PET-based analysis of tumor glucose metabolism and tumor hypoxia before and during anti-neoplastic treatment
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Chapter 7

Summary and general discussion
SUMMARY

Biological information obtained from imaging modalities such as Positron Emission Tomography (PET) prior to and during the course of radiation may provide valuable information required for radiation treatment optimization and adaptation [1]. PET can be used to adjust the radiation treatment plan by monitoring tumor biological characteristics, such as glucose metabolism and hypoxia [1]. This information may guide radiation oncologists to deliver higher doses of radiation to tumor subvolumes, e.g., by depicting metabolically active and/or hypoxic tumor cells, which are more radioresistant. Such strategies may be more suitable to improve the therapeutic ratio, i.e., improving tumor control without enhancing radiation-induced side effects, than escalating the dose to the entire tumor bed. Tumor hypoxia is an important contributor to radioresistance, which has been demonstrated in several tumor types [2-4]. Tumor hypoxia results from an imbalance between oxygen supply and consumption due to an abnormal structure and function of the microvessels supplying the tumor [5-7]. The response of cells to ionizing radiation is strongly dependent on oxygen levels [7]. An enhancement of radiation damage by oxygen is generally referred to as the oxygen-fixation hypothesis. When radiation is absorbed in biological material, free oxygen radicals are formed, which are highly reactive molecules that initiate a chain of events resulting in DNA damage [8]. In a hypoxic state, oxygen radicals are less likely to arise. Consequently, a higher radiation dose is needed to achieve the same tumor control rate in hypoxic tumors [7,8].

The gold standard in assessing tumor hypoxia is the Eppendorf electrode method [9]. This approach has been used to group patients based on their median pO2 values. However, this method is invasive, and can only be applied for well accessible superficial tumors. These limitations made clinicians concentrate on non-invasive techniques such as PET imaging with specific hypoxic tracers. Recently, Busk et al. [10] compared tumor oxygen levels as determined by gold standard Eppendorf electrodes with hypoxic areas as determined by FAZA-PET T/B ratio in an animal model. A significant correlation was found between the FAZA T/B ratio and oxygen pO2 values. In addition, the PET assisted hypoxia imaging has several advantages over Eppendorf electrode measurements: it is a non-invasive procedure; it generates three-dimensional images; and finally, it allows measuring multiple sites of tumors simultaneously. Moreover, PET is capable of visualizing the often heterogeneous pO2 distribution within the tumor volume without the need of multiple electrode measurements [11,12].

It is clear that tumor hypoxia is a major risk factor for failure after radiotherapy or chemoradiation due to increased radioresistance of hypoxic tumor cells. Precise delivery of higher radiation doses per fraction to the hypoxic sub volumes during the entire course of treatment may be a strategy to improve the therapeutic ratio by increasing local tumor control without inducing excess radiation-induced side effects.
effects. This requires methods that provide spatial information on tumor hypoxia prior to and during the course of radiation.

In this thesis, we focused on number of methodological issues related to the development of hypoxia guided radiation dose escalation strategies in HNSCC and NSCLC.

In chapter 2, the literature on different hypoxia tracers was summarized focusing on tumor hypoxia detection in NSCLC patients. The aim was to establish whether the presence of hypoxia could be used to predict outcome. The current clinical data do not offer sufficient evidence for superiority of any specific hypoxia PET tracer. As Fluoromisonidazole (FMISO) is a first generation hypoxia tracer, it has been excessively used to detect hypoxia in both humans and animals.

A more recently developed hypoxia tracer is fluoroazomycinarabinoside (FAZA), which also belongs to the nitroimidazole group. Preclinical studies indicated that FAZA is a promising hypoxia tracer in various tumor models [13]. These studies showed that FAZA is rapidly cleared from the circulation and normoxic tissues, and is excreted mainly via the renal pathway, thereby providing a more favourable tumor-to-background (T/B) ratio in most anatomical regions as compared to FMISO [14]. In addition, FAZA exhibited in vivo stability against enzymatic activity and therefore could be recommended as a potential tracer for tumor hypoxia in clinical studies [15].

FAZA-PET/CT imaging of tumor hypoxia is a valuable tool not only to identify the presence of hypoxia, but also to determine the spatial hypoxia distribution across the tumor volume. Apart from that, the fractional hypoxic volume based on FAZA-PET/CT showed that hypoxic areas are heterogeneously distributed throughout the tumor volume, reflecting a highly heterogeneous tumor microenvironment [16]. This information is required to develop radiation dose escalation strategies for precise targeting of hypoxic (sub)-volumes.

FDG (Fluorodeoxyglucose) is routinely used to assess tumor glucose metabolism [17]. The extent of FDG accumulation in solid tumors depends primarily on the over-expression of Glucose transporter 1 (GLUT-1) and glycolytic enzymes [18,19]. Up-regulation of glucose transporters (GLUTs) is observed also in hypoxic regions, [20], which is due to an increased hyperglycolysis driven by HIF. Tumors with a high SUVmax have higher HIF and GLUT-1 expression than tumors with a low SUVmax, as detected by FDG-PET [21]. Therefore, it has been assumed that the degree of tumor FDG uptake may reflect the level of tumor hypoxia and may therefore be used as a surrogate marker for tumor hypoxia. We have studied this issue and presented the results in Chapters 3 and 4.

In chapter 3, we estimated the potential added clinical value of the specific hypoxia tracer FAZA over
FDG, which is routinely used in the diagnostic work up, response evaluation and radiotherapy treatment planning of advanced-stage NSCLC. In this prospective study, we included eleven patients with stage III or stage IV NSCLC who underwent FDG and FAZA-PET before chemoradiotherapy. The spatial correlation between FDG and FAZA-uptake values was investigated using voxel-based analysis. All 11 patients showed clear uptake of FAZA in the primary tumor. No significant correlation was observed between FDG SUVmax and FAZA T/B ratio. The pattern of tumoral FDG uptake was rather homogeneous, whereas FAZA uptake was more heterogeneous. These findings support the notion that FDG and FAZA signals indeed reflect different biological functions if measured in the same tumor. Consequently, a poor correlation between these 2 tracers suggests a highly heterogeneous tumor microenvironment. A significant correlation between FDG-SUVmax and lesion size \(P = 0.002\) was observed indicating that larger tumors are generally more metabolically active than smaller tumors.

This study showed that the FAZA tumoral uptake pattern varied widely among tumors and that FAZA was more heterogeneously distributed than FDG. Moreover, FAZA PET-CT imaging detected heterogeneous distributions of hypoxic subvolumes within a homogeneous FDG background [16]. Therefore, when added to FDG, FAZA provided more specific information on tumor hypoxia different from that of FDG. Based on these results, we concluded that FAZA PET-CT provides additional information to FDG PET-CT and could be a promising tool for a more individualized treatment of advanced NSCLC, e.g. Hypoxia imaging during treatment could be a promising way to stratify patients who may benefit from hypoxia modification or dose escalation strategies.

**Chapter 4.** The results presented in Chapter 4 showed that loco-regional effects of chemotherapy on tumor hypoxia and tumor glucose metabolism can be better quantified and visualized when the FAZA uptake is measured per voxel. Besides the traditional SUVmax T/Background or T/Blood ratio approach, the voxel-by-voxel analysis was chosen in order to evaluate the tumor heterogeneity. In this study, we investigated how chemotherapy affected the individual tumor hypoxic areas measured with FAZA voxel-by-voxel analysis, as well as whether these changes correspond to metabolic effects as measured with the FDG. A voxel-by-voxel analysis is only a valid approach if corresponding tumor voxels are considered for comparison. Therefore different patient positioning between scans, tumor displacement and treatment induced changes of tumor volume need to be accounted for. One could consider imaging procedures where patient positioning during scanning is replicated using laser guides. However, these imaging procedures require additional staff training and more elaborate patient preparation. Another option is to completely rely on software to map corresponding tumor voxels. Our approach was a two-step approach where first a rigid registration was applied to the whole body CT scan in such a way that differences in patient positioning between the two PET scans were
accounted for. Once translation and rotation parameters were optimized to compensate differences in patient positioning, a deformable image registration was applied to the CT data to account for tumor movement and tumor volume changes. To allow a voxel-by-voxel analysis, tumor volume changes needed to be limited such that deformable registration would only compensate for local tumor movement [22,23]. Compensation for tumor volume changes should be avoided since it is uncertain how the deformable registration deals with the discrepancy in the number of tumor voxels. To check whether functional information within the tumor volume was not affected by the deformable registration we performed a straightforward inverse consistency check by applying a deformable registration in the reverse direction and looked at the correlation between the original and voxel values transformed by a forward and backward deformable registration. For this study, correlation coefficients were significant and acceptable, suggesting that the functional information within the tumor volume is preserved. However larger tumor volume changes due to successful therapy could pose limitations to this approach.

We showed that the FDG uptake measured by SUVmax decreased significantly after 2 cycles of chemotherapy ($p=0.02$). The voxel-by-voxel technique revealed an overall decrease in the FDG uptake after 2 cycles of chemotherapy. Furthermore, the baseline FDG SUV did not overlap neither with the FAZA T/B ratio ($R^2=0.05$) nor with the FAZA T/Blood ratio ($R^2=0.08$). After 2 cycles of chemotherapy, no relationship was found between FDG SUV and FAZA ($R^2=0.03$ and $R^2=0.08$, respectively) during follow up. Our result showed no significant association between hypoxia and glucose metabolism. Although hypoxia results in HIF activation and subsequently in an increased glucose metabolism, the overall hypoxia was not related to the FDG even after chemotherapy, as measured with FAZA. The traditional maximum intensity uptake measures (SUVmax, T/Bmax or T/Bloodmax) did not reflect the true changes in the activity of the whole tumor. The voxel-by-voxel analysis, by contrast, is able to detect heterogeneity changes within the tumor. Furthermore, this method allowed detecting heterogeneous responses between hypoxic and (highly) metabolic tumor areas. Therefore, future studies should incorporate volumetric analysis by the voxel-by-voxel approach instead of single hypoxic spot analysis as it brings more understanding of tumor biology and characterizes the heterogeneity response towards treatment.

In chapter 5, we performed a prospective observational cohort study using serial hypoxic imaging before treatment initiation and at several time-points during (chemo) radiotherapy in head and neck squamous cell carcinoma (HNSCC) and NSCLC patients in order to understand spatio-temporal dynamics of tumor hypoxia. The information rendered from sequential hypoxia imaging may allow us to define the optimal time point for the integration of hypoxia FAZA-PET/CT information into radiotherapy treatment planning to benefit from hypoxia modification or dose escalation strategies. In this study,
The spatio-temporal dynamics of tumor hypoxia and fractional hypoxic volumes (FHV) were evaluated using a voxel-by-voxel analysis based on a FAZA-T/B ratio of 1.4, at four time points in HNSCC patients, at baseline (FAZA-BL), at week one (FAZA-W1), two (FAZA-W2), and four (FAZA-W4) during CHRT and at three time points in NSCLC patients (baseline; W2, W4).

A detailed voxel-by-voxel analysis of FAZA-PET/CT scatter plots manifested a heterogeneous intratumoral hypoxic distribution. In short, four different types of cases were found: 1) increasing hypoxia, 2) decreasing hypoxia, 3) stable hypoxia, and 4) stable non-hypoxia. Ten out of twelve patients showed substantial pre-treatment tumor hypoxia representing a FHV ≥ 1.4 assessed by FAZA-PET/CT. Stable tumor hypoxia was observed in three out of five HNSCC patients and two out of five NSCLC patients at FAZA-W2. In three HNSCC patients and two NSCLC patients FHVs declined to non-detectable hypoxia levels at FAZA-W4 during CHRT, while two NSCLC patients, showed increasing FHVs.

In this regard, a well demarcated hypoxic area at FAZA-Week 2 of chemoradiotherapy is more appropriate for dose escalation and can be treated with spatially conformed doses by precisely targeting tumor hypoxia.

**Chapter 6** Response assessment in non-small cell lung cancer (NSCLC) is usually performed according to the RECIST criteria using CT scans of the thorax [24]. However, the reduction in tumor size can take several months, and radiation induced lung injury changes, such as inflammation and fibrosis can hamper response evaluation of the tumor and local control. FDG accumulation in tumor cells is related to biological characteristics of the tumor. Treatment induced changes, such as cell death or growth arrest, result in reduction of the FDG uptake. Therefore, this phenomenon can be referred to a sensitive marker for treatment response. Using the FDG-PET metabolic imaging can help us differentiate between radiation induced pneumonitis and tumor changes in lung cancer. In addition, it was observed that changes in tumor metabolism are more significant than anatomical changes in lung cancer.

The prognostic value of the residual FDG uptake in lung tumors treated with SABR has not been established. Therefore, we examined the prognostic value of the post-SABR FDG uptake at 12 weeks with respect to local control (LC), mediastinal failure (MF), distant failure (DF), overall survival (OS), and disease specific survival (DSS) in resectable but medically inoperable patients (e.g. due to concomitant cardiovascular disease) with stage I NSCLC and FDG-PET positive primary lung tumors. Our results suggest that the residual FDG uptake at 12 weeks after SABR predicts LC [25]. A trend was found towards a better DSS and even OS for post-SABR SUVmax< 5.0.

Therefore, a single FDG-PET scan at 12 weeks can be used to tailor further follow-ups. Patients with the
post-SABR SUVmax ≥ 5.0 should be considered as having an increased risk of local failure. Therefore, their follow-up should be intensified. Our results are in line with those of others [26-28].

Sasaki et al. [26] found that SUVmax 5.0 was the best cut-off to predict 2 year overall survival rate in patients with NSCLC (n = 162; 2-year OS, 94% vs 65%; P = 0.02). In a series of 44 patients with stage I NSCLC treated with surgery, Higashi et al. [29] found that patients with an SUVmax ≤ 5.0 had improved five year disease free survival (88% vs 17%) when compared with patients with an SUVmax of > 5.0. Hamamoto et al. [28] also divided the stage I NSCLC patients into the high SUVmax and low SUVmax tumor group with the cut-off point of SUVmax 5.0. In their study, pre-treatment high SUVmax of a primary tumor on FDG-PET scan was associated with poor local control. This indicates the close correlation between the primary SUVmax and patient outcome. Patients with increased glucose metabolism of tumor cells are associated with poorer prognosis. Therefore, the SUVmax, an indicator of local FDG uptake, may become one of the potential prognostic factors. Patients with a FDG SUVmax > 5.0 may be considered at increased risk of failure and may benefit from more effective approaches, for instance, higher radiation dose, and consequently improve treatment efficiency.

**General discussion and Future perspectives**

In NSCLC, locoregional failure rates between 30% and 55% at 3 years [30], while in stage III-IV HNSCC locoregional failure rates vary from 18% to 73% at 3 years [31]. Therefore, improving locoregional tumor control is still of major concern. Tumor hypoxia is a significant adverse prognostic factor and contributes to resistance for chemoradiotherapy. This has been demonstrated in several tumor types [2-4], including also in NSCLC and HNSCC [4,32-34].

Solid tumors contain mixture of normoxic and hypoxic cells. A radiation dose kills a greater population of normoxic cells than hypoxic cells because normoxic cells are radiosensitive [7]. As a consequence, a higher radiation dose is needed to achieve the same local control rate, in hypoxic tumors. Dose escalation is therefore an important strategy to overcome tumor hypoxia and thereby improving local tumor control and is expected to improve outcome in terms of overall survival as well.

However, from a clinical point of view, dose escalation is more complex. Dose escalation to the entire Gross Tumor Volume (GTV) will give rise to a higher dose to the normal tissues as well, leading to an increase of radiation-induced toxicity. In NSCLC, administering a prescribed dose of 60 to 66 Gy is already difficult to achieve in 5-10% of the cases without accepting an unacceptable risk of severe side effects such as pulmonary and/or cardiac toxicity. In HNSCC, dose escalation will result in an increase of acute and late radiation-induced toxicity such as xerostomia, dysphagia and mucosal ulcers which have a significant negative effect on quality of life after completion of treatment [35].
Therefore, dose escalation specifically to hypoxic areas within the tumor offers more opportunities to escalate the dose to the most radioresistant parts of the tumor without or minimally increasing the dose to the normal tissue.

In the past few years, highly sophisticated radiotherapy technologies have been introduced in the field of radiation oncology, such as intensity-modulated radiotherapy, which allows for dose painting that is, the delivery of a higher dose to specific tumor areas and subvolumes. This approach is only effective in the case of static hypoxia because the boost dose is delivered to the same region every day. In the case of dynamic hypoxia, a single high-dose fraction using stereotactic body radiotherapy delivered to the hypoxic region on the same day of the FAZA PET/CT may be more appropriate.

Radiotherapy techniques to achieve dose-escalation

The goal of radiation treatment planning is to specify the number of beams and the settings that together determine the way in which the beams are delivered to the target volume. This may result in a higher probability of a successful curative treatment with minimal radiation induced side effects. Three-dimensional conformal radiation therapy (3DCRT) allows directing beams at multiple angles, with each beam is shaped at its corresponding target projection. This type of treatment enables more conformal dose distribution to target volume compared to 2D planning. However this requires adequate quality assurance methods, including 3D dosimetry using phantoms. Most importantly, the risk of late complications may be increased if the 3DCRT technique does not compensate for the additional dose.

Intensity modulated radiation therapy (IMRT) has certain advantages over 3DCRT, namely, varying fluence over the cross-section of each beam. In IMRT, the modulation of the fluence within each field can yield a dose distribution that conforms closer to the target than when only uniform beam fluences are used. This allows delivering lower doses to organs at risk (OAR), compared to when 3DCRT is used. However, larger volumes are exposed to low doses with IMRT, which may increase the risk of radiation induced second malignancies. Recently, Madani et al. [35] evaluated adaptive IMRT planning in head and neck cancer patients based on “Dose Painting By Numbers” (DPBN) according to FDG-PET voxels. They reported that the median total dose of 85.9 Gy is feasible in a total of 32 fractions. However, they noted development of late onset mucosal ulcers at levels as high as 80.9 Gy and defined this level as a maximum tolerated dose. Although treatment options have expanded, the loco-regional recurrence rate is still relatively high, and a five-year overall survival rate is below 50% [36]. Therefore, new treatment techniques are needed to improve outcomes for this patient group.

The simultaneous integrated boost (SIB) method attempts to integrate the information obtained from
fractionation studies into the standard model of differential doses for IMRT delivery [37]. SIB method can still deliver treatment on a once daily basis but delivers higher fractions (> 2.0 Gy per fraction/day) to GTV. This accelerated delivery of higher radiation doses can address tumor hypoxia and proliferation, delivering a given dose in a shorter period of time. The advantage of SIB-IMRT consists in a better target conformity, less dose to critical structures and the option if dose escalation in the GTV. However, there is limited experience in normal tissue tolerance following SIB-IMRT in head and neck cancer; to date there is no universally agreed standard of dosage. However, SIB-IMRT is feasible and yields highly conformal dose distributions, but tissues embedded in the target volume may be at higher risk, and caution should be observed when applying higher than conventional fraction sizes. Therefore, the potential benefits and drawbacks of the SIB-IMRT should be carefully evaluated before the clinical implementation for each site. Special attention should be paid to the dose and dose fractions for each target volume.

Currently, Stereotactic ablative body radiotherapy (SABR) is considered as a treatment option for patients with medically inoperable early-stage non-small-cell lung cancer. SABR can be applied to deliver higher radiation doses to tumors with greater precision when compared with conventional techniques. SABR also offers the capability to deliver fractionated radio surgical treatment plans for bigger lesions, decreasing the radiation of adjacent healthy tissues to potentially minimize the rate of complications. Recent data from stage I and II NSCLC, from prospective single institutional trials indicate that local tumor control rates are > 88% can be achieved using SBRT [38]. However, distant metastases constitute the predominant failure pattern following SABR, a finding similar to that seen after surgery [38]. These outcomes suggest that higher dose may not necessarily lead to higher locoregional tumor control or overall survival. There have been several dose escalation studies of SBRT for lung cancer. In all such studies, SABR was found to be safe and feasible [27,28,39], except in patients with prior thoracic radiation. However, a subsequent phase II study demonstrated that this regimen should not be used for patients with tumors near the central airways due to excessive toxicity. In additional, there are several factors that might influence tumor control such as method of fixation, respiratory control, treatment planning strategy, size of PTV derived from GTV, also, it remains controversial whether the PTV should be irradiated homogeneously or heterogeneously. These factors might have an additional influence on locoregional tumor control. Therefore, new treatment techniques are needed to improve outcomes for this patient group.

Another technique, Intensity modulated proton therapy (IMPT), has a potential to overcome 3DCRT, SIB, SABR, IMRT shortcomings. Firstly, proton beam shows a significant increase in dose deposition at the end of the proton range [40]. The region of an increased dose is called the Bragg peak. Beyond the Bragg peak, dose deposition is negligible, which enables to spare healthy tissues surrounding the
tumor. Secondly, the depth of the Bragg peak can be controlled by alteration of protons’ energy. In this way, different energy levels can be achieved, which makes it possible to spread the Bragg peak covering the full target volume in depth. This approach will optimize local tumor control by introducing heterogeneous dose delivery, where the most active parts of the tumor receive higher dosage, unlike with conventional homogeneous approach. However, the characteristics of protons make IMPT highly vulnerable to uncertainties. These uncertainties arise from interfractional variations such as tumor shrinkage, patient weight, tissue density and patient set up. Some robust optimization methods for IMPT have been proposed to account for range and setup uncertainties such as probabilistic nonlinear programming and robust linear programming approaches. The resulting treatment plans showed reduced sensitivity to uncertainties [40].

**Drawbacks of dose escalation of hypoxia volumes**

Radiotherapy plays an important role in cancer treatment by effectively improving loco-regional tumor control. Studies by Lee N et al. [41] and Chao KS et al. [42] showed that tumor recurrence can occur within the whole tumor. Therefore, it has been hypothesized that dose escalation strategies should include the entire tumor volume rather than hypoxic areas alone. One trial by Cox et al. [43] showed no such effect in stage III NSCLC patients. The use of 69.6 Gy produced a statistically significant increase in survival relative to the use of 60 Gy. However, no additional increase in survival was found with the two higher total doses, 74.4 Gy and 79.2 Gy and the survival rates at 2 years were actually lower than 35% seen with 69.6 Gy. Rasey et al. [12] found that tracer uptake varied markedly and heterogeneously between tumors in the same region.

Tumor hypoxia can be heterogeneous. First, the amount of hypoxia present in tumors remarkably differs from patient to patient [6,8,9]. In addition, the intratumoral distribution of hypoxia may also depend on histologic tumor type [12]. Second, the severity of hypoxia in tumor cells depends on the increased diffusion distance between tumor and blood supply. Third, the distribution of oxygen status is variable, some parts of a tumor exhibiting higher levels of hypoxia than others due to differences in dynamic blood flow as a result of periodic episodes of opening and closing of blood vessels. Finally, the tumor cells that are hypoxic today may or may not be hypoxic at subsequent time points due to a changing tumor microenvironment and/or to treatment itself. However, given that data suggesting changes in tumor hypoxia may vary during the course of treatment, it is essential to distinguish geographically stable and dynamic hypoxia during therapy, because the choice of a dose escalation strategy to hypoxic areas will strongly depend on the dynamics of tumor hypoxia during the course of radiation.
The traditional maximum intensity uptake measures (SUVmax, T/Bgmax or T/Blmax) did not reflect the true changes in the activity of the whole tumor. They are characteristics of the single voxel with the least oxygenation status within the gross tumor volume (GTV). However, it is unlikely that single hypoxic voxel measurements within the GTV reflect the oxygenation status of the entire tumor volume. Therefore, voxel-by-voxel analysis, which provides detailed information about the hypoxic distribution across the entire tumor rather than a single voxel. The voxel-by-voxel analysis, by contrast, is able to detect heterogeneity changes within the tumor. Furthermore, this method allowed detecting heterogeneous responses between hypoxic and (highly) metabolic tumor areas. Therefore, future studies should incorporate volumetric analysis by voxel-by-voxel approach instead of single hypoxic spot analysis brings more understanding of tumor biology and characterizes the heterogeneity response towards treatment.

Clinical data on determining the actual time point for hypoxia based dose escalation is scarce. Very recently, Zips et al. [1] suggested that anticipating dynamics of tumor hypoxia on the basis of baseline FMISO-PET/CT would be inappropriate; because the majority of patients exhibited substantial tumor hypoxia at baseline and it remained questionable which parts of the tumor remain hypoxic. In addition, they determined the prognostic value of the FMISO uptake before and during chemoradiotherapy in locally advanced HNSCC patients (n=25). In this study, the hypoxic volume thresholds (\( \geq 1.4, 1.6, 1.8 \) and 2.0) were significantly correlated with a local failure at 1 (8-10 Gy) or 2 weeks (18-20 Gy) during treatment (n=8). In addition, baseline imaging parameters were not found to be good predictors for local recurrence. The authors concluded that hypoxic imaging at 1 or 2 weeks during treatment is a promising way to select patients that may benefit from hypoxic modification or dose escalation strategy.

The concept of voxel-based analysis can be used for voxel-wise dose prescription and dose escalation related to the PET tracer uptake. Very recently, researchers suggested that the DPBN is feasible according to the PET tracer voxel uptake in head and neck cancer patients using FMISO-PET images [44,45]. The DPBN strategy aims for a linear relationship between the dose prescription to a voxel and the underlying SUV value. In this way, the whole GTV of the primary tumor is considered. Very recently, Dieter et al. [46] evaluated the feasibility of using deformable image registration in adaptive DPBN in head and neck cancer patients. The median prescription dose to the dose painted target was 70.2 Gy (fractions 1-30) and to elective neck was 40 Gy (fractions 1-20). Acute grade 3 toxicity was limited to dysphagia in three out of ten patients and mucositis in another two out of ten patients. The authors concluded that adaptive DPBN using currently available tools is feasible. However, irradiation of smaller target volumes might have contributed to mild acute toxicity. In another study, Thorwarth et al. [44] estimated that the tumor control probability (TCP) would increase from 56% to 70% using the
DPBN based on FMISO-PET imaging. To this end, large clinical data of local tumor control and toxicity are needed to correlate dose volume parameters obtained by various dose summation methods with outcome and to allow a rational selection of the best methods. In future, next generation radiotherapy treatment planning systems should be able to deal with heterogeneous voxel-by-voxel prescriptions to deliver heterogeneously distributed doses accordingly [47,48].

CONCLUSIONS

In conclusion, PET/CT imaging of tumor hypoxia is feasible in HNSCC and NSCLC cancer patients. FAZA PET imaging allows detecting heterogeneous distributions of hypoxic subvolumes even within a homogeneous FDG background. Therefore, FAZA, when added to FDG, provides good information on tumor hypoxia and its heterogeneity. This can help in developing tools for guiding individualized treatment of advanced NSCLC and HNSCC. From our prospective observational cohort study, we observed a relatively stable tumor hypoxia at FAZA-Week 2 (W2) of CHRT, compared to FAZA-Baseline. Hence, FAZA-W2 of CHRT is a most suitable moment for dose escalation. It may also serve as a more reliable basis for integration of FAZA-PET/CT information into the radiotherapy treatment planning for hypoxia-directed dose escalation strategies. Additional studies are needed on the spatio-temporal dynamics of tumor hypoxia to stratify patients who may benefit from hypoxia based radiotherapy treatment planning.

Implementation of PET imaging for personalized adaptive radiotherapy treatment planning is a potentially promising approach that will modify the way treatments are prescribed and delivered to ultimately improve overall outcomes.
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