CHAPTER 1.1

General introduction, aims and outline of the thesis
GENERAL INTRODUCTION

Head and neck cancer comprises approximately 3% of malignancies worldwide (1-3). Most malignancies in the head and neck area are squamous cell carcinomas originating at the mucosal surface of the upper aerodigestive tract, which includes oral cavity, oropharynx, nasopharynx, hypopharynx, and larynx. Traditionally the use of tobacco and alcohol consumption has been recognized as the most important risk factors which account for approximately 75% of the head and neck cancers (4, 5). The combined use of these substances appears to be synergistic in the development of head and neck squamous cell carcinoma (HNSCC). It appears that smoking mainly increases the risk of laryngeal cancer and alcohol consumption is more associated with pharyngeal and oral cavity cancer (6). Patients are generally over 50 years of age with a male to female ratio of 70:30 (1). Presenting symptoms include hoarseness for laryngeal cancers. For pharyngeal cancers patients often present when the tumor is larger and results in dysphagia, a sore throat or ear pain. Patients may also present with one or more painless cervical nodes (6).

At early stages treatment usually consist of a single modality, most often surgery or radiotherapy. Whereas advanced disease is treated with combinations of surgery, chemotherapy and/or radiotherapy with salvage surgery in reserve (7-9). Radiotherapy is associated with better organ preservation compared to surgery and results in less problems with swallowing and speech and comparable survival rates (10). For this reason (chemo)radiotherapy is increasingly used in head and neck cancer. Early complications of radiotherapy include: radiation dermatitis, both xerostomia as excessive mucus production and a painful mucositis which all can result in problems with adequate intake of food and liquids (10). Therefore patients of require nasogastric feeding or a percutaneous gastronomy. Adding chemotherapy results in more acute toxicity. An added survival benefit of 6.5% for concomitant chemotherapy has been found (11). Cisplatin-based regimens are most frequently used. More recently the anti-epidermal growth factor receptor antibody cetuximab has shown to also increase overall survival when added to radiotherapy (12, 13). On the long-term radiotherapy results in less problems with body image and facial contour compared to extensive surgical procedures. Long-term side effects of radiotherapy may occur in up to 82% of patients and include xerostomia, soft tissue fibrosis, dysphagia and osteoradionecrosis of the mandible (10, 14). These long-term effects result in an impairment of the quality of life of long-term survivors of head and neck cancer (15, 16).

When residual disease after chemoradiotherapy is detected, salvage surgery may still be possible. The success rate of salvage surgery is the highest when it is performed as early as possible. In a study including patients with oropharyngeal carcinoma salvage surgery after 1-2 months was successful in 70% of early detected residues, compared to only 33% in later detected recurrences (8). The increasing use of non-invasive chemoradiotherapy warrants good surveillance protocols. Especially since symptoms caused by post-radiation changes and residual overlap. Both can present with hoarseness, pain, and swallowing complaints (17). Because taking repeated biopsies can exacerbate these symptoms and can cause infection, non-invasive methods of surveillance are preferred. Moreover, information obtained by imaging techniques may guide biopsies when indicated.
Five year overall survival (OS) in HNSCC is strongly dependent of tumor localization and disease stage varying from 59-78% for stage I, to 32-47% for stage IV M0 disease (18). Best survival is seen in laryngeal carcinoma (66% 5-year OS), and worst survival in hypopharyngeal carcinoma (32% 5-year OS) (18).

Recently the human papillomavirus (HPV), known for causing cervical cancer, has been recognized as a risk factor for developing oropharyngeal HNSCC (19-22). The HPV-16 genotype is considered the most important HPV subtype in oncogenesis (23). Patients with HPV-associated HNSCC are generally younger and often do not have a history of excessive alcohol and tobacco consumption (19, 20, 22). This may result in a delayed diagnosis. Generally these patients present with a small primary tumor and large lymph nodes (6). HPV-positive HNSCC is associated with a better prognosis than HPV-negative HNSCC (19, 20, 22).

Another important infectious causative of head and neck cancer, and more specifically nasopharyngeal cancer (NPC), is the Epstein-Barr virus (EBV) (24-26). Nasopharyngeal carcinoma differs from other HNSCC in the geographic distribution with a peak incidence in Southeast Asia (27). Another distinct feature of NPC is the excellent radiosensitivity compared to other forms of HNSCC (28).

Salivary gland tumors are a rare and very heterogeneous group of neoplasms. All salivary glands can be affected, however approximately 80% is located in the parotid gland. In the parotid gland approximately 25% of the lesions is malignant compared to up to 45% for submandibular gland tumors and up to 90% for sublingual gland tumors (29, 30). Pleomorphic adenomas are the most common benign salivary gland tumor (29, 30). These tumors are formed by epithelial and myoepithelial cells and harbor the ability to transform to malignant lesions (i.e. carcinoma ex pleomorphic adenoma). Warthin tumors are another relatively common benign salivary gland tumor (29, 30). This entity is a more homogeneous compact to the heterogeneous pleomorphic adenoma. Treatment of benign salivary gland tumors usually consists of surgical excision with wide surgical margins, often in the form of a superficial parotidectomy, to prevent disease recurrence (30). Benign salivary gland tumors need to be distinguished from malignant salivary gland tumors. This last group is characterized by local invasion, perineural spread and the ability to metastasize (31).

**Imaging**

In head and neck cancer imaging is used in: diagnosing disease, determining disease stage, monitoring treatment response and for follow-up after treatment. The most commonly used modalities are ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) (32).
Ultrasound is mainly used for nodal staging (33, 34). Advantages of ultrasound are the high spatial resolution, low costs, general availability and that the technique does not require ionizing radiation. Moreover ultrasound can easily be combined with fine needle aspiration (FNA) to obtain material for cytological assessment of lymph nodes suspicious of containing malignant tissue (33, 34). Disadvantages of ultrasound are the operator dependency and risk of a sampling error with FNA. Another disadvantage is that deeper structures (e.g. retropharyngeal nodes) cannot be assessed with this modality.

Computed tomography is a fast imaging technique with superior bone detail. Advantages of CT are the high spatial resolution, low acquisition times resulting in the virtual absence of motion artefacts. With the current generation of multidetector row CT systems slice thicknesses of less than 1 mm are widely used in clinical practice (32). However CT lacks soft tissue contrast, the technique requires ionizing radiation, dental implants may result in severe artefacts especially when the oral cavity is assessed, and the iodinated contrast used in contrast-enhanced CT imaging is relatively contraindicated in patients with renal impairment. This makes CT the modality of choice in patients:

- with contra-indications to MRI (e.g. claustrophobia, pacemakers, vascular clips or foreign metal bodies);
- at risk of cortical bone invasion (e.g. in the mandibular or skull base);
- who are unable to lay flat for a long period of time, have difficulty breathing or have problems with swallowing secretions.

Further, chest-CT is often used in patients who are at risk of pulmonary metastases.

Magnetic resonance imaging is the technique of choice for the visualization of soft tissue (e.g. muscle invasion, perineural spread, cartilage invasion and intracranial extension). Conventional MRI protocols for head and neck imaging usually include T1, T2, a sequence with fat-suppression (e.g. short-tau inversion recovery (STIR) or spectral attenuated inversion recovery (SPAIR)), and contrast-enhanced T1-weighted sequences (35). In MRI chelates of the paramagnetic element gadolinium are used as a contrast medium. Contrast accumulates in the extravascular space resulting in shortening of T1 and therefore signal enhancement of contrast-enhanced T1-weighted images (36). Malignant tissue induces increased vascularity resulting in increased contrast delivery and enhanced signal intensity. With the current 1.5T and 3T MRI systems slice thicknesses of 3-7 mm are clinically feasible to perform within an acceptable time (32). Due to the relatively long examination time, MRI is susceptible to motion artifacts caused by patient movement, swallowing and breathing. Besides providing anatomical information, MRI can also be used for acquiring functional imaging, which will be discussed below.

**Functional imaging**

The aforementioned techniques are considered anatomical since these techniques provide information on the location and size of a lesion, and the relation to nearby structures. Functional imaging techniques provide information on tissue functioning, with the anatomical detail being of secondary importance.
In MRI several functional imaging techniques are increasingly applied. In this thesis we focused on two types of functional imaging: Diffusion-weighted imaging (DWI) and perfusion weighted imaging, since these techniques are the main focus of imaging research in head and neck cancer.

Diffusion-weighted imaging is based upon measuring the random or Brownian motion of water molecules in tissue (37). By applying different diffusion gradients with different strengths tissues can be separated based on the amount of diffusion restriction. The amount of diffusion weighting depends on the timing and the strength of the gradient and can be quantified in a b-value. By comparing signal intensities at varying b-values, the signal decay can be quantified in an apparent diffusion coefficient. In order to calculate an ADC at least two different b-values are needed: typically a low (e.g. <150 s/mm$^2$) and a high b-value (e.g. >700 s/mm$^2$). The ADC can be calculated with the following formula:

$$\frac{S(b)}{S_0} = \exp (-b \cdot ADC)$$

Where $S_0$ represents the signal intensity with diffusion gradient b, and $S_0$ represents the signal intensity without diffusion gradients.

Restricted diffusion (i.e. low ADC values) in oncologic imaging is often caused by hypercellular tissue with limited extracellular space, and is therefore associated with the presence of malignancy (38-42) (Table 1). On the contrary, areas with ample extracellular space and a relatively low cell density are characterized by a high ADC value. Necrosis and inflammation generally meet these criteria (41, 43, 44) (Table 1).

<table>
<thead>
<tr>
<th>Signal intensity on high b-value image</th>
<th>Signal intensity on ADC map</th>
<th>Interpretation</th>
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</thead>
<tbody>
<tr>
<td>High</td>
<td>Low</td>
<td>Highly proliferative malignant tissue, abscess, viscous fluid or blood</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>Necrosis, fluids, adenocarcinoma with low cellularity</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Fibrosis, fat, susceptibility artifact</td>
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In the head and neck area diffusion restriction may be physiological in some tissues (e.g. in the parotid and submandibular salivary glands, thyroid glands, palatine tonsils and benign lymph nodes). When assessing these tissues, it is important to also look for other signs of malignancy (e.g. asymmetry or ingrowth in surrounding structures) (45, 46). An increase in ADC during and after treatment is associated with a favorable prognosis (38, 47, 48).
As the word ‘apparent’ indicates, true diffusion is not measured with the ADC concept. Especially at lower b-values, pseudorandom or ‘incoherent’ diffusion also contributes to the imaging signal. This incoherent movement is mainly caused by perfusion at the capillary level. Le Bihan et al. introduced a bi-exponential intravoxel incoherent motion (IVIM) model to account for this (37):

\[
\frac{S_b}{S_0} = (1 - f) \cdot e^{(-bD)} + f \cdot e^{(-bD^*)}
\]

Where \(S_b\) represents the signal intensity with diffusion gradient \(b\), and \(S_0\) represents the signal intensity without diffusion gradients. \(D\) is known as pure or slow diffusion coefficient, which is related to pure molecular diffusion. \(D^*\) is the fast or pseudodiffusion coefficient that resembles the perfusion related incoherent microcirculation and is about a factor of 10 greater than \(D\) in biological tissue (37, 49-51). Finally, \(f\) is the perfusion or (micro) vascular volume fraction, which depends on capillary geometry and blood velocity (37, 49). With this model several quantitative parameters can be acquired in order to further characterize lesions without the admission of contrast material (Figure 1).

Most often DWI is performed with an echo-planar imaging (EPI) sequence (38-40, 42, 43, 47, 48, 52-67). Advantages of EPI are the high signal intensity and image contrast, and the relatively short acquisition time (68). The main disadvantage of EPI-based imaging is frequent presence of susceptibility artifacts resulting in image distortion. In the head and neck area air-tissue boundaries and the presence of metallic implants (e.g. dental fillings or implants) may result in magnetic inhomogeneities, which can cause severe susceptibility artifacts, especially when EPI-based DWI is used. To deal with this turbo spin-echo (TSE) based sequences can be used. This sequence does not suffer from image distortion; however this is at the cost of a reduced signal-to-noise ratio and prolonged acquisition time (40, 69-72).

Perfusion-weighted imaging describes a group of imaging techniques in which pharmacokinetic modelling after the administration of intravenous contrast is used. It is hypothesized that malignant tissue can be characterized based on differences in vascular properties. Malignant tissue induces vessel formation of vessels with poor functionality, high permeability, tortuosity and density (73). Changes in these vascular properties can be measured and may provide information on tumor response to treatment (74-79). High expression of hypoxia-associated markers as hypoxia inducible factor 1α and carbonic anhydrase have been associated with an adverse prognosis (80).
Figure 1 Example of IVIM in a patient with a T4b squamous cell carcinoma originating from the hypopharynx. A) Shows the original diffusion weighted image with a b-value of 1000 s/mm². B) Shows the bi-exponential decay of signal intensity over b-values. At low b-values the pseudodiffusion coefficient (D*) is the main contributor to the signal decay over b-values. With increasing b-values the pure diffusion coefficient (D) becomes the main contributor to the signal decay. When using the intercept of D and the signal intensity at b=0 s/mm² f can be estimated. C), D) and E) are the D, D* and f map, respectively. The respective values can be acquired by drawing a region of interest of the tumor.

The most frequently used technique is dynamic contrast-enhanced imaging (DCE) (74-79, 81-105). This technique is based on the serial acquisition of T1-weighted images before, during and after the injection of intravenous contrast. Then, extravasation of the contrast material can be measured. The rate of extravasation is mainly determined by the amount of blood flow, the thickness and viability of the capillary wall (36, 106). The resultant changes in T1-signal caused by changes in the amount of contrast material can be quantified using pharmacokinetic modelling. The Tofts model is the most commonly used pharmacokinetic model in head and neck cancer (36, 106). With this model four different quantitative parameters can be obtained (Figure 2):
1. $K^{\text{trans}}$, the volume transfer constant between plasma and interstitial space. This parameter provides information on capillary permeability;
2. $k_\text{ep}$, the rate constant between interstitial space and plasma. With this parameter the flow from the interstitial space back to the capillaries can be estimated;
3. $v_e$, the fractional volume of the extracellular, extravascular space;
4. $V_p$, the plasma volume fraction.

With the use of other models even more parameters may be obtained. For example, use of the Brix model results in the parameters ‘amplitude scaling constant’ (AH) and ‘time of arrival of contrast medium’ (TA) (107).

Figure 2 Schematic picture of the Tofts model

Another approach is to analyze the time-dependent change in signal intensity during and after the administration of intravenous contrast. This results in parameters such as maximum contrast-index, initial area under the curve, time to peak, wash in and wash out (84, 88, 91-93, 108). These parameters are considered to be not directly related to tissue pathology and are more difficult to compare between patients. Therefore these parameters are considered to be semi-quantitative parameters.
Perfusion-weighted imaging can also be performed with another, less frequently used, method based on T2*-based sequences. This is referred to as dynamic susceptibility contrast (DSC) MRI (109-113). The accumulation of contrast material causes a transient darkening of tissue. It is assumed that the degree of darkening is linearly related to the concentration of contrast material. This produces surrogate parameters indicative of tissue perfusion (e.g. blood volume and blood flow) (109, 114).

Positron emission tomography (PET) differs from the other imaging modalities because it is a pure functional imaging modality. It is often combined with CT for attenuation correction and to combine functional with anatomical imaging for topographical determination of high uptake lesions. Imaging is performed after the administration of a positron emitting tracer. These emissions can be measured and reconstructed in a three-dimension image. The most commonly used tracer is $^{18}$F-Fluoro-deoxyglucose ($^{18}$F-FDG), which is a marker of tissue metabolism.

Malignant tissue has a relatively high metabolic rate compared to other tissues (115). This makes $^{18}$F-FDG a relative specific marker for the detection of malignancy. However, severe inflammation (e.g. during and after radiotherapy) can also result in focal $^{18}$F-FDG uptake which may compromise the sensitivity of $^{18}$F-FDG-PET-CT during and after treatment with (chemo)radiotherapy (116-122). Another disadvantage of $^{18}$F-FDG-PET-CT is the relatively low spatial resolution, which may result in false-negative findings in smaller lesions (123). Applications of $^{18}$F-FDG-PET-CT are detecting nodal and distant metastases, unknown primary lesions and synchronous second primary lesions (e.g. lung cancer is relatively common in patients with HNSCC due to the overlapping risk factors) (124).

AIMS AND GENERAL OUTLINE OF THE THESIS
The general aim of this thesis was to assess the role of functional imaging in HNC: from making the diagnosis and differential diagnosis, to determining patient prognosis and the detecting residual disease.

The main shortcomings of currently accepted imaging strategies are:

1. Selecting patients who are likely to respond to (chemo)radiotherapy is not possible with current imaging modalities. Preferably this is done before treatment.
2. The relatively limited sensitivity and specificity of anatomic imaging in the detection of residual and recurrent disease after treatment with (chemo)radiotherapy.
3. That reliable response evaluation with $^{18}$F-FDG-PET-CT can be performed from three months after treatment, when patients already received the complete treatment with the associated treatment toxicity.
We explored the potential of functional imaging techniques in head and neck cancer, as known from literature, in three reviews in Chapter 2. In Chapter 2.1 we focused on the diagnostic and prognostic potential of DCE. In Chapter 2.2 we used a comparable approach to assess the value of IVIM. In Chapter 2.3 we focused on the use of various types of functional imaging in early follow-up in order to identify the most promising techniques.

Before any technique can be applied in clinical practice, reproducibility needs to be assessed. Therefore we determined DWI reproducibility in Chapter 3.

In Chapter 4 we focused on the diagnostic potential of DWI. In Chapter 4.1 we assessed the value of whole-body-MR imaging because the presence of distant metastases currently rules out the chance of cure. In these patients therapy should focus on patient comfort and toxicity needs to be limited. Another patient population at risk of over-treatment are patients presenting with a lymph node metastasis with an unknown primary tumor. If the primary tumor cannot be found during disease staging, then the whole pharyngeal axis is treated with radiotherapy with associated toxicity. In Chapter 4.2 we therefore assessed if the use of DWI and \(^{18}\text{F}-\text{FDG-PET-CT}\) alone or combined resulted in increased detection of occult primary tumors. Another clinical challenge is the detection of residual HNSCC after treatment with (chemo)radiotherapy. Our main aim in Chapter 4.3 was to assess the added value of DWI to follow-up with \(^{18}\text{F}-\text{FDG-PET-CT}\) and in Chapter 4.4 to find the most optimal combination of imaging with the most relevant parameters.

Finally in Chapter 5 we assessed the prognostic potential of DWI. In Chapter 5.1 we focused on the combined use of DWI and contrast-enhanced imaging to determine if the use of intravenous contrast material can aid in determining diffusion restriction solely in the solid part of the primary tumor and lymph nodes. In Chapter 5.2 we used histogram analysis to assess the prognostic value of pre-treatment DWI and \(^{18}\text{F}-\text{FDG-PET-CT}\) in patients with HNSCC.
REFERENCES


