Summary

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 5% of all malignant tumors worldwide. Two thirds of the patients with HNSCC present with advanced disease. HNSCC’s metastasize to regional lymph nodes rather than spread hematogenously. Distant metastases usually occur late in the course of the disease. As locoregional treatment has improved significantly over these last few decades more patients are at risk to develop distant metastases and second primary tumours.

The presence of distant metastases at initial evaluation influences the prognosis and thus treatment selection: since no effective systemic treatment for disseminated HNSCC is currently available, patients with distant metastases are until recently generally not considered curable and often receive only palliative treatment. Overall survival for patients with distant metastases detected at initial screening is significantly poorer compared to patients with distant metastases missed during initial screening and detected during follow-up. Therefore, screening for distant metastases is important to avoid futile extensive treatments.

The aims of this thesis were to evaluate screening for distant metastases in head and neck cancer patients using $^{18}$FDG-PET, chest CT and integrated $^{18}$FDG-PET-CT (Chapters 2-7) and to evaluate the clinical practice of this screening in the Netherlands (Chapter 8).

In Chapter 2 a multicenter study is described in which screening for distant metastases in HNSCC patients with high risk factors was performed using $^{18}$FDG-PET and chest CT. The previously identified high risk factors were: three or more lymph node metastases,
bilateral lymph node metastases, lymph node metastases ≥ 6 cm, low jugular lymph node metastases, locoregional tumour recurrence and second primary tumours. A total number of 92 patients were included. \(^{18}\)FDG-PET showed a higher sensitivity to detect distant metastases (53% vs. 37%) and positive predictive value (80% vs. 75%) than chest CT. The combination of \(^{18}\)FDG-PET and chest CT had the highest sensitivity (63%). ROC analyses revealed that the area under the curve of \(^{18}\)FDG-PET was significantly higher as compared to chest CT. The addition of \(^{18}\)FDG-PET to chest CT showed a significant decrease in overtreatment, thus resulting in a decrease of futile mostly extensive treatments in these patients. Therefore, it was concluded that in HNSCC patients with high risk factors, pretreatment screening for distant metastases by chest CT was improved by whole-body \(^{18}\)FDG-PET.

Cost-effectiveness analyses of the different diagnostic strategies of chapter 2 are described in Chapter 3. The costs of the addition of \(^{18}\)FDG-PET as screening modality were calculated; if distant metastases were found with \(^{18}\)FDG-PET and missed using chest CT the total costs for curative treatment were deducted. All costs were calculated with the use of clinical scenario analysis. It was concluded that the addition of \(^{18}\)FDG-PET did not lead to additional costs due to its higher sensitivity in screening for distant metastases which results in a decrease of more expensive futile treatments.

In Chapter 4 interobserver variability in screening for distant metastases in head and neck cancer patients using \(^{18}\)FDG-PET and chest CT is investigated. Chest CT and \(^{18}\)FDG-PET scans of 69 HNSCC patients with high-risk factors who underwent screening for distant metastases were analyzed. All scans were independently read by two experienced radiologists or nuclear physicians who were blinded to the other
examinations and follow-up results. The interobserver agreement was determined and expressed in a weighted or unweighted kappa which corrects for agreement by chance. In case of disagreement between the two observers of each modality a final consensus reading was performed. A kappa of 0.516 was found for assessment of size on chest CT. Kappa values for origin (distant metastases or second primary tumour) and susceptibility of 0.406 and 0.512 for chest CT and 0.834 and 0.939 for $^{18}$FDG-PET were found, respectively. Overall, chest CT readings had a reasonable to substantial agreement, while $^{18}$FDG-PET readings showed an almost perfect agreement. These findings suggest that for optimal clinical assessment $^{18}$FDG-PET can be scored by one observer but chest CT should probably more often be scored by two observers in consensus or combined with $^{18}$FDG-PET.

A validation study is described in Chapter 5. A test cohort of 47 consecutive HNSCC patients with high risk factors for the development of distant metastases, who had previously undergone $^{18}$FDG-PET and chest CT with a minimum of 12 months follow-up, were retrospectively analyzed. In patients with locoregional control during follow-up the sensitivity and specificity were 55% (95% CI: 23-83%) and 97% (95% CI: 82-99%) respectively for chest CT, 55% (95% CI: 23-83%) and 100% (95% CI: 88-100%) respectively for $^{18}$FDG-PET and 73% (95% CI: 39-94%) and 100% (95% CI: 88-100%) respectively for the combination of $^{18}$FDG-PET and CT. The in chapter 2 proposed algorithm was considered to have been validated. In this algorithm all $^{18}$FDG-PET positive scans for distant metastases (regardless of interpretation of a solid lung lesion on CT) and CT scans with suspicious pulmonary lesions of less than 5 mm diameter (regardless of $^{18}$FDG-PET findings) are considered positive for distant metastases.
In Chapter 6 a retrospective study is described in which previously identified high risk factors for development of distant metastases were validated and the impact of time of detection of distant metastases on survival was evaluated. From a total of 301 HNSCC patients with high risk factors (three or more lymph node metastases, bilateral lymph node metastases, lymph node metastases ≥ 6 cm, low jugular lymph node metastases, locoregional tumour recurrence and second primary tumours) who were scheduled for extensive treatment and underwent pretreatment screening on distant metastases using chest CT and/or whole body $^{18}$FDG-PET(-CT), the high risk factors, the development and time point of distant metastases and survival were analyzed. Multivariate analysis revealed that bilateral lymph node metastasis was the strongest predictive factor. Locoregional recurrence and second primary tumours were the risk factors associated with the lowest cumulative incidence. If the risk factor locoregional recurrence was split into local en regional recurrences, regional recurrence was associated with a substantially higher risk than local recurrence. The validity of three or more lymph node metastases, bilateral lymph node metastases, low jugular lymph node metastases and regional recurrence as high risk factors for the development of distant metastases was confirmed. The more high risk factors a patient had the lower the 5-year distant metastases free survival was. The detection of distant metastases by pretreatment screening worsens the overall survival as compared to distant metastases detected during follow-up.

A retrospective cohort study is described in Chapter 7. In literature different intervals in follow-up term are used as reference standard to calculate sensitivity of screening modalities when screening for distant metastases in HNSCC patients. Longer follow-up
intervals result in a significant decrease of reported sensitivities. In this study 46 HNSCC patients with high risk factors to develop distant metastases who underwent pretreatment screening with $^{18}$FDG-PET/CT were retrospectively analyzed using different reference standards. In 16 patients (35%) distant metastases were detected during screening (6 patients) or during a mean follow-up of 39.4 months (10 patients). The sensitivity and negative predictive value were 83.3 and 97.2% when 6 months, 60.0 and 89.9% when 12 months and 37.5 and 72.2% when 30 months follow-up were used as reference standard, respectively. The outcome was comparable with reported studies with similar reference standards. This critical appraisal on the reference standards used in our and reported studies shows room for improvement for the detection of distant metastases to refrain more patients from unnecessary extensive locoregional treatment for occult metastatic HNSCC.

Chapter 8 describes a survey which was performed among the eight centers of the Dutch Head and Neck Society treating head and neck cancer in the Netherlands. The survey was performed with the same questionnaire which was used 10 years ago. The response rate was 100%. $^{18}$FDG-PET–CT and contrast-enhanced chest CT as screening modalities for the detection of distant metastases were routinely used. Compared to the prior survey a reduction of variation in indications and diagnostic techniques used for screening for distant metastases was observed during the last 10 years. Notably all but one center reported they would refrain from extensive treatment if a HNSCC patient would develop clinically manifest distant metastases within 6 months. Although the sensitivity of the diagnostic pathway needs to be improved, most centers were satisfied with the current diagnostic pathway.
In this thesis screening for distant metastases in HNSCC patients is investigated. To avoid futile extensive treatments in patients with high risk factors for the development of distant metastases screening should preferably be performed using a diagnostic tool with the highest sensitivity and accuracy. The combination of chest-CT and whole-body $^{18}$FDG-PET-CT is currently the best available method for screening for distant metastases in HNSCC patients. However, there still is room for improvement.