Cancer Imaging (2011) **11,** S147–S152
DOI: 10.1102/1470-7330.2011.9036

CI

e-med
www.e-med.org.uk

IMAGING IN RADIATION ONCOLOGY

Wednesday 5 October 2011, 11:30–13:00

Advances in radiotherapy: from 2D to 4D

Morten Høyer[a], Maria Thor[a,b], Sara Thörnqvist[a,b], Jimmi Søndergaard[a], Yasmin Lassen-Ramshad[a] and Ludvig Paul Muren[a,b]

[a]Department of Oncology and [b]Department of Medical Physics, Aarhus University Hospital, Aarhus, Denmark

Corresponding address: Morten Høyer, MD, PhD, Department of Oncology, Aarhus University Hospital, 8000 Aarhus C, Denmark.
Email: hoyer@aarhus.rm.dk

Abstract

Imaging techniques are increasingly integrated into modern radiotherapy (RT). Multimodal imaging is used to define the target for RT planning and imaging technology is also being integrated into linear accelerators, with the purpose to ensure delivery of radiation with high geometric accuracy. The integration of imaging in RT calls for a stronger collaboration between diagnostic radiologists and the professions involved in RT.

Keywords: *Radiotherapy; Intensity-modulated radiotherapy; Stereotactic radiotherapy; Image-guided radiotherapy; Adaptive radiotherapy.*

Introduction

Radiotherapy (RT) technology has improved considerably over the last decades. Inclusion of multiple imaging modalities and modern computer technology into treatment planning, together with the technological achievements of the linear accelerator (linac) has increased the precision of RT delivery considerably. In intensity-modulated radiotherapy (IMRT), the radiation dose distributions are shaped to the target with a steep fall in the dose to the neighbouring normal tissues[1]. Whereas conventional RT techniques (e.g. 4-field box techniques) resulted in a bath of high-dose radiation to a large volume, IMRT provides highly selective irradiation of the target. However, the steep dose gradients make IMRT more sensitive to uncertainties, e.g. caused by changes in shape and position of the target and normal tissues as well as variations in the daily set-up of the patient. High precision in delivery can be achieved by image-guided radiotherapy (IGRT) where the target is imaged immediately before treatment with the patient in the treatment position[2].

The present article provides a review of these novel technologies that have become standard and gives some examples of innovative areas within clinical RT.

Principles and definitions in radiotherapy

The nomenclature of the RT targets and organs at risk (ORs) have changed over time. Today we are using the ICRU-62 and -83 reports (Fig. 1)[3,4]. The gross tumour volume (GTV) is defined as the tumour visible by any imaging modality or by clinical examination. The clinical target volume (CTV) is formed by addition of a margin around the GTV to account for subclinical tumour infiltration and the internal target volume (ITV) by adding a further margin for internal intra- and inter-fractional movement of the target. Finally, a safety margin related to uncertainly in daily set-up at the treatment unit is added to form the planning target volume (PTV). An OR is defined as an organ receiving a radiation dose close to its tolerance. The treated volume receives a dose that may control the tumour and the irradiated volume receives a dose that may cause toxicity.

Imaging in radiotherapy planning

Computed tomography (CT) is the standard imaging modality in RT planning. Electron density information from CT allows exact radiation dose calculation and

1470-7330/11/000001 + 06

CT also has high geometric stability. In cases where CT is insufficient for target definition, additional magnetic resonance imaging (MRI) and positron emission tomography (PET) examinations may provide the necessary anatomical and/or functional information. In planning of prostate cancer MRI gives a more exact definition of the prostate, in particular at the apex of the prostate[5], and in the definition of brain tumours, MRI is also superior to CT (Fig. 2)[6]. [^{18}F]Fluorodeoxyglucose (FDG)-PET/CT may be superior to CT in specific cases such as advanced lung cancer. In bronchial cancer, FDG-PET/CT may be more accurate than CT in definition of the CTV, especially if the tumour causes collapse of the lung[7]. MRI and PET may also be better than CT for assessment of tumour response following RT of some tumours.

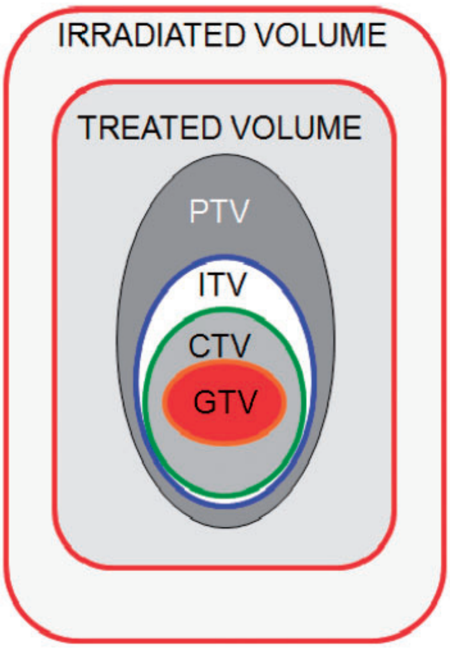

Figure 1 **Definitions of targets in the ICRU-62 and -83 reports (GTV, gross tumour volume; CTV, clinical target volume; ITV, internal target volume; PTV, planning target volume). For definitions, see text.**

Diffusion-weighted (DW)-MRI is promising in RT planning. Apparent diffusion coefficients (ADC) determined by DW-MRI correlate significantly with tumour cell density in cervical cancer and it is hypothesized that radiation dose should be intensified in volumes with high ADC values[8]. Dynamic contrast-enhanced MRI also seems promising in identification of cancer in the prostate, which may be useful for even further escalation of the radiation dose to focal tumour dense volumes[9]. PET/CT with hypoxic tracers (i.e. [^{18}F]misonidazole[10], [^{18}F]fluoroazomycin-arabinoside[11]) may identify hypoxic subvolumes of radioresistant tumours that need escalated radiation doses. Functional imaging of normal tissues may reveal subvolumes of, for example, brain, parotid glands, lung and liver, with high functionality, which therefore should be spared the radiation dose[12]. These techniques have yet to be tested in clinical trials.

With the need for electron density information from CT, high-resolution soft tissue information from MRI, and metabolic information from PET, there is a great demand for imaging co-registration[13]. Furthermore, accurate co-registration in IGRT can reveal information about deformations of the organs and enable voxelwise dose accumulation based on the actual dose delivered to the target and normal tissues during the treatment[14]. Rigid and deformable multimodal image

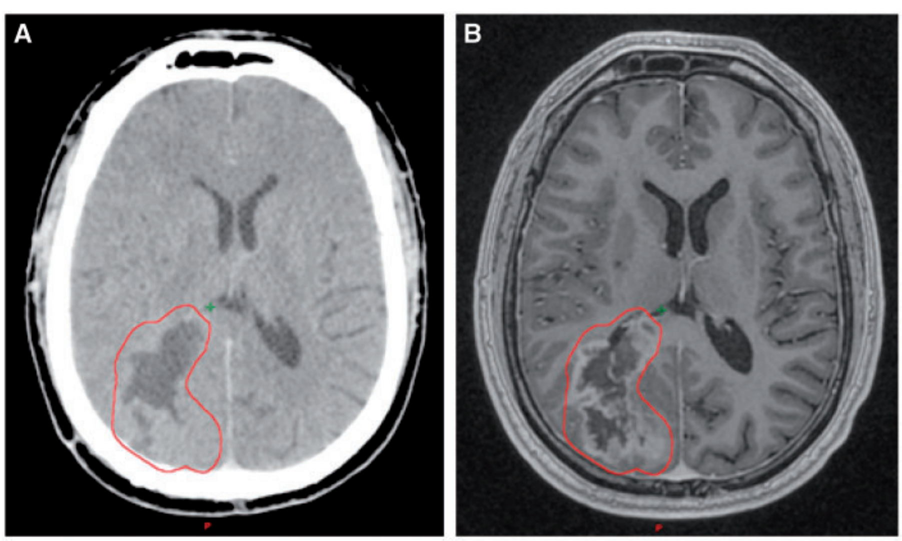

Figure 2 **Treatment planning CT (A) and preoperative MRI (B) with delineation of the gross tumour volume (GTV) for a patient with glioblastoma multiforme.**

co-registration software is now commercially available, but still has severe limitations for many organs and image modalities.

Intensity-modulated radiotherapy

IMRT can be used to obtain highly individualized irradiation of the primary tumour and elective lymph nodes, whenever desired, with sparing of the normal tissues (Fig. 2). IMRT planning using advanced treatment planning algorithms and powerful computers results in dose distributions conforming to the shape of the target with steep dose fall-off outside the target. By volumetric arc therapy (VMAT), the radiation is delivered during one or two perpendicular gantry rotations around the patient with constant movement of the MLC.

IMRT has been shown to be particularly beneficial in RT of head and neck cancer where it allows sparing of the parotid glands[15] as well as in RT of the prostate[16] and bladder cancer[17] where the radiation dose to the target can be escalated without increased rectal morbidity when treatment is delivered by the IMRT technique (Fig. 3). The steep dose fall close to the target periphery demands high precision in the treatment delivery. For this reason, IGRT procedures are essential when IMRT is used.

The terms dose sculpturing or dose painting by numbers are principles based on IMRT where the radiation dose is heterogeneously distributed over the target so that radioresistant subvolumes of the target characterized by hypoxia or high tumour cell density identified by functional imaging receive an escalated radiation dose, whereas more radiosensitive subvolumes receive the standard dose[18].

Stereotactic radiotherapy

Stereotactic radiotherapy (SRT) is a highly precise and conformal RT technique for treatment of small targets by use of a high number of treatment beams. Until recently it was guided by external coordinates, but now most SRT is guided by IGRT, which may improve the geometric precision even further and can also be delivered quickly and with less resources. SRT was originally developed for treatment of intracranial benign and malignant tumours and a dedicated RT machine, the gamma-knife, was invented for this specific purpose. Today, most centres use conventional linear accelerators for SRT of intracranial tumours[19].

Since 1995, stereotactic body radiation therapy (SBRT) has been used in the treatment of small primary or metastatic tumours outside the brain, primarily in the lungs and liver. The patients are often immobilized in a stereotactic body frame (SBF), but also frame-less techniques are used. In SBRT, the high dose volume is highly conformed to the shape of the target, formed by a high number of beams (Fig. 4). A number of studies have shown that SBRT leads to high local control rates together with a low risk for complications[20–22]. SBRT is often considered the primary alternative to lobectomy in patients with limited stage lung cancer who are unfit for thoracic surgery.

Image-guided radiotherapy

Previously, patients were set up at the treatment unit based on skin marks and room lasers. Portal X-ray films acquired at the first treatment session had poor resolution as mega-voltage (MV) beam quality was used to verify the patient position based on bony anatomy. Nowadays, there are numerous commercially available options including 2-D and 3-D imaging technology integrated into the linacs. These provide much better image quality to ensure correct daily set-up of the patient based on either bony structures, implanted fiducials (as for prostate cancer) or even the target (as for lung tumours).

The so-called electronic portal imaging device (EPID) enables the simplest online patient position verification method. 2-D images can be registered to digitally reconstructed radiographs (DRR) of the treatment planning CT scan. Due to the MV beam quality, the EPID still has a relatively poor soft tissue contrast. For this reason, vendors have integrated kilovoltage (kV) X-ray on the linear accelerators. This allows better 2-D image quality for alignment of the patients based on bony anatomy or fiducial marker match. Volumetric imaging based on the cone beam CT (CBCT) principle can be obtained by reconstruction of more than 500 planar images acquired during a rotation of the gantry around the patient (Fig. 5). This is possible with kV as well as the MV technique. In the tomo-therapy machine, an MV single-slice CT is integrated with a compact linear accelerator, which treats the patient in a slice-by-slice fashion. The CBCT has soft tissue resolution, which allows direct online target alignment prior to each treatment session. Commercially available software for automatic rigid co-registration of the CBCT and the treatment planning CT scan calculates the set-up error in the three orthogonal directions and three rotations. The magnitude of error can be directly transferred to the couch controller, which shifts the position (and rotation) of the treatment couch. Image acquisition, reconstruction and match only take a few minutes and are in many institutions operated by a radiotherapy technologist.

Use of IGRT considerably reduces the uncertainty related to movement of the target between the treatment sessions and IGRT is today considered as a standard in RT. For prostate cancer, CTV–PTV margins of 8–10 mm were needed to account for inter-fractional geometric uncertainties when a conventional set-up by skin marks and room lasers was used. By use of gold markers implanted in the prostate and daily IGRT, these margins

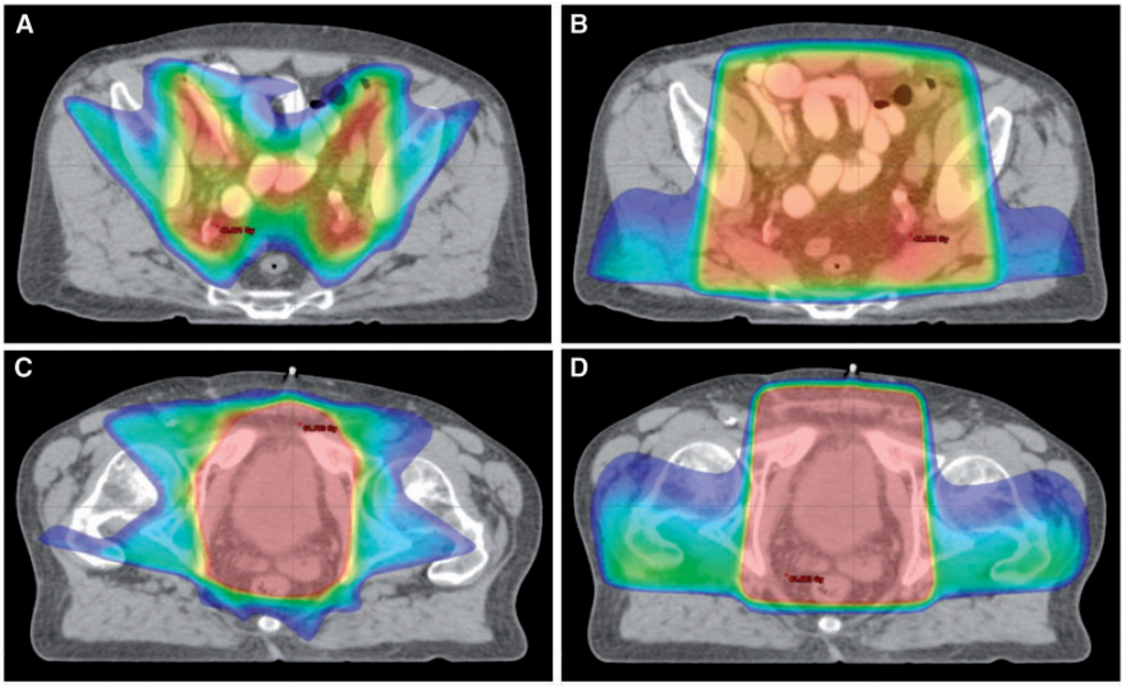

Figure 3 **IMRT (A + C) and conventional radiotherapy (CRT) (B + D) of two planes of the planning CT in a patient with urinary bladder cancer. The figure shows the improved conformation of the radiation dose to the target (bladder and pelvic lymph nodes) in IMRT compared to CRT.**

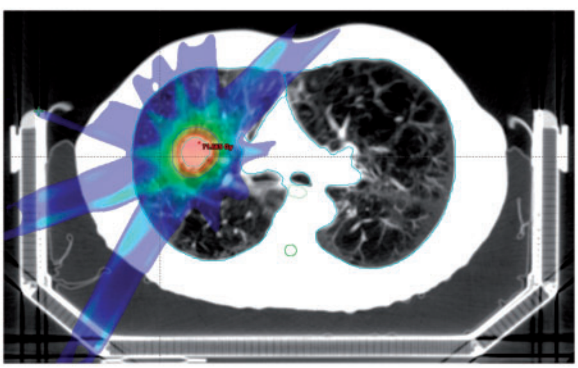

Figure 4 **SBRT for a limited stage non-small cell lung cancer. Colour wash indicates the 15-Gy dose level (in 3 fractions) in a 6-field SBRT plan with 67.5 Gy (in 3 fractions) prescribed to the clinical target volume (CTV).**

can be reduced to 2–7 mm[23]. Using systems enabling detection of the movement during the treatment session (intrafractional movement), the margin can be even further reduced[24]. In conventional RT for lung cancer, CBCT reduces the median set-up error from 5–6 mm to 2 mm when IGRT with a match on the vertebral column replaced conventional set-up by skin marks[25]. In SBRT for small lung tumours, the errors were reduced from 11 mm to 2 mm with the introduction of CBCT with a daily match on the lung tumour[26].

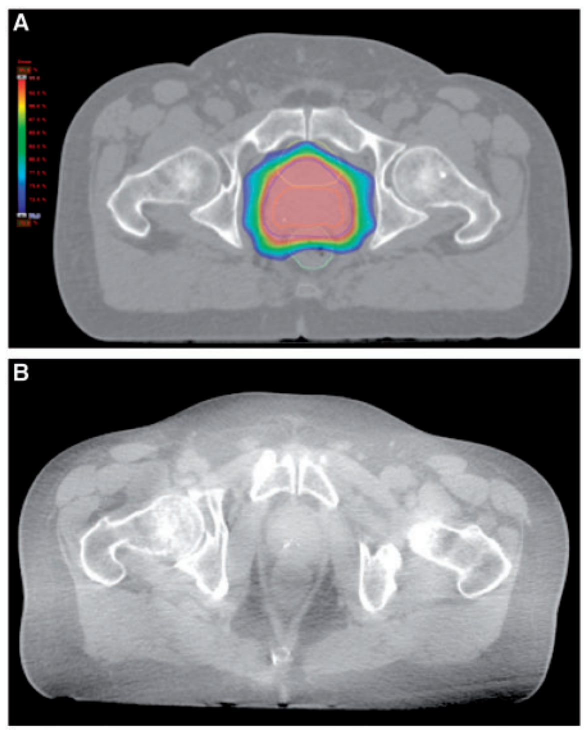

Figure 5 **IMRT for prostate cancer. The figure shows the treatment planning CT with dose colour wash (A) and kV CBCT acquired with the patient in treatment position on the treatment couch (B).**

Management of respiration-related target motion

Targets in the thorax and upper abdomen move with respiration and therefore there is a risk for a systematic positional error when RT planning CT acquisition and treatment are not in the same respiratory phases. For this reason, the RT planning CT for these patients is often acquired as a 4-D CT with simultaneous registration of the respiration. In the reconstruction, slices are sorted according to the respiratory phases and most often the mid-ventilation CT is used for RT planning. The simplest methods to minimize the respiratory motion are to acquire scans and treat the patient in a defined respiratory phase by active breathing technique[27] or apply pressure on the upper abdominal wall, which has been shown to reduce the internal target movement by 50%[28]. In RT of the left breast, deep inspiratory breathhold is often used to spare the left anterior descending coronary artery[29] with the aim of reducing the risk of treatment-related coronary morbidity. Both these methods are used in SBRT of lung and liver tumours.

Methods for tracking the target with the beam from the linear accelerator through continuous modulation of the MLC are currently under development. The methods demand exact online localization of the target by continuous imaging during delivery of the treatment[30]. The Cyper-knife is a small linear accelerator mounted on a robotic arm which moves synchronously with the respiration; today, this is the only commercially available beam-tracking RT system.

Adaptive strategies

The target and normal tissues may change considerably in size, shape or position during the course of treatment and this may lead to unintended distribution of the radiation dose. A collapse of the lung resolving due to regression of a central lung tumour may considerably change the position and lead to under-dosage of the lung tumour[31]. Similarly, shrinkage of large neck nodes during RT of head and neck cancer may lead to under-dosage of the cancer and over-dosage of the normal tissues[32]. Adaptive RT plans based on systematic feedback of daily or weekly imaging during the treatment course may compensate for anatomical changes and ensure full dose throughout the RT course[33]. A plan-of-the-day strategy means that the patient's RT plan is modified based on images acquired immediately before treatment. This method is especially useful for RT of bladder cancer which is challenging due to the day-to-day change in shape and size of the bladder.

Discussion

A number of normal tissues have a pronounced volume effect, meaning that radiation to decreased volume leads to decreased toxicity[34]. This is exploited in modern RT where IMRT with selective irradiation to targets can be delivered with a high-precision IGRT technique. High precision and normal tissue sparing allow dose escalation without further increase in morbidity and thereby increase the therapeutic ratio of RT.

However, the small margin may also lead to increased risk of geographic failure. Marginal failures have been reported in IMRT of head and neck cancer[35] and increased risk of biochemical failure has been reported in RT for prostate cancer if margins were too small[36]. Pathology examination of excised lung and liver tumours has demonstrated microscopic tumour extension 15 and 10 mm beyond the macroscopic border of lung and liver tumours, respectively[37,38]. This subclinical disease should be given particular attention in modern RT with highly conformal dose distributions.

There is a great demand for further development and integration of imaging techniques into RT. In 2011, the European RT field has celebrated the 30th anniversary of the separation of the European Society for Radiotherapy and Oncology (ESTRO) from the European Association of Radiology. However, modern management of cancer patients, including RT, needs multidisciplinary collaboration between both the radiological and radiotherapy specialties, as well as the many other specialties that are involved.

References

[1] Staffurth J. A review of the clinical evidence for intensity-modulated radiotherapy. Clin Oncol (R Coll Radiol) 2010; 22: 643–57.

[2] Jaffray DA. Image-guided radiation therapy: from concept to practice. Semin Radiat Oncol 2007; 17: 243–4. doi:10.1016/j.semradonc.2007.08.001.

[3] Purdy JA. Current ICRU definitions of volumes: limitations and future directions. Semin Radiat Oncol 2004; 14: 27–40. doi:10.1053/j.semradonc.2003.12.002.

[4] ICRU. ICRU reports 62 and 83. http://www.icru.org. 2011.

[5] Parker CC, Damyanovich A, Haycocks T, Haider M, Bayley A, Catton CN. Magnetic resonance imaging in the radiation treatment planning of localized prostate cancer using intra-prostatic fiducial markers for computed tomography co-registration. Radiother Oncol 2003; 66: 217–24. doi:10.1016/S0167-8140(02)00407-3.

[6] Jansen EP, Dewit LG, van HM, Bartelink H. Target volumes in radiotherapy for high-grade malignant glioma of the brain. Radiother Oncol 2000; 56: 151–6. doi:10.1016/S0167-8140(00)00216-4.

[7] Wu K, Ung YC, Hornby J, et al. PET CT thresholds for radiotherapy target definition in non-small-cell lung cancer: how close are we to the pathologic findings? Int J Radiat Oncol Biol Phys 2010; 77: 699–706. doi:10.1016/j.ijrobp.2009.05.028.

[8] Haack S, Pedersen EM, Jespersen SN, Kallehauge JF, Lindegaard JC, Tanderup K. Apparent diffusion coefficients in GEC ESTRO target volumes for image guided adaptive brachytherapy of locally advanced cervical cancer. Acta Oncol 2010; 49: 978–83. doi:10.3109/0284186X.2010.500619.

[9] Jackson AS, Reinsberg SA, Sohaib SA, et al. Dynamic contrast-enhanced MRI for prostate cancer localization. Br J Radiol 2009; 82: 148–56. doi:10.1259/bjr/89518905.

[10] Mortensen LS, Buus S, Nordsmark M, et al. Identifying hypoxia in human tumors: a correlation study between 18F-FMISO PET and the Eppendorf oxygen-sensitive electrode. Acta Oncol 2010; 49: 934–40. doi:10.3109/0284186X.2010.516274.
[11] Schuetz M, Schmid MP, Potter R, et al. Evaluating repetitive 18F-fluoroazomycin-arabinoside (18FAZA) PET in the setting of MRI guided adaptive radiotherapy in cervical cancer. Acta Oncol 2010; 49: 941–7. doi:10.3109/0284186X.2010.510145.
[12] Partridge M, Yamamoto T, Grau C, Hoyer M, Muren LP. Imaging of normal lung, liver and parotid gland function for radiotherapy. Acta Oncol 2010; 49: 997–1011. doi:10.3109/0284186X.2010.504735.
[13] Thornqvist S, Petersen JB, Hoyer M, Bentzen LN, Muren LP. Propagation of target and organ at risk contours in radiotherapy of prostate cancer using deformable image registration. Acta Oncol 2010; 49: 1023–32. doi:10.3109/0284186X.2010.503662.
[14] Thor M, Petersen JB, Bentzen L, Høyer M, Muren LP. Deformable image registration from CT to cone beam CT scans in radiotherapy for prostate cancer. Acta Oncol 2011; 50: 918–25.
[15] Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol 2007; 25: 4873–9. doi:10.1200/JCO.2007.11.5501.
[16] Zelefsky MJ, Fuks Z, Hunt M, et al. High-dose intensity modulated radiation therapy for prostate cancer: early toxicity and biochemical outcome in 772 patients. Int J Radiat Oncol Biol Phys 2002; 53: 1111–16. doi:10.1016/S0360-3016(02)02857-2.
[17] Sondergaard J, Hoyer M, Petersen JB, Wright P, Grau C, Muren LP. The normal tissue sparing obtained with simultaneous treatment of pelvic lymph nodes and bladder using intensity-modulated radiotherapy. Acta Oncol 2009; 48: 238–44. doi:10.1080/02841860802251575.
[18] Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MD-CRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000; 47: 551–60. doi:10.1016/S0360-3016(00)00467-3.
[19] Guckenberger M, Baier K, Guenther I, et al. Reliability of the bony anatomy in image-guided stereotactic radiotherapy of brain metastases. Int J Radiat Oncol Biol Phys 2007; 69: 294–301.
[20] Hoyer M, Roed H, Traberg HA, et al. Phase II study on stereotactic body radiotherapy of colorectal metastases. Acta Oncol 2006; 45: 823–30. doi:10.1080/02841860600904854.
[21] Kopek N, Paludan M, Petersen J, Hansen AT, Grau C, Hoyer M. Co-morbidity index predicts for mortality after stereotactic body radiotherapy for medically inoperable early-stage non-small cell lung cancer. Radiother Oncol 2009; 93: 402–7. doi:10.1016/j.radonc.2009.06.002.
[22] Baumann P, Nyman J, Hoyer M, et al. Stereotactic body radiotherapy for medically inoperable patients with stage I non-small cell lung cancer – a first report of toxicity related to COPD/CVD in a non-randomized prospective phase II study. Radiother Oncol 2008; 88: 359–67. doi:10.1016/j.radonc.2008.07.019.
[23] Kupelian P, Meyer JL. Prostate cancer: image guidance and adaptive therapy. Front Radiat Ther Oncol 2007; 40: 289–314.
[24] Poulsen PR, Muren LP, Hoyer M. Residual set-up errors and margins in on-line image-guided prostate localization in radiotherapy. Radiother Oncol 2007; 85: 201–6. doi:10.1016/j.radonc.2007.08.006.
[25] Borst GR, Sonke JJ, Betgen A, Remeijer P, van HM, Lebesque JV. Kilo-voltage cone-beam computed tomography setup measurements for lung cancer patients; first clinical results and comparison with electronic portal-imaging device. Int J Radiat Oncol Biol Phys 2007; 68: 555–61. doi:10.1016/j.ijrobp.2007.01.014.
[26] Worm ES, Hansen AT, Petersen JB, Muren LP, Praestegaard LH, Hoyer M. Inter- and intrafractional localisation errors in cone-beam CT guided stereotactic radiation therapy of tumours in the liver and lung. Acta Oncol 2010; 49: 1177–83. doi:10.3109/0284186X.2010.498435.
[27] McNair HA, Brock J, Symonds-Tayler JR, et al. Feasibility of the use of the Active Breathing Co ordinator (ABC) in patients receiving radical radiotherapy for non-small cell lung cancer (NSCLC). Radiother Oncol 2009; 93: 424–9. doi:10.1016/j.radonc.2009.09.012.
[28] Wunderink W, Mendez RA, de Kruijf W, de Boer H, Levendag P, Heijmen B. Reduction of respiratory liver tumor motion by abdominal compression in stereotactic body frame, analyzed by tracking fiducial markers implanted in liver. Int J Radiat Oncol Biol Phys 2008; 71: 907–15. doi:10.1016/j.ijrobp.2008.03.010.
[29] Korreman SS, Pedersen AN, Nøttrup TJ, Specht L, Nyström H. Breathing adapted radiotherapy for breast cancer: comparison of free breathing gating with breath-hold technique. Radiother Oncol 2005; 76: 311–18. doi:10.1016/j.radonc.2005.07.009.
[30] Poulsen PR, Cho B, Sawant A, Keall PJ. Implementation of a new method for dynamic multileaf collimator tracking of prostate motion in arc radiotherapy using a single kV imager. Int J Radiat Oncol Biol Phys 2010; 76: 914–23.
[31] Sonke JJ, Belderbos J. Adaptive radiotherapy for lung cancer. Semin Radiat Oncol 2010; 20: 94–106. doi:10.1016/j.semradonc.2009.11.003.
[32] Bhide SA, Davies M, Burke K, et al. Weekly volume and dosimetric changes during chemoradiotherapy with intensity-modulated radiation therapy for head and neck cancer: a prospective observational study. Int J Radiat Oncol Biol Phys 2010; 76: 1360–8. doi:10.1016/j.ijrobp.2009.04.005.
[33] Yan D, Vicini F, Wong J, Martinez A. Adaptive radiation therapy. Phys Med Biol 1997; 42: 123–32. doi:10.1088/0031-9155/42/1/008.
[34] Dearnaley DP, Khoo VS, Norman AR, et al. Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomised trial. Lancet 1999; 353: 267–72. doi:10.1016/S0140-6736(98)05180-0.
[35] Cannon DM, Lee NY. Recurrence in region of spared parotid gland after definitive intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2008; 70: 660–5. doi:10.1016/j.ijrobp.2007.09.018.
[36] Engels B, Soete G, Verellen D, Storme G. Conformal arc radiotherapy for prostate cancer: increased biochemical failure in patients with distended rectum on the planning computed tomogram despite image guidance by implanted markers. Int J Radiat Oncol Biol Phys 2009; 74: 388–91.
[37] Grills IS, Fitch DL, Goldstein NS, et al. Clinicopathologic analysis of microscopic extension in lung adenocarcinoma: defining clinical target volume for radiotherapy. Int J Radiat Oncol Biol Phys 2007; 69: 334–41.
[38] Mendez RA, Verheij J, Dwarkasing RS, et al. Comparison of macroscopic pathology measurements with magnetic resonance imaging and assessment of microscopic pathology extension for colorectal liver metastases. Int J Radiat Oncol Biol Phys 2010; doi:10.1016/j.ijrobp.2010.10.032.