Chapter 7

Summary and conclusions
SUMMARY

Squamous cell carcinomas (SCC) of the larynx have the highest incidence of all newly diagnosed patients with head and neck cancer. Accurate assessment of primary tumor extent and metastatic lymph node involvement is essential for optimal treatment of SCC. Current diagnostic procedures for detection and staging of primary and metastatic lesions, for evaluation of response to therapy and for detection of residual or recurrent disease, are performed by several modalities. These include physical examination, laryngoscopy under general anaesthesia, biopsies of all suspect areas and computed tomography (CT) or magnetic resonance imaging (MRI), ultrasound (US) and ultrasound guided fine needle aspiration (USgFNAC). Despite all these modern diagnostic modalities, the overall survival of patients with laryngeal or hypopharyngeal carcinomas has not increased over the last four decades. The current modalities have limitations in accurately detecting primary and residual/recurrent disease. These limitations may cause either over- or undertreatment with consequent effects on morbidity and survival.

Positron emission tomography (PET) is a functional imaging modality that enables determination of tissue metabolism and pathophysiology in vivo, and therefore of tumor tissue metabolism. In contrast to CT and MRI, PET is not hampered by anatomical or structural changes since it reflects metabolism and alterations therein. Investigating the feasibility of PET with L-[1-\textsuperscript{11}C]-tyrosine (TYR-PET) for clinical use in SCC of the larynx and hypopharynx is the purpose of this thesis. In Chapter 1, SCC of the larynx and hypopharynx are discussed in terms of epidemiology and current diagnostic procedures including its limitations. The aims of the thesis conclude Chapter 1.

Chapter 2 described the first published study on the clinical applications of TYR-PET in SCC of the larynx and hypopharynx. This feasibility study investigated the visualization of SCC of the larynx and hypopharynx by dynamic TYR-PET, and quantification of tumor activity by assessment of the Protein Synthesis Rate (PSR). In contrast to static scanning, in which the scanning procedure is performed in one position for a fixed time, starting at a certain time after injection of a radiopharmaceutical, dynamic scanning is performed in several successive images starting at the time of injection. The activity in tissues and blood can be followed in time and from the dynamic images time-activity curves can be obtained. Absolute quantification of metabolic tumor processes can be calculated by using these parameters in a kinetic model.

It was demonstrated that laryngeal and hypopharyngeal tumors can be clearly visualized with TYR, and a high sensitivity (100\%) for detection of this malignancies was found.

In the quantification of tumor metabolism, the carboxyl-labeled amino acid TYR appears to be an appropriate compound to determine protein synthesis activity in laryngeal and hypopharyngeal tumor. Quantification of the metabolic rates of the malignancies
and normal tissue, showed a significant difference between the PSR of tumor tissue and background tissue in all patients.

However, no additional information was obtained by quantification over visualization alone in detection of primary malignancies. Therefore, in vivo quantification of tumor metabolism by assessment of PSR using dynamic TYR-PET, seems not to be necessary in detection of previously untreated tumors.

Given the ability of dynamic TYR-PET for quantification of increased protein synthesis in tumor tissue in vivo, we have compared this method with several other, less elaborate, quantification methods in Chapter 3. For quantification of the protein synthesis rate (PSR), arterial cannulation with repeated blood sampling to obtain the plasma input function, and a dynamic TYR-PET study to calculate a time-activity curve, are necessary. In most PET studies, the standardized uptake value (SUV) method is used to quantify tumor activity. SUV can be calculated without repeated arterial blood sampling and prolonged scanning time, as required for determination of PSR, and is therefore less stressful for the patient. The relationship between PSR and SUV is largely unknown and different factors can cause wide variability in SUV. To determine the feasibility of noninvasive PET in head and neck oncology, the comparison of the absolute quantification method (PSR) with four different SUV methods (uncorrected SUV (SUV_{BW}); SUVs corrected for body surface area (SUV_{BSA}); for lean body mass (SUV_{LBM}) and Quetelet index (SUV_{QI})) was performed.

High correlation between the quantitative values (PSR) and the SUVs were described which offer the possibility to use noninvasive TYR-PET for reliable quantification of the metabolic tumor activity in primary laryngeal carcinomas.

One of the major problems in head and neck oncology is determination of tumor status after radiotherapy. Physical examination and conventional imaging by CT and MRI do not always accurately differentiate between residual or recurrent tumor and post treatment inflammation, fibrosis, edema or scarring. In Chapter 4, the accuracy and diagnostic value of TYR-PET for therapy evaluation of laryngeal carcinomas were discussed. We evaluated tumor response measurements with TYR-PET and conventional imaging (CT) in nineteen patients with laryngeal carcinomas. PET and CT studies were performed before definitive treatment. For determination of tumor status, a second TYR-PET scan was performed three months after radiotherapy. After treatment, sensitivity and specificity of TYR-PET for discrimination between residual tumor and benign post treatment tissue changes were both 100%, and for CT, 50% and 67%, respectively.

During the minimal follow-up period of 29 months, 6 patients had clinical suspicion of recurrent disease. In these six cases, a third TYR-PET, CT imaging and biopsies were performed. For detection of recurrent tumor during follow-up, sensitivity and specificity of TYR-PET were also 100%, and CT, 75% and 50%, respectively. We demonstrated that TYR-PET is an accurate imaging modality for therapy evaluation in detection of residual
and recurrent disease with higher sensitivity and specificity for discrimination of tumor status compared with conventional imaging.

Choosing the optimal treatment for an individual patient with squamous cell carcinoma of the larynx is a difficult challenge because of the unpredictable clinical behavior of this malignancy. The optimal choice of therapy depends mainly on the stage, type and location of the tumor as assessed by clinical and morphological examination. Although tumor stage is the only independent factor predicting treatment outcome of laryngeal cancer, the TNM classification has limitations in the management of a particular patient with head and neck cancer. Individual tumors with a similar clinical stage differ greatly in the response to radiotherapy. The factors influencing this unpredictable clinical behavior and decreased radio-curability are generally unknown. Despite the large number of histopathologic and biological studies that have been performed, there are currently no morphologic or cytologic markers available to predict outcome in head and neck cancer. A reliable method for assessing the clinical behavior and predicting the radio-curability of tumors would assist in therapy strategy and prognostic value. In Chapter 5, we evaluated whether quantitative PET using TYR has predictive value for survival and therapy outcome in patients with primary SCC of the larynx.

Cumulative survival was compared between patients with tumor PSR equal to or higher than the median (2.0 nmol/ml/min) and those with tumor PSR lower than the median and was found not to be significantly different (p=0.07). When the radiotherapy group was evaluated separately, the difference in survival was significant (p=0.03; 5-yrs survival, 30% vs. 73%) and high TYR uptake correlated with poor prognosis. In multivariate analysis, PSR was an independent predictive factor for survival. Because no significant difference (p=0.08) was found between patients with or without recurrence, no predictive value of PSR for disease recurrence could be demonstrated.

Therefore, prediction of survival of patients undergoing radiotherapy for laryngeal squamous cell carcinoma is feasible primarily by using dynamic TYR-PET to quantify metabolic tumor activity before treatment and may be of value for treatment strategy. The dispersion of quantitative values of the two groups is, however, a matter of concern, and larger series of patients are needed to assess the optimal cut-off value of TYR-PET for therapy planning. Furthermore, we did not observe a difference in survival for patients with larger tumors treated by surgery, suggesting the influence of other factors on metabolic tumor activity.

The behavior of malignancies is suggested to be related to metabolic activity of tumors. Mitotic activity, proliferation rate and differentiation are in vitro histological parameters of metabolic activity. In vivo, tumor metabolism can be assessed by PET. Chapter 6 described the relations between in vivo tumor metabolism using TYR-PET and in vitro biological activity as reflected by tumor grade, mitotic and proliferative activity of laryngeal squamous cell carcinomas.
Twenty-eight patients with histologically confirmed laryngeal carcinomas underwent dynamic TYR-PET before receiving definitive therapy. Different methods for quantification of tumor activity were performed: assessment of protein synthesis rate (PSR), calculation of standardized uptake value (SUV) and estimation of tumor-to-nontumor (T/N) ratio. All tumors were graded according to the UICC grading system, the percentage of mitotic figures was determined and proliferating cells were detected by immunostaining the Ki-67 protein. In the mean values of well differentiated (G1), moderately differentiated (G2) and poorly differentiated (G3) tumors, a relation was found between TYR uptake and grade, suggesting a relation between in vivo metabolic activity and tumor aggressiveness. No correlations were observed between mitotic activity or percentage of cells in proliferation and different quantification methods as measured by PET.

CONCLUSIONS AND FUTURE PERSPECTIVES

This thesis describes the first applications of TYR-PET in patients with SCC of the larynx and hypopharynx. We have demonstrated that TYR-PET is a reliable method for detection of laryngeal and hypopharyngeal carcinomas, and, by using a dynamic TYR-PET protocol, in vivo quantification of metabolic tumor activity is feasible by assessment of the PSR (chapter 2). In untreated laryngeal carcinomas, noninvasive quantification methods (SUV) can be used instead of the absolute quantification method (PSR) (chapter 3). TYR-PET proved to be an accurate imaging modality for therapy evaluation with higher sensitivity and specificity for discrimination of tumor status after treatment compared with conventional imaging (chapter 4). Pretreatment quantification of tumor activity may have prognostic value for SCC treated by radiotherapy (chapter 5). Between in vitro biological activity and in vivo metabolic activity, a relation exists in PSR and tumor grade (chapter 6).

Although future investigations are necessary to assess the exact clinical applications of TYR-PET in head and neck tumors, PET has already an established value for clinical oncology in enlarging our knowledge of metabolic tumor processes.

To predict the future of an imaging modality such as PET, the technical improvements in the other imaging modalities also need to be taken into account. These modalities will be evolving with improved resolution, faster acquisition, and improved injectable contrast. Although all of these other modalities will improve technically over time, their basic physical principles for image formation will not change: computed tomography (CT) will rely on attenuation of x-ray photons by tissue density, ultrasound (US) will rely on the reflection of high frequency sound waves on tissue planes, and magnetic resonance imaging (MRI) will rely on radio-frequency signals from tissues in a magnetic field. The basic principles of PET will continue to be based on the detection of photons emitted from the patient.

However, the potential variety of radiopharmaceuticals or radiotracers which may
be developed in the future, can offer interesting possibilities for diagnosis and therapy evaluation. Some disadvantages of TYR-PET may be overcome by the development of future radiopharmaceuticals. The necessity of a cyclotron for the production of TYR and therefore reduced distribution capacity, the prolonged dynamic scanning time and arterial cannulation for quantification may limit future applications. Possible solutions may be found in new or other radiolabeled amino acids. Special interest should be taken on artificial amino acids such as 1-aminocyclopentane carboxyl acid (ACPC), α-aminoisobutyric acid (AIB), $[^{18}\text{F}]$fluoro-L-phenylalanine and $[^{11}\text{C}]$-methyl]-alpha-aminoisobutyric and on artificial tyrosine analogues, as L-3-$[^{18}\text{F}]$fluoro-alpha-methyl-tyrosine (FMT) and O-2-$[^{18}\text{F}]$fluoroethyl-L-tyrosine (FET), L-3-$[^{123}\text{I}]$iodo-alpha-methyl-tyrosine (IMT). Also the proliferation tracers like $[^{18}\text{F}]$-fluoro-deoxy-L-fluorothymidine (FLT) and $[^{11}\text{C}]$-choline are considered to be potential tracers.

The continuing development of new and specific diagnostic and therapeutic tracers is one of the unique adaptive features of nuclear medicine and PET, which will maintain its role in clinical imaging and medicine. As some nuclear medicine procedures become obsolete because of competing imaging modalities, new tracers with better or different biological characteristics will evolve.