Imaging-based treatment adaptation in radiation oncology

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Abstract
In many tumor types a significant effort is put in patient-tailored adaptation of treatment to improve patient outcome and preferably reducing toxicity. These opportunities arose with the introduction of modern irradiation techniques (e.g., intensity modulated radiotherapy) combined with (functional) imaging for more precise target volume delineation. Based on functional CT, MRI and PET imaging, radiation target volumes are altered during the course of treatment or subvolumes inside the primary tumor are being defined for dose enhancement strategies. Moreover, normal tissue complication probability is being predicted using anatomical or functional imaging, e.g., CT or PET predicting radiation pneumonitis. Besides focusing, monitoring and adapting photon therapy for solid tumors, the role of PET for proton beam therapy verification is being highlighted. Finally, remaining challenges are discussed throughout the manuscript.
Introduction

The arsenal of modern oncological treatments includes surgery, high-precision radiotherapy, chemotherapy, targeted agents, immunotherapy, and combinations of these. Advanced imaging is a prerequisite for optimal patient management. In radiation oncology, positron emission tomography (PET) and magnetic resonance imaging (MRI) have become imaging modalities that play an increasing role in non-invasive characterization of the individual patient’s tumor prior to and during radiotherapy to facilitate treatment adaptation. Persisting tumor activity or early relapse after treatment places an unwanted burden to the patient due to exposure to ineffective but still toxic treatment. A switch to more effective treatment is at best postponed, but may be hampered or even prevented by previous treatment. Additionally, prolonged ineffective treatment is an increasing burden to the healthcare system in view of the high financial costs associated with modern therapies.

Rather than evaluating tumor response after administration of a substantial part or even completion of the treatment course, there is a shift towards (very) early assessment and prediction of (non)response and subsequent adaptation of treatment: [i] radiation dose-escalation or de-escalation to the biological subvolumes of voxels, [ii] addition, change or omission of concurrent chemotherapy enhancing the radiation effect but also increasing side-effects, or [iii] the tailored selection of targeted therapies, such as monoclonal antibodies and tyrosine kinase inhibitors (TKIs).

Furthermore, PET provides valuable information on tumor-surrounding normal tissues that can be spared with modern radiation treatment techniques, enables the selection of patients benefiting from systemic radiotherapy in the form of radiolabeled agents for local dose-enhancement, and it may guide combined photon and proton irradiation techniques. Finally, advanced image analysis techniques (Radiomics) and combination of PET with functional anatomical imaging modalities such as dynamic contrast enhanced or dual-energy computed tomography (DCE-CT of DE-CT) or diffusion-weighted magnetic resonance imaging (DWI-MRI) will irreversibly change assessment of tumors from mere measurement of size to multimodality delineation and characterization.
**Functional and molecular imaging modalities currently available**

18F-fluorodeoxyglucose (FDG) is the most widely used radiopharmaceutical for PET, depicting tumor metabolism. As numerous studies have shown the potential of FDG-PET for staging, target volume delineation, response assessment and relapse detection with impact on management of patients with a wide variety of cancer diagnoses, it has become the cornerstone of biological imaging in oncology(1,2). Although increased metabolism due to the Warburg effect and the changes therein provides an important reflection of tumor aggressiveness, more specific tracers to depict distinct tumor characteristics have been developed. For several decades it has been known that one of the major biological factors driving radiation resistance is tumor cell hypoxia. Hypoxia can be non-invasively visualized by means of PET imaging using dedicated tracers such as 18F-fluoromisonidazole (FMISO), 18F-fluoroazomycin arabinoside (FAZA) or 18F-HX4(3-7). Tumor cell proliferation can be depicted by the thymidine analogue 18F-Fluorothymidine (FLT) that has been validated against histopathological specimens in a broad variety of solid tumors and lymphomas [e.g.,(8-10)]. Apart from tracers depicting biometabolic tumor characteristics, e.g., angiogenesis and apoptosis, radiotracers assessing tumor receptor expression, e.g., human epithelial growth factor receptor-2 (HER2), and the epidermal growth factor receptor (EGFR), are increasingly being applied(11-14).

Besides novel radiopharmaceuticals, developments in hardware have revolutionized medical imaging. The introduction of combined PET/CT instead of stand-alone scanners has enhanced the potential and the impact of PET, and was responsible for increasing application of molecular imaging in radiotherapy practice(15). More recently, integrated PET/MRI has further advanced the impact of multimodality imaging. With functional techniques for both CT (e.g., DCE-CT and DE-CT) and MRI (e.g., dynamic contrast-enhanced; DCE-MRI, and DW-MRI) being in place, the simultaneous acquisition is likely to enhance adaptive treatment techniques.

**The use of (functional) MRI and CT in radiotherapy**

For its superior soft tissue resolution, conventional MRI is of pivotal importance for detection, local staging, and delineation of many cancer types (e.g., tumors in the pelvic area, head and neck, brain and sarcoma). When incorporating MRI in radiation treatment planning, dedicated image acquisition techniques and other technical issues may be necessary. Especially, geometric distortions can be significant (>10 mm) and thus need to be identified and addressed in the era of high-precision radiotherapy. With MRI systems being integrated with linear accelerators (MR Linac), real-time imaging
of tumor locations during the actual treatment delivery has been realized, facilitating precise delivery of dose to target while sparing surrounding normal tissues(16). Expanding the use of MR Linac for continuous adaption of radiotherapy, especially in tumors subjected to internal motion, e.g., breathing, seems straightforward.

For brachytherapy in cervical cancer, it is well-established that complete remission rates are favorable for MRI-guided brachytherapy as compared to conventional brachytherapy, resulting in high complete remission rates and a low frequency of local recurrence(17). As described by Kharofa et al.(18) the use of MRI during treatment in these patients will facilitate treatment adaptation, optimizing the coverage of the target volume while minimizing dose to organs at risk. DWI-MRI holds great promise for adaptive radiotherapy for it relies on the restriction of the diffusion of water molecules in areas of high cellularity. This restriction of diffusion is expressed as the Apparent Diffusion Coefficient (ADC). While already part of clinical practice in the diagnostic work-up of many tumor types with MRI, the role for DWI in adaptive radiotherapy is currently the subject of clinical studies. In an early study by Kim et al.(19), treatment induced changes in ADC were predictive for response to chemoradiotherapy in patients with squamous cell carcinoma of the head and neck (HNSCC) as early as one week after the start of therapy. In another study on HNSCC it was shown that patients with lower ADC values of the tumor after 4 weeks of radiotherapy had a higher risk for local-regional recurrence(20). Schmid et al.(21) reported MRI-morphologic features to predict for tumor response after chemoradiotherapy in 85 cervical cancer patients.

Besides static imaging, with or without contrast-enhancement, MRI offers a number of non-invasive functional features. Dynamic contrast enhanced MRI depicts perfusion and vascular permeability. By applying the appropriate pharmacokinetic models, it provides semiquantitative data on fluid transfer between the blood stream and the extravascular extracellular space. Blood oxygen level dependent (BOLD) MRI provides information on the ratio between oxygenated and deoxygenated hemoglobin in the blood(22). As deoxygenated hemoglobin is paramagnetic and oxygenated hemoglobin is not, BOLD imaging can provide information about the hypoxic status of tumors. Furthermore, it is feasible to measure the oxygenation status of tumors and tissues with MRI-based techniques, using oxygen dependent T1 relaxation times. An additional option is magnetic resonance spectroscopy (MRS) to study metabolic changes in tumors, assessing the relative concentrations of cancer cell metabolites. In a very promising French study, MRS obtained before radiotherapy allowed stratification of patients with glioblastoma multiforme according to therapy outcome(23). Combining all
data provided by functional MRI into a multiparametric data set provides an extensive characterization of tumors, e.g., in prostate cancer(24).

DCE-CT is slowly finding its way into clinical studies assessing tumor perfusion and treatment response. In a pilot study in 15 rectal cancer patients treated with chemoradiotherapy, Sahani et al.(25) found tissue blood flow (BF) to decrease and mean transit time (MTT) to increase after treatment. Baseline BF and MTT separated responders from non-responders. Similar results were reported in patients with colorectal cancer and hepatocellular carcinoma when monitoring response to treatment blocking the vascular endothelial growth factor, such as bevacizumab or sorafenib(26,27). Sauter et al.(28) extensively correlated DCE-CT [i.e., BF, blood volume, volume transfer coefficient (Ktrans), and standardized perfusion value] with 18F-FLT PET parameters [maximum and mean standardized uptake value (SUV) and metabolic tumor volume] and immunohistochemical analysis (Ki67, microvessel density) in 24 NSCLC patients. They reported 18F-FLT PET measures to correlate with Ki67, whereas microvessel density correlated with blood flow and volume, as well as with Ktrans. Just recently, Tixier et al.(29) found a significant correlation between intra-tumoral heterogeneity of 18F-FDG PET and tumor blood flow as detected by DCE-CT in advanced stage colorectal cancer. Dual-energy CT imaging, i.e., simultaneously acquisition of two CT scans with different kiloVoltage, will most certainly provide new possibilities for improve the accuracy of target volume delineation, and tumor and normal tissue characterization (Figure 1).

**PET for radiation treatment plan adaptation and normal tissue characterization**

In recent years, several studies and meta-analyses have shown that modern molecular and functional imaging with PET and (f-)MRI allows for imaging of prognostic parameters with respect to RT outcome(4,30).

Some studies have recently investigated imaging strategies to assess the response to therapy at a very early time point during (chemo)radiotherapy. Van Elmpt et al.(31) assessed 18F-FDG PET uptake patterns before and two weeks into (chemo)radiotherapy in 34 advanced stage NSCLC patients and reported a high decrease of the 18F-FDG-PET signal between both PET-scans to predict for a higher overall survival. In a similar Dutch study, Usmanij et al.(32) showed that a decrease in total lesion
glycolysis of more than 38% during the first two weeks of (chemo)radiotherapy was associated with a significantly longer progression free survival.

Several recent studies have shown the prognostic value of hypoxia PET imaging with respect to radiotherapy outcome for a variety of solid tumors (33-36). A study published by Zips et al. (36) underlined the prognostic value of 18F-FMISO PET imaging obtained before and after two weeks of (chemo)radiotherapy in 25 HNSCC patients, whereas baseline 18F-FMISO PET did not correlate with treatment outcome, providing a basis for the integration of hypoxia-PET into radiotherapy planning for hypoxia-directed dose escalation strategies. A Danish study even found 18F-FAZA PET imaging to stratify patients into groups according to loco-regional control (34). In a small study cohort, Dirix et al. (20) investigated different functional imaging modalities (18F-FDG and 18F-FMISO PET, T1-, T2-, DWI- and DCE-MRI) at various time points before and during primary radiotherapy in 15 HNSCC patients. In addition to a prognostic value of hypoxia PET, the authors reported that tumors developing a locoregional recurrence during follow-up had significantly lower ADC values on DWI-MRI during and after radiotherapy, and presented with significant differences in DCE-MRI compared to lesions that remained controlled. Molecular imaging of prognostic parameters and biological properties are essential prerequisites for an individual adaptation of treatment.

Troost et al. (10) found the SUV of the proliferation tracer 18F-FLT to precede volumetric changes on CT when repeatedly imaging ten oropharyngeal cancer patients. Subsequently, Hoeben et al. (37) assessed a larger cohort of 48 advanced stage HNSCC patients and reported a large decrease of the 18F-FLT PET signal in the first two or four weeks, respectively, to be associated with a better 3-year disease free survival (Figure 2). Preliminary findings on 18F-FLT PET in HNSCC patients receiving radiotherapy combined with the monoclonal anti-EGFR antibody cetuximab need confirmation by a larger interventional study (38). 18F-FLT may be a very powerful tool to stratify patients and adapt treatment accordingly (e.g., additional antiproliferative treatment by means of chemotherapy or EGFR-inhibition).

Based on the above described findings in exploratory imaging studies, a few centers have started phase I/II studies to investigate the potential and limitations of individualized RT strategies adapted on functional imaging information acquired before or during RT (31,39-41). To date, biological adaptation strategies consist mainly of concepts escalating the dose to functionally abnormal or radio-resistant sub-volumes inside the gross tumor volume (GTV), even though results from preclinical studies on this topic are eagerly being awaited. In order to systematically investigate the clinical feasibility and
toxicity of dose escalation in HNSCC, Leclerc et al. (40) performed a phase I clinical trial in which therapeutic planning target volumes (PTVs) were treated to three consecutive dose levels of 69 Gy, 72 Gy or 75 Gy in 30 fractions, respectively. Main results of the study were that dose escalation in this order of magnitude was effective and safe with no differences in toxicity between the three treatment arms. The first dose painting trial adapting the prescribed dose level individually based on 18F-FDG PET imaging was published in 2007 by Madani et al. (39). Within this phase I clinical trial, a total of 41 HNSCC patients were treated in two arms with dose levels of 72.5 Gy and 77.5 Gy, respectively to the 18F-FDG PET-derived biological target volume (BTV) using a simultaneous integrated boost (SIB) technique. One treatment-related death was reported in the experimental arm consequently halting the study. In 2011, the same Belgian group reported on a further dose painting study, escalating dose to a median of 80.9 Gy or 85.9 Gy, respectively, prescribed to the 18F-FDG PET avid region inside the GTV using a dose painting by numbers approach (42). For this study, three individually adapted treatment plans were generated: fractions 1-10 and 11-20 were planned based on the 18F-FDG PET derived BTV, whereas fractions 21-32 were planned conventionally. In 6 out of 21 patients recruited into this study dose limiting toxicity, i.e., mucosal ulcers, were observed and thus the maximum tolerated dose (MTD) was set at a median of 80.9 Gy. To date, the study presented by Madani et al. (42) is the only reporting MTD for dose escalation in HNSCC suggesting that there is only a very narrow window of additional dosing (total dose of approximately 70-80 Gy) available for personalized radiation strategies based on functional imaging. To reach additional efficacy in terms of loco-regional control, other strategies of treatment intensification are warranted.

Two currently recruiting prospective phase II clinical studies investigate the potential of escalating radiation dose based on 18F-FDG PET in NSCLC and HNSCC, respectively. First, the PET-boost trial for advanced stage NSCLC patients randomizes between dose-escalation to the entire primary tumor volume or to the 18F-FDG avid region inside the GTV at the same integral dose, whilst the dose to the affected lymph nodes remains unaltered (31). Second, the altered design of the ARTFORCE trial in HNSCC randomizes between standard irradiation (70 Gy in 35 fractions) or dose-painted redistribution of the radiotherapy regimen based on 50% of the maximum SUV contour within the GTV (GTV-FDG-PET), with a maximum total dose in the investigational arm of 84 Gy to 2% of the PTV-GTV-PET, which equals GTV-FDG-PET expanded by 3 mm.

A German mono-institutional randomized phase II study investigates the clinical feasibility of hypoxia dose escalation in HNSCC (41). Patients randomized into the experimental arm are treated with a 10% dose escalation, i.e., 77 Gy, to a hypoxic volume defined on basis of dynamic 18F-FMISO PET data.
The planned interim analysis for the first 20 patients recruited into this study showed that dose escalation in this order of magnitude is well tolerated(41). Furthermore, results of this study confirmed a prognostic model relating individual tumor control probability with the dynamic 18F-FMISO PET data established in an earlier study(43).

For clinical implementation of personalized radiotherapy approaches based on functional imaging data, a number of methodological issues need to be taken into account. Thus far, radiotherapy planning and dose calculation is predominantly performed on basis of a dedicated planning-CT. As a consequence, several functional imaging data have to be registered with robust and accurate registration algorithms that have to be validated beforehand(44). Hence, different algorithms and parameter settings may be required for the registration of data concerning different anatomical regions and different imaging techniques. In order to keep registration errors as small as possible and to guarantee a robust translation of the functional voxel-information into RT planning, acquisition of functional PET or MR images in RT treatment position is recommended(24,45). To account for biological and anatomical changes throughout the course of radiotherapy, adaptive treatment strategies appear promising also for biologically individualized RT based on functional PET or MR imaging(46).

Modern imaging equipment increasingly enables the acquisition of multiple functional images in parallel or sequentially with a short time interval between the single examinations. Houweling et al.(47) revealed 18F-FDG PET information to differ from ADC maps derived from DWI-MRI data for 18 HNSCC patients, resulting in different targets for potential dose painting strategies. Another study proposed a statistical model to combine different functional MRI data sets to derive a voxel-based probability of tumor presence for more accurate automatic contouring(48). The proposed model was validated against pathological information of prostatectomy specimen in 87 prostate cancer patients(48). In the advent of increasingly available multi-parametric functional imaging data from hybrid scanner such as combined PET/MR, methods to combine data containing different biological information – not only for target volume delineation - appear promising. Consequently, Alber and Thorwarth(49) proposed to integrate a voxel-based probability of tumor presence directly into the optimization process for radiotherapy planning. This formalism also takes into account the varying sensitivities and specificities of different imaging modalities as well as other sources of uncertainty, e.g., patient movement. An extension of this methodology would also allow combining multi-parametric image information to derive a probability map of radiation resistance inside the GTV. Figure 3 presents an example, in which 18F-FMISO PET data and ADC values derived from DWI-MRI were used to calculate a radiation sensitivity map which
subsequently served as input for a probability dose painting taking into account voxel-based radiation resistance values. Such approaches require validated classification data for a number of different functional data sets, so far only available from preclinical data.

A new approach to make use of imaging information for patient stratification and personalization of treatment is “Radiomics”. This recently proposed methodology makes use of a comprehensive quantification of tumor phenotypes by applying a large number of quantitative image features(50,51). In a recent extensive study Aerts et al.(50) presented a radiomic analysis of 440 features quantifying tumor image intensity, shape and texture, which were extracted from CT data of more than 1,000 NSCLC or HNSCC patients. The authors concluded that a prognostic radiomics signature capturing intra-tumor heterogeneity exists which is associated with underlying gene-expression patterns, and may thus identify a general prognostic phenotype in both patient cohorts. Consequently, this new emerging field converting medical images into minable data by extracting a large number of quantitative imaging features is a potentially powerful tool with respect to RT personalization.

Apart from tumor characterization and target volume definition, PET enables the detection of radiation-sensitive tissue sub-volumes in non-tumorous tissues, such as lung tissue prone to developing radiation pneumonitis. In a study by Petit et al.(52), a cohort of 101 prospectively recruited NSCLC patients was retrospectively analyzed to investigate the relationship between pretreatment 18F-FDG uptake in the lungs, the delivered radiation dose and radiation-induced lung toxicity (RILT). The study revealed that the risk of RILT increased with pre-treatment 18F-FDG uptake in the lungs. Consequently, the risk of RILT may decrease when avoiding sub-volumes in the lung with high FDG uptake by applying dedicated radiation planning techniques. A similar study investigated the potential of CT imaging to measure RILT(53). Here, changes in Hounsfield Units (HU) of CT scans acquired before and three months after RT were correlated with RILT. The authors report that HU changes were linearly correlated with radiation dose, which implies that HU changes identify the whole range of individual radiosensitivity on a continuous, quantitative scale. Moreover, a study by Nijkamp et al.(54) found a positive correlation of radiation dose with severity of acute esophagitis (AE) detected by means of 18F-FDG PET uptake after concurrent chemo-radiotherapy in 82 NSCLC. Thus, functional imaging using 18F-FDG-PET can be used to assess radiation sensitivities of normal tissue in order to enable for a better treatment in the future.
PET for *in vivo* treatment verification of proton and carbon ion beam therapy

Proton and carbon ion therapy are emerging radiotherapy techniques indicated for a variety of solid tumors (e.g., pediatric, chondrosarcoma, chordoma, neuro-oncological) in order to increase anti-tumor efficacy, to spare tumor-surrounding normal tissues, or a combination of both. However, for changes in tissue density occurring during fractionated particle therapy (e.g., mucus, weight loss) severely affect radiation dose deposition, one of the main challenges is the verification radiation dose delivery within the target.

In addition to the previously described possibilities for plan adaptation based on functional imaging, PET technology provides exciting opportunities for particle beam verification(55). During hadron irradiation, β+ emitters such as 11C or 15O are produced along the beam path and these can be visualized with PET, either online using in-room imaging equipment, or off-line a few minutes after particle dose administration(56). As a consequence, PET is a non-invasive means for almost instantaneous image-guidance in hadron therapy with an accuracy of proton and carbon ion beam range estimation of below a few millimeters(57). However, biological washout processes as well as patient motion are challenging accurate range verification with PET(58). Recently, methods have been developed that allow automatic range assessment and uncertainty estimation already during the treatment planning process for particle therapy(59).

A first small clinical study using an in-room PET system for proton range verification demonstrated its potential for *in vivo* treatment monitoring in proton therapy(60). A larger clinical study (MIRANDA) is currently recruiting patients in Germany with the aim to investigate the clinical feasibility and effectiveness of PET quality assurance for promoting the accuracy of proton and carbon ion beam therapy(61).

Due to the steep dose gradients obtained with particle beam therapy, this technique may be ideal for the clinical realization of biologically adapted therapy on the basis of functional imaging with PET or MRI. A few planning studies investigated the potential of proton beam therapy for dose painting and found better organ-at-risk sparing and therefore increased flexibility in terms of local dose escalation, e.g.(62,63). Also, the higher linear energy transfer of heavy ions may be of great value to overcome local radiation resistance, induced for example by tumor hypoxia(64).

Finally, PET may facilitate decision-making when combining photon and proton irradiation(65). On the one hand, particle therapy enables the assignment of highly conformal dose distributions, whereas photon treatment plans are very robust against motion and other sources of disturbance. As a
consequence, depending on the tumor entity, a combination of protons and photons may be used – also
due to a restricted availability of proton treatment facilities(65).
Molecular imaging in systemic radiotherapy and targeted therapy.

For systemic radiotherapy, *i.e.*, administration of radioactive agents that specifically bind to targets on cancer cells, molecular imaging has a special role, for drugs can be radiolabeled with therapeutic (alpha or beta-emitting) or diagnostic (gamma or positron-emitting) radionuclides. This concept called *theranostics* is a typical example of personalized treatment as the targeting of the therapeutic can be predicted and followed by a companion diagnostic imaging agent in every individual patient.

Treatment of differentiated thyroid cancer with iodine-131 is the earliest example of theranostics, applied now for more than 70 years. This targeted therapy exploits expression of the sodium/iodine symporter on thyroid cancer cells to detect and to treat thyroid cancer with 131I, providing excellent clinical outcome of this disease even in a metastatic setting(66,67). Another example of theranostics is the use of molecular imaging agents to detect and treat patients with metastatic neuroendocrine tumors (NET) with radiolabeled somatostatin-analogues or radiolabeled metaiodobenzylguanidine (mIBG)(68). With high affinity, these somatostatin-analogues specifically target somatostatin subtype receptors and mIBG of noradrenalin transporters, overexpressed in NET.

More recently, treatment of metastatic prostate cancer with radiopharmaceuticals is receiving considerable interest(69,70). Selection of patients with bone metastases of castration-resistant prostate cancer for treatment with the alpha-emitting calcium-analogue Radium-223 is performed with bone scintigraphy, depicting the sclerotic bone metastases amendable to 223Ra treatment. Although Marie Curie discovered radium-isotopes more than one century ago, 223Ra was only been approved for this indication in recent years. Novel radiolabeled agents targeting the PSMA-epitope on prostate cancer cells are being developed not only targeting and treating bony metastases but also soft-tissue tumor locations as well, again directly linking molecular imaging to targeted therapy(71). The monoclonal anti-CD20 antibody conjugated to 90Y, 90Y-ibritumomab tiuxetan (90Y-IT) is an FDA and EMA approved treatment for relapsed or refractory low-grade or follicular NHL(72). For the development of this therapeutic approach, the diagnostic companion agent (IT labeled with gamma-emitting radionuclide Indium-111) was used to evaluate the targeting of this monoclonal to the tumor sites.

This illustrates the role of molecular imaging to develop targeted therapies. The concept of molecular imaging of radiolabeled drugs is not only used as an adjunct to radioactive therapeutics, but is has also been embraced to elucidate mechanisms of action, heterogeneity of target expression and target accessibility for drugs that are already widely used in clinical practice, such as trastuzumab in HER2-positive metastatic breast cancer(73,74). It is not always necessary to develop new
radiopharmaceuticals to monitor and adapt treatment. A typical example is GIST tumors harboring an activating c-KIT mutation that can be targeted with imatinib. For imatinib also inhibits hexokinase, the driving enzyme for 18F-FDG accumulation in tumor cells, responding GIST tumors can become completely negative on 18F-FDG-PET within days and months before a volume response can be established(75). Conversely, failure to show an 18F-FDG response may provide valuable information to treat those non-responding lesions by surgery or (stereotactic) radiotherapy, while keeping the patient on treatment for the other, still responding lesions. Additionally, early metabolic response, reflected by decreased 18F-FDG-uptake early after start of treatment, may be associated with improved clinical outcome, as shown e.g. by Demetri et al.(76) in patients with GIST treated with sunitinib after imatinib failure. This opens a window of opportunity to adapt the dose or change treatment in those patients who fail to show a metabolic response.

Apart from its systemic effects, specific radiolabeled agents may well be combined with external beam radiotherapy (EBRT). One may postulate delivering high doses of systemic radiotherapy to antigen-expressing targets followed by EBRT to the tumor and elective treatment volumes. Consequently, the radiation dose to the target may substantially be increased without harm to surrounding radiation-sensitive normal tissue, thus widening the therapeutic window. Very recently, Koi and coworkers(77) treated three human squamous cell carcinoma models (UT-SCC-5, UT-SCC-8 and FaDu) with the 90Y-labelled anti-EGFR antibody cetuximab combined with EBRT (Figure 4). Varying therapeutic efficacy was reported for the models. As opposed to EGFR expression detected by immunohistochemical staining of tumor sections, 86Y-cetuximab-PET signal correlated to responsiveness to radiolabeled targeted treatment. At present, four clinical studies on the combination of EBRT and targeted agents are registered on www.clinicaltrials.gov covering brain metastases from solid tumors, NSCLC, and diffuse intrinsic pons glioma.

Exploiting molecular imaging to select patients prior to and establish non-response early during treatment aids the clinician in earlier adaptation of treatment, sparing the patient the side effects of ineffective drugs and society the cost of futile treatments. However, to wisely use and to avoid unnecessary proliferation of advanced imaging without proven impact on patient treatment and outcome, it is mandatory to address the development of companion diagnostics during early and late phase clinical trials, rather then introducing non-evidence based imaging technology in a clinical setting.
Conclusions/perspectives:

Adaptive (radiation) treatment on the basis of functional imaging includes various aspects that were addressed in this review article. With progress in image fusion, treatment plan summation and radiation techniques, and new combination treatments (radiotherapy, chemotherapy, monoclonal antibodies, tyrosine kinase inhibitors, and radiolabeled targeted agents), this field has just started to evolve.
REFERENCES


Figure 1. Perfused lung volume (color overlay) measured using a contrast-enhanced Dual Energy CT scan of a patient with a non-small cell lung cancer tumor inside the left lobe (shown in transverse, frontal and sagittal view). A large perfusion defect surrounding the tumor is clearly visible most probably caused by obstruction of the pulmonary vessels. Courtesy of W. van Elmpt, Department of Radiation Oncology (MAASTRO clinic), Maastricht University Medical Centre, The Netherlands and Marco Das, Department of Radiology, Maastricht University Medical Centre, The Netherlands.
Figure 2. 18F-FLT PET/CT before (chemo)radiotherapy (A and D), in the second week of treatment (B and E), and in the fourth week of therapy (C and F). The first row (A-C) shows a slow decrease in 18F-FLT uptake in a patient with a cT4N2bM0 supraglottic laryngeal carcinoma treated with chemoradiotherapy. This patient developed a local recurrence 7 months after the end of treatment and died of metastatic disease. The second row (D-F) shows a fast decrease of the 18F-FLT uptake in a patient with a cT3N1M0 supraglottic laryngeal carcinoma treated with radiotherapy only. This patient developed no tumor-related event after 32 months of follow-up. Reprinted with permission from(37).
Figure 3. Example of a 56-y old female with a squamous cell carcinoma of the base-of-tongue who underwent multi-parametric functional PET/MR imaging before the start of radiotherapy. (A) Combined 18F-FMISO PET/MR 3h post injection (T2 TIRM). (B) 18F-FMISO PET registered to the planning CT showing the different planning target volumes (PTV). (C) ADC map derived from DWI-MRI including a volume containing low ADC values (PTV<sub>ADC</sub>low) inside the PTV of first order. (D) Exemplary RT plan with dose escalation of 20% prescribed to PTV<sub>ADC</sub>low. (E) Probability map for radiation resistance of the tumor derived from a combination of 18F-FMISO PET and ADC. (F) Dose Painting radiotherapy plan directly optimized on the probability map shown in (E). Radiation treatment plans were optimized using the treatment planning system Hyperion® for a VMAT treatment with 2 arcs, 6 MV photons. Volumes of interest: PTV<sub>70Gy</sub> (red), PTV<sub>ADC</sub>low (yellow), PTV<sub>FMI</sub> (blue), PTV<sub>60Gy</sub> (green), PTV<sub>54Gy</sub> (orange), spinal cord (purple). Isodose Lines (from lowest to highest): 45, 51, 57.5, 66.5, 73, 77, 80 Gy.
Figure 4. (A) Pseudo-colored images of representative tumor sections of FaDu, UT-SCC-8 and UT-SCC-5 growing in NMRI mice (red: cetuximab, dark green: EGFR, dark blue: perfusion, Hoechst 33342, light blue: vascular endothelium, CD31, light green: hypoxia, pimonidazole, gray: necrotic area). (B) Representative PET images administered $^{86}$Y-cetuximab. Reprinted with permission from (77).
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