PET-based analysis of tumor glucose metabolism and tumor hypoxia before and during anti-neoplastic treatment
Bollineni, Vikram

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Chapter 1

General introduction
PET-based analysis of tumor glucose metabolism and tumor hypoxia before and during anti-neoplastic treatment

GENERAL INTRODUCTION

Concurrent chemoradiation (CHRT) is the principle treatment modality for patients with locally advanced non-small cell lung cancer (NSCLC). For locally advanced head and neck squamous cell carcinoma (HNSCC), CHRT is one of the major treatment modalities. Despite the addition of concurrent chemotherapy to radiation, locoregional failure still remains a significant problem for both patient groups. In NSCLC, locoregional failure rates between 30% and 55% at 3 years [1], while in stage III-IV HNSCC locoregional failure rates vary from 18% to 73% at 3 years [2]. Therefore, improving locoregional tumor control is still of major concern and is expected to improve outcome in terms of overall survival as well. The outcome for patients depends on several factors, such as on performance status, age, tumor stage, and tumor hypoxia and specifically in the case of HNSCC, human papilloma virus (HPV) status [3-6]. Tumor hypoxia is an important adverse prognostic factor and contributes to resistance for both chemotherapy and radiotherapy. This has been demonstrated in several tumor types [7], including also in NSCLC [8,9] and HNSCC [4,10].

Prognostic impact of hypoxia in HNSCC

Lehtio et al. [11], evaluated the relationship of fractional hypoxic volume (FHV) in HNSCC patients using fluoroerythronitroimidazole (FETNIM) PET with survival. Patients with a FHV greater than or equal to the median had a significantly worse survival than those with a FHV less than the median. In a study of 73 patients with HNSCC, pretreatment fluoromisonidazole (FMISO) uptake was found to be an independent prognostic factor for overall survival [12]. In another study that included 12 patients with HNSCC who received FMISO-PET scans prior to radiation, the authors concluded that FMISO uptake was predictive of treatment response to radiotherapy [13]. Rischin et al. [14] investigated the prognostic significance of FMISO-PET in patients with HNSCC receiving chemoradiation in combination with the hypoxia sensitizer tirapazamine (TPZ), and concluded that both baseline hypoxia and persistent hypoxia on FMISO scans in patients receiving a non-TPZ containing chemoradiotherapy regimen, was associated with a higher risk of locoregional failure.

A recent FAZA (Flouroazomycinacinabinoside) PET study in 40 patients with HNSCC treated by (chemo) radiotherapy, scans were made before and during therapy. There were 25/40 hypoxic tumors before FDG and 6/13 during treatment. Significantly poorer prognosis was observed of patients with hypoxic tumors (disease free survival, 60%), compared with non-hypoxic tumors (disease free survival, 93%) [15]. Varia et al. [16] also demonstrated the use of pimonidazole immunohistochemical assay in measuring hypoxic volume at cellular level in cervical carcinoma patients (n=10). In 9 out of 10 patients, the presence of tumor hypoxia was determined. Kaanders et al. [17] evaluated the correlation
between pimonidazole binding and treatment outcome in head and neck cancer patients (n=43). In this study, 2 year local control rates were 48% in patients with high pimonidazole binding and 87% in patients with low pimonidazole binding. In conclusion, the results of these clinical studies indicate that tumor hypoxia is an important adverse prognostic factor in HNSCC.

Prognostic impact of hypoxia in NSCLC

Several authors described the association between tumor hypoxia in NSCLC and outcome of radiotherapy of chemoradiation in terms of locoregional control and overall survival.

Eschmann et al. [18] determined the prognostic impact of FMISO-uptake in advanced NSCLC patients before curative radiotherapy (n=14). In this study, tumor recurrence and progression occurred in those patients whose FMISO-T/B [Tumor-to-Background] ratio >2.0 (n=5). In locally advanced stage (III-IV) NSCLC patients treated with radiotherapy and or chemotherapy, re-oxygenation as assessed with FMISO-PET early after treatment was associated with tumor response, whereas stable or increasing tumor hypoxia resulted in worse local tumor control [8].

Gagel et al. [8] prospectively studied the capacity of FMISO-PET hypoxic imaging to determine the tumor response early after chemotherapy in patients with unresectable locally advanced (stage III-IV) NSCLC (n=8). Five out of eight patients with a decreased FMISO uptake showed partial remission after chemotherapy, reflecting the fact that the re-oxygenation status resulted in good tumor response, while increased or stable hypoxia corresponded to worse local tumor outcomes. No association between initial high FMISO uptake and treatment outcome could be detected.

Dehdashti et al. [19] found that an arbitrarily selected T/M cut-off value 3.0 turned out to be accurate in distinguishing responders from non-responders, as detected by the 64Cu-ATSM [Cu(II)-diacetyl-bis (A/4-methylthiosemicarbazone) PET/CT in NSCLC patients. However, additional studies are needed to evaluate these cut-offs as accurate cut-offs in large groups of patients.

Li et al. [20] showed that hypoxia imaging with 99m TC-HL91 (99mTc labeled 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime) correlated well with the tumor response and patient survival rates in stage III inoperable NSCLC patients, where a high uptake of HL91 predicts a poor outcome after radiotherapy in NSCLC. They also showed that the HL91 SPECT imaging could identify the tumor oxygen status during radiotherapy in lung cancer. In this study, a randomly selected T/N cut-off value ≥ 1.47 showed a poor tumor response in stage III inoperable NSCLC patients.
Based on the accumulated evidence in literature, hypoxia PET results have been shown to have a prognostic value in small prospective series. Tumor hypoxia results in biological alterations that leads to a more aggressive disease phenotype and seems too associated with resistance to radiotherapy, the presence of PET-assessed tumor hypoxia could theoretically be used to predict outcome. This provides a basis for further studies allocating hypoxia modifying treatment according to hypoxic status of the tumor.

Types of tumor hypoxia

Tumor hypoxia is caused by an imbalance between oxygen supply and consumption, which may be due to structural and functional abnormalities of newly formed tumor vessels [21,22]. The periodic episodes of opening and closing of blood vessels can create dynamic or fluctuating blood supply to the tumor through immature, leaky vasculature which creates hypoxic environment in tumors [21].

In normal tissues, oxygenation levels are maintained by a compensatory mechanism which increases blood flow in times of increased demand. In tumor tissues such a compensation mechanism is lacking due to immaturity of the vessels and a decreased density. Consequently, increased oxygen demand may lead to hypoxia [23]. In fact multiple factors have been shown to contribute to the development of tumor hypoxia, including perfusion, diffusion and anemia:

a) Perfusion related hypoxia is caused by fluctuating blood flow in the tumor. The microvessels supplying the tumors are disorganized, chaotic and exhibit an irregular branching pattern such as dilations, blind ends and shunts [24]. There is an absence of flow regulation along with lack of smooth muscle cells and nervous components. This phenomenon is also called “acute hypoxia” because perfusion limited oxygen supply causes ischemic hypoxia which is often transient [25].

b) The enlarged diffusion distances in tumor may also lead to hypoxia in tumors, subsequently resulting in less oxygen and nutrients supply to cells far away from nutritive blood vessel. This is referred to as diffusion limited hypoxia and is also known as “chronic hypoxia”. Chronic hypoxia can also be caused by adverse diffusion geometry within tumor microvessels [25].

c) The third factor which can lead to hypoxia is a reduction of the oxygen transport capacity of the blood. Tumor-related or treatment-induced anemia cause reduced O₂ transport capacity of blood which leads to hypoxia. This is a common feature in cancer patients and oxygen levels go down already with a small reduction in hemoglobin levels below 1.1-1.86 mmol/l [23]. This will not be further addressed in this thesis.
Consequences of tumor hypoxia

Tumor hypoxia leads to cellular reactions and activation of number of molecular pathways, e.g. of Hypoxia Inducible transcriptional Factor 1 (HIF). HIF is a heterodimeric protein, highly expressed in most tumors [26]. HIF is the key feature of the hypoxia signaling pathway [27,28]. Under normoxic conditions, a group of enzymes called prolyl hydroxylases (PHDs) hydroxylate HIF allowing the Von Hippau Lindau (VHL) tumor suppressor gene to bind and promote HIF degradation. Whereas, under hypoxic conditions, the PHDs cannot hydroxylate HIF owing to the requirement of molecular oxygen and allowing for the stabilization of HIF. It then translocate to the nucleus and promotes transcription of hypoxia responsive elements (HREs) such as, [1] erythropoietin hormone (EPO) release promotes tumor cell survival and proliferation, [2] activation of Vascular Endothelial Growth Factor (VEGF) which is critical for the formation of new blood vessels (angiogenesis) in the tumor and [3] glycolytic enzymes stimulating anaerobic tumor metabolism for energy preservation to meet their demands leaving an acidic tumor environment after each cycle, [4] BNIP3 (Bcl-2 and 19-kilodalton interacting protein-3) which leads to genomic instability by evading apoptosis and [5] Epidermal Growth Factor Receptor (EGFR) which is associated with a more aggressive tumor behavior [26,29,30]. All these factors contribute to a more aggressive tumor phenotype and finally lead to multifactorial resistance against treatment (figure 1).

FIGURE 1: Schematic representation of hypoxia induced multifactorial resistance

Hypoxia detection

The aforementioned results clearly indicate that tumor hypoxia is associated with poor radiation response and worse locoregional control and survival. Therefore, assessment of tumor hypoxia in the clinical setting becomes increasingly important. Over the last decades, several techniques have been developed to quantify oxygenation status of tumors.
The gold standard procedure to assess tumor hypoxia is by using the *Eppendorf electrode*. This approach has been used to group patients based on their median pO2 values, but disregards a great deal of tumor heterogeneity information. Other disadvantages of this method are its invasiveness and that it is mainly applicable in well accessible superficial tumors.

Tumor hypoxia can also be determined by using *immunohistological techniques* by staining for various intrinsic or extrinsic markers of hypoxia. Immuno-histochemical staining methods provide the relative oxygen concentrations on an individual cell basis and enable distinguishing between viable and necrotic tissues. However, this technique also pose major limitations, such as the limited availability of only small tumor portions after biopsy and therefore a lack of a global picture of oxygenation status of the entire tumor. Furthermore, consensus regarding how to classify the different staining patterns is lacking and may severely hamper reproducibility and generalizability of results among different investigators [17]. These limitations made clinicians to concentrate more on non-invasive techniques such as Positron Emission Tomography (PET) imaging with specific hypoxia tracers.

*Nitroimidazole derivatives*, such as Fluormisonidazole (FMISO), are a hypoxia-specific tracer molecule used for clinical PET examinations [31]. At low oxygen levels (5-10 mmHg), the compound is reduced under hypoxic conditions specifically, forms a covalent bond with thiol groups in the cell, and finally detected by PET scanners [13]. In a recent study that was conducted to evaluate the reproducibility of FMISO, intratumoral distribution in 20 patients with head and neck cancer showed considerable variability in the intratumoral uptake that occurred between repeated FMISO-PET scans performed three days apart [31].

More recently, Fluoroazomycinarabinoside (FAZA) has been developed as a hypoxia tracer, because it exhibits more favorable tumor-to-background in most anatomical regions than FMISO [33]. In addition, FAZA exhibits *in vivo* stability against enzymatic activity, and therefore can be recommended as a potential tracer for hypoxia in clinical studies. Recently, Souatzoglou et al. evaluated the feasibility of FAZA-PET for the imaging of tumor hypoxia in eleven patients with head and neck cancer and concluded that FAZA-PET imaging is feasible and that adequate image quality can be achieved [33]. Another study, evaluated the role of FAZA PET imaging to identify hypoxia in order to plan radiation treatment in head and neck cancer patients. It was concluded that IMRT treatment planning based on FAZA uptake measurements is feasible [34].

One of the newly developed hypoxic tracer is HX4 ([18F]-3-Fluoro-2-{4-[(2-nitro-1H-imidazol-1-yl) methyl]-1H-1, 2, 3-trizol-1-yl}, a member of the 2-nitroimidazole family for the imaging of tumor
hypoxia. Recently, Van Loon et al. [35] studied the properties of HX4 in a phase I NSCLC trial (n=6), with proven stage IV disease, who had undergone prior surgery, chemotherapy and radiotherapy. The mean tumor to muscle ratio for HX4 uptake 120 min after injection was 1.40 (range 0.63-1.98). The authors claim that HX4 may have better pharmacokinetic properties than the recently used FMISO. Recently, Dubois et al. [36] validated heterogeneous HX4 tumor uptake and showed strong correlation with hypoxic fraction as measured by the percentage of pimonidazole positive pixels \( r=0.72; P<0.001 \).

Another well studied non-nitroimidazole hypoxic tracer is 64Cu-ATSM [Cu (II)-diacetyl-bis (A/4-methylthiosemicarbazonie). This compound undergoes reductive metabolism under hypoxic conditions, forming stable adducts that subsequently bind to macromolecules inside the cell, resulting in a PET signal [38]. Its higher membrane permeability as compared to nitroimidazole based tracers makes this tracer more attractive [19]. Takahashi et al. [38] found that the 64Cu-ATSM can be viewed as a promising PET tracer for hypoxia imaging. In their study, an abnormally intense uptake of the 64Cu-ATSM was observed in all patients with locally advanced lung cancer (n=6). This may be due to an enhanced hypoxic condition in the tumor.

Li et al. [20] also evaluated the relationship between changes in tumor oxygenation status during the course of radiotherapy (3DCRT) and the treatment outcome in pathologically proven stage III inoperable NSCLC patients (n=32), using serial hypoxia imaging with 99m TC-HL91 \( \text{[99mTc labeled 4,9-diaza-3,3,10,10-tetramethyldodecan-2,11-dione dioxime]} \). In their study, the median T/N value for 32 patients was 1.47 before radiotherapy. Patients with a T/N value <1.47 showed a better tumor response (81.0%) than patients with T/N value \( \geq 1.47 \) (25.0%) \( p=0.002 \).

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a non-invasive imaging technique that is currently being used for detecting hypoxic status of the tumor [40]. MRI has the advantage of both high spatial and temporal resolution and it can be repeated as needed. Cooper et al. [40] used Eppendorf electrodes to measure hypoxic status of the tumor in 30 patients with cervical carcinoma; DCE-MRI was performed prior to obtaining oxygenation data. Tumor oxygenation status was found to correlate with their semi quantitative DCE-MRI derived parameters. In another study of seven patients with HNSCC, statistically significant correlations were observed between DCE-MRI parameters and significant pimonidazole tissue staining of surgical specimen [40]. Several advanced MRI techniques are currently being used in the assessment of tumor hypoxia. BOLD MRI can measure hypoxia by the ratio of deoxy-haemoglobin to oxy-haemoglobin in blood whereas, TOLD MRI, Tissue Oxygen Level Dependent MRI estimates hypoxia by measuring tissue oxygenation status. However, as these techniques are technically complex and challenging, they are beyond the scope of this
thesis. However, the interested reader may refer to relevant publications in the subject [41].

**Strategies to overcome hypoxia**

The aforementioned studies clearly indicate that tumor hypoxia leads to a number of molecular responses and subsequent cellular mechanisms responsible for poor locoregional tumor control. Therefore, a number of strategies have been applied to overcome tumor hypoxia.

**Hyperbaric oxygen**

Hyperbaric oxygen (HBO) treatment can be used to improve oxygenation status of the tumor, by enhancing the amount of dissolved oxygen in the plasma and thereby increasing oxygen delivery to the tumor tissue [42]. HBO in combination with radiotherapy has been used clinically as a radiosensitizer, aiming to increase the DNA damage by means of radiation treatment [43]. However, in a recent pre-clinical study, in combination with radiotherapy and HBO in experimental head and neck cancer showed that although HBO did reduce the hypoxic status of the tumor, it did not have any effect on tumor growth, neither alone nor in combination with radiotherapy [44]. A review by Daruwalla et al. [45] based on ten clinical studies, HBO treatment of patients with cervical and bladder cancer did not offer any benefit. Therefore, the use of HBO in combination with radiotherapy still remains unclear and does not seem very promising.

**Hypoxic cell sensitizers**

Instead of trying to force oxygen into tissues by the use of pressurized oxygen tanks, the emphasis shifted to oxygen substitutes that diffuse into poorly vascularized areas of tumors and achieve the desired effect by chemical means [25,43]. Major effects have been directed at developing chemicals that can sensitize hypoxic cells which in principle mimic the effect of oxygen, and so have no sensitizing effect on normal tissues. The most widely studied hypoxic cell sensitizer is misonidazole, a member of the Nitroimidazole family [44]. In a randomized clinical trial performed by the Radiation Therapy Oncology Group (RTOG), the addition of misonidazole to radiotherapy showed no benefit [46]. However, the Danish multicenter randomized double-blind trial with another radiosensitizer, known as nimirazole, demonstrated an overall benefit in survival as well as locoregional tumor control [47]. A statistically significant improvement in locoregional tumor control was found in nimirazole treated patients compared to patients receiving radiotherapy and placebo (5-year actuarial rate of 49% versus 33%, P<0.002). This trend was also found in the overall survival but to a lesser, non-significant extent (26% versus 16%, 10-year actuarial values, P=0.32). A recent meta-analysis by Overgaard et al. found that in HNSCC the addition of hypoxic modifiers to radiotherapy significantly improved loco-regional
tumor control. Most hypoxic sensitizer trials have been performed using nimorazole. However, effective doses of this drug were found to cause peripheral neuropathy, which is the main reason why it has been kept from routine clinical use [43].

**ARCON: (Accelerated radiotherapy with carbogen and nicotinamide)**

ARCON is the combination of accelerated radiotherapy in combination with breathing hyperbaric oxygen and nicotinamide [48]. Based on the results of the meta-analysis on altered fractionation, accelerated radiotherapy is considered standard of care when radiotherapy is administered as single modality [49]. In this approach, carbogen breathing is added to overcome chronic hypoxia while nicotinamide is added to overcome acute hypoxia.

Breathing hyperbaric oxygen (100% oxygen) can lead to vasoconstriction, which may in result variations in tumor blood supply. This can be avoided if 5% carbon dioxide is added to oxygen, a mixture called carbogen. Nicotinamide is a vitamin B3 analogue that prevents transient fluctuations in tumor blood supply, which may cause acute hypoxia [50]. An approach using a combination of these additions was tested in a Dutch phase III clinical trial in which patients with locally advanced carcinoma of the larynx were randomly assigned to receive accelerated radiotherapy alone versus ARCON. No significant difference was noted in local tumor control, but this may be due to the lower dose to the primary tumor site when accelerated radiotherapy was combined with ARCON [50].

**Chemotherapy agents**

Another strategy to overcome radioresistance of tumors is the use of drugs that preferentially sensitize and selectively kill hypoxic cells [51]. Tirapazamine (TPZ) is a representative hypoxia activated pro-drug. TPZ exerts its cytotoxic effect through formation of radicals that initiate intracellular macromolecular damage, causing DNA double-strands brake [25]. However, a phase III randomized clinical trial in advanced HNSCC patients comparing TPZ, cisplatin and radiotherapy to cisplatin and radiotherapy showed no significant differences in either 2-year failure free survival, time to locoregional progression and quality of life [52]. It should be noted however, that the results of this study should be interpreted with caution as the results appear to be jeopardized by poor quality radiotherapy [53].

**Radiation dose escalation**

Gray et al. were the first to describe the role of tumor hypoxia in increasing tumor resistance to radiotherapy [54]. The degree of sensitization by oxygen is often quoted as oxygen enhancement
ratio (OER), which is the ratio of doses needed to achieve the same tumor control probability as in tissue with normal oxygenation status [55]. For ionizing radiations such as x-ray and \( \gamma \)-rays, the OER at high doses has a value of between 2.5 and 3.5. Increased oxygen concentration creates additional free radicals and consequently, increases the damage to the target tissue. Therefore, oxygenation status of the tumor is very important to the effects of irradiation [56]. 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 [22]. As a consequence, a higher radiation dose is needed to achieve the same local control rate, in hypoxic tumors [57]. Dose escalation is therefore an important strategy to overcome tumor hypoxia.

The presence of molecular oxygen mediates DNA damage through formation of oxygen free radicals which is less likely to occur in hypoxic conditions [21,22]. Hence higher radiation doses are required to combat tumor hypoxia. Martel et al. [58] estimated that a dose of at least 80 Gy is required to achieve a 50% locoregional control rate at three years. Recent studies showed that higher radiation doses significantly improve locoregional tumor control and overall survival rates. For instance, Rengan et al. [59] observed that an increase of 10 Gy resulted in a 36% decrease in local failure risk. In addition, Kong et al. [60] concluded that a 1 Gy radiation dose escalation was associated with a 3% reduction in the risk of death. However, increasing the radiation dose may also increase the dose to healthy tissues and thus to an increase in radiation induced side effects. Ideally speaking, only hypoxic areas of the GTV should receive such a higher dose.

Although tailored hypoxic tumor dose escalation appear a promising approach, the question arises as to whether this is practically feasible. First, this approach requires detection of tumor hypoxia by technologies that provide spatial information regarding tumor hypoxia. In addition, the choice of the radiation dose escalation technique [e.g. simultaneous integrated boost technique or single high dose stereotactic boost] highly depends of the course of hypoxia during the course of radiation treatment. Therefore, the development of such strategies demands a detailed knowledge of the time course of hypoxia and re-oxygenation. Unfortunately, this information is not yet available for human tumors.

PET imaging with hypoxia tracers can theoretically be combined with Intensity Modulated Radiotherapy (IMRT), to improve locoregional tumor control and subsequently survival of the patients with locally advanced disease. The ability of IMRT to accurately deliver higher radiation doses to hypoxic regions within the tumor as visualized by PET tracers, without increasing the normal tissue toxicity is very appealing. Several strategies are under development [IMRT with a simultaneous integrated boost, VMAT, protons]. To achieve the most optimal hypoxic subvolume dose escalation, the knowledge of
spatial-temporal dynamics of tumor hypoxia during the course of radiotherapy is essential.

**Which information is needed to overcome hypoxia by dose escalation?**

From a radiobiological point of view, dose escalation to the tumor is a logical strategy to overcome the adverse effects of hypoxia on radioresistance. 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 and dysphagia which both have a significant negative effect on quality of life after completion of treatment [61]. 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 tissues [60,61]. Although such strategy may appear obvious, dose escalation to hypoxic regions is rather complex issue as there are several factors that may introduce significant changes in the spatiotemporal dynamics of tumor hypoxia [10], including:

1) Tumor oxygenation patterns are heterogeneous among individual patients [10];

2) The severity of hypoxia in tumor cells depends on the diffusion distance between tumor and blood supply [25];

3) Tumor cells that are hypoxic today may or may not be hypoxic at subsequent time points due to a changing tumor microenvironment [4,10].

If the hypoxic subvolumes remain geographically stable during the course of chemoradiation, increasing the radiation dose in these subvolumes may allow improving local tumor control. On the contrary, such an approach is unlikely to be beneficial or may even harmful if the size and/or location of the hypoxic subvolumes change significantly during the treatment. Therefore, it is crucial to distinguish geographically stable and dynamic hypoxia during therapy as this will affect dose escalation strategies to intratumoral hypoxic areas during the course of irradiation. Then, we can optimize the timing and frequency of hypoxia imaging for the treatment planning.
Questions to be answered?

Dose escalation to hypoxic areas is a potentially promising but not yet proven radiotherapy approach. Before it can be clinically tested, several measures need to be addressed.

1. Radiation dose escalation to hypoxic areas requires accurate spatial information obtained by advanced imaging techniques, e.g. as determined from PET/CT imaging using hypoxic tracers.

2. In many centers, radiation treatment planning is already based on planning FDG-PET/CT. It has been suggested that tumoral FDG uptake correlates with tumor hypoxia and that high FDG uptake could be used as a surrogate for tumor hypoxia and that additional and specific PET-tracers to detect hypoxia are unnecessary [13]. However, this correlation remains to be determined.

3. It has been hypothesized that dose escalation to hypoxic areas is most effective if the most hypoxic areas receive the highest radiation dose. In general, radiation treatment planning is performed prior to treatment and assumes a more or less stable situation during the entire course of treatment. However, based on the previously mentioned findings, this is very unlikely. During radiation, the spatial distribution of hypoxia is likely to change due to cytotoxic treatment, tumor shrinkage and hypoxia transience. The extend of these changes during the course of treatment and the possible consequences with regard to dose escalation strategies remain to be determined as well.

Aims of this thesis

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 subvolumes 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. This requires methods that provide spatial information on tumor hypoxia prior to and during the course of radiation. The studies described in this thesis will focus on a number of methodological issues related to the development of hypoxia-guided radiation dose escalation in HNSCC and NSCLC.

More specifically, the aims of this thesis are:

1) To get insight on the role of PET to image tumor hypoxia in NSCLC and its potential use for radiotherapy treatment planning, including to summarize the different hypoxia tracers, to investigate whether tumor hypoxia is present in NSCLC, and finally to describe whether the
presence of hypoxia as demonstrated on PET scans can be used to predict outcome. For this purpose, a systematic review of literature was performed and the results of this review are described in [Chapter 2].

2) To determine the potential added clinical value of the specific hypoxia tracer FAZA over the commonly used FDG in the treatment of advanced NSCLC patients. The amount of tumor FDG uptake may reflect the level of hypoxia and may therefore be used as a surrogate marker for tumor hypoxia. The results of a prospective study including patients with NSCLC investigating this putative assumption are described in [Chapter 3].

3) To investigate how chemotherapy affects areas of tumor hypoxia as measured with FAZA uptake and whether these changes correspond to metabolic effects as measured with FDG in NSCLC patients [Chapter 4].

4) To quantify spatio-temporal dynamics of tumor hypoxia using serial hypoxic imaging before and at several time-points during (chemo)radiotherapy in head and neck and non-small cell lung cancer patients [Chapter 5].

5) To investigate the prognostic value of post-Stereotactic ablative body radiotherapy (SABR) FDG uptake at 12 weeks with respect to treatment outcome in medically inoperable patients with stage I NSCLC or FDG-PET positive primary lung tumors [Chapter 6].

Eventually, chapter 7 contains the general discussion and proposals for future directions.
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