Clinical applications of L-[1-11C]-tyrosine PET in laryngeal cancer
Boer, Jurjan Rudolf de

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Chapter 1

Introduction
INTRODUCTION

Squamous cell carcinoma of the larynx comprises approximately 2% of all malignant tumors. In head and neck cancer, laryngeal carcinoma has the highest incidence of all newly diagnosed patients. The incidence of laryngeal carcinomas varies largely throughout the world. In South American countries as Brazil and Argentina the incidence is 19.9/10^5/yr, whereas in the United States and France estimated rates are 12.5/10^5/yr and 11.4/10^5/yr, respectively. Japan has the lowest incidence rates with 1.8/10^5/yr. With approximately 690 new cases in the Netherlands, the annual incidence is 8 per 100,000 persons. The age of patients with primary laryngeal cancer ranges between 50-70 years. Female patients tend to be 5-10 years younger on first presentation of the disease. In the last decade, the male: female ratio has changed from 20:1 to almost 10:1. Location of laryngeal tumors is on the vocal cords (glottic) in 2/3 of the cases, in approximately 1/3 of the cases above the vocal cords (supraglottic), and in less than 3% under the vocal cords (subglottic).

Hypopharyngeal cancer occurs less frequent than laryngeal cancer and has an annual incidence of 1.3 per 100,000 persons in the Netherlands. Predisposing factors for both laryngeal and hypopharyngeal carcinomas are abuse of tobacco and alcohol, although the importance of alcohol in the etiology of laryngeal cancer remains unclear.

CURRENT PROCEDURES AND LIMITATIONS IN HEAD AND NECK ONCOLOGY

Accurate assessment of primary tumor extent and metastatic lymph node involvement is essential for both planning and evaluation of therapy. To diagnose squamous cell carcinomas of the head and neck region, several diagnostic modalities are used in clinical practice. Physical examination, including indirect laryngoscopy and palpation of cervical lymph nodes, endoscopy 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) are the standard diagnostic procedures in a patient suspected of having a head and neck tumor.

In spite of all current diagnostic modalities, several clinical problems exist in detection and staging of primary and metastatic lesions, in the optimal choice of therapy of primary tumors, in the evaluation of response to therapy and in the detection of residual or recurrent disease. These clinical problems are outlined below.

Detection

Physical examination
The first step in the assessment of primary tumors of the head and neck region is inspection of all mucosa lining of the upper aerodigestive tract by indirect laryngoscopy. However,
visual interpretation of suspected tumor tissue is not very accurate since some parts of the mucosa are not properly visualized in this way. Consequently, direct laryngoscopy under general anaesthesia is required.

The neck is examined for possible lymph node metastases by palpation, but the drawback of this procedure is the high overall error rate 4.

**Direct laryngoscopy and tissue sampling**

During direct laryngoscopy, which is performed under general anaesthesia, information about tumor size and superficial tumor extension of all subsites is obtained and biopsies are taken from suspect areas for histological investigation. Sampling of tissue from the macroscopic most malignant part of the tumor is of the utmost importance. Unfortunately, in squamous cell carcinomas of the larynx and hypopharynx, intratumor heterogeneity occurs whereas only a small part of the tumor is biopsied and histologically studied. Biopsies from a non-representative area of the tumor can therefore result in a histological sampling error. Some laryngeal tumors even have submucosal growth and can be missed by biopsy, resulting in false negative histological results 5.

Although laryngoscopy obtains superior information about superficial tumor extension, no information is obtained about tumor infiltration in surrounding or deeper tissues, cartilage destruction or lymph node metastases.

**Radiological imaging**

Advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) can assess tumor extension in surrounding tissues. Although CT and MRI have improved detection and staging of head and neck tumors, the ability of these techniques to delineate primary and metastatic lesions accurately is limited 6, due to the fact that CT and MRI monitor primary tumors and lymphogenic metatases by size and structural changes in anatomy. Primary tumors that do not distort tissue planes, lymphogenic metastases that are not enlarged and small tumors may not be detected by CT or MRI. On the other hand, soft tissue swelling by inflammation or edema, inflammation around tumor tissue, and enlarged reactive lymph nodes can be interpreted as viable tumor tissue 7.

Presence of lymphogenic metastases in the neck can be assessed by several radiological imaging modalities. MRI, CT, ultrasound (US) and US guided fine needle aspiration (USgFNAC) have improved the overall error rate of palpation. Still the error rates for CT range from 7.5% to 28%, and for MRI 16% is reported 4,8. Differentiation between malignant and benign lesions with US has not been possible until the introduction of FNAC. However, the accuracy of this technique depends strongly on the skills of the investigator 9.
Staging

All previously mentioned modalities are used also for assessing the accurate stage of head and neck tumors. Staging is described using the TNM classification developed by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC). In laryngeal and hypopharyngeal squamous cell carcinomas the T-stage (Tumor) refers to the local extent of the tumor and ranges from T1 to T4. In contrast to tumors outside the head and neck region in which T-staging is determined by tumor size, T-staging of laryngeal and hypopharyngeal squamous cell carcinomas depends mainly on the location of the tumor in different anatomical subsites of the larynx and hypopharynx, and vocal cord fixation. N-stage (Nodus) refers to the presence of regional lymphogenic metastases in the neck and ranges from N0-N3 and the M-stage (Metastasis) refers to the absence (M0) or presence (M1) of distant metastases.

The TNM classification system serves as a guideline in the management of squamous cell carcinomas of the larynx and hypopharynx. The TNM classification system allows for exchange of data between oncological centers and makes statistical analysis of groups of patients possible. Until now the TNM classification system is the only proven independent factor predicting treatment outcome of laryngeal and hypopharyngeal cancer. Nevertheless, it has its limitations in planning therapy of an individual patient. Despite a similar T-classification, individual tumors may differ greatly in the response to (radio)therapy. The factors influencing this unpredictable clinical behaviour and decreased radiocurability are generally unknown.

Therapy

In general, the curative therapy options for carcinomas of the head and neck are surgery, radiotherapy (RT), a combination of both or a combination of chemotherapy and radiotherapy. Treatment with CO₂-laser evaporation or photodynamic therapy is restricted to a very small group of superficial growing tumors. The best choice of treatment of patients with laryngeal and hypopharyngeal carcinoma is still under investigation and depends on curability, functional ability after treatment and low complication risk.

Most small tumors (T1, T2 and small volume T3) are usually treated by RT in daily irradiation sessions for five to seven weeks for a total absorbed tumor dose of 70 Gy. For a selected minority of patients, restricted surgical procedures such as hemi- or supraglottic laryngectomies are possible. All these treatment options allow preservation of laryngeal function, including the voice, and therefore quality of life.

Patients with advanced bulky lesions (T3 and T4) will undergo a total laryngectomy with or without a partial pharyngectomy. For these patients preservation of the laryngeal function is not possible. In some centers, treatment of advanced tumors is performed by RT alone or RT in combination with chemotherapy, with salvage surgery...
(total laryngectomy) reserved for local recurrence\textsuperscript{19}. Unresectable tumors are currently treated by RT in combination with chemotherapy.

In the middle stages (T3 glottic laryngeal, T2 and T3 supraglottic laryngeal and T2 hypopharyngeal cancer) the optimal choice between RT alone or surgery with or without postoperative RT, remains under debate and investigation\textsuperscript{14-16}. Surgery will remove the entire tumor, but also the laryngeal function. RT allows preservation of the voice, but if irradiation fails and results in tumor recurrence, salvage surgery is the only therapeutic option left. The patient still loses the laryngeal function, has endured a total RT course on the head and neck region and has a increased risk of developing complications after salvage surgery due to diminished recovery capacity of irradiated tissue\textsuperscript{20}.

**Therapy evaluation**

Another clinical and radiological problem emerges once treatment has been given. There are no techniques available which can monitor the response of tumor tissue during and after therapy adequately. Frequent clinical follow-up, direct laryngoscopy, and CT or MRI are the current tools to evaluate therapy response.

Previous mentioned radiological problems for detection and staging of head and neck tumors with CT or MRI also occur during therapy evaluation. Differentiation between tumor recurrence or residual tumor on one hand, and post-treatment tissue reactions (inflammation, edema, necrosis, fibrosis and scarring) on the other, is often difficult. These factors limit the sensitivity and specificity of interpretation of anatomical imaging modalities, such as CT and MRI\textsuperscript{21,22}.

**Detection of residual or recurrent tumor**

In up to 50\% of the patients with laryngeal or hypopharyngeal cancer, residual or recurrent disease occurs after radiotherapy\textsuperscript{12,19}. In patients suspected of residual or recurrent disease, laryngoscopy under general anaesthesia and CT/MRI are performed. During laryngoscopy, visual differentiation can be difficult between post-treatment edema, soft tissue swelling and recurrent tumor tissue. Biopsies of suspect areas, for confirmation of residual or recurrent disease, may reveal false-negative results by missing viable tumor. Deep or repeated biopsies may be needed to detect submucosal tumor growth, but should be performed with caution since the capacity of irradiated tissue to recover is diminished\textsuperscript{20}.

Despite all current diagnostic modalities, the overall survival of patients with squamous cell carcinomas of the larynx and hypopharynx has not increased over the last four decades. Each of previous mentioned limitations in diagnosing, staging and monitoring patients with laryngeal and hypopharyngeal cancer may cause either over- or undertreatment
with consequent effect on morbidity and survival. Therefore, for improvement of therapy strategy and treatment results, imaging techniques which are able to delineate primary and metastatic lesions accurately and which can identify persistent and recurrent disease may be of great value.

**POSITRON EMISSION TOMOGRAPHY**

Nuclear medicine techniques have introduced a different kind of information as compared to conventional radiological imaging techniques as CT, MRI or US. In nuclear medicine, intravenously administered radioactive radiopharmaceuticals are used to obtain an image of the distribution of the radiopharmaceutical in the human body, whereas radiological techniques are based on differential absorption of radiation of an external source. In the past decades the development of new radiopharmaceuticals and the improvement of equipment for imaging in nuclear medicine has contributed to a more functional approach in clinical oncology. Because no direct relation exists between size of tumors and the number of viable malignant cells, and since metabolic alterations may precede structural alterations, metabolic tumor imaging techniques may become additional in the management of malignancies.

In conventional nuclear medicine, the radionuclides which have an established role in clinical oncology are Technetium-99m (\(^{99m}\)Tc), Gallium-67 (\(^{67}\)Ga), Thallium-201 (\(^{201}\)Tl) and Iodine-131 (\(^{131}\)I). These single photon γ-radiation emitting radionuclides, bound to a so-called "biomolecule", use a specific aspect of tumor pathophysiology and tumor biochemistry for diagnostic tumor localization. A gamma camera is used to detect the radiation, and distribution images are obtained. Limitations of conventional nuclear medicine are the relatively low resolution images and the difficulty for quantification of the amount of radioactivity per volume unit. Both these drawbacks relate to the physical properties of the radio-isotopes used.

Positron Emission Tomography (PET) is the latest development in nuclear medicine and has already established a substantial potential for applications in clinical oncology. PET differs from conventional nuclear medicine in the use of positron emitting radionuclides, and the technique allows more accurate visualization and quantification of metabolic processes in vivo.

**Positron emission**

In contrast to conventional nuclear medicine, PET uses radio-isotopes that emit positrons. Of the elements known in nature, many have isotopes with a relative shortage of neutrons, or - in other words - an abundance of positive charge in the nucleus. This shortage makes the nucleus unstable, with stability being restored if a negative charge is caught (electron capture), or a positive charge is expelled (positron emission). A positron is to be seen
as a particle with the same weight as an electron, but with a positive charge. Positrons travel a short distance in tissue before annihilating with an electron, converting their mass into energy, according to Einstein’s formula $E=mc^2$ and abiding the physical laws of conservation of energy and of impulse. This creates two 511 keV-photons (gamma radiation) moving in opposite directions under an angle of 180° (figure 1). The most frequently used radio-isotopes applied in PET are Carbon-11 ($^{11}$C), Nitrogen-13 ($^{13}$N), Oxygen-15 ($^{15}$O) and Fluorine-18 ($^{18}$F).

![Figure 1.](image)

A positron emitted from a positron emitting radionuclide, travels a short distance before annihilation with an electron. The energy and impulse the annihilation produces are translated in the creation of two 511 keV-photons (γ radiation) moving in directions under an angle of 180°. Emitted photons can be absorbed by detectors of the PET camera, which surround the patient as detector rings. If the capture of a photon by two opposite detectors coincides within 20 nsec., the signal is caused by annihilation.

**PET imaging**

PET imaging is performed by a PET camera which makes use of the fact that the two annihilation photons have a fixed energy and are emitted into opposite directions. Emitted photons can be absorbed by detectors in the PET camera. Each detector has connection to many opposite detectors. If the capture of a photon by two opposite detectors coincides within 20 nsec., the signal is caused by annihilation. The line at which this annihilation has taken place (“coincidence line”) is then known, and owing to the multitude of these coincidence lines in combination with mathematical reconstruction algorithms, the distribution of annihilation in the field of view can be reconstructed into an image. And since the radio-isotope is linked to a biomolecule, the image represents also the distribution of the radiopharmaceutical in the body. This feature of dedicated PET cameras, which surround the patient as a ring of multiple detectors, makes it possible to record the quantity and spatial location of the positron emitter within the body.

Positron emission scanning can be performed statically and dynamically. Static
scanning is performed in one position for a fixed time, starting at a certain time after injection of a tracer. Usually scanning starts after the tracer level in tissue has reached a plateau phase. A static scan monitors metabolic tumor activity at one specific moment, and is well suited for visualization of the activity in three dimensions (transaxial, coronal and sagittal).

Dynamic scanning is performed in several successive images starting at the time of injection. The activity in tissues can be followed in time and from the images, time-activity curves can be obtained. In addition, (arterial) blood samples can be taken at fixed time intervals. By combining the data from tissue and blood in a kinetic model, metabolic (tumor) processes can be quantified.

PET applications

In clinical oncology imaging, the role of PET is rapidly increasing. Most PET tumor imaging has been performed with the radiopharmaceutical 2-[18F]-fluoro-2-deoxy-D-glucose (FDG), a glucose analogue. One of the many biochemical alterations of tumor cells is an increased glucose metabolism, and FDG as radiotracer for tumor metabolism has already established several applications in PET imaging of cancer 23,24.

In head and neck oncology, FDG-PET can provide important information in staging primary tumors 25 including nodal staging in the neck 26,27 and assessment of distant metastases and second primaries 28,29. Also in the detection of unknown primary cancer 25,30, recurrent disease 28,31,32, and in the evaluation of therapy 26, FDG-PET has proven to be more accurate compared with conventional imaging modalities. In quantitative studies, FDG-PET may provide an independent prognostic factor for survival of patients with head and neck cancer 32,33.

However, FDG is a tracer with a high sensitivity but its specificity is relatively low due to the uptake in tissues with increased glucose metabolism other than malignancies. For instance, increased FDG uptake is described in inflammatory tissues, benign lesions, biopsy sites, tonsil tissue, salivary glands and post-irradiation tissues 34.

An increase of amino acid metabolism in malignant tumor cells is another biochemical alteration present in tumor cells 35. Amino acid tracers probably will be more specific because amino acids play a minor role in the metabolism of inflammatory cells as compared to FDG 36. The majority of the amino acid PET studies have been performed with L-[methyl-11C]methionine (MET) 36,37. The preference for this tracer is the result of the easy and reliable chemical synthesis. In humans, no accumulation of MET was found in focal inflammatory tissues and uptake by macrophages and necrotic tissue is negligible. However, methyl-labeled methionine reflects amino acid transport rather than protein synthesis and is also involved in other metabolic pathways, such as transmethylation and polyamine synthesis. The complicated metabolism of methionine has made it impossible to construct a precise metabolic model and therefore absolute quantification is not possible.
L-[1-11C]-Tyrosine (TYR), a carboxyl-labeled amino acid tracer, appears to be a more appropriate compound to determine protein synthesis activity in tumor tissue\textsuperscript{38}. Due to the relatively simple pathway of TYR, kinetic modelling has been constructed, and absolute quantification by calculation of the Protein Synthesis Rate (PSR) is possible. The TYR-PET model has been developed and validated in animal experiments and patients studies\textsuperscript{36,39-42} and may be of interest in the management of patients with squamous cell carcinomas of the head and neck.

**PURPOSE OF THE THESIS**

The purpose of this thesis is to investigate the feasibility of PET with L-[1-11C]-Tyrosine (TYR-PET) for clinical use in squamous cell carcinomas of the larynx and hypopharynx. The emphasis of the clinical studies is given on in vivo tumor analysis, visualization and quantification, detection, evaluation of therapy, and prognosis of laryngeal and hypopharyngeal carcinomas.

The aims of this thesis are:

1. To establish the value of TYR-PET in metabolic tumor imaging and quantification of squamous cell carcinomas of the larynx and hypopharynx.
2. To assess the diagnostic accuracy (sensitivity/specificity) of TYR-PET compared to conventional diagnostic modalities.
3. To establish the potential of TYR-PET for monitoring therapy in laryngeal and hypopharyngeal carcinomas.
4. To establish the prognostic value of TYR-PET.
REFERENCES


