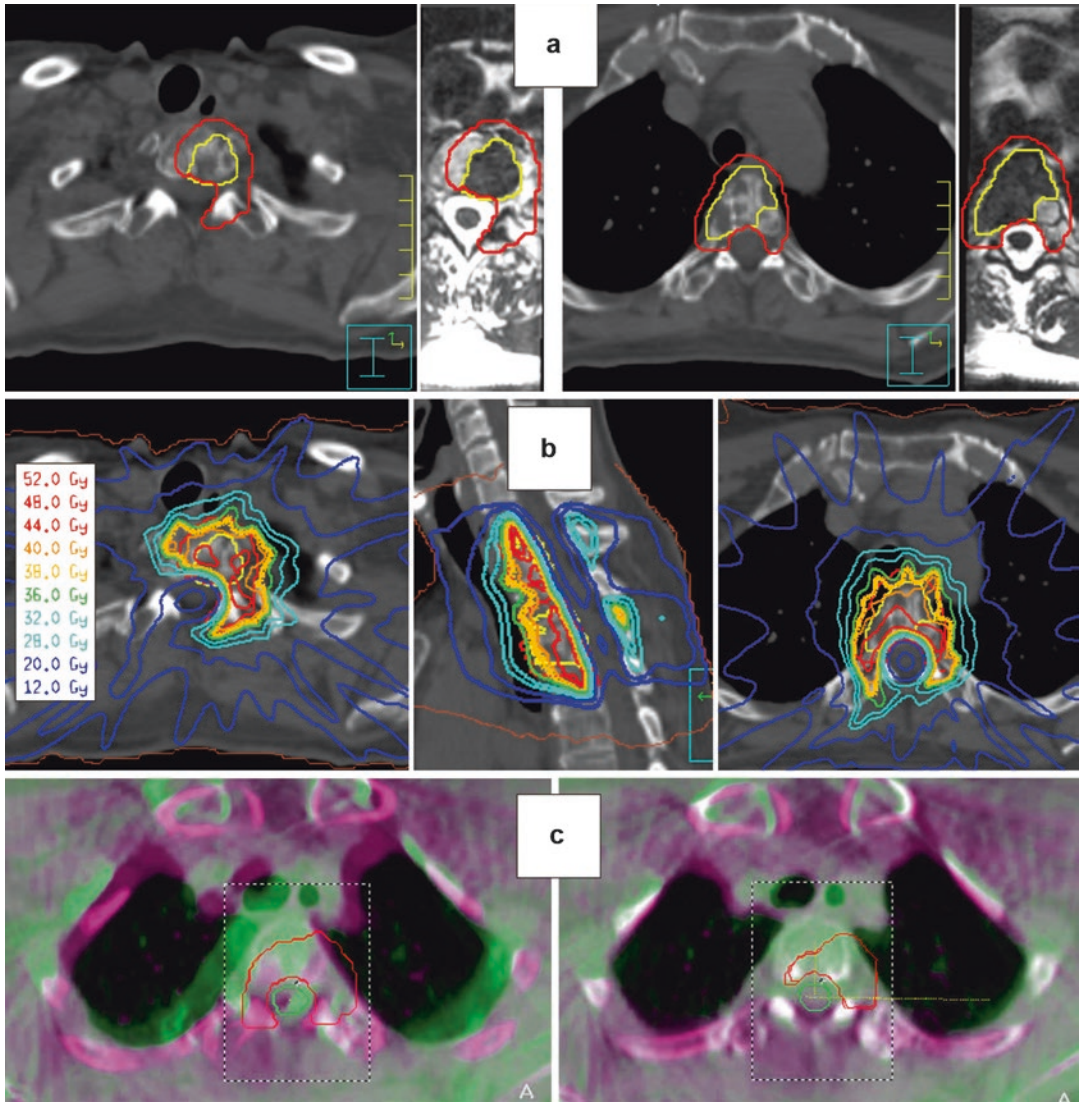

Fig. 8 Case example of a reirradiation for a spinal metastasis in a 62-year-old male patient with metastatic prostate cancer. Medical history: 2010: primary diagnosis of localized prostate cancer; antihormonal therapy, rejection of local therapy. January 2015: locally invasive prostate cancer, several bone metastases including the thoracic spine; laminectomy Th3-6 and tumor debulking; and dorsal instrumentation Th1-Th8. March 2015: postoperative radiotherapy to residual tumor with 5×4 Gy. January 2016: local progression with epidural growth Th4-5; reirradiation with 10×3 Gy. (**a**) Spinal metastases with GTV (*yellow*) based on the MRI and PTV (*red*); (**b**) IMRT dose distributions with a total dose of 40 Gy to the PTV and a maximum dose of 15 Gy to the spinal cord; (**c**) image-guidance using cone-beam CT with superposition of planning CT and verification cone-beam CT before (*left*) and after (*right*) image registration

achieved in 13/16 patients and 5/12 patients, respectively. No acute or late toxicity grade >II was observed. Further data are needed for confirmation of these promising results. Sterzing et al. reported on reirradiation of spinal metastases in 36 patients: The initial irradiation dose was 36.3 Gy on average, and after an interval of 17.5 months a dose of 34.8 Gy was delivered using TomoTherapy IMRT (Sterzing et al. 2010). Promising rates of pain reduction and local control were reported and no severe toxicity was observed.

4 Three and Four Dimensional Treatment Plan Evaluation

If possible, the dose distribution of the first radiotherapy series should be available for treatment planning and plan evaluation. Information on maximum doses or DVH data of the first radiotherapy series is insufficient because of the missing spatial relationship to the current treatment. If this information about the previous dose distribution is not available, for example, because the patient had been treated with 2D conventional planning, this radiotherapy series should be resimulated in the current planning CT. However, one needs to be aware that the resimulation may not reflect the situation at the first irradiation course, because the patient's anatomy could have changed, for example, due to the recurrent tumor or weight changes.

Three-dimensional dose distributions need to be evaluated carefully in terms of target coverage and especially in terms of normal tissue doses. DVHs are helpful tools for evaluation of the dose distributions, but one needs to be aware of the limitations of DVHs, where all spatial information is lost.

If the first treatment series was a 3D-CRT or IMRT irradiation and the treatment plan is digitally available, one could accumulate the dose distributions of the first and the current treatment series for a better risk assessment of the reirradiation. Accumulation of two dose distributions delivered at different times is called 4D dose calculation or 4D planning. Three important issues need to be considered for this 4D dose accumulation.

1. Data about recovery of normal tissue and their modeling in treatment planning and evaluation are rare. Accumulation consequently simulates a worst case scenario without any recovery.
2. Accumulation of physical doses would require conventional fractionation throughout the target and OARs, which is infrequently the case. Single-fraction doses different from 2 Gy should be weighted according to their biological effectiveness using the linear-quadratic model prior to dose accumulation. Calculation of 2 Gy-equivalent total doses (Lebesque and Keus 1991; Maciejewski et al. 1986) is an elegant method, resulting in numbers, which can be compared to tolerance doses for a single course of radiotherapy (Marks et al. 2010).
3. The patient's anatomy of the previous and the current treatment plan is certainly different, which makes 1:1 dose accumulation in the current CT data set misleading. A critical organ could have been displaced by the recurrent tumor, and this displacement of the critical organ in the current CT image relative to the situation of the first treatment course has to be considered in the process of dose accumulation (Fig. 9). Deformable registration between both image data may need to be performed and the

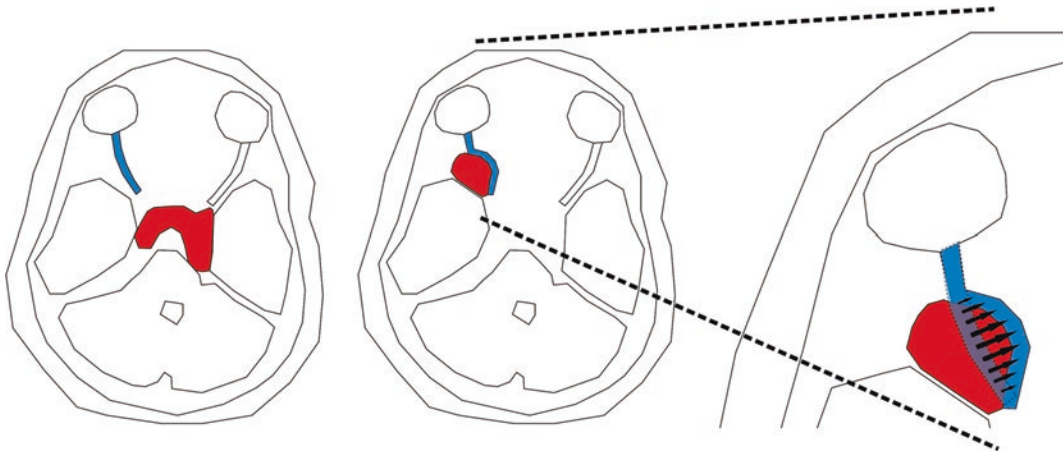

Fig. 9 Illustration of a recurrent skull base tumor (*red*), which causes a displacement of the right optical nerve (*blue*). Accumulation of the dose to this optical nerve from both irradiation series needs to account for this displacement by means of deformable image registration (indicated by vectors)

resulting deformation map applied to the previous dose distribution: The deformed previous dose distribution and the current dose distribution are then accumulated and displayed in the current CT data set with the recurrent tumor and preset location of the relevant OARs (Jumeau et al. 2015). Several commercial solutions are nowadays available to perform such dose accumulations; however, methods to allow the user to evaluate the uncertainty of the deformable registration and subsequent accumulation are missing. Therefore, residual dose distributions, especially in situations with large anatomical change, have to be evaluated carefully (van Rijssel et al. 2014).

5 Stereotactic Radiotherapy and Image Guidance

In the reirradiation situation, the target volume is usually limited to the recurrent macroscopic tumor without extensive elective CTV margins in order to reduce normal tissue exposure (Mantel et al. 2013). Stereotactic intracranial radiotherapy and stereotactic body radiotherapy (SBRT) in combination with image guidance (IGRT) provide an accurate means of highly conformal treatment delivery and patient positioning which can further spare organs-at-risk during reirradiation (Guckenberger et al. 2014).

Patient setup for daily radiotherapy has traditionally been performed by alignment of the room lasers with patient skin marks. This procedure assumes that there is a fixed, rigid relationship between the skin marks and the actual target volume. However, this method of patient setup is one of the major uncertainties in the radiotherapy delivery process contributing significantly to the safety margins (Hurkmans et al. 2001). Patient-specific uncertainties are imperfect alignment of the patient to the laser, mobility of the skin relative to the bony anatomy, and mobility of the tumor relative to the bony anatomy. These setup errors are especially important for treatment plans with steep dose gradients between the target and the organ-at-risk: For IMRT treatment of spinal metastases, it has been shown that patient setup errors as small as 1 mm can increase the dose to the spinal cord by a clinically relevant amount (Guckenberger et al. 2007a) (Fig. 10). Consequently, highly conformal treatment plans using IMRT or Protons pose a significant risk of target underdosage and/or OAR overdosage unless precise patient setup is ensured.

The stereotactic technique has been proven as highly effective for accurate patient setup. Stereotactic radiotherapy has traditionally been defined by a system of external coordinates. This stereotactic system is rigidly fixated to the patient and forms the basis for treatment planning with definition of the isocenter position and patient setup before treatment. In the cranial region, this has been traditionally practiced in an invasive fashion, where the stereotactic frame is fixated to the patient's skull. This offers best accuracy of patient setup; however, the invasiveness of the procedure requires planning and treatment finished within 1 day by means of radiosurgery. Noninvasive techniques for fractionated regimes were developed using thermoplastic mask or bite-block systems; the tradeoff to perform a fractionated treatment courses was a slightly reduced accuracy of patient setup. Initially developed for intracranial treatments, the stereotactic technique has been successfully adopted for extracranial stereotactic radiotherapy (Fig. 11).

Recently, image-guidance techniques have been developed, which are located in the treatment room and allow for daily verification of the patient setup with online correction of setup errors before the start of treatment. It has been shown that these IGRT techniques are at least equivalent in terms of patient setup accuracy compared to invasive frame-based stereotactic radiosurgery in the cranial region (Ramakrishna et al. 2010). The accuracy of patient setup for fractionated stereotactic radiotherapy in the cranial (Guckenberger et al. 2007b) and extracranial region (Guckenberger et al. 2006) is improved with IGRT compared to frame-based stereotactic patient positioning. Additionally, sufficient soft-tissue contrast in these verification images or implantation of radio-opaque markers make verification of the actual tumor position possible, which is important for targets, where mobility

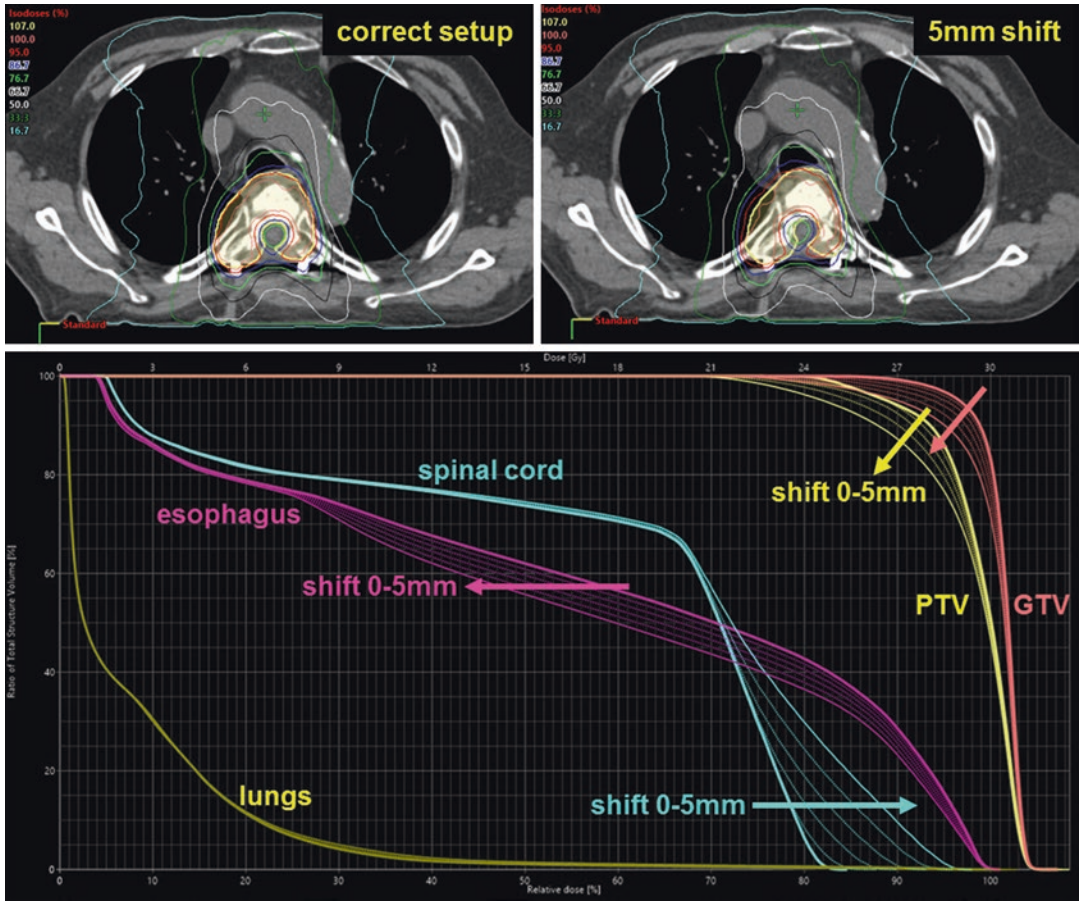

Fig. 10 Effect of set-up errors on dose to organ-at-risk: *Upper left image*: Dose distribution in the axial plane in VMAT plan for a spinal metastasis. *Upper right image*: Simulation of patient set-up error with a lateral shift of 5 mm to the left *Lower image*: Dose to the spinal cord: The *yellow* DVH curve displays the prescribed PTV dose according to the treatment plan. The *turquoise* DVH curves are dose distributions to the spinal cord resulting from simulated set-up errors. DVH curves for the esophagus and GTV are shown in *lilac* and *pink*, respectively

independent from bony anatomy has been described (Fig. 12). A treatment using daily image guidance with online correction of setup errors for high-precision radiotherapy is considered as "frame-less stereotactic radiotherapy": The stereotactic frame is replaced by image guidance with the patient's image as the "system of coordinates" for isocenter localization (Haertl et al. 2013). The available technologies of IGRT are summarized in Table 2.

Some issues, which are considered as especially important in the reirradiation situation, should be discussed.

In the primary course of radiotherapy, IGRT mainly aims at precise as possible delivery of the planned dose to the target volume. This may be different in the reirradiation situation, where precise as possible sparing of the OAR is the primary goal of IGRT. Precise targeting the tumor versus precise avoidance of the OAR could result in different displacement vectors for IGRT in cases where the spatial relationship between target and OAR changed in comparison to the planning situation. Possible causes are shrinkage/progression of the recurrent tumor during radiotherapy or a shift of the tumor position towards the OAR. Such non-rigid patient deformations cannot be corrected with a single couch displacement. Firstly, registration of the whole planning image with the

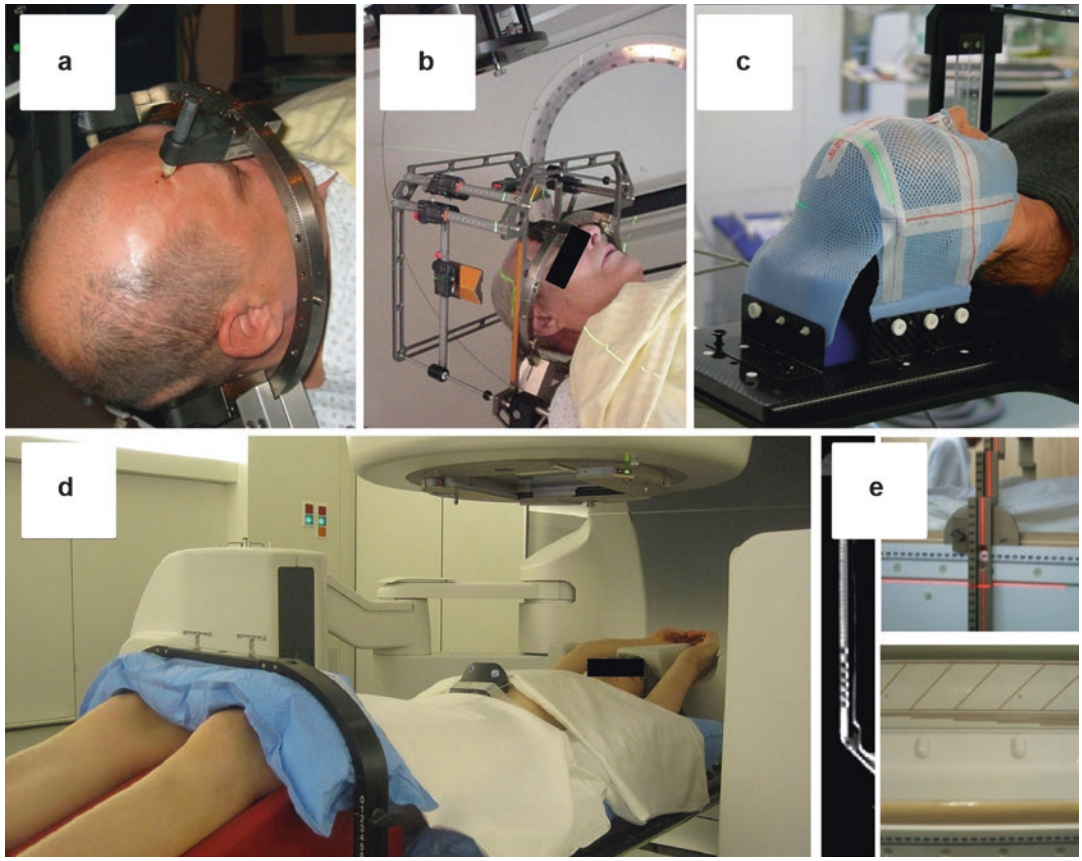

Fig. 11 Stereotactic patient setup: Cranial stereotactic radiotherapy with invasive fixation of the stereotactic ring (**a**) and the attached stereotactic frame with the system of external coordinates (**b**). Thermoplastic mask used in image-guided stereotactic radiotherapy (**c**). Stereotactic body radiotherapy using the Stereotactic bodyframe with a customized vacuum cushion (**d**) and a system of external coordinates (**e**)

whole verification image will result in a single registration vector, which will neither correctly display the situation for the target nor the OAR. Consequently, one should limit the region of interest (ROI) for image registration in IGRT to the volume, which is intended to be treated most precisely: This can be the target or the OAR. Larger uncertainties for volumes outside this ROI then need to be considered. Two separate registrations with the ROI for image registration around the target and around the OAR allow the evaluation of relative motion between these two structures. A compromise could be made to achieve an acceptable level degree of accuracy on the target and OAR level; in cases of changes beyond a certain threshold, replanning should be considered.

Additional irradiation dose due to IGRT could also be an issue of concern in the reirradiation situation. However, similar to the primary course of radiotherapy, the rationale for using IGRT should be evaluated on an individual patient basis before the treatment with consideration of the planned dose distribution and expected setup uncertainties. Additionally, most IGRT systems allow adaptation of imaging parameters to the clinical situation: for example, for cone-beam CT imaging, collimation, and the number of projection images, voltage and mAs influence the imaging dose significantly: If no soft-tissue contrast is needed, the dose for a single cone-beam CT can be reduced to less than 1 mSv (Sykes et al. 2005), which is certainly of limited clinical relevance, even if reirradiation is performed.

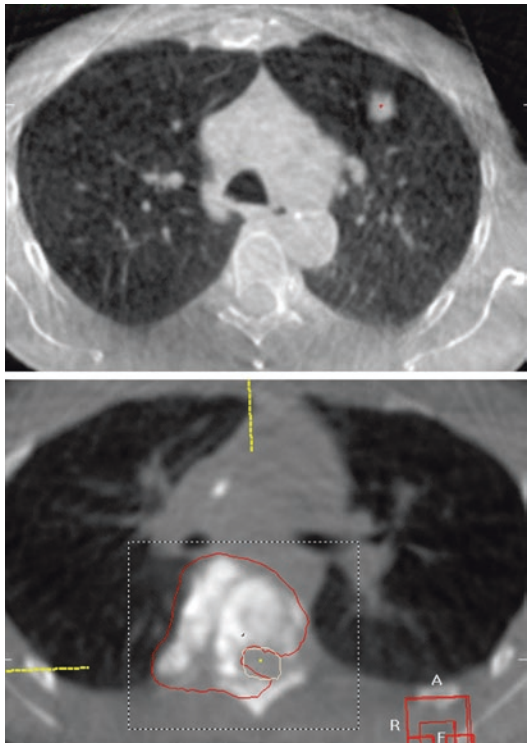

Fig. 12 Image quality of kilo-voltage cone-beam CT for image guidance: *upper image*: targeting of a lung nodule; *lower image*: targeting of a (GTV in *red*) spinal metastasis

Before the IGRT era, frame-based stereotactic radiosurgery with invasive fixation of the frame to the patient's skull offered significantly increased accuracy compared to the noninvasive fractionated approaches. One had to choose between highest accuracy and a fractionated treatment. This is not the case anymore when IGRT is used: Today, the same accuracy can be achieved with IGRT during a fractionated course of treatment. This could be beneficial especially in the reirradiation scenario: Fractionated irradiation may reduce late complications compared to hypo-fractionated regimes or radiosurgery taking advantage of the well-known difference in repair capability between tumors and late responding tissues.

Clinical results using stereotactic patient setup or image guidance in the reirradiation situation are promising, although they can currently not yet be considered standard of practice. Cranial reirradiation frequently used stereotactic patient setup for maximum (re-)positioning accuracy. Detailed clinical results are described in the respective chapter of this book. For example, fractionated stereotactic reirradiation of recurrent high grade gliomas has resulted in acceptable rates of toxicity and promising overall survival compared to historical controls after application of hypo-fractionated doses up to 40 Gy (Shepherd et al. 1997) or stereotactic radiosurgery (Kong et al. 2008). The addition of modern targeted drugs or chemotherapy like temozolomide (Combs et al. 2008), gfitinib (Schwer et al. 2008), or bevacizumab (Gutin et al. 2009; Cuneo et al. 2012) to stereotactic reirradiation may further improve outcome. Similarly, repeated stereotactic radiosurgery has been proven to be feasible for patients with progressive brain metastases with 1-year local control rates of up to 78 % depending on tumor histology (Minniti et al. 2016).

A small number of studies reported clinical results using SBRT in the reirradiation situation. For instance, initial results have been published for recurrent head-and-neck cancer (Rwigema et al. 2010; Heron et al. 2009), lung cancer after previous thoracic radiotherapy (Fig. 13) (Kelly et al. 2010; Poltinnikov et al. 2005; Kilburn et al. 2014), or recurrent gynecological cancer (Guckenberger et al. 2010; Deodato et al. 2009). For lung cancer, small field SBRT for thoracic reirradiation seems to be safe with promising rates of local control exceeding conventional techniques, although overall survival appears to be highly dependent on systemic progression. In contrast, SBRT reirradiation for head-and-neck cancer is limited by the risk of severe late adverse events, which are however less frequent than in patient series with conventional techniques. In summary, SBRT for recurrent extracranial tumors is still in an early stage of establishment, where no recommendations regarding total dose, fractionation, and radiation tolerance of normal tissue are possible.

6 Intrafractional Motion Management

Intrafractional changes of the tumor position could result in decreased target dose coverage with the consequence of reduced local control;

Table 2 Image-guided technologies

	Technique	Radiation dose	3D information	Soft tissue contrast	Real-time imaging	Imaging in treatment position	Pros	Cons
Electronic portal imaging device (EPID)	Use of therapeutic MV beam	None to high	Limited	Very low	Possible	Yes	No doses for imaging of treatment fields; in-beam imaging; real-time imaging	High doses unless imaging of treatment fields; very limited soft tissue contrast; implanted markers required for soft tissue tumors
Stereoscopic kV X-ray	Two stereoscopic X-ray sources and panels	Low	Limited	Low	Possible	Yes	Real-time imaging	Limited soft tissue contrast; implanted markers required for soft tissue tumors
In-room CT scanner	CT on rail; mobile CT scanner	Medium	Full	Excellent	No	No	Volume imaging; best image quality; respiration-correlated imaging	Movement of patient and treatment couch necessary
kV cone-beam CT	Installed orthogonal to treatment beam	Medium	Full	Good	No	Yes	Volume imaging; respiration-correlated imaging	Worse image quality compared with in-room CT imaging
MV cone-beam CT and helical MV CT	MV CBCT: use of treatment beam and EPID; TomoTherapy™	High	Full	Acceptable	No	Yes	Volume imaging; minimized metal artifacts	Suboptimal soft tissue contrast; high imaging doses
Ultrasound	B-mode acquisition and targeting	None	Good	Acceptable	No	Yes	No additional irradiation dose	User dependency; risk of target displacement due to pressure
Active electromagnetic markers	Implanted active electromagnetic markers (Calypso)	None	Limited	None	Yes	Yes	Real-time online information with high frequency	No anatomical information; implanted markers required
Surface scanner	Laser- or video-based surface scanner	None	Surface only	None	Yes	Yes	Real-time imaging; complete surface imaged	Suboptimal correlation between surface and target position for many tumor sites

No absolute values of radiation doses are stated because imaging parameters can be adjusted in most of the systems with large differences in imaging doses; it is distinguished between no additional irradiation dose, low, medium, and high additional irradiation dose

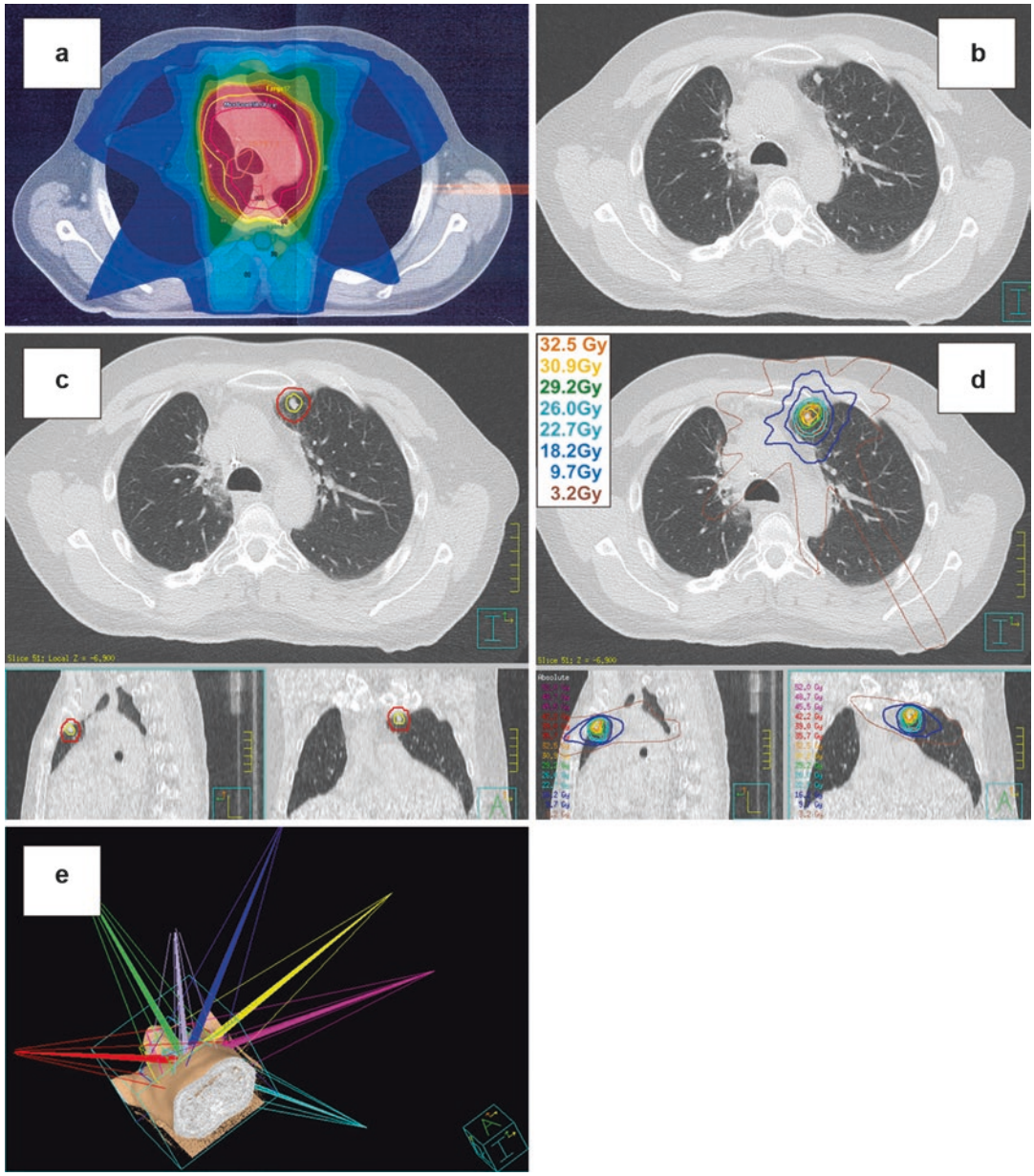

Fig. 13 Case example of retreatment for a solitary lung metastasis with SBRT. Medical history**:** 2007: Primary NSCLC (adeno carcinoma) right lower lobe; three cycles of neo-adjuvant chemotherapy; surgery with lobectomy and mediastinal lymph node dissection; tumor stage: ypT2 ypN2 M0; postoperative adjuvant chemotherapy; postoperative radiotherapy to the mediastinum (55.8 Gy); 2008: Solitary brain metastasis treated with radiosurgery; 2009: Solitary lung metastasis treated with radiosurgery of 26 Gy; (**a**) adjuvant radiotherapy after surgical treatment of N2 disease, (**b**) solitary lung metastasis, (**c**) target volume for SBRT GTV (*yellow*) and PTV (*red*), (**d**) dose distribution of SBRT with delivery of a single fraction of 26 Gy to the 80 % isodose, and (**e**) beam arrangement for SBRT

similarly, intrafractional motion of the OAR could result in increased risk of toxicity. Four sources of intrafractional uncertainties need to be considered: (1) Regarding *motion of the patient* him- or herself, one can distinguish between voluntary motion due to poor compliance and

involuntary motion, for example, due to pain, cough, or uncomfortable positioning. (2) *Breathing motion* is a major source of uncertainty in the thoracic and upper abdominal region: Motion amplitudes up to 3 cm for targets located in the chest (Seppenwoolde et al. 2002) or upper abdomen (Brandner et al. 2006) have been described. The predominant direction of breathing-induced tumor motion is the cranio-caudal direction with increased motion amplitudes in the caudal compared to the cranial parts of the lung. Analogously, the influence of breathing motion in the abdominal region decreases from the diaphragm towards caudal. (3) The influence of *cardiac motion* on tumor and OAR position variability is in order of magnitude between 1 and 4 mm. (4) It has been shown that *changes in the filling of hollow organs*, especially rectum and bladder, may influence doses to the target and OAR significantly (Polat et al. 2008). Additionally, peristaltic motion might lead to an additional uncertainty in the dose to the organs-at-risk.

6.1 Patient Motion Management

As described above, we distinguished between voluntary motion and involuntary intrafractional patient motion. The most effective way to reduce involuntary patient motion due to pain is to ensure a comfortable patient setup by using support devices for head, arms, knees, and feet and adjust these to the individual patient. Additionally, appropriate pain medication is essential, which is especially important in the reirradiation situation, where the local tumor is frequently associated with significant pain to the patient. Patient motion due to cough or dyspnea could be reduced by medication or oxygen supply during treatment, respectively.

Passive immobilization is standard practice in primary radiotherapy for many cancer sites, and identical devices should be used in the reirradiation situation: for example, head-shoulder masks or bite-blocks for irradiation in the head-and-neck region and thermoplastic vacuum cushions for immobilization of arms, leg, and the whole body. For total body immobilization in a vacuum cushion, a double-vacuum technique has been developed, where a second vacuum is applied underneath a foil, which is wrapped around the patient: A low pressure underneath the foil presses the patient into the vacuum cushions for effective and comfortable immobilization (Fuss et al. 2004). There is sometimes a tradeoff between immobilization and comfort of the patient: A patient in an uncomfortable positioning device will not be immobilized effectively, whatever device is used. It should also be mentioned that the previously discussed techniques of frame-less image-guided stereotactic radiotherapy still require effective immobilization: Image-guidance aims at minimization of interfractional setup errors, whereas immobilization aims at minimization of intrafractional uncertainties.

Different systems are available for intrafractional monitoring of the patient stability: for example, surface scanners or infrared markers positioned on the surface of the patient. If predefined thresholds of patient motion are violated, interruption of the irradiation should be performed. The patient's surface is then only a surrogate for the actual target position: Target motion independently from patient motion needs to be considered. It is consequently most accurate to repeat image guidance.

6.2 Breathing Motion Compensation

The first step in compensation of breathing motion is quantification of this uncertainty in a patient individual fashion at treatment planning. Fluoroscopic planar imaging is a frequently used technique for measurement of breathing-induced motion of pulmonary tumors; for targets in the upper abdomen, mobility of the diaphragm is used as a surrogate for the actual tumor motion. The advantage of fluoroscopic imaging is the possibility to monitor range and pattern of motion for a longer period of time. Disadvantages are the limitations of 2D planar imaging, where a proportion of pulmonary tumors are not visible and evaluation of the 3D motion trajectory is difficult.

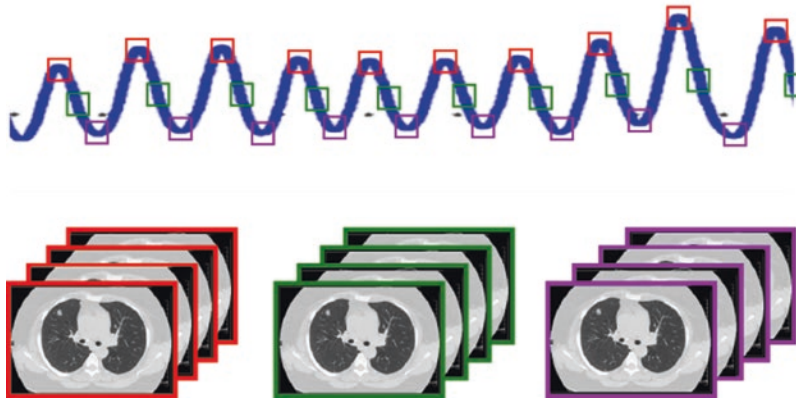

Fig. 14 Respiration correlated 4D-CT: In contrast to conventional CT imaging, each axial patient position is imaged for the duration of at least one breathing cycle by using small table pitches (highly redundant data acquisition). Images or projection data acquired at corresponding phases of the breathing cycle are then sorted/binned such that multiple CT phases at different phases of the breathing cycle are reconstructed

Implantation of radiopaque markers into the target for fluoroscopic 4D imaging is frequently practiced in the lung and liver region; however, the risk of a pneumothorax needs to be considered. The current gold standard for treatment planning is the respiration correlated CT (4D-CT), which allows with a single image acquisition the reconstruction of multiple CT series at different phases of the breathing cycle (Fig. 14). Besides evaluation of the patient individual motion pattern and range, another advantage of respiration correlated CT imaging for treatment planning is the reduction of motion artifacts in the CT images, which could result in incorrect size and shape of the target volume (Fig. 15).

In general, three techniques for breathing motion compensation can be distinguished. (1) Treatment in free breathing, (2) treatment in free breathing with dynamic beams chasing the target or with a dynamic couch performing compensatory motion to keep the target fixed relative to linac coordinates (tracking), and (3) gated beam delivery in only a specific phase of the breathing cycle or in a breath-hold technique. A summary of available motion management strategies is presented in Table 3.

The most frequently used technique treats the patients while they are breathing freely and continuous delivery of static beams is performed.

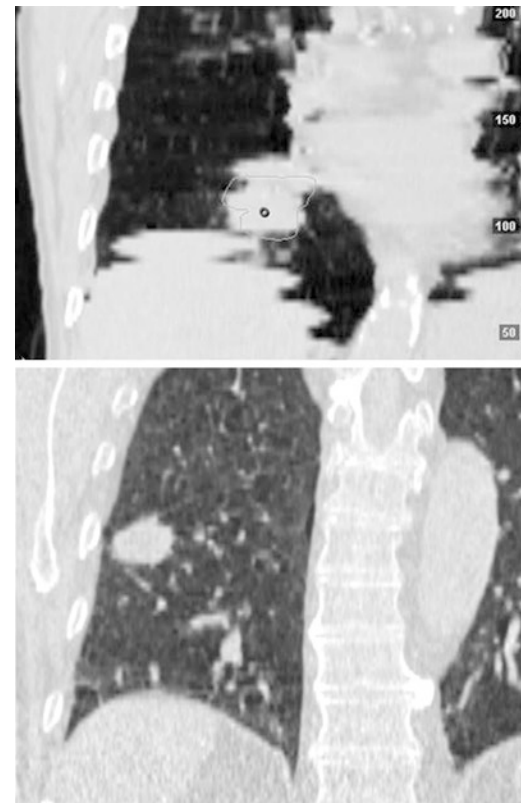

Fig. 15 Two pulmonary tumors, which were highly mobile in fluoroscopy. (*Upper image*) Significant motion artifacts in conventional 3D-CT imaging of the pulmonary target and the dome of the diaphragm; (*Lower image*) absence of motion artifacts in respiration correlated 4D-CT imaging

Table 3 Breathing motion management strategies

Breathing motion management technology	Safety margins	Complexity of treatment planning and delivery	Proportion of beam on time of total treatment time	Comments
Free breathing (ITV)	Large based on internal target volume concept	Low	Optimal	Unnecessary large safety margins
Free breathing (stochastical)	Reduced with mid-ventilation concept	High	Optimal	Preferable for motion amplitudes up to 15–20 mm
Mechanical abdominal compression	Reduced compared to free breathing	Low	Optimal	Only for patients with predominant tumor motion in craniocaudal direction; dependent on patient tolerance
Breath–hold technique	Small	Medium	Patient dependent (pulmonary function and compliance)	Adequate pulmonary function and patient compliance required; reduction of irradiated lung tissue when practiced in inhalation breath-hold technique
Gated beam delivery	Small	High	Low	Significant prolongation of the total treatment time
Tumor tracking	Small	Very high	Optimal	Highly complex

With patients breathing freely, the target volume needs to be adjusted such that it encompasses the tumor completely in all phases of the breathing cycle according to ICRU 62. However, it has been shown that this geometrical target volume concept uses unnecessary large safety margins with the consequence of large volumes of normal tissue within the PTV; smaller safety margins are possible if a stochastic target volume concept is applied (Engelsman et al. 2005). The so-called mid-ventilation concept has been proposed for irradiation in free breathing, where treatment planning and image guidance are based on the average tumor position; this was shown to reduce safety margins significantly compared to the traditional ITV target volume concept (Wolthaus et al. 2008). Recently, intensity-modulated, inverse treatment planning is more frequently used for tumors that move due to respiration. Several studies have evaluated the interplay effect between the motion of the tumor and the motion of the MLC with the conclusion that over a large number of beams and fractions or a high dose per fraction, the interplay effect averages out and is in the order of magnitude of 1–3 % (Ehrbar et al. 2016; Chan et al. 2014).

Tumor tracking is defined as a technique, where the treatment delivery adjusts dynamically to changes of the target position during the breathing cycle. Up to now tracking has been performed clinically using three different techniques: the CyberKnife, the Vero system, and MLC tracking. Most studies have been performed using the CyberKnife, a linear accelerator mounted on an industrial robot, which moves synchronously with breathing motion of the target (Seppenwoolde et al. 2007). The Vero system is a gimbaled linac system, which tracks the tumor using the treatment beam (Depuydt et al. 2014). Another technique, where the irradiation beam chases the moving tumor, makes use of a dynamic multileaf collimator (MLC) (Keall et al. 2006, 2014): The MLC shape is adjusted in real-time to changes of the target position. The third approach is different: A static beam delivery technique is combined with a dynamic couch,

where compensatory couch motion opposite to the target motion aims at keeping the target fixed in the beam aperture (Wilbert et al. 2008; Lang et al. 2014).

Gated beam delivery differs significantly, as the irradiation is only performed in a specific phase of the breathing cycle or in breath-hold technique; the irradiation is then paused at the other phases of the breathing cycle. This gated beam delivery results in a significant reduction of the "effective" target motion at cost of prolonged total treatment time (Underberg et al. 2005).

The choice of the appropriate motion management strategy should be dependent on the motion range of the pulmonary target. For motion amplitudes less than 15–20 mm, which is the majority of the patients, there is only a small benefit of gating and tracking in terms of margin reduction (Sonke et al. 2009; Guckenberger et al. 2009b) and treatment with the patient breathing freely is preferable. The benefit of gating and tracking increases for larger motion amplitudes. However, the availability of tracking is currently still limited and gating prolongs the treatment delivery time substantially. Keeping the total treatment time as short as possible is essential as longer treatment times were shown to result in increased intrafractional patient motion and drifts of the target (Purdie et al. 2007).

Similar to treatment planning, 4D target motion needs to be integrated into pretreatment patient setup using image guidance and intrafractional target position monitoring. Different technologies for pretreatment and intratreatment 4D imaging are available. Evaluation of the patient's surface and establishment of a correlation model between the surface motion and the target motion is frequently performed; however, interfractional and intrafractional changes of this correlation model are well known. Pretreatment respiration correlated 4D cone-beam CT is clinically available allowing for precise patient setup with full consideration of breathing motion in the IGRT process (Sonke et al. 2005); however, continuous intrafractional 4D imaging is not possible with this technology. Intrafractional 4D target monitoring has been described using stereoscopic X-ray imaging or using the electronic portal imaging device; however, implantation of markers is necessary for visualization of the targets as described previously.

Regardless which motion management strategy and which technology is chosen, it is important to have a consistent 4D work flow for treatment planning and treatment delivery: A systematic integration of breathing motion into all steps of imaging for treatment planning, target volume definition, image guidance, and treatment delivery is essential (Korreman et al. 2008).

6.3 Management of Cardiac Motion

Only limited research has been performed on the magnitude of cardiac motion and the influence of it on the dose distribution. For lung tumors, a displacement of 1–4 mm, depending on the distance between the tumor and the cardiac or aortic wall, was reported (Seppenwoolde et al. 2002). This might lead to an increase in target volume of about 10 % and in some cases to a reduction in target coverage (Chen et al. 2014). For esophageal tumors, the displacement can be up to 10 mm depending on the location of the tumor (Palmer et al. 2014).

Cardiac motion can be compensated with the motion management techniques described above. However, one needs to take into consideration that cardiac motion has a higher frequency compared to respiratory motion, and therefore, it is important that the applied motion management technique has a short delay between the detection of the motion and the compensation of the motion.

6.4 Management of Motion Due Variable Filling of Hollow Organs

Variability of the target position due to changes of the filling of hollow organs is well known in primary radiotherapy, for example, of prostate cancer. Whereas intrafractional variability of the bladder filling is clearly dependent on the total

treatment time, changes of the rectal filling could occur on a much shorter timescale and are not predictable.

Several noninvasive and nontechnological techniques have been shown to reduce interfractional and intrafractional target position variability. A diet protocol was shown to reduce moving fecal gas during acquisition of cone-beam CT images (intrafractional motion) and reduce interfractional prostate position variability (Smitsmans et al. 2008). Daily emptying the rectum before treatment by patient-applied rectal enemas has also been shown to reduce interfractional prostate position variability (Fiorino et al. 2008). Similar positive effects are expected for locally recurrent tumors with close relationship to the rectum. Rectal balloons have been shown to fixate the prostate (Wachter et al. 2002); however, the effect of the balloon on different tumor locations or local recurrences is probably small. Daily catheterization of the urinary bladder and refilling with a defined volume of normal saline reduce interfractional bladder volume variability, and a drinking protocol might reduce intrafractional bladder volume variability.

If real-time intrafractional monitoring of the target position is intended, identical technologies as described in the breathing motion management part can be applied. Additionally, electromagnetic transponders may be implanted into or in the vicinity of the tumor and their position can be monitored with a high frequency of 10 Hz.

Two issues may be different between primary radiotherapy and reirradiation regarding intrafractional motion management. Firstly, many patients are in considerable pain because of the locally recurrent tumor, and effective pain medication is difficult in a number of patients; consequently, comfortable patient positioning and a fast treatment delivery work flow are highly important. Techniques, which minimize the total treatment time (e.g., VMAT), may reduce intrafractional uncertainties more efficiently and simultaneously improve patient comfort compared to highly sophisticated techniques, which prolong the treatment time (e.g., gated beam delivery or repeated cone-beam CT scanning during treatment).

Though the implantation of markers into or around the macroscopic tumor is considered a safe procedure in the primary course of radiotherapy, literature data about the safety in the reirradiation situation are missing. The patient's anatomy may be altered due to previous surgery, and radiation-induced fibrosis may increase complication rates. Consequently, the use of imaging systems which do not require invasive implantation of markers may be preferable for retreatments.

7 Adaptive Radiotherapy

Besides changes of the target position, more complex changes have been described during the course of fractionated radiotherapy: for example weight loss of the patients, progression and regression of the macroscopic tumor, changes of oedema, effusion, and pulmonary atelectasis. Such systematic changes of the patient's anatomy compared to the planning situation could influence the delivered dose distributions, and an adaptation of the treatment plan should consequently be considered (Fig. 16).

Adaptive radiation therapy has been defined as a closed-loop, iterative process where the treatment plan is modified based on feedback measurements performed during treatment (Yan et al. 1997). Adaptive radiotherapy is a technique to deal with all uncertainties during a course of radiotherapy; however, this chapter will concentrate on systematic shape and volume changes of the macroscopic tumor and changes of the patient's weight and shape.

The process of adaptive radiotherapy can be divided into several steps. The first step is evaluation of the patient individual random and especially systematic changes compared to the planning stage. If these changes exceed a certain threshold, an adaptation of the treatment plan is performed: This could be an adjustment of the isocenter position as well as replanning to deal with more complex changes. Ideally, this is not only an adaptation of the treatment plan to the current situation but takes changes, which occurred during the treatment course so far, into account (e.g., planning of a compensatory higher

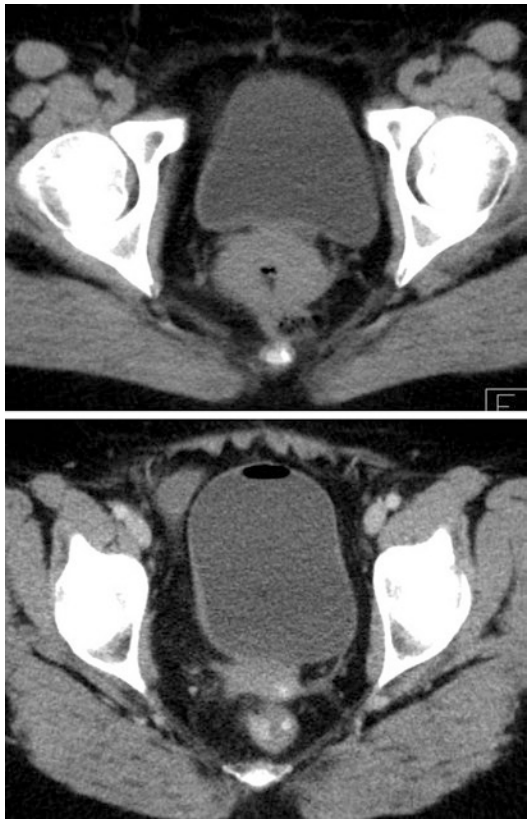

Fig. 16 Locally recurrent cervical cancer: size of the macroscopic tumor at the time prior to treatment planning (*upper image*) and after delivery of a conventionally fractionated dose of 46 Gy (*lower image*); this CT image with significant tumor regression was used for adaptive planning of an SBRT boost

dose to a cold-spot volume). After the adaptation is performed, the feedback loop is re-entered (Fig. 17).

Systematic volume changes of the macroscopic tumor have been described in primary radiotherapy for advanced stage NSCLC, where a continuous decrease of the GTV by 1.2 % per day has been reported (Kupelian et al. 2005). This continuous tumor shrinkage has been confirmed by other groups, whereas progressive disease during radio (chemo) therapy seems to be rare. Similar findings of continuous GTV shrinkage were made during primary radiotherapy for other cancer sites, for example, head-and-neck cancer (Barker et al. 2004) and cervical cancer (Mayr et al. 2006). Shrinkage of the tumor could release pressure from the surrounding tissue with the consequence of critical structures moving into the high dose regions. Additionally, adaptive replanning depending on daily bladder filling has shown to reduce dose to normal tissue considerably (Vestergaard et al. 2013).

Weight loss is a frequently observed phenomenon in cancer patients and is an established prognostic factor for overall survival in a number of cancer sites (Fearon et al. 2011). Weight loss during a course of radiotherapy may have multiple causes, for example, oral, pharyngeal, or esophageal mucositis, diarrhea, simultaneous chemotherapy, or loss of appetite. All means of

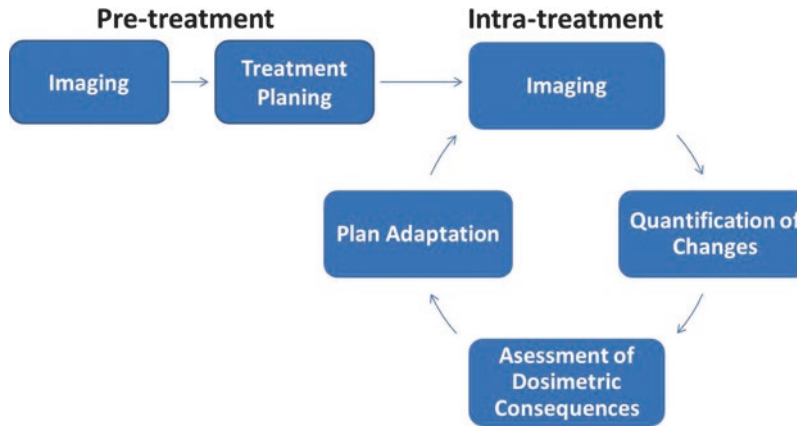

Fig. 17 Schematic illustration of an adaptive feedback loop

prevention and treatment of weight loss should be undertaken. However, if significant weight loss occurs during treatment, it could influence radiotherapy in a clinically relevant way. Weight loss could make immobilization devices like thermoplastic head masks less effective, resulting in increased setup uncertainties or alter dose distributions due to changes of the patient's geometry.

Several issues remain to be solved until adaptation of the treatment beams to a shrinking tumor will find its way into routine clinical practice of primary radiotherapy. The additional work load of replanning needs to be considered. Reliable and fast nonrigid image registration tools are required for dose accumulation of treatment plans, which were planned on different CT data sets. There are no valid data about thresholds and optimal time during the radiotherapy course, when and how frequently adaptation should be performed. There may also be a certain risk of shrinking the treatment fields: Microscopic disease could be excluded from the PTV with the consequence of underdosage and decreased local control.

There are no data in the literature about this type of adaptive radiotherapy specifically in the reirradiation situation. However, one could argue that the risk of normal tissue damage is significantly increased for reirradiation, justifying adaptive radiotherapy despite the increased work load and accepting a potential miss of microscopic disease. Additionally, it is not only the tumor, which might change during the course of radiotherapy: As described above, pulmonary atelectasis, effusions, and edemas could change and alter doses to critical OARs or the target volume. Adaptation of the treatment plans to such changes of the normal tissue could be considered as a safe approach of adaptive radiotherapy and should be performed when observed.

Literature

Ang KK et al (2001) Extent and kinetics of recovery of occult spinal cord injury. Int J Radiat Oncol Biol Phys 50(4):1013–1020

Barker JL Jr et al (2004) Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. Int J Radiat Oncol Biol Phys 59(4):960–970

Biagioli MC et al (2007) Intensity-modulated radiotherapy with concurrent chemotherapy for previously irradiated, recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 69(4):1067–1073

Bortfeld T, Webb S (2009) Single-arc IMRT? Phys Med Biol 54(1):N9–N20

Brandner ED et al (2006) Abdominal organ motion measured using 4D CT. Int J Radiat Oncol Biol Phys 65(2):554–560

Bzdusek K et al (2009) Development and evaluation of an efficient approach to volumetric arc therapy planning. Med Phys 36(6):2328–2339

Chan C et al (2014) Intensity-modulated radiotherapy for lung cancer: current status and future developments. J Thorac Oncol 9(11):1598–1608

Chao KS et al (2000) Intensity-modulated radiation therapy in head and neck cancers: the Mallinckrodt experience. Int J Cancer 90(2):92–103

Chen T et al (2014) Frequency filtering based analysis on the cardiac induced lung tumor motion and its impact on the radiotherapy management. Radiother Oncol 112(3):365–370

Combs SE et al (2008) Radiochemotherapy with temozolomide as re-irradiation using high precision fractionated stereotactic radiotherapy (FSRT) in patients with recurrent gliomas. J Neurooncol 89(2):205–210

Cuneo KC et al (2012) Safety and efficacy of stereotactic radiosurgery and adjuvant bevacizumab in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 82(5):2018–2024

Dearnaley DP et al (1999) Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 353(9149): 267–272

Deodato F et al (2009) Stereotactic radiotherapy in recurrent gynecological cancer: a case series. Oncol Rep 22(2):415–419

Depuydt T et al (2014) Treating patients with real-time tumor tracking using the Vero gimbaled linac system: implementation and first review. Radiother Oncol 112(3):343–351

Dresen RC et al (2010) Absence of tumor invasion into pelvic structures in locally recurrent rectal cancer: prediction with preoperative MR imaging. Radiology 256(1):143–150

Duprez F et al (2009) Intensity-modulated radiotherapy for recurrent and second primary head and neck cancer in previously irradiated territory. Radiother Oncol 93(3):563–569

Ehrbar S et al (2016) Three-dimensional versus four-dimensional dose calculation for volumetric modulated arc therapy of hypofractionated treatments. Z Med Phys 26(1):45–53

Engelsman M et al (2005) How much margin reduction is possible through gating or breath hold? Phys Med Biol 50(3):477–490

Even-Sapir E et al (2004) Detection of recurrence in patients with rectal cancer: PET/CT after

abdominoperineal or anterior resection. Radiology 232(3):815–822
Fearon K et al (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12(5):489–495
Fiorino C et al (2008) Evidence of limited motion of the prostate by carefully emptying the rectum as assessed by daily MVCT image guidance with helical tomotherapy. Int J Radiat Oncol Biol Phys 71(2):611–617
Fuss M et al (2004) Repositioning accuracy of a commercially available double-vacuum whole body immobilization system for stereotactic body radiation therapy. Technol Cancer Res Treat 3(1):59–67
Goitein M (2010) Trials and tribulations in charged particle radiotherapy. Radiother Oncol 95(1):23–31
Gollub MJ et al (2013) Prognostic aspects of DCE-MRI in recurrent rectal cancer. Eur Radiol 23(12):3336–3344
Grosu AL et al (2005) Reirradiation of recurrent high-grade gliomas using amino acid PET (SPECT)/CT/MRI image fusion to determine gross tumor volume for stereotactic fractionated radiotherapy. Int J Radiat Oncol Biol Phys 63(2):511–519
Guckenberger M et al (2006) Cone-beam CT based image-guidance for extracranial stereotactic radiotherapy of intrapulmonary tumors. Acta Oncol 45(7):897–906
Guckenberger M et al (2007a) Precision required for dose-escalated treatment of spinal metastases and implications for image-guided radiation therapy (IGRT). Radiother Oncol 84(1):56–63
Guckenberger M et al (2007b) Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. Int J Radiat Oncol Biol Phys 69(1):294–301
Guckenberger M et al (2009a) Is a single arc sufficient in volumetric-modulated arc therapy (VMAT) for complex-shaped target volumes? Radiother Oncol 93(2):259–265
Guckenberger M et al (2009b) Potential of image-guidance, gating and real-time tracking to improve accuracy in pulmonary stereotactic body radiotherapy. Radiother Oncol 91(3):288–295
Guckenberger M et al (2010) Stereotactic body radiotherapy for local boost irradiation in unfavourable locally recurrent gynaecological cancer. Radiother Oncol 94(1):53–59
Guckenberger M et al (2014) Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. Strahlenther Onkol 190(1):26–33
Gutin PH et al (2009) Safety and efficacy of bevacizumab with hypofractionated stereotactic irradiation for recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 75(1):156–163
Haertl PM et al (2013) Frameless fractionated stereotactic radiation therapy of intracranial lesions: impact of cone beam CT based setup correction on dose distribution. Radiat Oncol 8:153
Hashimoto T et al (2006) Repeated proton beam therapy for hepatocellular carcinoma. Int J Radiat Oncol Biol Phys 65(1):196–202
Hatakeyama T et al (2008) 11C-methionine (MET) and 18F-fluorothymidine (FLT) PET in patients with newly diagnosed glioma. Eur J Nucl Med Mol Imaging 35(11):2009–2017
Heron DE et al (2009) Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. Int J Radiat Oncol Biol Phys 75(5):1493–1500
Hurkmans CW et al (2001) Set-up verification using portal imaging; review of current clinical practice. Radiother Oncol 58(2):105–120
ICRU (1993) International commission on radiation units and measurements: prescribing, recording and reporting photon beam therapy, report 50. ICRU, Bethesda
ICRU (1999) International commission on radiation units and measurements: prescribing, recording and reporting photon beam therapy, report 62. ICRU, Bethesda
Ito K et al (1992) Recurrent rectal cancer and scar: differentiation with PET and MR imaging. Radiology 182(2):549–552
Jingu K et al (2010) Focal dose escalation using FDG-PET-guided intensity-modulated radiation therapy boost for postoperative local recurrent rectal cancer: a planning study with comparison of DVH and NTCP. BMC Cancer 10:127
Jumeau R et al (2015) Optimization of reirradiation using deformable registration. Int J Radiat Oncol Biol Phys 93(3):E599
Keall PJ et al (2006) Geometric accuracy of a real-time target tracking system with dynamic multileaf collimator tracking system. Int J Radiat Oncol Biol Phys 65(5):1579–1584
Keall PJ et al (2014) The first clinical implementation of electromagnetic transponder-guided MLC tracking. Med Phys 41(2):020702
Kelly P et al (2010) Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. Int J Radiat Oncol Biol Phys 78(5):1387–1393
Kilburn JM et al (2014) Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment. Radiother Oncol 110(3):505–510
Kong DS et al (2008) Efficacy of stereotactic radiosurgery as a salvage treatment for recurrent malignant gliomas. Cancer 112(9):2046–2051
Korreman SS, Juhler-Nottrup T, Boyer AL (2008) Respiratory gated beam delivery cannot facilitate margin reduction, unless combined with respiratory correlated image guidance. Radiother Oncol 86(1):61–68
Kupelian PA et al (2005) Serial megavoltage CT imaging during external beam radiotherapy for non-small-cell lung cancer: observations on tumor regression during treatment. Int J Radiat Oncol Biol Phys 63(4):1024–1028
Lang S et al (2014) Development and evaluation of a prototype tracking system using the treatment couch. Med Phys 41(2):021720
Lax I et al (1994) Stereotactic radiotherapy of malignancies in the abdomen. Methodological aspects. Acta Oncol 33(6):677–683

Lebesque JV, Keus RB (1991) The simultaneous boost technique: the concept of relative normalized total dose. Radiother Oncol 22(1):45–55

Lee JK et al (1981) CT appearance of the pelvis after abdomino-perineal resection for rectal carcinoma. Radiology 141(3):737–741

Lee N et al (2007) Salvage re-irradiation for recurrent head and neck cancer. Int J Radiat Oncol Biol Phys 68(3):731–740

Lee IH et al (2009) Association of 11C-methionine PET uptake with site of failure after concurrent temozolomide and radiation for primary glioblastoma multiforme. Int J Radiat Oncol Biol Phys 73(2):479–485

Leksell L (1951) The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 102(4):316–319

Leksell L (1968) Cerebral radiosurgery. I. Gammathalanotomy in two cases of intractable pain. Acta Chir Scand 134(8):585–595

Liang J et al (2015) Trajectory modulated arc therapy: a fully dynamic delivery with synchronized couch and gantry motion significantly improves dosimetric indices correlated with poor cosmesis in accelerated partial breast irradiation. Int J Radiat Oncol Biol Phys 92(5):1148–1156

Lin R et al (1999) Nasopharyngeal carcinoma: repeat treatment with conformal proton therapy – dose-volume histogram analysis. Radiology 213(2): 489–494

Loeffler JS et al (1990) The treatment of recurrent brain metastases with stereotactic radiosurgery. J Clin Oncol 8(4):576–582

Maciejewski B, Taylor JM, Withers HR (1986) Alpha/beta value and the importance of size of dose per fraction for late complications in the supraglottic larynx. Radiother Oncol 7(4):323–326

Mackie TR et al (1993) Tomotherapy: a new concept for the delivery of dynamic conformal radiotherapy. Med Phys 20(6):1709–1719

Mahan SL et al (2005) Evaluation of image-guided helical tomotherapy for the retreatment of spinal metastasis. Int J Radiat Oncol Biol Phys 63(5):1576–1583

Mantel F, Flentje M, Guckenberger M (2013) Stereotactic body radiation therapy in the re-irradiation situation – a review. Radiat Oncol 8:7

Marks LB, Ten Haken RK, Martel MK (2010) Guest editor's introduction to QUANTEC: a users guide. Int J Radiat Oncol Biol Phys 76(3 Suppl):S1–S2

Marnitz S et al (2015) Which technique for radiation is most beneficial for patients with locally advanced cervical cancer? Intensity modulated proton therapy versus intensity modulated photon treatment, helical tomotherapy and volumetric arc therapy for primary radiation – an intraindividual comparison. Radiat Oncol 10:91

Marucci L et al (2006) Conservation treatment of the eye: conformal proton reirradiation for recurrent uveal melanoma. Int J Radiat Oncol Biol Phys 64(4):1018–1022

Mayr NA et al (2006) Serial therapy-induced changes in tumor shape in cervical cancer and their impact on assessing tumor volume and treatment response. AJR Am J Roentgenol 187(1):65–72

Meerwein CM et al (2015) Post-treatment surveillance of head and neck cancer: pitfalls in the interpretation of FDG PET-CT/MRI. Swiss Med Wkly 145:w14116

Milker-Zabel S et al (2003) Clinical results of retreatment of vertebral bone metastases by stereotactic conformal radiotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 55(1):162–167

Minniti G et al (2016) Repeated stereotactic radiosurgery for patients with progressive brain metastases. J Neurooncol 126(1):91–97

Munck Af Rosenschold P et al (2015) Impact of [18F]-fluoro-ethyl-tyrosine PET imaging on target definition for radiation therapy of high-grade glioma. Neuro Oncol 17(5):757–763

Nakamura K et al (2014) Recent advances in radiation oncology: intensity-modulated radiotherapy, a clinical perspective. Int J Clin Oncol 19(4):564–569

Nieder C et al (2006) Update of human spinal cord reirradiation tolerance based on additional data from 38 patients. Int J Radiat Oncol Biol Phys 66(5): 1446–1449

Niyazi M et al (2012) Re-irradiation in recurrent malignant glioma: prognostic value of [18F]FET-PET. J Neurooncol 110(3):389–395

Otto K (2008) Volumetric modulated arc therapy: IMRT in a single gantry arc. Med Phys 35(1):310–317

Palmer J et al (2014) Motion of the esophagus due to cardiac motion. PLoS One 9(2):e89126

Pauleit D et al (2005) O-(2-[18F]fluoroethyl)-L-tyrosine PET combined with MRI improves the diagnostic assessment of cerebral gliomas. Brain 128(Pt 3):678–687

Plastaras JP, Berman AT, Freedman GM (2014) Special cases for proton beam radiotherapy: re-irradiation, lymphoma, and breast cancer. Semin Oncol 41(6): 807–819

Polat B et al (2008) Intra-fractional uncertainties in image-guided intensity-modulated radiotherapy (IMRT) of prostate cancer. Strahlenther Onkol 184(12):668–673

Poltinnikov IM et al (2005) Combination of longitudinal and circumferential three-dimensional esophageal dose distribution predicts acute esophagitis in hypofractionated reirradiation of patients with non-small-cell lung cancer treated in stereotactic body frame. Int J Radiat Oncol Biol Phys 62(3):652–658

Popovtzer A et al (2009) The pattern of failure after reirradiation of recurrent squamous cell head and neck cancer: implications for defining the targets. Int J Radiat Oncol Biol Phys 74(5):1342–1347

Purdie TG et al (2007) Cone-beam computed tomography for on-line image guidance of lung stereotactic radiotherapy: localization, verification, and intrafraction tumor position. Int J Radiat Oncol Biol Phys 68(1):243–252

Ramakrishna N et al (2010) A clinical comparison of patient setup and intra-fraction motion using frame-based radiosurgery versus a frameless image-guided

radiosurgery system for intracranial lesions. Radiother Oncol 95(1):109–115
Rieken S et al (2013) Analysis of FET-PET imaging for target volume definition in patients with gliomas treated with conformal radiotherapy. Radiother Oncol 109(3):487–492
Rwigema JC et al (2010) Fractionated stereotactic body radiation therapy in the treatment of previously-irradiated recurrent head and neck carcinoma: updated report of the University of Pittsburgh experience. Am J Clin Oncol 33(3):286–93
Schwer AL et al (2008) A phase I dose-escalation study of fractionated stereotactic radiosurgery in combination with gefitinib in patients with recurrent malignant gliomas. Int J Radiat Oncol Biol Phys 70(4):993–1001
Seppenwoolde Y et al (2002) Precise and real-time measurement of 3D tumor motion in lung due to breathing and heartbeat, measured during radiotherapy. Int J Radiat Oncol Biol Phys 53(4):822–834
Seppenwoolde Y et al (2007) Accuracy of tumor motion compensation algorithm from a robotic respiratory tracking system: a simulation study. Med Phys 34(7): 2774–2784
Shepherd SF et al (1997) Hypofractionated stereotactic radiotherapy in the management of recurrent glioma. Int J Radiat Oncol Biol Phys 37(2):393–398
Smitsmans MH et al (2008) The influence of a dietary protocol on cone beam CT-guided radiotherapy for prostate cancer patients. Int J Radiat Oncol Biol Phys 71(4):1279–1286
Smyth G et al (2013) Trajectory optimization for dynamic couch rotation during volumetric modulated arc radiotherapy. Phys Med Biol 58(22):8163–8177
Sohn M, Weinmann M, Alber M (2009) Intensity-modulated radiotherapy optimization in a quasi-periodically deforming patient model. Int J Radiat Oncol Biol Phys 75(3):906–914
Sonke JJ et al (2005) Respiratory correlated cone beam CT. Med Phys 32(4):1176–1186
Sonke JJ et al (2009) Frameless stereotactic body radiotherapy for lung cancer using four-dimensional cone beam CT guidance. Int J Radiat Oncol Biol Phys 74(2):567–574
Sterzing F et al (2010) Spinal cord sparing reirradiation with helical tomotherapy. Cancer 116(16):3961–3968
Stieler F et al (2011) Reirradiation of spinal column metastases: comparison of several treatment techniques and dosimetric validation for the use of VMAT. Strahlenther Onkol 187(7):406–415
Sykes JR et al (2005) A feasibility study for image guided radiotherapy using low dose, high speed, cone beam X-ray volumetric imaging. Radiother Oncol 77(1): 45–52
Teoh M et al (2011) Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol 84(1007):967–996
Terakawa Y et al (2008) Diagnostic accuracy of 11C-methionine PET for differentiation of recurrent brain tumors from radiation necrosis after radiotherapy. J Nucl Med 49(5):694–699
Underberg RW et al (2005) Benefit of respiration-gated stereotactic radiotherapy for stage I lung cancer: an analysis of 4DCT datasets. Int J Radiat Oncol Biol Phys 62(2):554–560
van Herk M (2004) Errors and margins in radiotherapy. Semin Radiat Oncol 14(1):52–64
van Rijssel MJ et al (2014) A critical approach to the clinical use of deformable image registration software. In response to Meijneke et al. Radiother Oncol 112(3):447–448
Verellen D et al (2007) Innovations in image-guided radiotherapy. Nat Rev Cancer 7(12):949–960
Vestergaard A et al (2013) Adaptive plan selection vs. re-optimisation in radiotherapy for bladder cancer: a dose accumulation comparison. Radiother Oncol 109(3): 457–462
Wachter S et al (2002) The influence of a rectal balloon tube as internal immobilization device on variations of volumes and dose-volume histograms during treatment course of conformal radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 52(1):91–100
Wilbert J et al (2008) Tumor tracking and motion compensation with an adaptive tumor tracking system (ATTS): system description and prototype testing. Med Phys 35(19):3911–9921
Wolthaus JW et al (2008) Comparison of different strategies to use four-dimensional computed tomography in treatment planning for lung cancer patients. Int J Radiat Oncol Biol Phys 70(4):1229–1238
Yan D et al (1997) Adaptive radiation therapy. Phys Med Biol 42(1):123–132