PET Imaging in Head and Neck Cancer Patients to Monitor Treatment Response: A Future Role for EGFR-Targeted Imaging
Laura K. van Dijk1,2, Otto C. Boerman2, Johannes H.A.M. Kaanders1, and Johan Bussink1

Abstract
Approximately 50,000 new cases of head and neck squamous cell carcinoma (HNSCC) are diagnosed worldwide each year and subsequently treated with surgery, chemotherapy, radiotherapy, and/or targeted therapy. The heterogeneity of the patient population in terms of treatment response drives the search for tumor-specific biomarkers. Imaging of biomarkers can reveal patient-specific responses to therapies and, if assessed early after the start of treatment, may allow adaptation of treatment regimens. In this review, tracers that have been tested to monitor treatment efficacy in HNSCC by PET scanning prior to and early after the onset of treatment are discussed. An important imaging target for this application in HNSCC patients is the EGFR. It steers the pathways related to proliferation, hypoxia, DNA damage repair, and apoptosis, all treatment-resistance mechanisms. The anti-EGFR antibody cetuximab has been labeled with various radionuclides and has been tested as an imaging biomarker in several HNSCC models. These studies suggest that EGFR-targeting tracers can be used to monitor EGFR receptor expression in HNSCC and have the potential to noninvasively monitor cetuximab treatment and steer individualized treatment regimens. Multiple factors can influence the uptake of EGFR-targeting tracers. Here, we discuss the relevance of gene and protein overexpression, mutations, and amplifications related to EGFR signaling. In addition, monoclonal antibody properties and the effect on the host immune system represent the accessibility of the drug targets; (iv) the expression influence the uptake of EGFR-targeting tracers. Here, we discuss the relevance of gene and protein overexpression, mutations, and amplifications related to EGFR signaling. In addition, monoclonal antibody properties and the effect on the host immune system are reviewed in light of the future role of EGFR-targeted imaging in HNSCC. Clin Cancer Res; 21(16); 3602–9. ©2015 AACR.

Introduction
For most head and neck squamous cell carcinomas (HNSCC), treatment is with curative intent and consists of surgery and/or radiotherapy, with or without concurrent chemotherapy or targeted therapy. However, approximately 50% of patients with locally advanced disease will develop recurrences or metastases within 2 years. Chemotherapeutics, such as cisplatin and 5-fluorouracil (5-FU), are routinely applied in combination with radiotherapy for treating locally advanced HNSCC, which has been shown to have a benefit over radiotherapy alone (1). Targeted therapies are being investigated, of which the majority focuses on targeting the EGFR. The EGFR is overexpressed in most epithelial malignancies, including HNSCC, is involved in pathways related to the tumor microenvironment and tumor cell metabolism, and controls cell survival mechanisms such as proliferation, hypoxia, DNA damage repair, and apoptosis (2). Cetuximab, a chimeric monoclonal antibody against the EGFR, is the only agent approved for use in HNSCC patients. Combining radiotherapy with cetuximab resulted in improved disease-free survival (DFS) and overall survival (OS; ref. 3). However, less than 15% of the patients benefitted from the addition of cetuximab.

In this review, we discuss PET tracers for HNSCC and their potential as imaging biomarkers, focusing on repetitive assessments. The EGFR imaging studies performed so far are reviewed. The strengths and pitfalls of EGFR monitoring, such as receptor expression, mutations, and amplifications, are addressed.

Repetitive Imaging in Head and Neck Cancer
The response to treatment is influenced by tumor microenvironmental factors, such as tumor oxygenation, proliferation, intrinsic radioresistance, and acquired drug resistance (4). Microenvironmental differences between tumors can be detected and quantified, for example by determining protein expression profiles by immunohistochemistry. Immunohistochemical analysis is a widely applied technique on biopsy material; however, biopsy sampling is an invasive procedure and prone to sampling errors. Further, repeated biopsy is unattractive because anesthesia is often required.

A noninvasive method for biomarker detection is radionuclide imaging using single-photon emission computed tomography (SPECT) or PET. The strengths of radionuclide imaging are 5-fold: (i) it registers the whole tumor in contrast to biopsy studies; (ii) multiple lesions may be detected and analyzed simultaneously; (iii) it targets only those areas that are systemically accessible, representing the accessibility of the drug targets; (iv) the expression of a specific target of a drug or resistance mechanism can be visualized; and (v) it allows for repetitive noninvasive assessments. Of special interest are evaluations where PET scans are acquired before and during treatment (Table 1). As such, the patient serves...
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Abbreviations: CR, complete response; CRT, chemoradiotherapy; EFS, event-free survival; ICT, induction chemotherapy; LPFS, local progression-free survival; LRC, locoregional control; LRF, PMR, partial metabolic response; SUV_{max}, maximum standard uptake value; T/B_{max}, maximum tumor-to-blood.
as his/her own control, thereby visualizing and quantifying the effects of the intervention in that particular patient.

**Metabolism**

$^{18}$F-labeled fluorodeoxyglucose ($^{18}$F-FDG) is the most widely applied tracer for PET, visualizing tumor cell metabolism. In HNSCC patients, $^{18}$F-FDG PET has been used for tumor volume assessment and staging and has prognostic potency as well (5). Hentschel and colleagues (6) showed that the 2-year OS was 88% for patients with $\Delta$SUV$_{\text{max}}$ $> 50\%$ measured 1 to 2 weeks after the start of concomitant chemoradiotherapy, relative to only 38% for patients with $\Delta$SUV$_{\text{max}}$ $< 50\%$ ($P = 0.02$). Abgral and colleagues (7) conducted $^{18}$F-FDG baseline scans and a second scan after two cycles of induction chemotherapy, which was then followed by chemoradiation. The median event-free survival (EFS) was 19 months (range, 4–25 months) and 10 months (range, 8–13 months) for responders and nonresponders, which correlated to 1-year EFS rates of 100% and 20%, respectively ($P = 0.0014$). Other studies of similar design have confirmed that a decrease of more than 50% in SUV$_{\text{max}}$ can predict clinical outcome (6, 9). $^{18}$F-FDG PET has been tested clinically for a potential role in response monitoring of EGFR-targeting therapies. Schmitz and colleagues (10) reported a partial response to preoperative administration of cetuximab in 18 of 19 patients, which corresponded to a $\Delta$SUV$_{\text{max}}$ of below $-25\%$ as measured at baseline and before surgery. A similar design by Adkins and colleagues (11) in 10 patients showed that a partial response corresponded to a mean decrease of $\Delta$SUV$_{\text{max}}$ below $48\%$ as measured before and after 8 weeks of cetuximab infusion. Although study numbers were limited, $^{18}$F-FDG could be further investigated as a potential early marker of cetuximab activity in HNSCC.

**Hypoxia**

The presence of tumor hypoxia is a common aspect of HNSCC and is a well-known cause of resistance to radiotherapy and chemotherapy (12). Hypoxia assessed by means of serial $^{18}$F-fluoromisonidazole ($^{18}$F-FMISO) PET imaging in HNSCC is of prognostic value. Dixit and colleagues (13) showed in 15 HNSCC patients that tumor-to-blood ratios ($T/B_{\text{max}}$) measured before and during chemoradiotherapy correlated negatively to DFS. Persistent $^{18}$F-FMISO uptake has also been correlated to locoregional failure (LRF) and local recurrence (LC; refs. 14, 15). $^{18}$F-FMISO imaging and especially dynamic scans could be relevant for response monitoring, especially with intensity-modulated radiotherapy (IMRT), to guide hypoxic subvolume delineation for adaptive radiotherapy (16, 17).

$^{18}$F-Fluoroozomicin-arabinoside ($^{18}$F-FAZA) accumulates in hypoxic cells by the same mechanism as $^{18}$F-FMISO. However, it is less lipophilic than $^{18}$F-FMISO and clears more rapidly from the blood, resulting in improved tumor-to-background contrast. Mortensen and colleagues (18) showed images with good tumor-to-background contrast in HNSCC patients as early as 2 hours after injection, encouraging further studies.

Pretreatment $^{62}$Cu-labeled (diacetyl-bis(N4-methylthiosemicarbazone)) ($^{62}$Cu-ATSM), for quantifying hypoxia, which was shown to have prognostic value for response to chemoradiotherapy, could be predicted by high pretreatment SUV$_{\text{max}}$ ($> 5.0$; ref. 19). This was supported by results from another recent study in which high pretreatment $^{62}$Cu-ATSM tumor uptake correlated with a reduced PFS (20). However, it is not known to what extent $^{62}$Cu-ATSM reflects tumor hypoxia is questionable. In a preclinical study evaluating $^{64}$Cu-ATSM, a negative correlation was found between hypoxia and tracer uptake in the tumor when assessed at early time points (<16 hours; ref. 21).

**Proliferation**

Tumors with high proliferative activity have been shown to be resistant to chemoradiotherapy (22). A study in 48 HNSCC patients analyzed the change in proliferation rate with $^{18}$F-labeled 3-fluoro-3-deoxy-thymidine ($^{18}$F-FLT) uptake and found that an SUV$_{\text{max}}$ decrease of $\geq 50\%$ between pretreatment and the first 2 weeks of treatment was associated with significantly better DFS (88% vs. 63%; $P = 0.035$; refs. 23, 24). Similar results were obtained by Kishino and colleagues (25), confirming the ability of $^{18}$F-FLT to monitor tumor response to chemoradiotherapy.

Even though the tracers mentioned above have demonstrated prognostic value, many methodological differences have influenced these study results (21, 26). The potential of these tracers for monitoring targeted therapy response should be more extensively studied in multicenter trials with larger cohorts and improved standardization.

**Potential of EGFR Imaging in Head and Neck Cancer**

EGFR as a biomarker

An imaging target in HNSCC is the EGFR, as it is involved in the regulatory pathways in all the radiotherapy-resistance mechanisms, such as hypoxia, proliferation, and intrinsic radioresistance (Fig. 1). The EGFR is one of the most dominantly expressed receptors in HNSCC: More than 80% of cases of HNSCC exhibit an increased membraneous expression of this ErbB family member (27). Its natural ligands are growth factors, including EGF, TGF$\alpha$, and heparin-binding EGFR-like growth factor (HB-EGF), some being overexpressed in HNSCC as well. EGFR activation steers, among others, the EGFR-phosphatidylinositol 3-kinase/protein kinase B (EGFR-Pi3K/akt) and the EGFR-RAS/ERK pathways responsible for DNA repair, proliferation, angiogenesis, and inhibition of apoptosis (28–30). The EGFR can also be activated by stress factors such as irradiation, and, as a consequence, effectors within the hypoxia-inducible factor-1 (HIF-1) pathway can enable tumor cell survival via vascular protection and decreased sensitivity to antioxidant molecules (31). Following activation, the EGFR can be internalized and degraded or recycled back to the cell membrane (32). In addition, the EGFR can be translocated to the nucleus and can regulate cell proliferation and DNA repair, which has been associated with poor patient outcomes (31).

The monoclonal antibodies cetuximab and panitumumab bind to the EGFR and prevent the conformational change in the receptor and thus inhibit dimerization and receptor signaling, subsequently incapacitating tumor cells to overcome radiation damage. Immunohistochemical analyses of EGFR expression in tumor samples produced conflicting results in an evaluation of its prognostic value (33, 34). A recent meta-analysis of over 3,000 HNSCC patients revealed that EGFR overexpression is correlated to a decreased OS, but not to a decreased DFS. This indicates that other tumor factors and analytic differences play an important role: Tumor sites, study regions, and scoring system were found to be mostly responsible for the discordance between the studies (35). EGFR expression predicts response to accelerated radiotherapy: a significant benefit in locoregional tumor control was seen in HNSCC patients with...
high EGFR expression ($P = 0.01$) but not in patients with low EGFR expression ($P = 0.85$; ref. 36). Similar results were obtained in another large randomized study (37). However, no role for EGFR as a predictive marker for EGFR-inhibitor treatment has been found. In a large clinical trial, no association between immuno-histochemical EGFR status and cetuximab benefit was found (38).

In addition, in HNSCC the EGFR gene copy number did not correlate with cetuximab response (39–41).

**EGFR imaging**

In the search for potential imaging biomarkers, cetuximab and cetuximab analogues have been labeled with several PET radionuclides, including $^{124}$I, $^{64}$Cu, $^{89}$Zr, and $^{86}$Y (42). Most studies so far were carried out in animal models. In 2005, Perk and colleagues (43) labeled cetuximab with $^{89}$Zr, $^{86}$Y, and $^{177}$Lu and found that the biodistribution of the radiolabels in mice with A431 xenografts was similar. Several studies showed that $^{89}$Zr-cetuximab tumor uptake correlated with EGFR expression determined immunohistochemically (44, 45). Aerts and colleagues (46) found a discrepancy as intermediate EGFR-expressing tumors had a higher uptake of $^{89}$Zr-cetuximab than those with high EGFR expression. This was most likely due to the use of an EGFR-saturating protein dose of the tracer in these models (100 mg/mouse). $^{89}$Zr-cetuximab dosimetry has recently been studied in patients with colorectal cancer, showing that the liver received the highest absorbed dose of $0.61 \pm 0.09$ mSv/MBq$^{-1}$ (47). The ultimate aim is to apply these tracers for treatment monitoring and response prediction. In addition, anti-EGFR tracers could potentially aid in determining nodal metastatic disease. Treatment monitoring using repetitive imaging has been studied in HNSCC xenografts with $^{111}$In-labeled cetuximab-F(ab$^\prime$)$_2$. This tracer could visualize changes of EGFR.
expression, and tumor uptake was correlated with response to the combination of irradiation and cetuximab (48, 49). In addition, a reduced uptake of $^{111}$In-cetuximab-F(ab’)$_2$, in the posttreatment scan compared with the pretherapy scan correlated with response to treatment, while resistance to therapy was characterized by a significantly increased $^{111}$In-cetuximab-F(ab’)$_2$ tumor uptake. The rapid kinetics of F(ab’)$_2$ tracers and the promising preclinical results indicate that this tracer has potential clinical value and should be further investigated.

**Considerations**

Multiple factors can influence the uptake of EGFR-targeting tracers. Response to cetuximab treatment and the correlation with EGFR-tracer uptake can be differentially affected by tumor and host microenvironmental factors.

**Overexpression, mutations, and amplifications**

EGFR alterations present in HNSCC include EGFR overexpression and increased EGFR gene copy number (40, 41). Even though the EGFR expression level has prognostic value, EGFR inhibition efficacy depends on factors affecting downstream signaling (31). The EGFR can be bypassed due to dependency on other ErbB pathways, the receptors of which are also known to be overexpressed in HNSCC, albeit usually to a lesser extent than EGFR (50). EGFR-independent pathways can support tumor growth, for example, through activation of several G protein-coupled receptors (GPCR). These GPCRs can activate AKT and ERK via protein kinase C (PKC) or activate the EGFR tyrosine kinase in a tyrosine-protein kinase CSK (Scrib-dependent) manner, resulting in continued tumor cell proliferation (51). In addition, cetuximab ineffectiveness can be related to mutations in the downstream signaling cascade of the EGFR. For example, the PIK3CA gene encoding for the p110-alpha subunit of PI3K is often amplified in HNSCC and promotes cellular proliferation (52). In addition, the tumor suppressor protein p53, as in many other cancers, is mutated in the majority of cases of HNSCC and also influences tumor proliferation (53).

A number of studies have investigated EGFRVIII, the truncated constitutively active EGFR variant III (54). It harbors mutations in the extracellular binding domain and influences monoclonal antibody binding, thereby affecting inhibition of downstream signaling pathways (55). Recently, a large study by Khattri and colleagues (56) evaluated EGFRVIII expression in 638 HNSCC samples, and found that less than 0.4% of the tumors were EGFRVIII-positive, indicating that the role of EGFRVIII in HNSCC is limited.

**Immune response mechanisms**

The antibody-dependent cellular cytotoxicity (ADCC) that cetuximab supposedly elicits has gained considerable interest (57). The antibody-dependent cellular cytotoxicity (ADCC) that cetuximab supposedly elicits has gained considerable interest (57). The fragment crystallizable (Fc) region of an immuno-globulin G1 (IgG1) antibody can bind several immune cells via the antibody-binding receptor FcγRIIa on natural killer cells, dendritic cells, monocytes, or other granulocytes. This initiates the release of specific enzymes that could degrade the tumor cells it is bound to (58). If ADCC is a significant contributor to tumor response in cetuximab treatment, results obtained in preclinical research may not be representative for the clinical situation as there is no adaptive immunity that can generate a specific immune response in murine xenograft models due to the lack of T cells in these animals. Recently, it has been shown that EGFR-specific T lymphocytes in cetuximab-treated HNSCC patients may contribute to antitumor activity relevant to clinical response (59). Therefore, the effect of cetuximab can be underestimated by the absence of adaptive ADCC-driven tumor cell kill in xenograft models.

Another characteristic of EGFR-targeting tracers is that they bind to EGFR expressed on normal tissues as well. As the EGFR is present in many normal human epithelial tissues, it can elicit a multitude of side effects (60). In the skin, EGFR inhibition deregulates normal keratinocyte proliferation, differentiation, and migration, resulting in an acneiform rash (61). In HNSCC patients, a correlation between the intensity of cutaneous rash and the effectiveness of cetuximab has been suggested (62). The interaction between rash and cetuximab response is currently under further investigation in a phase IV trial (NTC01553032, ref. 63). If confirmed, the severity of skin rash may aid in selecting patients for less toxic regimens (i.e., radiotherapy with cetuximab) or more intense regimens (i.e., chemoradiotherapy).

Treatment with monoclonal antibodies can elicit immunologic human anti-mouse antibody responses (HAMA) in patients, which subsequently can evoke allergic reactions and reduce monoclonal antibody efficacy (64). This was primarily seen in the first-generation antibodies of murine origin. Chimeric antibodies such as cetuximab contain fewer murine epitopes, but might still instigate a HAMA response and/or hypersensitivity reaction (65). Panitumumab targets the EGFR and is a fully human IgG2 monoclonal antibody, which therefore does not evoke a HAMA response. However, panitumumab could still induce a human anti-human antibody (HAA) formation and hypersensitivity reactions because of a higher number of effector T-cell epitopes and a smaller number of immune-suppressing regulatory T-cell epitopes on the engineered antibody (66). Panitumumab is currently used to treat colorectal cancer (67). In addition, $^{68}$Zr-panitumumab is currently being tested clinically as an EGFR-monitoring tracer in HNSCC (68).

**Properties of monoclonal antibodies**

Cetuximab has a half-life of 95 ± 24 hours in humans (69). If used as an imaging agent, it is present in the circulation for weeks, impeding rapid serial imaging. In mice, cetuximab has a half-life of approximately 40 hours, and optimal images with $^{111}$In-labeled cetuximab can be acquired 3 to 7 days after injection (32, 70). To facilitate earlier imaging and allow quick repeated assessments, the use of radiolabeled F(ab’)$_2$, Fab’ fragments, or other small formats of cetuximab might be a solution (71, 72). These fragments exhibit rapid clearance from the blood and rapid tumor penetration, while retaining the affinity of cetuximab IgG (71, 73). Especially in relation to monitoring treatment regimens, it would be an advantage if early repeated imaging would enable earlier adaptation of the therapeutic regimen. In addition, tumor cells can exhibit rapid turnover, especially in hypoxic tumors (<49 h; ref. 74). Hence, rapid assessment with antibody fragments could more accurately reflect receptor expression. This is in contrast to intact IgG tracers, which require delayed imaging for optimal tumor-to-background contrast and thus could potentially overestimate EGFR targetability.

As cetuximab is administered in relatively high doses for treatment purposes, application of an EGFR tracer directed against the same epitope is not possible during cetuximab treatment due to EGFR saturation. Therefore, the timing of
image acquisition in relation to the administered therapeutic dose is essential.

Conclusions
For treatment response monitoring, agents such as $^{18}$F-FDG and proliferation- or hypoxia-related tracers have been used. Radiolabeled EGFR inhibitors such as cetuximab have great potential to assess EGFR expression before and during treatment. Clinical research works toward a role for these tracers to monitor treatment response, thereby allowing adaptation of treatment regimens when necessary. Current and future studies will demonstrate the effectiveness of such strategies in the HNSCC patient population and ultimately could enable individualized treatment.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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