Acta Oncologica, 2008; 47: 1193–1200

informa
healthcare

ORIGINAL ARTICLE

Broadening the scope of Image-Guided Radiotherapy (IGRT)

CARLO GRECO[1] & C. CLIFTON LING[2]

[1]*Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, New York, USA and* [2]*Department of Medical Physics, Memorial Sloan Kettering Cancer Center, New York, New York, USA*

Abstract
The recent wave of enthusiasm for image guidance in radiation therapy is largely due to the advent of on-line imaging devices. The current narrow definition of image-guided radiotherapy (IGRT), in fact, essentially connotes the use of near real-time imaging during treatment delivery to reduce uncertainties in target position and should therefore be termed IGRT-D. However, a broader (and more appropriate) context of image-guidance should include: (1) detection and diagnosis, (2) delineation of target and organs at risk, (3) determining biological attributes, (4) dose distribution design, (5) dose delivery assurance and (6) deciphering treatment response through imaging i.e. the 6 D's of IGRT. Strategies to advance these areas will be discussed.

The concept of image guidance in radiation therapy is far from being new. In fact, the first use of x-ray tubes for cancer therapy involved the same kV radiation source for both imaging and treatment. Recently, image guidance has derived significant impetus from the commercial availability of advanced on-line volumetric imaging technologies that permit treatment delivery verification in near real-time. However, the commonly adopted definition of image-guided radiation therapy (IGRT) appears too narrow, primarily connoting the use of near real-time imaging for treatment delivery verification and set-up correction [1]. Thus, the above approach should be abbreviated as IGRT-D for image-guided radiation therapy delivery.

A broader and more appropriate context of IGRT should include (1) detection and diagnosis, (2) delineation of target and organs at risk, (3) determining biological attributes, (4) dose distribution design, (5) dose delivery assurance and (6) deciphering treatment response through imaging. That is, the 6 D's of IGRT. Target definition, biological attribute determination, and deciphering treatments response are the most challenging aspects of IGRT and strategies to advance these areas are needed for the benefits of IGRT to be brought to full fruition.

Detection and diagnosis

The foundation of non-invasive medical imaging can be traced back to the discovery of x-rays. Since then, an impressive armamentarium of morphological imaging techniques has been developed. Screening programs based on imaging are routinely used for the early detection of cancer. Examples of these are mammography for breast cancer [2] low-dose high resolution-CT for lung cancer [3,4] and virtual endoscopy for colon cancer [5]. It is believed that appropriate use of screening may result in improvements in cause-specific survival [6]. Of course, not only is the role of screening one of detection of the disease, but to do so at an early stage where cure rates are significantly higher. As a consequence of early disease detection, organ- and function-sparing have increasingly become the mainstay approach for the treatment of cancer in many anatomical sites [7–10]. It is expected that the role of cancer detection and diagnosis will continue to evolve with more-thorough and effective screening programs that can establish the presence of malignancy at increasingly earlier stages when it can be effectively treated by non-invasive treatment approaches such IGRT. The safety and efficacy of single fraction or highly hypofractionated IGRT regimens are becoming

Correspondence: C. Clifton Ling, Department of Medical Physics, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. E-mail: lingc@mskcc.org

(Received 8 May 2008; accepted 29 May 2008)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.1080/02841860802241956

more established. Predictive assays (proteomics and genomics) may provide reliable information on the true extent of the disease, discerning between patients who may be cured with a local form of treatment only *vs*. patients likely to already harbor microscopic dissemination. Under these circumstances, IGRT may, indeed, become the quintessential tool for non-invasive tumor ablation as an alternative to surgery in many clinical settings.

Undoubtedly, with current imaging techniques many lesions continue to evade detection. Recent technological advances have brought in the clinical realm high-resolution multi-detector CT and whole-body MR imaging, whose respective roles and cost-effectiveness in oncology imaging are yet to be determined [11–13]. Positron emission tomography (PET) has been around in the research arena for many years, and only recently has it gained widespread acceptance in the clinical practice. PET with the glucose analogue ^{18}F-fluorodeoxyglucose (FDG) is now one of the standard methods for *in vivo* imaging and staging of various malignancies [14]. PET- and MR-based novel imaging probes, capable of tracking specific molecular pathways as well as tissue functions, are currently being developed and tested. Non-invasive characterization of tissue abnormalities should lead to higher accuracy in the differential diagnosis between malignant and benign lesions. Molecular probes for imaging *in vivo* gene expression (e.g. oncogenes such as *myc* or tumor suppressor genes such as *p53*) [15,16], telomerase activity, over-expressed receptors (e.g. HER-2/neu) [17,18], apoptosis [19], protease activity, hypoxia [20] and angiogenesis [21] are being scrutinized for this purpose. The next decade, therefore, will likely witness a paradigm shift in which morphological multi-modality imaging will be heavily integrated with molecular-functional imaging. Indeed, the prototype of this approach is represented by hybrid PET/CT scanners in which the relatively poor resolution and lack of anatomical detail of the PET component is rectified with the hardware-fused CT images [22]. FDG-PET/CT has clearly been shown to yield higher overall sensitivity and specificity than either modality alone [23,24]. In non-small cell lung cancer the use of ^{18}F-FDG-PET imaging has been shown to result in stage shift. Patients considered amenable to radical irradiation, based on the assessment of CT scans only, are often found to already harbor distant metastasis on PET/CT re-evaluation, changing the radiotherapy approach from a radical to a palliative one [25].

The role of novel PET tracers in the detection of primary and recurrent tumors is still largely investigational, but appears to be of promise. For instance, in the context of early biochemical relapse following radical local treatment for prostate cancer, conventional imaging modalities are of little of no value in detecting local *vs*. nodal disease. New PET tracers such as ^{11}C-choline and ^{11}C-acetate may aid early detection of local recurrences or minimal nodal involvement *vs.* distant disease, thus effectively selecting patients who may be salvaged by high-dose loco-regional radiotherapy [26,27].

Another promising integration of morphological and functional imaging is represented by MRI and magnetic resonance spectroscopy (MRS). MRS is a non-invasive technique which may provide biochemical and metabolic information associated with tumor growth and development. In the diagnosis of prostate cancer, the choline/citrate ratio measured by MRS has been frequently described as a promising tool to discriminate between benign hyperplasia and malignancy [28].

Delineation of target and organs at risk

Radiation therapy is currently going through a series of technical and conceptual revolutions that are leading to the safe delivery of radiation to unprecedented dose levels. Advances in treatment delivery accuracy (IGRT-D) currently allow safe administration of curative treatments in a single session or highly hypofractionated regimens. The resulting dose escalation to the tumor is expected to bring about both an improvement in local tumor control and in cause-specific survival with excellent morbidity profiles. Current research efforts are aimed at the incorporation of high-quality imaging in the process of target volume delineation with the specific aim to minimize uncertainties and reduce exposure to normal tissues. The sharp dose gradients and the precise dose distributions associated with highly conformal treatment plans (e.g. IMRT, stereotactic radiotherapy), in fact, are less forgiving and therefore demand more accurate delineation of the target and the surrounding critical structures at planning. Indeed, target volume delineation is likely the largest source of uncertainty in the planning phase of IGRT.

The advent of high-speed helical scanners has led to the so-called CT simulation, which, by combining the simulation and CT-scan acquisition into one single session, minimizes systematic uncertainties and produces greater operational efficiency [29]. The 3D- data set of the patient in treatment position with appropriate immobilization devices in place, may be reconstructed through dedicated software to carry out the so-called *virtual simulation*, in which digitally reconstructed radiographs (DRR's) are generated for viewing, decision-making and documentation. All of these factors make CT simulation an integral ingredient of IGRT. However, the

limitations of CT imaging in the delineation of target and critical structures in many anatomical sites have become quite obvious. Concerns have been raised about the large inter- and intra -observer variability due to the uncertainties in tumor and critical organs extensions on CT images [30–34].

MRI provides improved soft tissue contrast, relative to CT, particularly for central nervous system structures, and within the abdominal and pelvic regions. MRI has, therefore, become a fundamental imaging modality for target and critical structure delineation for intracranial, head and neck, liver and pelvic tumors [35,36]. MRI by itself is not sufficient for treatment-planning purposes since it does not provide electronic densities required for dose calculations and may suffer from potential image distortion [37]. However, its inherent multi-planar capability and increased imaging functionality outweigh its drawbacks, and efficient MR distortion assessment and correction algorithms together with robust image co-registration software can overcome these limitations and permit optimal use of MRI for treatment-planning. Recently, new contrast media, such as super paramagnetic iron oxide nano-particles for abnormal lymph node identification have been developed, yielding an unprecedented diagnostic accuracy [38]. If these findings are confirmed in larger studies, this technique may turn out to be an invaluable tool in target volume delineation of involved lymph-node areas, especially in the pelvic region.

The vast potential of advanced MRI has recently led to the proposition of integrated machines coupling a high-field MRI system and a linear accelerator [39]. Indeed, this approach may usher a new era in IGRT in which advanced target localization and treatment are tightly integrated.

Recently, the advent of PET/CT devices with co-registered functional and anatomical data, has opened new exciting possibilities for target volume delineation [40]. PET/CT imaging is rapidly being embraced by the radiation oncology community as a tool to potentially improve target volume accuracy for treatment optimization [41]. A significant impact of PET-derived contours has been observed with respect to the CT-only in studies mostly dealing with lung cancer and cancer of the head and neck [41–44].

Several studies have dealt with the feasibility of incorporating FDG-PET information into contour delineation with the aim to reduce inter-observer variability, a well-known concern in radiotherapy treatment-planning. Although still present, following target delineation with PET/CT, inter-observer variability is somehow reduced compared to conventional CT-only contouring [45,46].

PET/CT may provide improved therapeutic ratios compared to conventional CT planning. Increased target coverage and often reduced target volumes, in fact, may potentially result in PET/CT-based planning to yield better tumor control probability through dose escalation, while still complying with dose/volume constrains for normal tissues [47,48]. Although a PET-based reduction in GTV might theoretically enable more normal tissue sparing, it may also confer an undue risk of marginal miss. This approach, therefore, should be used with caution until more evidence is gathered from studies comparing PET findings with the "gold standard" histopathological assessment [49].

Despite the widespread excitement in the incorporation of PET/CT data in treatment-planning, the optimal method to accurately determine the volume and shape of the GTV using PET information still remains an unresolved issue [50–52]. Recently, studies comparing different segmentation techniques have appeared in the literature [45,53–56]. A general consensus, however, is still lacking. Notwithstanding, in the not-so-far future, tissue contouring for treatment-planning will likely become more automatic with minimal interventions from physicians, thus effectively minimizing inter-observer variability. A potential problem exists when the contours determined from different imaging modalities conflict. Computer-aided diagnosis (CAD) intelligent rules to decide which contour should be used will be required. These CAD strategies will, of course, have to rely on histopathological correlations with imaging findings [49].

Target motion due to respiration is a major concern for tumors situated in the thoracic and abdominal regions. Traditionally, a margin commensurate to the amplitude of motion is added around the CTV to account for target misplacement during delivery. The recent development of ultra-fast multislice CT has opened a new dimension in radiotherapy and allows time-resolved (4D) CT imaging of the patient breathing cycle [57]. Recently, the feasibility of 4D-PET/CT acquisition has also been shown [58]. The 4D approach obviously allows a significant tightening of the margin required, thereby reducing non-target dose and the risk of radiation-induced toxicity. Reproducibility issues at treatment delivery, however, still need to be resolved for this technique to become routine clinical implementation [59,60].

Determining biological attributes

Many biological factors govern the response of tumors and normal tissues to radiation. In the past, attempts to decipher the biological connotations of

the tumor and the use of predictive assays to forecast the probability of successful radiation treatment were largely unsuccessful. More recently, the dawn of biological imaging has ushered in the promise that non-invasive modalities such as nuclear medicine and magnetic resonance imaging can provide biological information [61].

At present, there is much interest in tumor hypoxia in the management of cancer. Hypoxia is a well-known determinant of treatment outcome because hypoxic cells are significantly more resistant than aerobic cells to ionizing radiation [20,62]. Non-invasive PET-imaging of tumor hypoxia is a promising approach. Hypoxia-specific radiotracers have been evaluated in preclinical trials at MSKCC (^{64}Cu –ATSM, ^{18}F-FMISO and ^{124}I-IAZGP) [63–68]. Recently, a clinical evaluation of PET imaging with ^{18}F-FMISO has been performed in patients with head and neck cancer to explore the feasibility of dose-painting hypoxic regions with IMRT [69]. The dose to the hypoxic region could be escalated by approximately 20% to a prescription dose of 84 Gy, while keeping the organs at risk at the same tolerance levels. For these hypoxic regions to be targeted appropriately by dose-painting during fractionated radiotherapy, geographic consistency over time is crucial. Evaluation of whether the pre-treatment hypoxia images were invariant over time was performed obtaining two additional PET scans separated by 3 days [70]. Significant changes in the hypoxic regions of the target were observed in a subset of patients compromising the coverage of hypoxic tumor volumes achievable by dose-painting IMRT [71].

Angiogenesis a well-known determinant of tumor growth and has recently become a key therapeutic target through anti-angiogenetic agents. The feasibility of measuring vessel-related parameters such as perfusion and microvessel density is currently being explored through MRI [72].

There is potential in applying non-invasive imaging to guide targeted therapy such as the use of anti-EGFR agents. Her2/neu antibodies and small-molecule inhibitors labeled for PET imaging have recently been developed with the aim of identifying tumors potentially responsive to EGFR-target therapies [73].

Dose distribution design

The introduction of IMRT represented a significant advance in improving the conformal dose distribution relative to the target and surrounding normal tissues. Early on following the introduction of IMRT, the optimal number of beams required and preferred beam angles were subject of intense scientific debate. In general, it was found that 5-9 beams were sufficient to produce highly conformal distributions, and that further increase in the number of beams led to diminishing returns [74].

Radiation delivery with beams from 360°, as in intensity-modulated arc therapy (IMAT) and tomotherapy, while not necessarily producing clinically superior dose distribution, obviates the need to specify the number and directions of beams [75].

IMRT has opened the doors to the concept of dose-painting, i.e. depositing dose non-uniformly within the target to improve clinical outcome. One possible application is to increase dose to hypoxic regions as described previously [76].

Recently the concept of theragnostic imaging for radiation oncology has been put forward [77]. According to this principle, advanced imaging modalities allow micro-environmental variations or cellular phenotypes that modulate the effect of radiation to be mapped in three dimensions. Dose-painting by numbers is a strategy by which the dose distribution delivered by inverse planned intensity-modulated radiotherapy is prescribed in four dimensions based on the outcomes of the imaging studies. For instance, painting by numbers based on the intensity of uptake in FDG-PET images has been proposed [78]. It must be emphasized, however, that these are hypothetical proposals that require clinical studies for validation.

Dose delivery assurance

An ideal image guidance system for radiation treatment delivery should have three essential elements: 1) 3D volumetrics of soft tissues including tumors, 2) efficient acquisition and comparison of the 3D volumetrics, and, 3) an efficacious process for clinically meaningful intervention [1]. Many of the commercially available devices fall short of these ideals. However, in the absence of an ideal system, a sub-set of the features may suffice for specific disease sites and clinical applications. 2D MV imaging combined with a well-thought-out correction protocol may be sufficient for brain and H&N where bony landmarks can reliably determine the target position and critical organ locations. In disease sites where the target moves relative to the bony landmarks (e.g. prostate), implanted radio-opaque markers (e.g. gold seeds) provide surrogates of the target position for 2D imaging. However, bony anatomy and radio-opaque markers provide primarily surrogates of the center of the target position with less emphasis on normal tissue or changes in tumor conformation.

Assuming an ideal image guidance system such that 3D images of tumor/soft tissues can be acquired efficiently and daily comparison between the 3D

images and the reference 3D volumetrics can be performed quickly prior to treatment, then both systematic and random errors would be corrected on a daily basis. Then, a margin around the target would be unnecessary, except in disease site with intra-fraction uncertainties. The complexity of IGRT-D is compounded at sites that experience motion—most commonly due to respiration [79]. Yet, respiratory control and IGRT-D are distinct processes and one does not imply the other. Eventually, the tools of IGRT-D may provide approaches to better monitor and/or facilitate respiration controlled treatment.

If image guidance during radiation delivery allows for the reduction of unnecessary dose to normal tissues, dose escalation and improved local control may ensue. Viewed in this perspective, IGRT-D is a continuation of the progress begun with 3DCRT and IMRT, processes that permit increased tumor dose while keeping normal tissue toxicity at bay. As with 3DCRT and IMRT, clinical trials would be needed to validate this hypothesis. The above is predicated upon the absence of disease outside the delineated target volume. Advanced imaging techniques are needed to validate this assumption. If advanced imaging (e.g. MRI) and treatment were combined in a single unit, then pertinent biological and physiological information (e.g. tumor cell density and hypoxia) could be used for real-time feedback and control of dose distributions using IGRT-D [39].

Deciphering treatment response

Molecular imaging is rapidly emerging as a powerful tool in the interpretation of post-irradiation treatment response. For instance, comparison of pre-treatment and post-treatment FDG-PET uptake may be used as a predictor of therapeutic response. Significant decreases in standard uptake values (SUV) SUV post-irradiation have been associated with better outcomes in various disease sites [80–82]. However, radiation-induced metabolic changes affecting FDG uptake can also be non-specific and significant increases in SUV have been observed as a result of inflammation [83]. FDG uptake has been shown to be sensitive to the microenvironment and appears to be positively correlated with hypoxia and negatively correlated with proliferation and perfusion [63]. More encouraging data will likely emerge from novel tracers. Cellular proliferation may be measured with radiolabeled nucleosides, such as ^{18}F-fluorothymidine (FLT). In an experimental model, changes in FLT uptake post-irradiation have been shown to be more pronounced than FDG and correlate well with the proliferating cell nuclear antigen labeling index [84]. Therefore, FLT may turn out to be a useful imaging agent to monitor the early response to therapy in cancer patients.

MRI is an emerging tool to assess the effects of radiation. Studies using diffusion, perfusion and contrast uptake appear to be of great promise for quantitative evaluation of treatment effects and early prediction of outcome [85]. The apparent diffusion coefficient (ADC) measured by diffusion-weighted MRI can map the thermally induced motion of water molecules in tissues. This may provide valuable insights into tissue microstructure and enable an early assessment of response following locoregional therapy both on the tumor [86] and normal tissues [87].

The availability of reliable early surrogates of post-irradiation treatment response will likely open new avenues in the radiotherapeutic management of cancer with better disease-tailored approaches in which treatments may be modified *en-route* on the basis of the outcomes of predictive imaging studies.

Summary

Radiotherapy is an image-guided intervention and its evolution is ontogenetically linked to that of medical imaging. The commonly-adopted definition of IGRT, as the use of near real-time imaging for verifying treatment delivery, therefore, appears too narrow. A broader and more appropriate definition of image-guided radiotherapy should thus include many other key imaging steps involved in the process.

Imaging plays a pivotal role in the initial diagnostic and staging work-up of the disease. These steps are crucial for the appropriate treatment intent to be selected. The ultimate goal of IGRT is that radiation dose be delivered to an accurately-defined target volume exactly as planned. To this end, CT-based target delineation is known to be prone to considerable uncertainty. Therefore, metabolic imaging is actively being pursued with the aim to improve accuracy in target volume delineation and to minimize inter-observer variability. Biological imaging attempts to characterize the tumor in order to map regions of inherent radioresistance or of high clonogenic activity, where dose intensification (i.e. dose painting) may be in required to maximize tumor control. If unaccounted for, target motion may compromise the efficacy of exquisitely-defined treatment plans. Despite all efforts to accurately define the target and to immobilize the patient for enhanced set-up reproducibility, residual uncertainties in the position of the tumor and surrounding critical structures may persist. The sharp dose gradient of dose distributions associated with highly conformal

treatment plans demands for accurate target localization and guidance during treatment delivery. 3D volumetric tools for near real-time verification are now widely available and appropriate correction strategies are being developed. The availability of this new technology is paving the way for the safe implementation of high-dose single fraction or highly hypofractionated regimens, whose clinical benefits are rapidly emerging in various disease sites. Finally, imaging studies capable of predicting the ultimate outcome are actively being investigated and may eventually enable *en-route* correction of the treatment strategy. However, it must be borne in mind that IGRT, as defined above, is still in its infancy and many technical issues need to be resolved. In particular, robust tools for automatic target and normal tissue delineation, effectively removing what is likely the largest source of uncertainty in IGRT, are required.

Acknowledgements

This work is supported in part by PO1 CA59017 from the National Institutes of Health, USA.

References

[1] Ling CC, Yorke E, Fuks Z. From IMRT to IGRT: Frontierland or neverland? Radiother Oncol 2006;78:119–22.
[2] Armstrong K, Moye E, Williams S, Berlin JA, Reynolds EE. Screening mammography in women 40 to 49 years of age: A systematic review for the American College of Physicians. Ann Intern Med 2007;146:516–26.
[3] Miller A, Markowitz S, Manowitz A, Miller JA. Lung cancer screening using low-dose high-resolution CT scanning in a high-risk workforce: 3500 nuclear fuel workers in three US states. Chest 2004;125:152S–153S.
[4] Mazzone P, Obuchowski N, Mekhail T, Meziane M, Ahmad M. Lung cancer screening: Is it time for a change in policy? Cleve Clin J Med 2007;74:441–8.
[5] Torres C, Szomstein S, Wexner SD. Virtual colonoscopy in colorectal cancer screening. Surg Innov 2007;14:27–34.
[6] Olsen AH, Njor SH, Lynge E. Estimating the benefits of mammography screening: The impact of study design. Epidemiology 2007;18:487–92.
[7] Baxter NN, Garcia-Aguilar J. Organ preservation for rectal cancer. J Clin Oncol 2007;25:1014–20.
[8] Mehta PS, Harrison LB. Function and organ preservation in adult cancers of the head and neck. Expert Rev Anticancer Ther 2007;7:361–71.
[9] Rodel C, Weiss C, Sauer R. Trimodality treatment and selective organ preservation for bladder cancer. J Clin Oncol 2006;24:5536–44.
[10] Veronesi U, Zurrida S. Breast conservation: Current results and future perspectives at the European Institute of Oncology. Int J Cancer 2007;120:1381–6.
[11] Schaefer JF, Schlemmer HP. Total-body MR-imaging in oncology. Eur Radiol 2006;16:2000–15.
[12] Schmidt GP, Baur-Melnyk A, Herzog P, Schmid R, Tiling R, Schmidt M, et al. High-resolution whole-body magnetic resonance image tumor staging with the use of parallel imaging versus dual-modality positron emission tomography-computed tomography: Experience on a 32-channel system. Invest Radiol 2005;40:743–53.
[13] Shiau MC, Bonavita J, Naidich DP. Adenocarcinoma of the lung: Current concepts in radiologic diagnosis and management. Curr Opin Pulm Med 2007;13:261–6.
[14] Wood KA, Hoskin PJ, Saunders MI. Positron emission tomography in oncology: A review. Clin Oncol (R Coll Radiol) 2007;19:237–55.
[15] Weber WA. Use of PET for monitoring cancer therapy and for predicting outcome. J Nucl Med 2005;46:983–95.
[16] Mankoff DA, Shields AF, Krohn KA. PET imaging of cellular proliferation. Radiol Clin North Am 2005;43:153–67.
[17] Artemov D, Mori N, Ravi R, Bhujwalla ZM. Magnetic resonance molecular imaging of the HER-2/neu receptor. Cancer Res 2003;63:2723–7.
[18] Artemov D, Bhujwalla ZM, Bulte JW. Magnetic resonance imaging of cell surface receptors using targeted contrast agents. Curr Pharm Biotechnol 2004;5:485–94.
[19] Collingridge DR, Glaser M, Osman S, Barthel H, Hutchinson OC, Luthra SK, et al. In vitro selectivity, in vivo biodistribution and tumour uptake of annexin V radiolabelled with a positron emitting radioisotope. Br J Cancer 2003;89:1327–33.
[20] Chapman JD. Measurement of tumor hypoxia by invasive and non-invasive procedures: A review of recent clinical studies. Radiother Oncol 1991;20(Suppl 1):13–9.
[21] Haubner R. Alphavbeta3-integrin imaging: A new approach to characterise angiogenesis? Eur J Nucl Med Mol Imaging 2006;33(Suppl 1):54–63.
[22] Schoder H, Yeung HW, Larson SM. CT in PET/CT: Essential features of interpretation. J Nucl Med 2005;46: 1249–51.
[23] Branstetter BF, Blodgett TM, Zimmer LA, Snyderman CH, Johnson JT, Raman S, et al. Head and neck malignancy: Is PET/CT more accurate than PET or CT alone? Radiology 2005;235:580–6.
[24] Lardinois D, Weder W, Hany TF, Kamel EM, Korom S, Seifert B, et al. Staging of non-small-cell lung cancer with integrated positron-emission tomography and computed tomography. N Engl J Med 2003;348:2500–7.
[25] Mah K, Caldwell CB, Ung YC, Danjoux CE, Balogh JM, Ganguli SN, et al. The impact of (18)FDG-PET on target and critical organs in CT-based treatment planning of patients with poorly defined non-small-cell lung carcinoma: A prospective study. Int J Radiat Oncol Biol Phys 2002;52: 339–50.
[26] Scattoni V, Picchio M, Suardi N, Messa C, Freschi M, Roscigno M, et al. Detection of lymph-node metastases with integrated [(11)C]choline PET/CT in patients with PSA failure after radical retropubic prostatectomy: Results confirmed by open pelvic-retroperitoneal lymphadenectomy. Eur Urol 2007.
[27] Greco C, Cascini GL, Tamburrini O. Is there a role for positron emission tomography imaging in the early evaluation of prostate cancer relapse? Prostate Cancer Prostatic Dis 2008.
[28] Shukla-Dave A, Hricak H, Kattan MW, Pucar D, Kuroiwa K, Chen HN, et al. The utility of magnetic resonance imaging and spectroscopy for predicting insignificant prostate cancer: An initial analysis. BJU Int 2007;99:786–93.
[29] Sherouse GW, Bourland JD, Reynolds K, McMurry HL, Mitchell TP, Chaney EL. Virtual simulation in the clinical setting: Some practical considerations. Int J Radiat Oncol Biol Phys 1990;19:1059–65.
[30] Fiorino C, Reni M, Bolognesi A, Cattaneo GM, Calandrino R. Intra- and inter-observer variability in contouring prostate

and seminal vesicles: Implications for conformal treatment planning. Radiother Oncol 1998;47:285–92.
[31] Foppiano F, Fiorino C, Frezza G, Greco C, Valdagni R. The impact of contouring uncertainty on rectal 3D dose-volume data: Results of a dummy run in a multicenter trial (AIROPROS01-02). Int J Radiat Oncol Biol Phys 2003;57:573–9.
[32] Geets X, Daisne JF, Arcangeli S, Coche E, De PM, Duprez T, et al. Inter-observer variability in the delineation of pharyngo-laryngeal tumor, parotid glands and cervical spinal cord: Comparison between CT-scan and MRI. Radiother Oncol 2005;77:25–31.
[33] Van de SJ, Linthout N, de MJ, Vinh-Hung V, Claassens C, Noppen M, et al. Definition of gross tumor volume in lung cancer: Inter-observer variability. Radiother Oncol 2002;62:37–49.
[34] Senan S, Chapet O, Lagerwaard FJ, Ten Haken RK. Defining target volumes for non-small cell lung carcinoma. Semin Radiat Oncol 2004;14:308–14.
[35] 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 intraprostatic fiducial markers for computed tomography coregistration. Radiother Oncol 2003;66:217–24.
[36] Voroney JP, Brock KK, Eccles C, Haider M, Dawson LA. Prospective comparison of computed tomography and magnetic resonance imaging for liver cancer delineation using deformable image registration. Int J Radiat Oncol Biol Phys 2006;66:780–91.
[37] Khoo VS, Joon DL. New developments in MRI for target volume delineation in radiotherapy. Br J Radiol 2006;79(Spec No 1):S2–S15.
[38] Harisinghani MG, Barentsz J, Hahn PF, Deserno WM, Tabatabaei S, van de Kaa CH, et al. Noninvasive detection of clinically occult lymph-node metastases in prostate cancer. N Engl J Med 2003;348:2491–9.
[39] Raaijmakers AJ, Hardemark B, Raaymakers BW, Raaijmakers CP, Lagendijk JJ. Dose optimization for the MRI-accelerator: IMRT in the presence of a magnetic field. Phys Med Biol 2007;52:7045–54.
[40] Gregoire V, Haustermans K, Geets X, Roels S, Lonneux M. PET-based treatment planning in radiotherapy: A new standard? J Nucl Med 2007;48(Suppl 1):68S–77S.
[41] Greco C, Rosenzweig K, Cascini GL, Tamburrini O. Current status of PET/CT for tumour volume definition in radiotherapy treatment planning for non-small cell lung cancer (NSCLC). Lung Cancer 2007.
[42] van Baardwijk A., Baumert BG, Bosmans G, van KM, Stroobants S, Gregoire V, et al. The current status of FDG-PET in tumour volume definition in radiotherapy treatment planning. Cancer Treat Rev 2006;32:245–60.
[43] Ashamalla H, Guirgius A, Bieniek E, Rafla S, Evola A, Goswami G, et al. The impact of positron emission tomography/computed tomography in edge delineation of gross tumor volume for head and neck cancers. Int J Radiat Oncol Biol Phys 2007.
[44] van BA, Baumert BG, Bosmans G, van KM, Stroobants S, Gregoire V, et al. The current status of FDG-PET in tumour volume definition in radiotherapy treatment planning. Cancer Treat Rev 2006;32:245–60.
[45] Ashamalla H, Rafla S, Parikh K, Mokhtar B, Goswami G, Kambam S, et al. The contribution of integrated PET/CT to the evolving definition of treatment volumes in radiation treatment planning in lung cancer. Int J Radiat Oncol Biol Phys 2005;63:1016–23.
[46] Fox JL, Rengan R, O'Meara W, Yorke E, Erdi Y, Nehmeh S, et al. Does registration of PET and planning CT images decrease interobserver and intraobserver variation in delineating tumor volumes for non-small-cell lung cancer? Int J Radiat Oncol Biol Phys 2005;62:70–5.
[47] Madani I, Duthoy W, Derie C, De GW, Boterberg T, Saerens M, et al. Positron emission tomography-guided, focal-dose escalation using intensity-modulated radiotherapy for head and neck cancer. Int J Radiat Oncol Biol Phys 2007;68:126–35.
[48] Paulino AC, Koshy M, Howell R, Schuster D, Davis LW. Comparison of CT- and FDG-PET-defined gross tumor volume in intensity-modulated radiotherapy for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2005;61:1385–92.
[49] Daisne JF, Duprez T, Weynand B, Lonneux M, Hamoir M, Reychler H, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: Comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. Radiology 2004;233:93–100.
[50] Paulino AC, Johnstone PA. FDG-PET in radiotherapy treatment planning: Pandora's box? Int J Radiat Oncol Biol Phys 2004;59:4–5.
[51] Gregoire V. Is there any future in radiotherapy planning without the use of PET: Unraveling the myth. Radiother Oncol 2004;73:261–3.
[52] Gregoire V, Haustermans K, Geets X, Roels S, Lonneux M. PET-based treatment planning in radiotherapy: A new standard? J Nucl Med 2007;48(Suppl 1):68S–77S.
[53] Biehl KJ, Kong FM, Dehdashti F, Jin JY, Mutic S, El N, I, et al. 18F–FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: Is a single standardized uptake value threshold approach appropriate? J Nucl Med 2006;47:1808–12.
[54] Black QC, Grills IS, Kestin LL, Wong CY, Wong JW, Martinez AA, et al. Defining a radiotherapy target with positron emission tomography. Int J Radiat Oncol Biol Phys 2004;60:1272–82.
[55] Davis JB, Reiner B, Huser M, Burger C, Szekely G, Ciernik IF. Assessment of 18F PET signals for automatic target volume definition in radiotherapy treatment planning. Radiother Oncol 2006;80:43–50.
[56] Nestle U, Kremp S, Schaefer-Schuler A, Sebastian-Welsch C, Hellwig D, Rube C, et al. Comparison of different methods for delineation of 18F-FDG PET-positive tissue for target volume definition in radiotherapy of patients with non-Small cell lung cancer. J Nucl Med 2005;46:1342–8.
[57] Low DA, Nystrom M, Kalinin E, Parikh P, Dempsey JF, Bradley JD, et al. A method for the reconstruction of four-dimensional synchronized CT scans acquired during free breathing. Med Phys 2003;30:1254–63.
[58] Nehmeh SA, Erdi YE, Pan T, Yorke E, Mageras GS, Rosenzweig KE, et al. Quantitation of respiratory motion during 4D-PET/CT acquisition. Med Phys 2004;31:1333–8.
[59] Ford EC, Mageras GS, Yorke E, Ling CC. Respiration-correlated spiral CT: A method of measuring respiratory-induced anatomic motion for radiation treatment planning. Med Phys 2003;30:88–97.
[60] Yorke E, Rosenzweig KE, Wagman R, Mageras GS. Interfractional anatomic variation in patients treated with respiration-gated radiotherapy. J Appl Clin Med Phys 2005;6:19–32.
[61] Ling CC, Humm J, Larson S, Amols H, Fuks Z, Leibel S, et al. Towards multidimensional radiotherapy (MD-CRT): Biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000;47:551–60.
[62] Hockel M, Schlenger K, Aral B, Mitze M, Schaffer U, Vaupel P. Association between tumor hypoxia and malignant progression in advanced cancer of the uterine cervix. Cancer Res 1996;56:4509–15.

[63] Pugachev A, Ruan S, Carlin S, Larson SM, Campa J, Ling CC, et al. Dependence of FDG uptake on tumor microenvironment. Int J Radiat Oncol Biol Phys 2005;62:545–53.

[64] Wen B, Burgman P, Zanzonico P, O'donoghue J, Cai S, Finn R, et al. A preclinical model for noninvasive imaging of hypoxia-induced gene expression; comparison with an exogenous marker of tumor hypoxia. Eur J Nucl Med Mol Imaging 2004;31:1530–8.

[65] Zanzonico P, Cai S. Comparative microPET tumor imaging of F18-labeled fluoro-deoxyglucose (FDG) and fluoro-misonidazole (FMiso) using animal-specific positioning molds. J Nucl Med 2003;44(Suppl):116.

[66] Zanzonico P, O'Donoghue J, Chapman JD, Schneider R, Cai S, Larson S, et al. Iodine-124-labeled iodo-azomycin-galactoside imaging of tumor hypoxia in mice with serial microPET scanning. Eur J Nucl Med Mol Imaging 2004;31:117–28.

[67] Zanzonico P, Campa J, Polycarpe-Holman D, Forster G, Finn R, Larson S, et al. Animal-specific positioning molds for registration of repeat imaging studies: comparative microPET imaging of F18-labeled fluoro-deoxyglucose and fluoro-misonidazole in rodent tumors. Nucl Med Biol 2006;33:65–70.

[68] O'Donoghue JA, Zanzonico P, Pugachev A, Wen B, Smith-Jones P, Cai S, et al. Assessment of regional tumor hypoxia using 18F-fluoromisonidazole and 64Cu(II)-diacetyl-bis(N4-methylthiosemicarbazone) positron emission tomography: Comparative study featuring microPET imaging, Po2 probe measurement, autoradiography, and fluorescent microscopy in the R3327-AT and FaDu rat tumor models. Int J Radiat Oncol Biol Phys 2005;61:1493–502.

[69] Lee NY, Mechalakos JG, Nehmeh S, Lin Z, Squire OD, Cai S, et al. Fluorine-18-labeled fluoromisonidazole positron emission and computed tomography-guided intensity-modulated radiotherapy for head and neck cancer: A feasibility study. Int J Radiat Oncol Biol Phys 2008;70:2–13.

[70] Nehmeh SA, Lee NY, Schroder H, Squire O, Zanzonico PB, Erdi YE, et al. Reproducibility of intratumor distribution of (18)F-fluoromisonidazole in head and neck cancer. Int J Radiat Oncol Biol Phys 2008;70:235–42.

[71] Lin Z, Mechalakos J, Nehmeh S, Schoder H, Lee N, Humm J, et al. The influence of changes in tumor hypoxia on dose-painting treatment plans based on (18)F-FMISO positron emission tomography. Int J Radiat Oncol Biol Phys 2008;70:1219–28.

[72] Leach MO, Brindle KM, Evelhoch JL, Griffiths JR, Horsman MR, Jackson A, et al. The assessment of antiangiogenic and antivascular therapies in early-stage clinical trials using magnetic resonance imaging: Issues and recommendations. Br J Cancer 2005;92:1599–610.

[73] Pal A, Glekas A, Doubrovin M, Balatoni J, Namavari M, Beresten T, et al. Molecular imaging of EGFR kinase activity in tumors with 124I-labeled small molecular tracer and positron emission tomography. Mol Imaging Biol 2006;8:262–77.

[74] Stein J, Mohan R, Wang XH, Bortfeld T, Wu Q, Preiser K, et al. Number and orientations of beams in intensity-modulated radiation treatments. Med Phys 1997;24:149–60.

[75] Cao D, Holmes TW, Afghan MK, Shepard DM. Comparison of plan quality provided by intensity-modulated arc therapy and helical tomotherapy. Int J Radiat Oncol Biol Phys 2007;69:240–50.

[76] Popple RA, Ove R, Shen S. Tumor control probability for selective boosting of hypoxic subvolumes, including the effect of reoxygenation. Int J Radiat Oncol Biol Phys 2002;54.921–7.

[77] Bentzen SM. Dose painting and theragnostic imaging: Towards the prescription, planning and delivery of biologically targeted dose distributions in external beam radiation oncology. Cancer Treat Res 2008;139:41–62.

[78] Vanderstraeten B, Duthoy W, De GW, De NW, Thierens H. [18F]fluoro-deoxy-glucose positron emission tomography ([18F]FDG-PET) voxel intensity-based intensity-modulated radiation therapy (IMRT) for head and neck cancer. Radiother Oncol 2006;79:249–58.

[79] Chang J, Mageras GS, Yorke E, De AF, Sillanpaa J, Rosenzweig KE, et al. Observation of interfractional variations in lung tumor position using respiratory gated and ungated megavoltage cone-beam computed tomography. Int J Radiat Oncol Biol Phys 2007;67:1548–58.

[80] Allal AS, Slosman DO, Kebdani T, Allaoua M, Lehmann W, Dulguerov P. Prediction of outcome in head-and-neck cancer patients using the standardized uptake value of 2-[18F]fluoro-2-deoxy-D-glucose. Int J Radiat Oncol Biol Phys 2004;59:1295–300.

[81] Erdi YE, Macapinlac H, Rosenzweig KE, Humm JL, Larson SM, Erdi AK, et al. Use of PET to monitor the response of lung cancer to radiation treatment. Eur J Nucl Med 2000;27:861–6.

[82] Mac Manus MP, Hicks RJ, Matthews JP, McKenzie A, Rischin D, Salminen EK, et al. Positron emission tomography is superior to computed tomography scanning for response-assessment after radical radiotherapy or chemoradiotherapy in patients with non-small-cell lung cancer. J Clin Oncol 2003;21:1285–92.

[83] Arslan N, Miller TR, Dehdashti F, Battafarano RJ, Siegel BA. Evaluation of response to neoadjuvant therapy by quantitative 2-deoxy-2-[18F]fluoro-D-glucose with positron emission tomography in patients with esophageal cancer. Mol Imaging Biol 2002;4:301–10.

[84] Sugiyama M, Sakahara H, Sato K, Harada N, Fukumoto D, Kakiuchi T, et al. Evaluation of 3'-deoxy-3'-18F-fluorothymidine for monitoring tumor response to radiotherapy and photodynamic therapy in mice. J Nucl Med 2004;45:1754–8.

[85] Chenevert TL, Meyer CR, Moffat BA, Rehemtulla A, Mukherji SK, Gebarski SS, et al. Diffusion MRI: A new strategy for assessment of cancer therapeutic efficacy. Mol Imaging 2002;1:336–43.

[86] Mardor Y, Pfeffer R, Spiegelmann R, Roth Y, Maier SE, Nissim O, et al. Early detection of response to radiation therapy in patients with brain malignancies using conventional and high b-value diffusion-weighted magnetic resonance imaging. J Clin Oncol 2003;21:1094–100.

[87] Dirix P, De KF, Vandecaveye V, Stroobants S, Hermans R, Nuyts S. Diffusion-weighted magnetic resonance imaging to evaluate major salivary gland function before and after radiotherapy. Int J Radiat Oncol Biol Phys 2008.