SUMMARY

Nowadays, a combination of concurrent chemotherapy and radiotherapy (CRT) is applied to patients with advanced staged head and neck squamous cell carcinomas (HNSCC), with locoregional control and organ preservation as the main treatment goals. Although acceptable locoregional control rates are accomplished, the chance of residual disease remains considerable. Prediction of treatment outcome prior to CRT could lead to a non-standard treatment choice in an individual patient. Part 1 of this thesis addresses this topic. The purpose of these chapters was to investigate an association between pretreatment quantitative $^{18}$F-fluoro-2-deoxyglucose positron emission tomography – computed tomography ($^{18}$F-FDG-PET-CT) and diffusion-weighted MRI (DW-MRI)-values and the presence of biologically active human papillomavirus (HPV) in oropharyngeal cancer.

Traditional prognostic factors such as tumor size and lymph node invasion provide insufficient information concerning treatment outcome. Identification of additional prognostic factors, may lead to individually customized treatment and thereby possible higher responses to treatment and less treatment-induced side effects. The Standardised Uptake Value (SUV) is a semi-quantitative measurement of $^{18}$F-FDG tracer uptake in PET-CT and it has been suggested that patients with low pretreatment SUV-values generally have a more favourable outcome. However, patients with HPV-positive oropharyngeal squamous cell carcinoma (OPSCC) also show more favourable treatment response rates and prognosis as compared with HPV-negative patients. We evaluated SUV-values in HPV-negative and HPV-positive OPSCC using a retrospective study in chapter 2. Forty-four patients underwent pretreatment $^{18}$F-FDG-PET-CT of which twenty-seven patients were HPV-positive. HPV-positive patients had significantly smaller primary tumor volumes than HPV-negative patients. SUV-values are volume dependent because of the partial volume effect. The SUV-value in HPV-positive was 3.9 units lower than in HPV-negative tumors after correction for tumor volume. Therefore, we concluded that low pretreatment SUV-values in HPV-positive OPSCC, which are associated with a better prognosis, may be explained by HPV-induced tumor changes.

DW-MRI characterizes biologically relevant tumor features and the Apparent Diffusion Coefficient (ADC) may provide prognostic information. A few studies have shown that HNSCC with relatively low pretreatment ADC-values respond better to CRT than tumors with higher ADC-values. HPV-related tumors have distinct histological features compared with HPV-negative OPSCC and in chapter 3 we investigated the possible association between ADC-values and the presence of HPV in patients with OPSCC. Forty-four patients underwent pretreatment DW-MRI of which twenty-two patients...
were HPV-positive. ADC-values were not significantly different between HPV-negative- and HPV-positive tumors. Apparently, the differences in histological features between HPV-positive and HPV-negative OPSCC do not translate into different pretreatment ADC-values in our study cohort. Long-term follow-up studies with DW-MRI and HPV are needed to investigate if ADC-values and HPV-status are independent prognostic factors in OPSCC patients.

Predicting treatment outcome early during CRT is another potential way of treatment prediction and could hypothetically lead to a treatment switch in patients who are not likely to benefit from CRT, thereby preserving postoperative radiotherapy as an option after surgery if indicated. This kind of treatment prediction the subject in part 2 of this thesis.

Chapter 4 describes a prospective pilot study which explores the predictive value of DW-MRI and 18F-FDG-PET-CT early during CRT on locoregional outcome in patients with HNSCC. DWI is generally performed using echo-planar imaging (EPI), but non-EPI-DWI, such as Half-fourier acquisition single-shot turbo spin-echo (HASTE)-DWI can be an alternative. These techniques are also compared in this chapter. Eight patients with advanced HNSCC underwent DW-MRI (with both EPI- and HASTE-sequences) and 18F-FDG-PET(-CT) pretreatment, two weeks after the start of CRT and three months after CRT. No local recurrences were detected during follow-up. Median ADC$_{EPI}$-values in primary tumors increased during treatment, whereas ADC$_{HASTE}$ did not increase. SUV decreased with 62% from baseline PET to PET during treatment. Two regional recurrences were diagnosed. Early during treatment, ADC$_{EPI}$ tended to be higher for patients with regional control than for patients with a recurrence. This difference was not seen with ADC$_{HASTE}$. A trend was seen for a higher change in SUV in patients with regional control than in patients with a regional recurrence. These preliminary results suggest that HASTE-DWI seems to be inadequate in early CRT response prediction, compared to EPI-DWI which has potential to predict locoregional outcome early after the start of CRT.

In case of residual disease after CRT, a ‘salvage’ surgery may be considered, but this is associated with substantial morbidity and complications and will only be done after viable tumor has been proven histopathologically. Consequently, response evaluation is routinely performed 12 weeks after CRT in the VU University Medical Center with an examination under general anesthesia (EUA) to evaluate the primary tumor (response evaluation). Ultrasound-guided fine needle aspiration cytology (FNAC) is performed in case of residual neck disease. However, false negative biopsies due to sampling error within the residual mass and false positive results from FNAC regularly
occurs. Moreover, the discrimination between residual tumor and aspecific changes with conventional imaging is unreliable since post-treatment changes, including oedema, fibrosis and necrosis, hamper accurate assessment. Part 3 of this thesis addresses this clinical dilemma. The purpose of these chapters was to evaluate clinical practice concerning response evaluation in the Netherlands and to evaluate the accuracy of two functional imaging techniques to detect locoregional residual disease after CRT in HNSCC.

In chapter 5 the current clinical practice on response evaluation after CRT for advanced OPSCC is described, through a questionnaire sent to clinicians in all eight head and neck cancer centers of the Dutch Head and Neck Oncology Cooperative Group. Response evaluation was routinely performed with various methods in five institutions (62.5%) and in one institute (12.5%) only if clinical evaluation was difficult. Two centers (25%) did not perform response evaluation. A substantial variation in the diagnostic policy and the methods used for response evaluation after CRT for advanced OPSCC in the Netherlands was found. We concluded that there is a need for national guidelines concerning response evaluation in patients with advanced oropharyngeal cancer.

In chapter 6 the results of the REACTION-study, a prospective study, are described. The purpose was to evaluate the accuracy of $^{18}$F-FDG-PET-CT, DW-MRI and combined PET-CT/DW-MRI assessment to detect local residual disease after CRT, in patients with advanced OPSCC. Forty-six patients were included and underwent response evaluation with $^{18}$F-FDG-PET-CT, DW-MRI and an EUA three months after completion of CRT. Imaging was assessed by two observers per modality and combined PET-CT/DW-MRI reading was performed. Local residual disease was diagnosed in 5 patients. For PET-CT and DW-MRI, sensitivity was 75.0% and 60.0% at a specificity of 82.9% and 95.1%, yielding a NPV of 97.1% and 95.1%, respectively. Combined PET-CT/DW-MRI reading yielded a sensitivity of 100.0% at a specificity of 92.7%. This study suggests that PET-CT and DW-MRI seem to be reliable tools to rule out residual primary tumor, possibly making routine EUA superfluous. Combined PET-CT/DW-MRI reading may be superior to PET-CT and DW-MRI alone, but further research should assess this role of PET-MRI.

Chapter 7 evaluates the accuracy of DW-MRI and $^{18}$F-FDG-PET-CT to detect residual lymph node metastases after CRT in patients with advanced (N2-N3) pretreatment nodal disease of HNSCC. Retrospectively, routinely performed DW-MRI ($n=73$) and $^{18}$F-FDG-PET-CT ($n=58$) 3 months after CRT were assessed by two radiologists and two nuclear medicine physicians. Five patients had residual regional disease. DW-MRI showed a sensitivity of 60% and a specificity of 93%, versus 100% and 84% for PET-CT, respectively. A
statistical combination of PET-CT and DW-MRI showed a sensitivity of 100% and a specificity of 95%. PET-CT recognised all regional residues and DW-MRI recognised most patients with regional control. A combined approach seemed to increase the specificity of PET-CT alone, without compromising sensitivity of PET-CT alone.

An exploration of the diagnostic accuracy and cost-effectiveness of four response evaluation strategies to detect local residual disease in 46 oropharyngeal cancer patients treated with CRT, is performed in chapter 8. Besides the reference strategy, i.e. EUA for all patients, we considered three imaging strategies, namely $^{18}$F-FDG-PET-CT-based selection for EUA, DW-MRI-based selection for EUA and a combination of $^{18}$F-FDG-PET-CT and DW-MRI to select for EUA. All analyses were conducted using a decision-analytic model based on trial data of the patients from chapter 6 and scientific literature. The EUA strategy led to 96% correct diagnoses and the expected costs were €468 per patient whereas 89% of EUA indications were unnecessary. The DW-MRI strategy was the least costly strategy (€297 per patient), but also led to the lowest proportion of correct diagnoses, i.e. 93%. The PET-CT strategy (€1177 per patient) and combined imaging strategy (€1395 per patient) were dominated by the EUA strategy due to respectively a smaller or equal proportion of correct diagnoses, at higher costs. Based on our model results, the combined PET-CT and DW-MRI strategy is preferred over immediate EUA since it reaches the same diagnostic accuracy while leading to substantially less unnecessary EUA indications. This strategy costs only an additional €927 per patient. However, if healthcare resources are limited, DW-MRI is the strategy of choice because of lower costs while still providing a large reduction in unnecessary EUA indications.