CHAPTER 1

INTRODUCTION AND OUTLINE OF THESIS
CHAPTER 1
HEADC AND NECK SQUAMOUS CELL CARCINOMA

Etiology and staging

Head and neck squamous cell carcinoma (HNSCC) refers to malignant tumors that originate from the epithelium of the upper aerodigestive tract including the oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses (Figure 1). Squamous cell carcinoma consists of malignant cells with squamous differentiation. HNSCC is the sixth most common cancer, accounting for approximately 4% of all malignant tumors worldwide. The estimated incidence is 630,000 per year with a mortality-rate of 350,000. In the Netherlands approximately 3000 new patients are diagnosed with HNSCC every year.

Tobacco smoking and excessive alcohol consumption are well-known risk factors. Several other factors are also associated with the development of HNSCC, like human papillomavirus (HPV) and Epstein-Barr virus (EBV) and genetic and immunological predisposition.

The stage at diagnosis is an important parameter as it mostly determines the treatment plan and prognosis of patients with HNSCC. Staging is performed according to the TNM system of the International Union Against Cancer which consists of the extent of the primary tumor (T), the involvement of regional cervical lymph node metastasis (N) and the presence of distant metastasis (M). Based on this system, clinical stages I-IV can be established; tumors localised within the organ of origin are stage I and II, stage III represents local extension or with cervical lymph node metastasis and stage IV means more advanced cancer, i.e. primary tumor extension beyond the organ of origin and extensive nodal disease or distant metastasis. About one third of the patients present with early staged disease (stage I and II), while two third presents with advanced staged disease (stage III and IV), especially patients with oropharyngeal cancer.

Oropharyngeal squamous cell carcinoma and HPV

The oropharyngeal region is a part of the pharynx and comprises the tonsils, base of tongue, vallecula, posterior pharyngeal wall and the soft palate (including uvula) (Figure 1). Over the last decades, it has been well established that HPV is an important etiological factor in the development of particularly squamous cell carcinomas in the oropharynx (OPSCC), most commonly in the base of tongue and tonsils. Approximately 570 new patients with OPSCC are diagnosed every year in the Netherlands of which 175 patients...
have HPV-positive carcinomas \(^3\). The incidence of oropharyngeal cancer is increasing in North-western Europe and Northern America \(^{13-17}\), despite successful attempts to control tobacco and alcohol consumption, suggesting an increased contribution of HPV. Prevalence-rates of HPV-positive OPSCC vary around the world. As mentioned before, prevalence rates of HPV-positive OPSCC in the Netherlands are approximately 30\% \(^{18}\), while prevalences of 72\% \(^{19}\) are reported in the United States. HPV-positive OPSCC characteristically occurs in younger (<50 year) white male patients without a history of smoking and alcohol abuse \(^7,13\). HPV-positive and HPV-negative OPSCC are distinct disease entities \(^{20}\); HPV-related tumors have distinct histological features \(^{21,22}\) and have a different genetic route to cancer \(^{23,24}\).

The HPV genome consists of double-stranded DNA and produces two oncoproteins E6 and E7. These oncoproteins play a role in oncogenesis by inactivation of apoptotic pathways, disruption of cell cycle control and activation of cellular proliferation. The E6 oncoprotein inactivates and promotes degradation of the tumor suppressor p53, thereby disrupting normal apoptosis \(^{25,26}\). The E7 oncoprotein blocks the function of retinoblastoma (RB) pocket proteins, which leads to cell cycle entry and hereby allowing the virus to replicate \(^{27,28}\).

![Figure 1.](image)

Anatomy of the head and neck region, with sites of origin of tumors in the head and neck region including oropharyngeal subsites.
Therapy and prognosis

Three modalities are used in the treatment of HNSCC: surgery, radiotherapy and chemotherapy, which can be used separately but often a combination of these therapies is needed. Formerly, patients with advanced but resectable HNSCC were treated with a combination of surgery and postoperative radiotherapy, often leading to functional and cosmetic morbidity, inducing a diminished quality of life. Unresectable HNSCC was treated by radiotherapy with or without chemotherapy. Nowadays, non-surgical protocols are applied in the treatment regimen of resectable tumors as well, intending to preserve organ function and to maintain quality of life. This application of organ preservation protocols resulted in considerable locoregional control rates and it appeared that intensified radiotherapy schemes (accelerated or hyperfractionated) and combinations of chemotherapy and radiotherapy (CRT) all contribute to an increased control rate. At present, in the Netherlands most commonly used concomitant CRT with cisplatinum comprises 7 weeks of radiotherapy (70 Gray in 35 fractions) combined with three courses of intravenous cisplatinum (100 mg/kg) on day 1, 22 and 43.

Non-surgical treatment is associated with acute and long-term side effects; common complaints with radiotherapy are xerostomia, impairment in speech and difficulties in swallowing. Fibrosis of the neck with reduced mobility and pain are also not unusual. Chemoradiotherapy with cisplatinum may be accompanied by serious toxic side effects as cisplatinum is ototoxic, neuro- and nephrotoxic. Therefore, chemoradiotherapy is only appropriate for patients with a good health performance and normal kidney function. Accelerated radiotherapy (6 fractions a week) in combination with cetuximab (400 mg/m$^2$, followed by 250 mg/m$^2$ a week) is an alternative for elderly patients or patients with a poor performance status or decreased creatinine clearance. Adding cetuximab to radiotherapy alone leads to a significantly better locoregional control and survival. Cetuximab appears to be well endured, however, acute and chronic toxic skin effects do occur, such as a rash, discomfort and itching.

Prognosis is linked to the clinical stage at diagnosis. Patients with early stages HNSCC (stadium I and II) generally have a fairly good prognosis (80-90% 5-year survival rate), in contrast to patients with advanced disease (stadium III and IV), who have a much worse prognosis (40-50% 5-year survival rate). However, patients with HPV-positive OPSCC show more favourable treatment responses and survival rates as compared with HPV-negative OPSCC, despite the fact that patients with HPV-positive OPSCC more often present with regionally advanced disease.
Response evaluation

Fairly low locoregional residual and recurrent tumour rates indicate that CRT is an acceptable treatment option for patients with HNSCC. However, after failure of CRT, surgical salvage treatment may be curative if residual locoregional disease of initially resectable HNSCC is detected timely. In case of late detection and delayed salvage surgery, locoregional control and survival rates rapidly decrease. An examination under general anesthesia (EUA) (with eventual biopsies) is considered to be the most reliable procedure to detect local residual disease and since salvage surgery is associated with considerable morbidity and a high risk of complications, it will only be performed after histopathological confirmation of viable tumor cells obtained during EUA. Consequently, current clinical practice in the VU University Medical Center is to perform stringent response evaluation, i.e. EUA, routinely 12 weeks after the end of CRT. However, due to the acceptable locoregional control rates after CRT, many patients are exposed to unnecessary anaesthesia and biopsies in irradiated areas, potentially inducing inflammation and pain.

Timely detected residual neck disease after CRT for HNSCC can often be successfully salvaged with a neck dissection. A neck dissection is a relatively safe procedure with generally good therapeutic results. Nevertheless, it is associated with certain risks and complications, especially after previous radiation therapy. Surgical complications, such as bleeding, infection and chylous leakage can occur. Moreover, cutaneous nerves are sacrificed during the operation and can result in insensitivity of the neck or a dull neck pain. Also, the accessory nerve can be damaged, leading to shoulder impairment. Clinical palpation of the neck is most commonly used as diagnostic tool to assess the neck after CRT. If the presence of a residual lymph node is suspected, an ultrasound-guided fine needle aspiration cytology (FNAC) can be performed. On the other hand, planned neck dissection after CRT in all patients with initial N2-N3 disease is also advocated because the presence of residual neck disease cannot be safely predicted with currently used clinical methods.

The assessment of local and regional treatment response varies widely between institutions. It mostly includes a combination of physical examination and imaging. Depending on the initial TNM-stage and local guidelines, outpatient follow-up visits and imaging, such as computed tomography (CT), magnetic resonance imaging (MRI) or ultrasound-guided FNAC are performed. However, discrimination of malignant and aspecific changes after CRT with CT and conventional MRI is unreliable since post-treatment changes, including
oedema, fibrosis and necrosis, hamper accurate assessment \(^\text{46,47}\). Manikantan et al. recommended to perform imaging (CT or MRI) 3-6 months after CRT for the purpose of establishing a new baseline situation for later reference \(^\text{48}\). During recent years, functional imaging with positron emission tomography-computed tomography (PET-CT) and diffusion-weighted MRI (DW-MRI) became available. PET-CT has been gradually incorporated as a part of the post-treatment assessment. DW-MRI is a relatively newer technique and is mostly used for scientific research but in some institutions clinicians already rely on DW-MRI for response evaluation after CRT.

**Treatment prediction**

HNSCCs have a heterogeneous response to treatment \(^\text{38,39}\) and the possible value of imaging parameters as predictive factors for treatment outcome are under investigation. Current traditional prognostic factors, such as TNM-stage, HPV-status, tobacco smoking and alcohol consumption are insufficient to classify patients into risk groups. Identification of other prognostic characteristics could lead to patient selection for tailored treatment regimens and possibly result in higher responses to treatment and less treatment-induced side effects. Tumor characteristics can be assessed by imaging prior to treatment or changes can be evaluated early during treatment. For PET-CT, several studies have shown that patients with high pretreatment standardized uptake values (SUV)-values generally have a less favourable outcome, so it seems that a high rate of glucose metabolism is a characteristic of aggressive tumor behaviour \(^\text{49-52}\). For DW-MRI, it has been suggested that HNSCC with relatively low pretreatment apparent diffusion coefficient (ADC)-values respond better to CRT than tumors with higher pretreatment ADC-values \(^\text{53-56}\). However, it is unknown if these reported associations are partly or even completely attributed to the HPV-status, as patients with an HPV-positive OPSCC respond better to CRT than HPV-negative patients.

In patients with resectable HNSCC, CRT with eventual salvage surgery for residual disease in reserve is preferred. However, salvage surgery after CRT is associated with considerable risks and a high incidence of complications \(^\text{57}\). Another important disadvantage of salvage surgery after (chemo)radiotherapy is the fact that, although it may be indicated on the basis of the pathology results of the surgical specimen, postoperative radiotherapy is rarely possible thus limiting the outcome of this treatment. Therefore, a primary non-surgical treatment may not be the choice of treatment in all patients. Prediction of therapy outcome early during treatment could select patients who are likely not to benefit from CRT. This selection of patients may spare a
certain number of patients from ineffective treatment and may allow a treatment switch to surgery in these patients, preserving postoperative radiotherapy (if indicated) as an option. Several clinical studies have indicated the potential of functional imaging with PET-CT or DW-MRI early during CRT as a predictor of treatment response.

**PET-CT**

*General principles*

Conventional imaging methods such as CT and MRI are primarily anatomical imaging techniques using the physical properties of tissues (absorption of X-rays and proton densities, respectively) to differentiate abnormal from normal tissue. PET-CT is a functional imaging technique which detects the distribution of specific radioactive tracers and combines imaging of metabolically active tissues with anatomical information (Figure 2).

*Figure 2.*

An example of a $^{18}$F-FDG-PET-CT image depicting high $^{18}$F-FDG uptake in a right base of tongue cancer and a large ipsilateral lymph node metastasis.

PET imaging uses the administration of a molecule which is labelled with a positron emitter (PET tracer). Positron emitters are radioactive atoms with a positive charge. These radionuclides undergo positron decay through emission of a positron. Depending on the characteristics of the original isotope, the positron has kinetic energy which defines the distance of motion the positron travels in matter. After travelling a distance or range in matter, the positrons lose their kinetic energy through ionisation and interactions with electrons. After losing its kinetic energy, the process of annihilation will take place and the positron will combine with a free electron. This results in the emission of two photons with an equally shared energy of 511 keV in opposite direction ($180^\circ \pm 25^\circ$) from the annihilation site (Figure 3).
The distribution of the PET tracer within the body can be imaged by a PET scanner, which can be integrated with CT or MRI. Positron imaging uses multiple rings of detectors placed surrounding a patient to detect the directional relationship of two simultaneously emitted photons. Coincidence imaging is used by two opposing detectors to detect a pair of photons, thereby assuming that the point of annihilation occurred within the volume between the ring of detectors. The source of emission (detected event) can be localized along a straight line joining the two detectors and passing through the point of annihilation; the line of response (LOR) (Figure 4). Time-of-flight information is used to further localize the position of annihilation. By accurately measuring the detection times, the time difference in the detection times can provide information about where along the LOR the annihilation happened.

---

**Figure 3.** Positron decay and annihilation

**Figure 4.** Coincidence detection of annihilation photons
Currently, mostly PET-CT scanners are employed in the clinical field; a combination of a PET camera and a CT is used in which the patients move sequentially on a common bed from CT to PET acquisition. The CT scan aids in localizing the lesions visualized by PET and is also used for attenuation correction. Due to photoelectric absorption in a patient, the number of detected photons is reduced, which is called attenuation. However, the relatively poor soft-tissue contrast of CT can be a disadvantage using CT as the supplementary anatomical modality with PET, and coupling PET with MRI can be relevant in clinical situations in which the soft-tissue contrast of MRI outperforms that of CT, for example after radiotherapy in the head and neck area. The first generation of hybrid-PET-MRI systems are emerging into the clinical field permitting combined PET and MRI evaluation.

**18**Fluoro-2-deoxyglucose**

In the last decades, several positron emitting radioactive isotopes have been developed worldwide, but **18**Fluoro-2-deoxyglucose (**18**F-FDG) is the most widely used tracer in oncological PET studies. **18**F-FDG contains the positron emitter fluorine-18 (**18**F, \( t_{1/2} = 110 \) minutes). **18**F-FDG is a glucose analogue and can measure glucose metabolism in malignant tissue. Higher concentrations of **18**F-FDG accumulate in malignant tumors than in normal tissue, due to increased glycolytic activity of the cancer cells. However, physiological uptake occurs in the brain, myocardium and sometimes the colon and the tracer is cleared by the renal system. Also, unwanted uptake may be seen in the neck musculature and vocal folds, due to movement or talking and uncomfortable waiting conditions. Brown adipose tissue (BAT) is closely localized to lymph nodes in the head and neck region and **18**F-FDG uptake in BAT can be another source of false-positive results. The administration of β-adrenergic antagonists, such as propranolol, prior to **18**F-FDG injection can reduce tracer uptake in BAT.

**Acquisition**

PET-CT examinations are started by the intravenously administration of an amount of **18**F-FDG, depending on the body mass index, after 4-6 hours of fasting. Blood glucose levels are measured prior the **18**F-FDG administration and should be <10 mmol/L. Hereafter, the patients rests for 60 minutes in a dark room to avoid unwanted uptake in muscles. Low-dose CT scanning is performed prior to emission scanning for attenuation correction and anatomical localization. During PET scanning, images are acquired for one to four minutes
per bed position and the scan trajectory usually extends from mid femur to cranial vault. In the VU Medical Center a dedicated head and neck protocol is used for head and neck cancer patients, consisting of a scan trajectory from jugular notch to orbit with 4 min emission scans/bed position while the patients are scanned with the arms alongside their body. This protocol is performed prior to the whole body protocol (2 min emission scan/bed position, arms up).

Applications in head and neck oncology

Over the last decades, $^{18}$F-FDG-PET-CT has been increasingly employed in HNSCC for a number of clinical applications. First, PET-CT appeared to be of additional value in tumor staging; i.e. the detection of distant metastasis and simultaneous secondary primary tumors in advanced staged HNSCC. Secondly, in case of cervical lymph node metastasis from an unknown primary tumor, PET-CT has been reported to locate occult primary tumors in up to 44% of these patients. Thirdly, PET-CT has a high accuracy in monitoring response to (chemo)radiotherapy (i.e. response evaluation) and for the detection of residual or recurrent tumor during follow-up, both at the primary site and the neck. In a meta-analysis, the pooled sensitivity and specificity of PET (with or without CT) for the detection of local residual/recurrent disease were 79.9% and 87.5%, respectively and 72.7% and 87.6% for the detection of regional recurrent disease. Newer implementations of $^{18}$F-FDG-PET-CT concern radiotherapy treatment planning and prediction of response to CRT. PET-CT may improve and facilitate delineation of the primary tumor and lymph node metastasis in HNSCC for radiation treatment purposes. PET-CT also has shown to be of predictive value in HNSCC; high pretreatment $^{18}$F-FDG uptake is a poor prognostic factor. Another approach is predicting treatment outcome early during chemoradiotherapy; clinical studies report associations between decline in $^{18}$F-FDG uptake in the early phase of CRT and a positive treatment outcome.

Qualitative and quantitative interpretation

PET-CT scans can be interpreted in a qualitative (i.e. visual) or a quantitative manner. Visual assessment of images is clinically practicable for both nuclear medicine physicians and referring physicians because it provides instantaneous evaluation. However, qualitative interpretation is a subjective task and interobserver variation can occur. A validated interpretation system assists in clarifying equivocal findings found and can improve systematic and reproducible visual review. Until recently there had been no established
interpretation-system for response evaluation in head and neck cancer. In 2014, the Hopkins criteria were validated with substantial interobserver agreement in a retrospective series of 214 patients. These criteria use a qualitative 5-point scale in which scores 1, 2 and 3 are considered negative for tumor and scores 4 and 5 are considered positive for tumor (Table 1).

**Table 1. Hopkins Criteria for Head and Neck PET/CT**

| Score | 
|-------|-----------|------------------------------------------------|
|       | **18F-FDG-uptake pattern** | **Response category** |
| 1     | 18F-FDG uptake at the primary site and nodes less than IJV | Complete metabolic response |
| 2     | Focal 18F-FDG uptake at the primary site and nodes greater than IJV but less than liver | Likely metabolic response |
| 3     | Diffuse 18F-FDG uptake at the primary site or nodes is greater than IJV or liver | Likely postradiation inflammation |
| 4     | Focal 18F-FDG uptake at the primary site or nodes greater than liver | Likely residual tumor |
| 5     | Focal and intense 18F-FDG uptake at the primary site or nodes | Residual tumor |

Quantification of 18F-FDG uptake can also be used and possibly further improve diagnostic accuracy. The SUV is a semi-quantitative measurement of tracer uptake measured by drawing a Volume of Interest (VOI) using a 3-dimensional region-growing algorithm. For each VOI, the pixel with maximum SUV within the VOI (SUV<sub>max</sub>), the average of a few pixels around the pixel with SUV<sub>max</sub> (SUV<sub>peak</sub>), the average SUV using an adaptive threshold of 50% (SUV<sub>mean</sub>), 18F-FDG-avid tumor volume (metabolic active tumor volume; MATV) and Total Lesion Glycolysis (TLG), calculated as product of SUV<sub>mean</sub> and MATV, can be obtained.

The standardization of the imaging procedure, the interpretation and report on the results of 18F-FDG-PET-CT in oncologic imaging has led to the applicability of 18F-FDG-PET-CT in multicentre studies and increased the value to evidence-based medicine. For this harmonisation of 18F-FDG-PET-CT, procedure guidelines were formed in 2010 and an updated version was published by the European Association of Nuclear Medicine (EANM). In these guidelines, a common quality control/quality assurance procedure is described to support the accuracy of quantification, in which repeatability and reproducibility are important factors. In this manner, consistency between scanners and institutions is secured in case these guidelines are pursued.
DIFFUSION-WEIGHTED MRI

General principles

DW-MRI is a relatively new MR imaging technique within the oncologic applications. DW-MRI has several advantages; it can be included on most MRI scanners in addition to existing clinical imaging protocols, taking only a few extra minutes, and without the need for contrast administration. DW-MRI characterizes micro-environment and cellularity of tissues based on differences in the random Brownian motion of water protons, which is mainly influenced by the amount of extracellular space and the presence of cell membranes. In malignant tumors a higher cell density with limited extracellular space is seen, leading to a reduction in mobility of the water protons and consequently a restriction of Brownian displacement. Tissues containing inflammation or necrosis will have lower cell density leading to higher proton mobility (Figure 5 and 6).

Figure 5.
An example of a DW-MRI image depicting a left base of tongue carcinoma with an ipsilateral lymph node metastasis. Axial STIR MR image on the left, axial DWI b=1000-image in the middle and axial DWI ADC-map on the right.
In a highly cellular environment (left), water diffusion is restricted because of reduced extracellular space and by cell membranes, which act as barrier to water movement. In a less cellular environment (right), relative increase in extracellular space and defective cell membranes allows water diffusion.

DW-MRI uses two additional equally large but opposite motion-probing gradients. The first gradient dephases each water proton which is rephased by the second gradient in case of stationary water protons. Proton movement between the first and second pulse results in incomplete rephasing which leads to signal loss in the DWI images related to the amount and speed of the diffusion motion. The b-value of a DWI sequence measures the amount of diffusion weighting applied, determined by the strength, time of applied gradients and duration between the paired gradients. By repeating the sequences and measuring signal intensities with increasing b-values, the progressive signal decay over the images can be quantified using the ADC, showing an inverse correlation with tissue cellularity. Hypercellular tissue will show limited signal decay with increasing b-value, with persistent high signal intensity on DW-images with a high b-value, resulting in low ADC-values. On the contrary, hypocellular tissue will show signal decay with increasing b-value with low signal intensity on DW-images with a high b-value, resulting in high ADC (Figure 7) \(^64,86\).
Stationary molecules are unaffected by gradients and measured signal intensity is preserved. By contrast, moving water molecules acquire phase information from first gradient, which is not entirely rephased by second gradient, thereby leading to signal loss. Hence, water diffusion is detected as attenuation of measured MR signal intensity. RF= radiofrequency pulse.

**Figure 7. Principle of DW-MRI**

**Acquisition**

Up to now, no uniform imaging protocol for DW-MRI is available. The comparability and quality of DWI-images is influenced by various acquisition parameters such as type of scanner, field strength, choice of b-values and DWI-method (pulse sequence). The selection of b-values is pivotal to implement standardized head and neck DW-MRI protocols. The application of high b-values (b-values between 500 and 1000 sec/mm\(^2\)) enables the detection of remote water molecule movements and should be chosen carefully as (too) high b-values result in lower signal-to-noise-ratio (SNR). Using low b-values (b-values <100 sec/mm\(^2\)), fast moving water molecules are visualised, i.e. intravascular molecules and fast moving water molecules will show the strongest signal loss. In clinical practice, a combination of three b-values is most often used. This combination of b-values is also important; the use of only low b-values will result in high ADC-values and represents both diffusion and perfusion effects. The use of mainly high b-values results in lower ADC-values and better depicts the true diffusion in the tissue.
DW-imaging is susceptible to artefacts, particularly in the inhomogeneous head and neck region, containing a variety of tissues including bone, fat, muscle, glandular tissue and air. Moreover, movement-related problems, like swallowing, breathing, coughing, speaking and jaw movements impede imaging of the head and neck. DW-MRI protocols in HNSCC can be performed with an Echo-planar Imaging (EPI)-sequence or non-EPI sequence. With EPI-DWI, imaging of a relatively large volume with multiple b-values is possible due to a short acquisition time. However, EPI-DWI is sensitive to geometric distortions, which is especially strong near interfaces between soft tissue and air or bone. If artefacts are too detrimental, a non-EPI technique, such as half-fourier acquisition single-shot turbo spin-echo (HASTE) or periodically rotated overlapping parallel lines with enhanced reconstruction (PROPELLER), may be an alternative. However, non-EPI-DWI protocols are time-consuming, especially with the inclusion of multiple b-values. Furthermore, detection of tumoral lesions is more difficult due to a lower SNR. DW-MRI protocols in HNSCC are most commonly performed with EPI-DWI and this is probably the most promising technique in HNSCC.53,59,88

Applications in head and neck oncology

In the past, mainly anatomical imaging methods such as CT and MRI were performed in the diagnostic work-up of patients with HNSCC because they provide detailed information on the extent of the primary tumor and regional nodal metastases. However, small lesions may remain undetected due to morphological and size-related criteria on conventional imaging. Moreover, differentiation between malignant and aspecific post-treatment changes can pose a difficult dilemma since postradiotherapy changes obscure accurate assessment on these conventional images.46,77 Although relatively little experienced is gained with DW-MRI so far, clinicians more and more rely on functional imaging with DWI, which can be employed for several clinical purposes. First, a few studies studied the diagnostic accuracy of DW-MRI for detection of primary tumors in HNSCC89,90, although DWI does not seem to be superior to other techniques such as PET-CT to detect a primary tumor.91 Second, DW-MRI is increasingly used in staging of the neck for differentiating metastatic from benign lymph nodes and may be more accurate than nuclear imaging, especially in the detection of subcentimeter metastatic lymph nodes92-94. As with PET-CT, several studies investigated the value of DW-MRI in the prediction of treatment outcome before or during treatment. ADC-values seem to be a prognostic factor in HNSCC; several studies have shown that tumors with relatively low baseline ADC-values have better outcome than
tumors with high ADC-values \(^{53-56}\). For predictive imaging during treatment, DW-MRI is suggested as a predictive factor for tumor response during CRT. An early treatment-induced ADC increase is seen in tumors with complete remission \(^{53,58,59}\). Finally, DW-MRI is employed in post-treatment imaging for the purpose of monitoring treatment response and detecting tumor recurrence. Literature suggests that ADC-values are significantly lower in residual tumor \(^{59,95}\) and tumor recurrences \(^{88,96,97}\) than in postradiotherapy changes.

**Qualitative and quantitative interpretation**

The acquisition of adequate conventional images prior to DWI imaging is a prerequisite for performing DW-MRI, ideally with the same slices at the same slice position and orientation to provide anatomical co-registration, as well as observing morphological findings. As with PET-CT, DW-MRI scans can be interpreted qualitatively by means of visual assessment and quantitatively by measuring ADC-values. Qualitative interpretation has similar advantages and disadvantages as with PET-CT. However, no established visual assessment system for DW-MRI is available. In the current literature, qualitatively interpretation is mostly performed by visual assessment of the signal intensity on high b-value images and their corresponding ADC-maps \(^{85,96}\). Absence of hyperintensity on b=1000 images are regarded negative for malignant tumor. Hypercellular tissue, like malignant tumor, is characterized by a high signal intensity on b=1000 DW-images compared to the surrounding tissue corresponding to low ADC-values. However, restricted diffusion can also be seen in normal structures in the head and neck area such as Waldeyer’s ring because these structures also have high cellularity \(^{98}\). Areas of high signal intensity on high b-values images should always be assessed with their corresponding ADC-maps to filter out areas of T2 shine-through. The ‘T2 shine through’ effect indicates a hyperintensity related to the intrinsic T2-weighting of DW-images and is a result from the long tissue T2-relaxation times. Tissue changes induced by CRT (oedema, necrosis) can be seen as high signal intensity but also as low signal intensity on b=1000 images and usually show high values on the corresponding ADC-map (Table 2) \(^{99}\).
Table 2. Qualitative interpretation guidelines for DW-MRI

<table>
<thead>
<tr>
<th>Signal intensity on high b-value images</th>
<th>Signal intensity on ADC-map</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Generally, high cellular tumor; rarely abscess, viscous fluids or blood products</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
<td>T2 shine-through; liquefactive necrosis</td>
</tr>
<tr>
<td>Low</td>
<td>High</td>
<td>Fluid; necrosis; low cellularity; tumor with gland formation</td>
</tr>
<tr>
<td>Low</td>
<td>Low/intermediate</td>
<td>Fibromuscular issues; fat; fibrous tissue with low water content</td>
</tr>
</tbody>
</table>

Quantitative evaluation can be performed through the calculation of ADC-values and is probably less prone to inter- and intra-observer variability compared to visual assessment \(^{87}\). Currently, ADC-values are acquired by manually drawing a region of interest (ROI) on the native DWI images over the primary tumor or lymph node metastasis on one section or multiple ROIs on several sections to calculate ADC from the entire lesion. Necrotic components of the lesion of interest should be excluded from the ROI. Basic descriptives, such as mean, median, minimum, maximum, standard deviation and range are computed over the delineations.

Up to now, literature on DWI in oncologic head and neck imaging is conducted in single institutions without modifications in MR imaging systems or imaging protocols. Quantitative imaging parameters, such as ADC-values, can be affected by the selected MR imaging systems, sequences and imaging protocols. However, the reproducibility of ADC-values among different MR imaging systems and among sequences has not been established. Reproducibility should be validated across different systems and centers before multicentre DWI studies can be undertaken.
AIM AND OUTLINE OF THESIS

As outlined in this introduction, treatment prediction prior to or during CRT in patients with HNSCC is an area of interest in scientific research. Besides treatment prediction, there is also need for improvement of current response evaluation after treatment. The purposes of the research described in this thesis were to evaluate the accuracy of two imaging techniques (namely: $^{18}$F-FDG-PET-CT and DW-MRI) to predict locoregional residual HNSCC before and during CRT and to detect locoregional residual disease after CRT.

This thesis is composed of three parts. The aim of part 1 (prediction prior to treatment) was to investigate an association between pretreatment imaging parameters and the presence of HPV and to explore whether these are independent prognostic factors. The identification of additional pretreatment prognostic tumor characteristics may lead to customized treatment regimens and thereby higher treatment responses in individual patients. Differences in glycolytic characteristics between HPV-negative and HPV-positive OPSCC, as measured with pretreatment $^{18}$F-FDG-PET-CT, were evaluated in chapter 2. In chapter 3, we analysed the association between ADC-values, derived from DW-MRI, and the presence of biologically active HPV in patients with OPSCC.

The potential predictive value of these imaging techniques early during CRT on locoregional outcome is explored in part 2 (prediction during treatment). Chapter 4 describes the evaluation of the potential predictive value of EPI- and HASTE-DWI and $^{18}$F-FDG-PET-CT early during chemoradiotherapy on locoregional outcome in HNSCC.

The objective of part 3 (response evaluation) was to evaluate current response evaluation strategies and the accuracy of $^{18}$F-FDG-PET-CT and DW-MRI to detect locoregional residual disease after CRT in HNSCC. A questionnaire on the clinical practice concerning response evaluation after CRT for advanced OPSCC in all eight head and neck cancer institutions of the Dutch Head and Neck Oncology Cooperative Group is presented in chapter 5. Thereafter, the accuracy of response evaluation using $^{18}$F-FDG-PET-CT, DW-MRI and combined PET-CT/DW-MRI for advanced staged OPSCC was prospectively researched in chapter 6. In chapter 7, we retrospectively evaluated the accuracy and interobserver variation of these imaging techniques to detect residual lymph node metastases after CRT in advanced staged HNSCC. Finally, an estimation of the cost-effectiveness of the imaging techniques in the selection of patients for response evaluation in comparison with an examination under general anesthesia, is performed in chapter 8.

In chapter 9, a general discussion and future prospects about the topics in this thesis are presented.
REFERENCES


