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Contents

1

General introduction

The Larynx represents the junction of the upper and lower portions of the airway. It serves to protect the lower airways, facilitates respiration, and plays a key role in phonation. In adult humans, the larynx is found in the anterior neck at the level of the C3–C7 vertebrae. It connects the inferior part of the pharynx (hypopharynx) with the trachea. The larynx extends vertically from the tip of the epiglottis to the inferior border of the cricoid cartilage. Its interior can be divided into the supraglottis, glottis and, subglottis. Simplified one can say that the glottis consists of the vocal cords, the supraglottis is the region above and the subglottis the region below the vocal cords. The supraglottis is mainly derived from the 4th branchial arch, while the glottis and subglottis are mainly derived from the 6th branchial arch. The glottis and subglottis have therefore their lymphatic drainage towards the upper paratracheal nodes and lower deep jugular nodes while the supraglottic area drains upon the upper jugular vein nodes.

More than 97% of the laryngeal malignancies originate from the mucosa and are squamous cell carcinoma. Only a mere 3% of the laryngeal malignancies do not originate from the mucosa. Adenoid cystic carcinoma counts for 2%, neuroendocrine carcinoma and, sarcoma for the other 1% of the non-squamous cell carcinoma of the larynx[1]. In this paper, we will focus only on squamous cell carcinoma of the larynx (laryngeal cancer). Although only 1 % of all newly discovered malignancies, laryngeal cancer is the most frequent type of head and neck cancer in the Netherlands. The number of new patients with laryngeal cancer is approximately 700 a year in the Netherlands.

In the Netherlands, 60 % of the tumors originate in the glottic area, 35% in the supraglottic and 2% in the subglottic, although there is a tendency of an increase of supraglottic and a decline of glottic laryngeal cancer in the Netherlands[2].

Risk factors

Laryngeal cancer is highly associated with tobacco smoking. In fact, it is the main risk factor to develop glottic or supraglottic cancer. There is a strong correlation between the level of exposure per day and the inhalation level. In supraglottic cancer alcohol intake is definitely a risk factor synergetic to tobacco smoking[3]. Further known risk factors for as well glottic and supraglottic are toxic agents (e.g., asbestos, polycyclic aromatic hydrocarbons, wood dust, coal dust, and cement dust) related to occupation[4].

The major part of the patients are males and between 50 and 70 years old at the time of diagnosis. Consequently, it is expected that the sex ratio will shift because more women have become smokers, while the number of men smoking has declined. Unfortunately, in the short term, no decline is expected in the number of patients who will develop laryngeal cancer because the effects of smoking linger up to 20 years after quitting smoking.

Staging

For more than 2.5 decades, the treatment of HNC in the Netherlands has been centralized and restricted to the centers of the Dutch Head and Neck Oncology Cooperative Group (DHNOCG, Nederlandse Werkgroep Hoofd-Halstumoren) and their affiliated centers. Patients are staged and treated according to the guidelines of The National comprehensive cancer network (NCCN). In this dissertation, the primary sites are staged according to the 7th edition. The 7th UICC staging edition of the larynx, regarding the primary site, is shown below.

Tx Primary tumor cannot be assessed
Tis Carcinoma in situ

Supraglottic	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of the base of tongue, vallecula, medial wall of the pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease. Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid or esophagus)
T4b	Very advanced local disease. Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis	
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of the neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottic	
T1	Tumor limited to the subglottis
T2	Tumor extends to the vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Signs and symptoms

Persistent hoarseness is an early symptom of glottic cancer. Even small irregularities on the free side of the vocal cord gives rise to hoarseness. Glottic cancers usually commence at the free side of the vocal cords, which makes diagnosis at an early stage possible.

On the other hand, supraglottic cancers need to have a certain volume to change the voice (hot potato voice), cause globus feelings or dysphagia and have infiltrated deeply to cause (referred) pain. Supraglottic cancers are therefore usually diagnosed at a more advanced stage. Moreover, in contrast to the glottic area, the supraglottic area has rich lymphatic drainage, which results in a considerably higher number of regional metastasis in supraglottic cancer.

The diagnosis of laryngeal cancer has to be confirmed by a biopsy, showing squamous cell carcinoma. Consequently, a laryngoscopy has to be performed to inspect the larynx and take appropriate biopsies. Recent advancements in transnasal endoscopy have enabled a shift from an examination with biopsy under general anesthesia to an office-based examination with flexible endoscopic biopsy under topical anesthesia [5]. A positive biopsy and photo documentation is sufficient for a tumor, which is limited to one vocal cord without involvement, of the anterior or posterior commissure. For all the other stages of laryngeal tumors a CT or MRI, of the head and neck area has to be performed according to current guidelines[2]. The DHNOCG has no preference for one of the modalities and consequently both CT and MRI are used to stage the neck. In case of doubt, Ultra Sound guided Fine Needle Aspiration Cytology (USgFNAC) has to be performed to stage the neck. USgFNAC has the highest sensitivity and specificity rates of all modalities regarding lymph nodes. No recommendations are made regarding distant metastases and second primaries, but almost all the institutes in the Netherlands perform a contrast-enhanced thoracic CT on a routine base to rule out metastases or a simultaneous second primary.

The treatment of laryngeal cancer has focused on optimizing local control and organ preservation. According to the most recent national guidelines, endoscopic CO_2 laser resection is preferred above radiotherapy for favorable T1 supraglottic and glottic laryngeal cancers, due to the lower morbidity, shorter treatment duration and the possibilities for an organ-preserving treatment in case of recurrent disease[2]. The recommended treatment for T2 laryngeal cancer is radiotherapy. For T3 laryngeal cancer, however, the guidelines are less clear. The 2010 Dutch Guidelines recommend organ sparing treatment (if possible) by using concomitant chemoradiation or accelerated radiotherapy and laryngectomy if organ preservation is deemed impossible[2, 6]. For T4 tumors with a volume of less than $3cm^3$ the first choice of treatment is chemoradiation. When the tumor volume is too high, or organ preservation is not possible a laryngectomy will be performed and will be followed by postoperative radiotherapy. If concomitant chemotherapy is not possible one can still choose for accelerated radiotherapy in favorable cases.

A local recurrence is defined as the reappearance of cancer after treatment at the site at which it is originally detected within a certain time period. In the head and neck region, we usually use a distance of less than 2 cm from the original tumor location and a time frame of 5 years[7].

The local recurrence rate of laryngeal carcinoma reported after non-surgical treatment depends highly on the subsite and tumor stage. A review of Mendenhall et al. shows that T1b tumors have a 93%, T2a 80%, T2b 70%, T3a 63% and T4a an 81% 5-year cause-specific survival rate [8].

A review of Robin et al. shows for supraglottic cancers a five-year survival after radiotherapy of 60.8% for T1 tumors, 55.2% for T2, 31.2% for T3 and for T4 32.9%. The lower survival rate of supraglottic cancer is for a part related to the subsite, but the overall survival rate includes also deaths not related to the primary site[9]. The better survival rate and recurrence rate of T4 compared to T3 glottic and supraglottic cancers can be explained. Unfavorable and large volume T3 tumors will receive definite radiotherapy, while only low volume and favorable T4 tumors will receive definite radiotherapy [10].

Whereas primary laryngeal cancer is relatively easy to diagnose, the diagnosis of post-radiation residual disease is much more difficult. Post-radiation residual disease has a scattered submucosal growth pattern and can be embedded in edema and inflammatory tissue. This makes residual laryngeal cancer hard to differentiate from radiotherapy adverse effects.[11]

Early radiotherapy related changes are caused by the death of replicating cells due to DNA damage, either directly or by generation of reactive oxygen species. This damage and subsequent cell death lead to structural breakdown and general loss of function. Ciliated epithelium, blood vessels, and secretory glands appear especially sensitive. These early changes result in edema, erythema, sloughed tissues and, inspissated secretions[11,12,13]. Late radiotherapy related changes result from vascular damage and fibrosis. These changes are progressive and irreversible. Arterial vessels and the capillary microvasculature undergo changes that lead to obliterating endarteritis, ultimately causing ischemia and hypoxia of affected tissues. Loss of 60% to 80% capillary density may occur in irradiated tissue. The loss is largely incapable of microvascular recovery, due to irreversible fibroblast and stromal damage. The larynx of the patients may demonstrate progressive edema, muscle fibrosis, cricoarytenoid joint fixation, sloughing of tissue, perichondritis with eventual frank cartilage necrosis, and/or fistula formation. Laryngeal edema results from increased vascular permeability in the setting of decreased lymphatic and vascular outflow[11,12,14,15,16].

Models have indicated that laryngeal edema was correlated with a mean dose to the larynx of more than 50Gy[17].

System of classifying Radiotherapy related changes according to Chandler[16].

	Possible Symptoms	**Possible Signs**
Grade I	Slight hoarseness and mucosal dryness	Slight edema and presence of telangiectasias
Grade II	Moderate hoarseness and mucosal dryness	Moderate edema and erythema, some vocal cord hypomobility
Grade III	Severe hoarseness with dyspnea, moderate odynophagia, and dysphagia	Marked edema, skin changes anterior neck, severely impaired or fixed unilateral vocal cord
Grade IV	Respiratory distress, severe pain, and odynophagia, weight loss, dehydration	Fistula, fetid odor, fever, severe skin changes anterior neck and laryngeal airway obstruction due to edema

Flexible or indirect laryngoscopy is the first choice to visualize residual disease. However, as have been mentioned above, it can be hard to distinguish residual disease from adverse radiotherapy effects. An endolaryngeal biopsy is necessary to confirm the diagnosis, although a negative biopsy cannot by definition rule out the residual disease. According to Brouwer et al. an average of 1,5 endolaryngeal scopies is necessary to prove residual disease. To reject the diagnosis of residual disease an average of 3,0 endoscopies are necessary[18].

There are several reasons to limit the number of scopies. Endolaryngeal biopsies have to be taken while the patient is under general anesthesia. Although limited, general anesthesia has its own morbidity and mortality. A more important reason is the vulnerability and bad

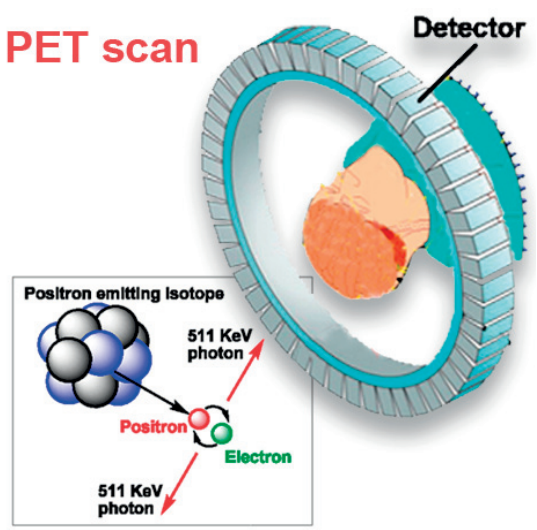
healing capacity of the post-radiation laryngeal mucosa[19]. Manipulation and especially biopsy taking has, therefore, be limited. Also, from an economic point of view, it is desirable to keep the number of endoscopies limited. General anesthesia and the use of an operation theatre is expensive and time of access to an OR is limited. Facilities have to be used as efficiently as possible[20].

Imaging techniques are used to help to differentiate between recurrences and adverse effects of radiotherapy. Nowadays CT and MRI of the head and neck are part of the routine work-up of patients. The specificity and sensitivity of both imaging techniques range from 60 to 70%[21]. Unfortunately, a 70% sensitivity rate is regarded too low to sustain from a laryngeal endoscopy in case of negative scan findings [21]. Consequently, alternatives are being explored. One such alternative to MRI or CT is positron emission tomography (PET)[22].

PET visualizes biochemical and (patho-)physiological processes in living organisms. Positron emitting radio isotopes are coupled chemically to organic molecules, thus yielding radiopharmaceuticals. The radiopharmaceuticals are injected intravenously, spread through the body and show an accumulation of the radiopharmaceutical on locations where the pathophysiological process studied is active.

Positron emitting radionuclides decay by emission of a positron from the nucleus which subsequently annihilates with an electron (from the surrounding tissue), according to the formula

$$e^{+} \text{ (positron)} + e^{-} \text{ (electron)} \longrightarrow \gamma\,(511\text{KeV}) + \gamma(511\text{KeV})$$



The emitted positron is the anti-particle of an electron. Each positron is emitted from the unstable nucleus with determined kinetic energy, depending on the radioisotope used. When the positron is expelled, it will bounce around, losing kinetic energy in the collisions and it will come to a standstill. Depending on the original kinetic energy the positrons on average have a wider or smaller range, which is related to the resolution of the PET-scan. Since there is an abundance of electrons in the tissue the positron will meet an electron in a short time, and the two will annihilate, transforming the masses of both into energy (1022keV) according to Einstein's formula $E=mc^2$. In order to abide by the law of momentum, in the vast majority of cases, the energy is released in the form of 2 quanta of gamma-radiation in the opposite direction with a fixed energy of 511 keV. Modern PET-camera's make use of this typical way of decay, thus yielding a "clean" signal with high sensitivities[23].

Malignancies usually have a higher level of metabolism than normal tissues, a raised protein synthesis, and DNA-turnover, or show overexpression of certain receptors. Consequently, the uptake of radiolabeled proteins, sugar, and nucleotides is usually higher in malignancies than the surrounding tissues. Most importantly, tumor cells have a relatively high level of glucose metabolism, caused by a suppression of the citric acid cycle. Cancer cells will continue to use glucose to produce ATP despite an abundance of oxygen, while normal cells will switch to fatty acids and citric acid in the presence of enough oxygen[24]. These differences in biochemical activity make it possible to visualize malignancies[25].

PET has a significant role in the diagnostic process of Head and Neck cancer. Nowadays a PET is advised by the Dutch Head and Neck Society for tumors with a high tendency to develop distant metastases, more specified bilateral, low jugular nodes or nodes larger than 6 cm [26].

Although the national tumor board has no preference for an imaging modality for unknown primaries in the head and neck area, in daily practice all Dutch head and neck centres perform an [^{18}F]-FDG-PET scan combined with a CT head, neck and thorax. A systematic review of Wong et al. shows that [^{18}F]-PET/CT diagnoses primary cancers in 38.5% of the cases, after previous negative imaging[27].

Radiotherapy planning can be more accurate by delineating the tumor by [^{18}F]-FDG-PET[28,29,29,30,31]. A sharp delineation of the tumor is important to determine the area which has to receive the highest doses of radiation. The area should not be smaller than the actual tumor to avoid under treatment. On the other side the area should not be larger than the actual tumor to avoid damage to vital organs surrounding the tumor.

Especially the work of Daisne shows that PET can delineate the tumor more accurately than CT or MRI. As a result, the side effects of the radiotherapy can be reduced without an incline of recurrent disease[32,33,34].

Imaging recurrent or residual disease after radiotherapy could become one of the most important areas of use for PET. Recent prospective studies show much better results as compared to CT or MRI[22,35,36]. A systemic review of Wong et al. shows that post treatment [^{18}F]-FDG-PET/CT has a sensitivity of 87% and a specificity of 93% for revealing local failure. This results in a high NPV which can obviate the need for invasive procedures or unnecessary follow-up imaging in the case of a negative [^{18}F]-FDG-PET/CT result, although with a relatively low PPV[37]. An excellent multi-institutional study conducted by Mehanna shows that [^{18}F]-PET-CT-guided active surveillance of the N+ neck after chemoradiation showed similar survival outcomes as planned neck dissection but resulted in considerably fewer neck dissections, fewer complications, and lower costs, supporting its use in daily practice[38].

For the head and neck region, metabolic imaging has almost become synonymous to [^{18}F]-FDG-PET. A drawback of [^{18}F]-FDG is the uptake in activated macrophages and in hypoxic conditions. The conditions in the early phase after radiotherapy are characterized by non-vital tumor cells and macrophages dominating the former tumor site, regardless the presence of residual disease or not[39,40]. The uptake of sugars and therefore [^{18}F]-FDG is relatively high in non tumor tissue during these conditions. This will make it difficult for [^{18}F]-FDG-PET to distinguish between adverse radiation effects and residual disease, resulting in excellent negative but poorer positive predictive values.

Most malignancies show a much wider alteration of metabolism, like amino acid, nucleoside and cell membrane metabolism. Several amino acids, the nucleoside thymidine and the precursor for the biosynthesis of phospholipids choline are incorporated in radiopharmaceuticals, which could be alternatives to [^{18}F]-FDG. In theory, these radiopharmaceuticals should be able to delineate malignancies at least as good as [^{18}F]-FDG. For the purpose of this thesis, we will focus on methionine.

The uptake of methionine is high in tumor cells but low in inflammatory tissues. Moreover, it is relatively easy to produce and connect with a C-11 group ([^{11}C]-MET). It could, therefore, be a good alternative to [^{18}F]-FDG[41]. [^{11}C]-MET is an established radiopharmaceutical and has been used on a large scale to visualize intracranial lesions[42,43,44,45,46]. Although on a smaller scale [^{11}C]-MET has also been successfully used in visualizing primary head and neck cancer[47,48,49,50,51].

The aims of this thesis are to investigate the role of [^{18}F]-FDG and alternatives of [^{18}F]-FDG, in particular [^{11}C]-MET, in the detection of local recurrent laryngeal carcinoma after (chemo) radiation.

In **Chapter** 2 we describe the results of a randomized controlled multicenter trial (RELAPS: REcurrent LAryngeal carcinoma after radiotherapy, PET Study). The study is conducted to improve the yield of direct laryngoscopy by setting its indication via PET, randomizing patients either to direct laryngoscopy with biopsies under general anesthesia (conventional strategy) or to [^{18}F]-FDG PET only followed by direct laryngoscopy with biopsies under general anesthesia. The clinical significance of the PET-based diagnostic strategy is evaluated, in relation to the number of futile indications for direct laryngoscopy under general anesthesia.

In **Chapter 3** a quantification of medical costs is presented. The mean medical costs of the PET-based strategy versus the conventional strategy are studied. Costs are subdivided for diagnostic, treatment and follow-up phases. A sensitivity analysis is performed to examine the impact of different input parameters.

In **Chapter 4** we give an overview of alternative radiopharmaceuticals to [^{18}F]-FDG for metabolic imaging of head and neck cancer, and we will try to define future developments.

In **Chapter 5** a pilot study is conducted to assess whether the radiopharmaceutical [^{11}C]-MET will be suitable for imaging small primary laryngeal cancers.

In **Chapter 6** we describe the results of the sequel to the RELAPS study. In this multicenter trial, an [^{18}F]-FDG and [^{11}C]-MET PET followed by direct laryngoscopy biopsies under general anesthesia is performed. In this study, we test the hypothesis that [^{11}C]-MET-PET has a higher positive predictive value than [^{18}F]-FDG-PET without a decline in the negative predictive value, in detecting recurrent disease in patients with clinical suspicion on recurrent laryngeal carcinoma after radiotherapy.

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2

Effectiveness of an 18F-FDG-PET based strategy to optimize the diagnostic trajectory of suspected recurrent laryngeal carcinoma after radiotherapy: The RELAPS multicenter randomized trial

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Abstract

Purpose

The purpose of this study is to evaluate the efficacy of [^{18}F]-FDG-PET as first-line diagnostic investigation, prior to performing a direct laryngoscopy with biopsy under general anesthesia, in patients suspected of recurrent laryngeal carcinoma after radiotherapy.

Patients and methods

150 patients suspected of recurrent T2–4 laryngeal carcinoma at least two months after prior (chemo)radiotherapy with curative intent for resectable disease were randomized to direct laryngoscopy (CWU: conventional workup strategy) or to [^{18}F]-FDG-PET only followed by direct laryngoscopy if PET was assessed 'positive' or 'equivocal' (PWU: PET based workup strategy), to compare the effectiveness of these strategies. Primary endpoint was the number of indications for direct laryngoscopies classified as unnecessary based on absence of recurrence, both on direct laryngoscopy and on six month follow up. Safety endpoints comprised resectability of recurrent lesions and completeness of surgical margins following salvage laryngectomy.

Results

Intention-to-treat analyses were performed on all randomized patients (CWU: n = 74, PWU: n = 76). Tumor recurrence was similar in both groups: 45 patients (30%; 21 CWU, 24 PWU) within six months. In 53 patients in the CWU arm (72%, 95% CI: 60–81) unnecessary direct laryngoscopies were performed compared to 22 in the PWU arm (29%, 95% CI: 19–40) ($p < 0.0001$). The percentage of salvage laryngectomies (resectability) and positive surgical margins were similar between CWU and PWU (81%, 63% respectively, $p = 0.17$, and 29%, 7%, respectively, $p = 0.20$). The prevalence of the combination of local unresectability and positive margins is in the CWU group 24% and in the PWU group 8%. No difference ($p = 0.32$) in disease specific survival between both groups was found.

Conclusion

In patients with suspected laryngeal carcinoma after radiotherapy, PET as the first diagnostic procedure can reduce the need for direct laryngoscopy by more than 50% without jeopardizing quality of treatment.

Introduction

For most patients with residual or recurrent laryngeal carcinoma who have been treated by chemo)radiation for initially resectable disease, timely detection increases the likelihood of successful surgical salvage. Dysphonia, dyspnoea, or local primary site pain, especially if progressive, can be a sign of recurrent laryngeal carcinoma. However, differentiating tumor and sequelae of radiotherapy is often difficult: in one study only 50% of all patients with severe edema or necrosis had residual or recurrent cancer (1). Current clinical practice mandates direct laryngoscopy with biopsy under general anesthesia – an invasive, expensive procedure with a low yield of recurrence of 53% at a first attempt (2). Depending on T-stage, between two and five direct laryngoscopy procedures are usually required to detect one recurrence within a time period of six months after suspicion was first considered (2). After a first negative direct laryngoscopy, 31% of patients will manifest a proven recurrence within the subsequent six months of observation (2). In addition, biopsy itself exacerbates post-radiotherapy changes, which further reduces the sensitivity of subsequent procedures. Current imaging techniques offer no help: neither CT nor MRI can reliably differentiate cancer from post-irradiation changes in laryngeal carcinoma (3). However, positron emission tomography shows potential to improve the yield and allow for better tissue targeting of direct laryngoscopy and biopsy. In a systematic review, the pooled sensitivity and specificity of 18F-fluorodeoxyglucose positron-emission tomography ([^{18}F]-FDG-PET) for the detection of recurrent laryngeal carcinoma after radiotherapy were reported as 89% and 74%, respectively, with a mean prevalence rate of recurrence of 50% (3). Experience from the centers of the Dutch Head and Neck Society (NWHHT) reported that the interobserver variability in scoring PET scans from a pilot study was reasonable (κ = 0.55) (4). A randomized controlled trial was required to determine the utility of [^{18}F]-FDG-PET in distinguishing post-treatment changes from cancer and thus decrease unnecessary direct laryngoscopies.

The goal of RELAPS (REcurrent LAryngeal carcinoma after radiotherapy PET Study) was to compare the current conventional (traditional) workup comprising direct laryngoscopy and biopsy to a strategy with PET as a first diagnostic test to select patients for such a workup. The primary outcome measure was the number of 'unnecessary' indications for direct laryngoscopies under general anesthesia, defined as the number of patients with procedures where no local recurrence could be detected by biopsy or during follow-up.

Methods

Patients

Eligible patients were clinically suspected (at indirect or flexible laryngoscopy or because of patient's complaints) of local residual or recurrent disease at least two months after completed (chemo)radiotherapy with curative intent for a resectable T2–4 laryngeal carcinoma, with a clinical indication for direct laryngoscopy and biopsy under general anesthesia (abbreviated as 'direct laryngoscopy'). Exclusion criteria were age below 18 years, clinically evident recurrence (in which case direct laryngoscopy would only be indicated to confirm recurrence histopathologically and assess its extent; such procedure would be performed regardless of imaging results), and pregnancy. The eligibility criterion of the minimal interval between radiotherapy and randomization was changed after trial commencement from four to two months to investigate the target group in daily clinical practice, because high negative predictive values of PET after eight weeks were reported (5).

The protocol was published (6) and approved by ethics committees as required in The Netherlands and Belgium. All patients provided written informed consent. Seven University and two Community Hospitals recruited patients for the study that was designed in collaboration with the Dutch Head and Neck Society (NWHHT).

Randomization and masking

Patients were enrolled by the treating physician, registered at the Comprehensive Cancer Centre Amsterdam by telephone and then centrally randomized to either the conventional workup comprising direct laryngoscopy and biopsy under general anesthesia (CWU), or to [^{18}F]-FDG-PET, with direct laryngoscopy under general anesthesia only in cases with positive or equivocal PET findings (PWU). Allocation was performed by a central office on-site computer combined with allocations kept in a locked, unreadable computer file that investigators can access only after the characteristics of an enrolled participant are entered. A stratified permuted-block procedure randomized patients to the groups on a 1:1 ratio. Strata comprised current smoking (yes/ no), institute of treating physician, and T-stage (T2/T3–4). Neither patients, investigators nor central office personnel were masked to the diagnostic group chosen by the allocation procedure.

Procedures

Patients in the CWU group underwent direct laryngoscopy under general anesthesia, combined with biopsies when indicated during direct laryngoscopy at the discretion of the attending head and neck surgeon. If direct laryngoscopy (with biopsies) was negative or equivocal, this procedure was repeated within six weeks, unless clinical signs and symptoms

had decreased or resolved. In the PWU group, patients with a negative PET scan received no further investigations (imaging or direct laryngoscopy) for at least another three months, except in case of progression of clinical signs or symptoms. In both study groups, patients with histopathologically proven recurrence were considered for total (or partial) laryngectomy based on an assessment of resectability. This assessment included MRI or CT of head and neck and chest X-ray, CTchest, ultrasound guided fine-needle aspiration cytology and/or PET(-CT) where indicated.

After an initial negative PET or negative direct laryngoscopy, the head and neck surgeon evaluated the patient every four to eight weeks, for at least a period of 12 months. Outpatient clinic visits, hospital admission, operative procedures, additional imaging and histological recurrence of tumor, the results of any surgical procedure, and death were documented during the follow-up period.

Data were collected by the assistant investigator (LvdP). The principal (RdB) and assistant investigator had access to all data and vouch for the completeness and accuracy of the reported data and analyses. Statistical analyses were performed by a clinical statistician (HvT).

PET(-CT) scans were performed in the local head and neck center, per protocol within two weeks after inclusion of each patient. Patients fasted for 6 h before the scan. A 20 min head and neck acquisition of images was started 1 h after injection of 100–587 MBq [^{18}F]-FDG (dose dependent on body weight and scanner) and the scanned trajectory included skull base to clavicle. The data supplied by the physician contained the pre-treatment stage, site and side location of the laryngeal carcinoma, and the date of the cessation of the last dose of radiation treatment. Results were communicated to the referring clinician by phone and confirmed in a written report. Assessment of the PET images was performed visually by the local nuclear medicine physician. The larynx was assessed by degree of abnormal uptake, anatomical confidence and side, and summarized in a three-point scale: negative, equivocal, or positive regarding local tumor status. The PET report also included information on lymph node involvement and distant metastases in the field of view (extending beyond head and neck area according to local preference).

The primary efficacy parameter was the difference in the number of unnecessary indications for direct laryngoscopies between the CWU and PWU arms after 6 and 12 months of date of clinical suspicion for recurrent cancer (i.e. from randomization). An indication for direct laryngoscopy was classified as unnecessary if no recurrence was diagnosed on direct laryngoscopy nor subsequently within the reference follow-up period of 6 months (primary period) or 12 months (secondary period) from date of clinical suspicion of cancer.

Importantly, in the CWU group an indication for direct laryngoscopy was considered justified (necessary) in all cases where recurrence was diagnosed within the reference follow-up period (tumor positive pathology), even if the original direct laryngoscopy found no recurrence (false negative result). To guard against possible adverse effects of PET delaying detection of potentially resectable recurrences safety end points comprised resectability of recurrent lesions (percentage of laryngectomies performed in case of recurrence) and surgical margins of a salvage laryngectomy (percentage of positive margins of laryngectomy specimen).

Statistical analysis

With a reduction (from 38% to 13%) as our aim, a sample size calculation on Fisher's Exact test with a two-sided significance level of 0.05 and a power of 85%, revealed a requirement of 59 evaluable patients per group (6). In the anticipation that 20% of patients would not be evaluable a total of 150 patients were randomized equally to the two study arms. Because of the expected low risk of PET imaging and the relatively short accrual time, no interim statistical analysis was planned. Efficacy analyses were performed according to the intention-to-treat principle, followed by per-protocol-analyses. Logistic regression was performed to account for potentially confounding variables (age, smoking and clinical stage at presentation before radiotherapy). Proportions were tested using the Chi-square statistic or Fisher's Exact test if considered more appropriate. Continuous variable was compared using *t*-tests or Wilcoxon two-sample rank test in case of non-normal distribution. Time-to-event analysis was performed using the method of Kaplan–Meier. Disease-specific survival was defined as time from randomization to death due to disease (laryngeal cancer) and overall survival included all deaths irrespective of the cause of death. For overall survival the log-rank and cox-proportional hazard analysis were used to compare groups and to calculate hazard ratios and 95% confidence intervals. Disease-specific survival between the groups (at 12 months) was compared in the context of competing risks using Gray's method (7).

Results

Patients

Between February 2005 and February 2009, 150 patients attending eight collaborating centers, members of the Dutch Head and Neck Society, and one Belgian center (seven university and two community/categorical hospitals) were randomly assigned to the CWU (n = 74) or the PWU strategy (n = 76).

The groups were balanced with respect to the baseline characteristics of the patients, except for age (Table 1). Randomization resulted in an equal distribution of symptoms and findings after diagnostic flexible endoscopic laryngoscopy (see Appendix). The median time from completion of radiotherapy to entry into the study was 10 and 7 months for CWU and PWU, respectively. In the PWU group 54 patients underwent PET only and 21 patients PET/CT. Median delay between injection of [^{18}F]-FDG and scan was 60 min (range 42–99). All patients were normoglycemic at PET (mean serum glucose: CWU 5.6, PWU 5.8). The median (IQR) time interval between randomization and the first direct laryngoscopy was 18 days (12–24) in CWU patients, vs. 27 days (17–40) in patients with positive or equivocal PET in the PWU group ($p = 0.0002$), and 84 days (57–134) for PWU patients with progression of clinical signs and symptoms who underwent direct laryngoscopy despite a negative PET (Wilcoxon two-sample test).

The number of tumor recurrences was similar in both groups: 45 patients (30%; 21 CWU, 24 PWU) within six months and 48 (32%; 23 CWU, 25 PWU) within 12 months. Likewise, time from randomization to recurrence was similar (HR = 0.93, $p = 0.81$). Laryngectomy was performed in 81% (95% CI 57–94) of CWU vs. 63% (95% CI 41–80) of PWU patients with a recurrence ($p = 0.17$, Table 2). Median time from randomization to laryngectomy with positive resection margins was six (n = 5; range 1–33) and one (n = 1) months for CWU and PWU, respectively. In the CWU group, four patients had no salvage laryngectomy because of: metastases (n = 2) and non-tumor related factors (n = 2). In the PWU group, nine biopsy positive patients did not proceed to laryngectomy because of: unresectable primary tumor (n = 1), metastases (n = 2), non-tumor related factors (n = 6). The prevalence of positive resection margins was not significantly different between the groups (CWU 29% (95% CI 10–56), PWU 7% (95% CI 2–32); $p = 0.2$). The prevalence of the combination of local unresectability and positive margins is in the CWU group 24% (5 positive margins/ 21 recurrences) and in the PWU group 8% (1 local unresectable + 1 positive margins/24 recurrences).

Table 1. Baseline characteristics of the patients.

Variable	Conventional strategy CWU (N = 74)	18F-FDG-PET based strategy PWU (N = 76)
Gender – No. (%)		60 (79%)
Male	58 (78%)	16 (21%)
Female	16 (22%)	
Age		64 (11)
Mean (SD) – year	60 (9)	38 (50%)
<65 year – No. (%)	52 (70%)	38 (50%)
≥65 year – No. (%)	22 (30%)	
Primary tumor site – %		43 (57%)
Supraglottic	39 (53%)	33 (43%)
Glottic	34 (46%)	
Subglottic	1 (1%)	
Primary tumor stage – %		44 (58%)
T2	43 (58%)	25 (33%)
T3	27 (37%)	7 (9%)
T4	4 (5%)	
Primary node stage – %		61 (80%)
N0	60 (81%)	6 (8%)
N1	6 (8%)	
N2a		3 (4%)
N2b	2 (3%)	6 (8%)
N2c	6 (8%)	
N3		
Previous treatment – %		72 (95%)
Radiotherapy	70 (95%)	4 (5%)
Chemoradiotherapy	4 (5%)	

Table 2. Follow-up of the patients.

Variable	Conventional strategy CWU (N = 74)	18F-FDG-PET based strategy PWU (N = 76)	p-Value
Direct laryngoscopies per patient – No. 6 months			p = 0.027
0 laryngoscopies	2	20	(Cochran-Armitage trend test)
1 laryngoscopies	53	39	
2 laryngoscopies	19	14	
3 laryngoscopies	-	1	
4 laryngoscopies	-	1	
5 laryngoscopies	-	-	
Direct laryngoscopies per patient – No. 12 months			p = 0.028
0 laryngoscopies	2	17	(Cochran-Armitage trend test)
1 laryngoscopies	49	41	
2 laryngoscopies	20	16	
3 laryngoscopies	2	1	
4 laryngoscopies	1	-	
5 laryngoscopies	-	1	
Local disease within 6 months – No. (%)	21 (28)	24 (32)	
Local disease within 12 months – No. (%)	23 (31)	25 (33)	0.95
Total deaths – No. (%)			
Cumulative at 6 months	5 (7)	13 (17)	
Cumulative at 12 months	5 (7)	19 (25)	0.003[a]
Disease specific deaths – No. (%)			
Cumulative at 6 months	3 (4)	8 (11)	
Cumulative at 12 months	3 (4)	9 (12)	0.08[b]
Salvage surgery – No. (%)			
Local disease with salvage within 6 months	17 (81)	15 (63)	
Local disease with salvage within 12 months	18 (78)	16 (64)	0.44

[a] Logrank p-value at 12 months.

[b] Gray's test at 12 months.

Primary outcome

Indication for direct laryngoscopy was classified as unnecessary in 53 (72%) CWU compared to 22 (29%) PWU patients (difference 43%, 95% CI: 27–58; $p < 0.0001$). This absolute difference in unnecessary indications for direct laryngoscopies of 43% can be interpreted as 2.3 patients to be evaluated with PET (95% CI: 1.7–3.7) to avoid at least one unnecessary indication for direct laryngoscopy. Direct laryngoscopies were unnecessary after PET in 19/54 (35%, 95% CI: 23–49) and after PET/CT in 3/21 (14%, 95% CI: 3–36, $p = 0.13$) PWU patients.

Adjustment for potential confounders (stratification factors and age) did not essentially change this difference. Current smoking was associated with an increased probability for an unnecessary direct laryngoscopy ($p = 0.02$, Logistic regression). Seven patients died within six month follow-up without overt recurrence. In all per-protocol analyses (excluding three patients) the difference in unnecessary direct laryngoscopies between CWU and PWU remained significant. In none of the prespecified subgroup analysis a difference in number of unnecessary indications for direct laryngoscopies was found between PET and PET/CT.

Thirty PET findings were true negative and one was false negative. The latter concerned a PET/CT with negative PET but positive (diagnostic) CT, followed by a direct laryngoscopy within one month; however, the patient refused total laryngectomy. In the PWU arm, in 22/44 patients (50%; 95% CI: 36–64) direct laryngoscopies did not yield a tumor-positive biopsy (difference with CWU 21%; 95% CI: 1–41; $p = 0.03$), this group comprised 12 positive and 10 equivocal PET scans.

Between 6 month and 12 month follow-up, three local recurrences were identified (two CWU, one PWU). In all three patients the (first) direct laryngoscopy after randomization had shown no evidence of recurrent disease.

The flow chart of the included patients is presented in Fig. 1.

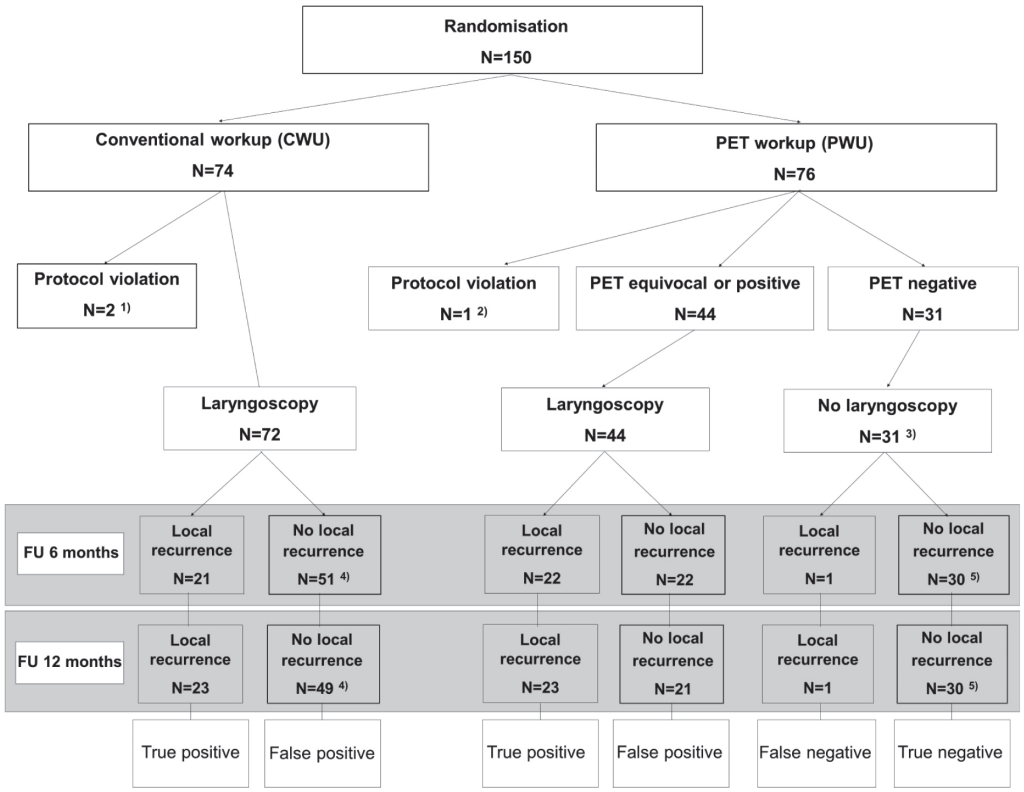

Fig. 1. Flow chart of included patients, based on six-month follow-up. (1) two patients: no laryngoscopy, (2) one patient: no PET, local tumor, (3) one patient: although PET was negative, laryngoscopy was performed, (4) two patients: follow-up <6 months, (5) three patients: follow-up <6 months.

With 12 months as the reference follow-up period, indication for direct laryngoscopy was classified as unnecessary in 69% (95% CI 57–79) of CWU, compared to 28% (18–39) of PWU patients ($p < 0.0001$). Stratified analyses and per protocol analyses were highly similar to the six-month results. At 12 months after randomization, the total number of tumor-negative biopsies taken during direct laryngoscopy was 81 in the CWU arm vs. 58 in the PWU arm ($p = 0.04$).

Follow-up

The mean number of outpatient clinic visits in the first year was similar: 6 CWU vs. 5 PWU independent of the PET results in the latter arm. In the first six months of follow-up five CWU patients died: due to progressive disease (n = 3: 2 local and 1 locoregional disease); cardiovascular disease (n = 1); and chest dyspnea without evidence of recurrence (n = 1).

In the same period 13 PWU patients died; due to progressive disease (n = 8: 3 local, 1 regional disease and 4 distant metastases), cardiovascular disease (n = 3), infection (n = 1), and primary lung cancer (n = 1). In three of four patients with distant metastases these had already been identified by PET. In the next six months another six patients died, all in the PWU group, due to progressive disease (n = 1: distant metastases after laryngectomy), cardiovascular disease (n = 1), primary pulmonary carcinoma (n = 2), car accident (n = 1), and pulmonary edema without evidence of cancer (n = 1). No difference (p = 0.32) in disease specific survival between both groups was found. Disease specific and overall survival Kaplan–Meier curves for the first 36 months are shown in Figs. 2 and 3.

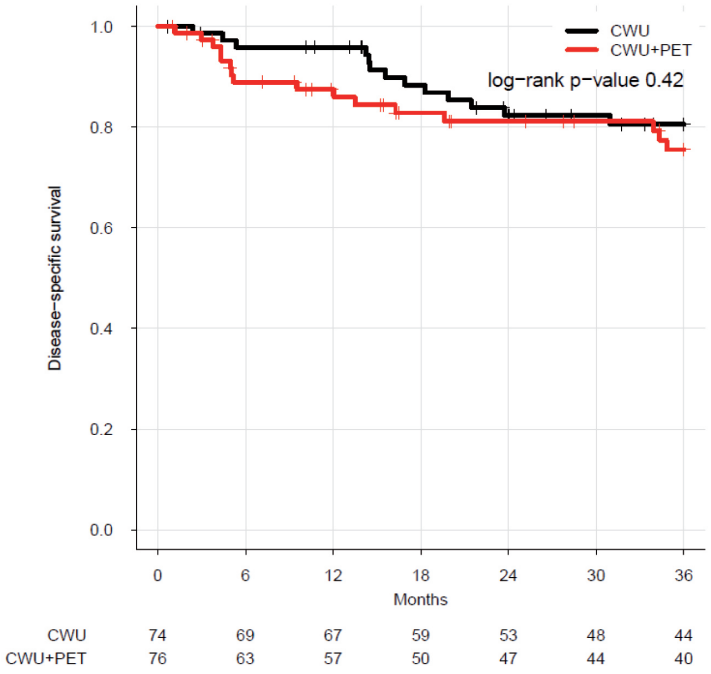

Fig. 2. Disease specific survival for CWU and PWU arms.

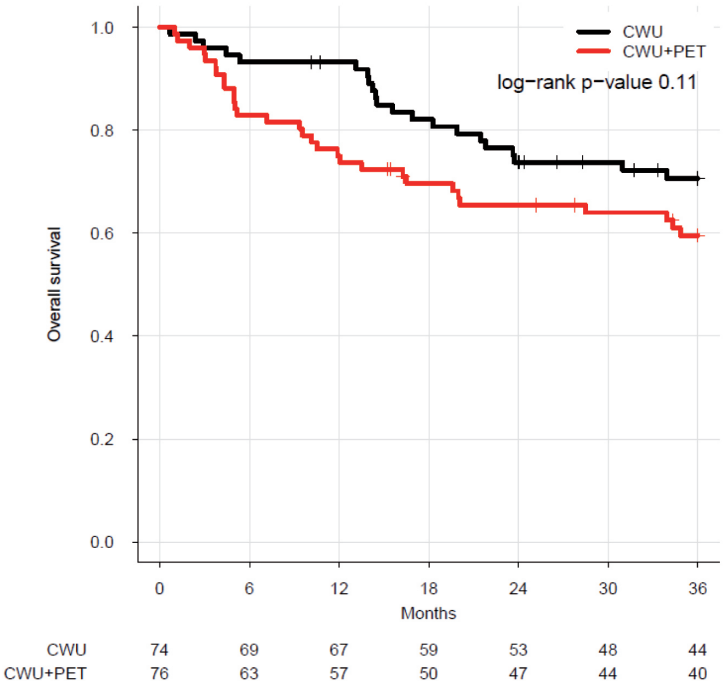

Fig. 3. Overall survival for CWU and PWU arms.

Discussion

This trial demonstrates that a diagnostic strategy including [^{18}F]-FDG-PET can effectively exclude disease recurrence in patients treated for laryngeal carcinoma, strongly and safely reducing the need for invasive procedures such as direct laryngoscopy.

Without the need for hospitalization and anesthesia, and lacking bothersome side effects, PET is clearly a more acceptable procedure for these patients than direct laryngoscopy. A reduction in unnecessary procedures also increases efficiency of expert personnel and saves resources. PET also allows entire body scanning in the same setting, enabling the detection of regional and distant metastases (8–10).

A prerequisite to forego a diagnostic technique (in this case direct laryngoscopy) is diagnostic safety. Preferably detection of recurrent disease should not be delayed, and any delay should not worsen prognosis. This trial documented such safety of the [^{18}F]-FDG-PET based strategy: results of the operability of a recurrence and surgical margins of

the salvage laryngectomy in the PWU group were comparable with the CWU group. The decision to perform a salvage laryngectomy depends on several factors: unresectability but also comorbidity, patient's wish (refusal) and metastases. The main reason to consider a local recurrent laryngeal cancer unresectable is that positive margins are expected. Since adjuvant options after previous radiotherapy are very limited, patients with such a recurrence will not undergo salvage laryngectomy. Therefore, it is better (with more power) to combine patients with local unresectable recurrence and positive margins and compare this number in both groups as a proxy for safety. The PWU group did not worse than the CWU group. Also, time to laryngectomy with positive resection margins was not increased in the PWU group as compared to the CWU group. The disparity in number of deaths within 12 months seems to be coincidental and not due to undetected disease. This is confirmed by the similar disease specific survival between both groups after follow-up of 36 months.

Only one [^{18}F]-FDG-PET scan was false negative. False negative results are most frequently ascribed to size (<10 mm) (11). In this specific case it concerned a PET/CT scan, and because the CT scan was positive the negative PET was inconsequential: a direct laryngoscopy was performed without delay. In our proposed PET based strategy (without CT), this recurrence would have been missed and a laryngectomy would have been postponed unnecessarily. This case is remarkable because combination of PET and CT in an integrated PET/CT scanner in some series particularly reduces the false-positive rather than the false-negative observations, thereby improving specificity (8,12,13). In our subgroup analyses, maybe due to small groups, the number of unnecessary indications for direct laryngoscopies in PET and PET/CT scanned patients was not significantly different. Gupta et al. found in a meta-regression analysis no significant difference between post-treatment stand-alone PET and integrated PET/CT (14).

Strengths of this study include the randomized design and the follow up. Also, the study was embedded in the routine clinical practice in a wide range of participating hospitals, including both university and community settings, which increases its generalizability. A diagnostic imaging technique is considered 'effective' if it not only provides more accurate data than existing modalities, but also improves patient management, and ultimately it should contribute to have a favorable impact on health status at reasonable costs. In this study we provide not only indicative data as in an accuracy study but also information on the actual effectiveness of PET.

Although PET is able to decrease the number of direct laryngoscopies substantially, still 50% of patients selected for direct laryngoscopy underwent this procedure unnecessarily, leaving room for further improvement.

In conclusion: This trial shows that in patients suspected of recurrent or persistent laryngeal cancer only those with positive or equivocal PET findings should undergo a confirmatory direct laryngoscopy. This strategy seems to be safe and will reduce the number of unnecessary invasive procedures by more than 50%.

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3

Recurrent Laryngeal Carcinoma PET Study (Relaps): Cost Analysis Of 18F-FDG Pet In Patients With Suspected Recurrent Laryngeal Cancer Previously Treated With Radiotherapy

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Objectives

The aim of this study was to investigate the potential benefits and cost consequences of introducing 18F-Fluorodeoxyglucose Positron Emission Tomography ([^{18}F]-FDG-PET) in the diagnostic work-up of patients with suspected recurrent laryngeal cancer after radiotherapy.

Methods

REcurrent LAryngeal carcinoma PET Study (RELAPS), a prospective multicenter randomized controlled trial, recruited 150 patients from eight head and neck cancer centers in the Netherlands and one center in Belgium. Two diagnostic algorithms were compared to the reference standard: (1) Conventional work-up (CWU); direct laryngoscopy with biopsy under general anesthesia, and (2)[^{18}F]-FDG-PET work-up (PWU) followed by laryngoscopy; only for positive or equivocal findings. Standard reference comprised histopathology and clinical follow-up of 6- and 12-months, respectively. Diagnostic performance of [^{18}F]-FDG-PET and indication of unnecessary operations were efficacy measures. Dutch healthcare perspective was used to obtain input parameters from hospital databases, patient records, literature and publicly available sources. Costs were expressed in 2014 Euros. Sensitivity analysis was performed.

Results

Indication for direct laryngoscopy was classified unnecessary in 49 CWU patients (68%, 95%CI: 56-79) compared to 21 PWU patients (28%, 95%CI: 18-40) ($p< 0.0001$). The absolute difference between groups at 12-months was 40%. [^{18}F]-FDG-PET had a sensitivity of 96% (95%CI, 78%-100%), specificity of 59% (95%CI, 44%-72%), a positive predictive value of 52% (95%CI, 37%-68%) and a negative predictive value of 97% (95%CI, 83%-100%). Results at 6-months follow-up were similar. Total mean medical costs per patient for PWU and CWU were € 11,302 and € 11,784 (6-months), and € 12,670 and € 13,776 (12-months), respectively. The incremental costs were in favor of the PWU patients (€ 482 (6-months), € 1,105 (12-months)). Sensitivity analyses showed that the most influential parameters were hospitalization, treatment-related operations and cost of PET.

Conclusions

The introduction of [^{18}F]-FDG-PET in the diagnostic trajectory of laryngeal cancer patients with suspected recurrence after radiotherapy is feasible, safe and favorable from clinical and economic perspectives.

4

Alternative PET tracers in head and neck cancer. A review

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Abstract

Positron emission tomography (PET) has become a standard in staging Head and Neck cancer. While 18F-fluoro-2-deoxy-D-glucose ([^{18}F]FDG-PET) is the most frequently used radiopharmaceutical, glycolysis is not the only metabolic process that can be visualized. Different PET tracers can also be used to visualize other metabolic processes and in this manner, the disadvantages of FDG-PET can be avoided. In this review, we describe a comprehensive overview of alternatives to FDG that can be used in identifying head and neck cancer. The potential advantages and disadvantages of these radiopharmaceuticals are discussed.

Keywords
PET, Amino acids, Nucleoside, Hypoxia, Monoclonal antibodies

Introduction

Most malignancies show an altered metabolism, which can be visualized by positron emission tomography (PET), a technique commonly used for in vivo molecular imaging. In head and neck oncology, PET has become more and more synonymous to[^{18}F]-FDG-PET. [^{18}F]-FDG-PET is now commonly used in diagnosing high-staged tumors and unknown primaries, and more recently, as a therapy evaluation after (chemo-)radiation and for a better delineation of the tumor before radiotherapy. [^{18}F]-FDG-PET, 18F-fluoro-2-deoxy-D-glucose, is a sugar derivative, which visualizes glucose metabolism. However, increased glycolysis is just one part of the changed metabolism in malignancies and most malignancies show a much wider alteration of metabolism. In this review, we focus on the alternatives to [^{18}F]-FDG-PET for the head and neck region. A search of the Cochrane, MEDLINE and Cancer Lit databases that cover articles entered between January 1984 and March 2012 was performed. All articles with key words 'PET' and 'head and neck cancer' were reviewed to explore what alternative PET methods to[^{18}F]-FDG-PET have been used.

Alternatives to[^{18}F]-FDG-PET

Amino acids

Amino acids are building blocks of proteins and precursors for many other bio-molecules. Furthermore, they are crucial in many metabolic cycles. Many of these processes are up-regulated in cancer cells, leading to an increased need for amino acids. Several amino acid-based radiopharmaceuticals have been developed. In vitro and in vivo studies have shown an enhanced uptake of amino acid-based radiopharmaceuticals in malignancies compared to the surrounding tissues. In contrast to[^{18}F]-FDG-PET, the uptake of amino acid-based radiopharmaceuticals is low in hypoxic inflammatory tissues. Conditions in the early phase after radiotherapy are characterized by hypoxia and inflammation. In theory, amino acid-based radiopharmaceuticals should therefore be better suited to differentiate between post-radiation inflammation and residual cancer.

Radiolabeled amino acids

Amino acids have been successfully labeled to ^{11}C, and ^{18}F. [^{11}C]-labeled amino acids are easier to produce and more stable. Unfortunately, however, the short half-life of [^{11}C]-labeled amino acids urges the use of an on-site cyclotron, which has hampered its use on a larger scale. Consequently, whereas in the past, [^{11}C]-labeled amino acids were extensively studied, nowadays research is focused on fluorinated analogs with longer half-life.

L-[Methyl-11C]-methionine ([^{11}C]MET)

[^{11}C]-MET has been the most frequently used radiolabeled amino acid. The main reason is the convenient production that allows rapid synthesis with high radiochemical yields without the need for complex purification steps. After injection, [^{11}C]-MET is rapidly distributed and a high uptake is immediately observed in the liver, kidney, pancreas and salivary glands [1]. There is some [^{11}C]-MET uptake in inflamed tissue, but the uptake of [^{11}C]-MET in tumor cells is significantly higher. Autoradiography shows [^{11}C]-MET uptake predominantly in viable tumor cells, with low uptake in macrophages and non-viable tumor cells [2]. In addition to the large-scale[^{11}C]-MET use in visualization of intracranial tumors, lymphoma, melanoma, breast, pelvic, parathyroid and lung cancer have also been visualized with [^{11}C]-MET. Preclinical studies validating [^{11}C]-MET in the evaluation of (chemo) therapy, showed a faster decline of [^{11}C]-MET in the post-radiation phase compared to [^{18}F]-FDG [3, 4]. Minn et al. [5] reported that [^{11}C]-MET was better correlated with tumor proliferative activity in squamous head and neck carcinoma than FDG, a finding that might be due to the relation of methionine to DNA metabolism. Up to now there have been only a limited number of studies dealing with methionine in head and neck cancer. The number of patients included has been small and the results alternating, which make the findings hard to interpret. Our search revealed eight studies dealing with head and neck cancer and [^{11}C]-MET-PET, three feasibility studies, two in which [^{11}C]-MET and [^{18}F]-FDG-PET were compared and three evaluations of therapy studies [6–12]. The three feasibility studies showed that 68 of the 70 tumors were visualized with [^{11}C]-MET-PET. Unfortunately, only in one study, the population was homogeneous, with only small laryngeal tumors [12]. The other two studies included different head and neck subsites and stages with variable histology. The studies of Lindholm and Geets compared [^{18}F]-FDG and [^{11}C]-MET in 37 patients with untreated head and neck cancer. Again all subsites, stages and histology were included. [^{18}F]-FDG and [^{11}C]-MET visualized the same 36 tumors [8–10]. Cook compared [^{11}C]-MET and [^{18}F]-FDG and concluded that [^{18}F]-FDG showed better anatomical details and [^{11}C]-MET had a better tumor background ratio. Physiological activity of [^{11}C]-MET in bone marrow and salivary glands did not interfere with the visualization of the primary site, but it was observed that it could hamper the visualization of lymph node metastases at level I and II [1]. In the study by Lindholm, [^{11}C]-MET-PET was performed before and after radiotherapy. All patients with an SUV of more than 3.1 after radiotherapy had residual disease, while three of the ten patients with a post-radiotherapy SUV of less than 3.1 showed residual disease. This resulted in a sensitivity rate of 0.75 and specificity of 0.70 [8]. Nuutinen performed a PET before radiotherapy and 2 weeks after completing radiotherapy in 13 patients. In all patients, the SUV dropped, but there was no difference in the SUV values between the patients who were disease free 2 years later and those who developed a recurrence [11]. In contrast, Chesnay described that a 25 % or more decrease in the SUV correlated with a tendency to respond better to chemotherapy. In their study, a [^{11}C]-MET-PET was

performed before and 2 weeks after three courses of cisplatin and 5-FU in 14 patients with a T3 or T4 hypopharyngeal cancer. After 2 years, 83 % of the group with a 25 % decline or more in the SUV was alive. The group with a decline of less than 25 % showed a survival rate of only 57 % [6]. These publications show that the excellent results obtained with [^{11}C]-MET in vitro are not confirmed in vivo and are more or less similar to those obtained with [^{18}F]-FDG, although, especially with regards to therapy evaluation, there is not much data. As mentioned before, the specificity of [^{18}F]-FDG is low in the early post-radiation phase and [^{11}C]-MET could be a viable alternative. To answer this question, however, more research would be necessary.

L-1-[11C]-Tyrosine (TYR)

Another essential amino acid is tyrosine. Tyrosine can be labeled with ^{11}C as well as with ^{18}F, in the form of fluormethyl-tyrosine or fluor-ethyl-tyrosine. The few studies (five) concerning TYR and head and neck carcinoma show promising results [13–17], the laborious production process is a serious limitation to using TYR on a larger scale. TYR is, therefore, now largely replaced by either MET or fluorine- labeled analogs. L-3-[^{18}F]-Fluoro-alpha-methyltyrosine (FMT). In experimental tumors, FMT shows a higher contrast of tumor to normal tissue and a higher uptake compared to both [^{18}F]-FDG and [^{11}C]-MET in preclinical studies [3, 18–20]. Murayama et al. [3] showed in an animal study a much steeper decline of FMT compared to [^{18}F]-FDG shortly after irradiation of an induced tumor, which is of special interest because results obtained with [^{18}F]-FDG in humans in the early post-radiation phase have been disappointing. Unfortunately, the results obtained in vivo are less impressive and comparable to those obtained with ^{11}C-labeled amino acids. However, most of the FMT studies deal with intracranial tumors, and only a few publications report about extracranial tumors. These studies show a sensitivity of FMT, which is comparable to or somewhat lower than that obtained with [^{18}F]-FDG but with a better specificity. There is only one report dealing with head and neck cancer and FMT. A FMT and [^{18}F]-FDG-PET were performed in 36 patients with an untreated maxillofacial malignancy by Miyakubo. FMT and F[^{18}F]-DG visualized all malignancies, but FMT showed a better contrast between tumor and surrounding tissues [21]. As from one single study, one cannot come to any conclusion, so more studies need to be conducted.

O-(2-[^{18}F] Fluorethyl)-L-tyrosine (FET)

There are four studies dealing with head and neck cancer and FET; one feasibility and in three in which a FET and a F[^{18}F]-DG-PET were performed. A feasibility study by Pauleit et al. [22] showed that all eight head and neck cancers, as well as the other two squamous cell carcinomas were visualized by FET, in contrast to adenocarcinoma, of which none of the 28 was visualized. The first study included 21 patients with suspicion of squamous cell carcinoma of the head and neck. All 21 patients received a [^{18}F FDG and FET-PET before

treatment. The sensitivity of FET was 75 % and the specificity 95%. The sensitivity of [^{18}F]-FDG was 93 % and the specificity 79 % [23]. The second study was conducted by Balogova. Twenty-seven patients were included, 15 for initial staging and 12 for therapy evaluation after radiation. The sensitivity of [^{18}F]-FDG and FET was 95 and 64 %, and the specificity 63 and 100 %, respectively [24]. A study including 13 patients showed a sensitivity for [^{18}F]-FDG and FET of respectively 89 and 70 % and a specificity of 50 and 90 % [25]. All authors came to the same conclusions: although a better specificity compared to [^{18}F]-FDG was confirmed, FET did not appear to be suited as a first-line PET tracer in head and neck squamous cell carcinoma imaging due to insufficient sensitivity and therefore cannot replace [^{18}F]-FDG for staging head and neck tumors. However, it was useful in the few selected cases to favor a wait and see attitude after radiation when a F[^{18}F]-DG positive and FET negative lesion was found. These findings indicate that FET may become a supplement to FDG in case of a positive FDG-PET during treatment evaluation.

Nucleosides

Nucleosides are the building stones of DNA and therefore directly linked to cell proliferation. The only nucleoside that has been clinically used is thymidine.

Thymidine (FLT)

The nucleoside thymidine is exclusively linked to DNA. Thymidine is phosphorylated by the enzyme thymidine kinase one (TK1) and phosphorylated thymidine is trapped intracellular. During DNA synthesis, TK1 activity increases almost tenfold and is an accurate reflection of cellular proliferation [26]. 11C and 18F-labeled thymidine are available as tracers. ^{11}C-thymidine has never been used for clinical purposes in the literature. In contrast, much more is known about ^{18}F-labeled thymidine (FLT). Results of FLT studies obtained by visualizing primary breast, esophageal cancer and melanoma are comparable to the results obtained with FDG. There have been four head and neck studies [27–30]. Cobben and Been visualized primary laryngeal cancers. These three small studies (17,19 and 14 patients, respectively) showed sensitivity rates of ca. 85 % for both FLT and [^{18}F]-FDG [27, 29]. Been's study included post-radiation patients as well. Three of the 14 patients developed recurrent disease after primary radiotherapy, 2 were visualized by [^{18}F]-FDG and 1 by FLT. Troost et al. [28] demonstrated in 10 stage II or higher head and neck carcinomas an elevated uptake in metastatic as well in non-metastatic lymph nodes. This resulted in sensitivity of 100 % and specificity of 16.7 %. One could conclude from these studies that the results obtained with FLT in staging head and neck cancer have not been promising. Far more interesting are the results obtained in therapy evaluation because a decrease in the cellular proliferation rate is one of the earliest events in the response to successful tumor treatment. Murayama irradiated mice with inoculated squamous cell carcinoma. The tumor uptake of FLT decreased in the first day after radiation while the uptake of [^{18}F]-FDG decreased after 7

days and MET after 3 days [3]. FLT declines rapidly during radiation, most likely because the surviving cancer cells will not be in a proliferating phase. Therefore, a sharp decline in the uptake of FLT does not necessarily mean an excellent response to radiotherapy. Three clinical head and neck cancer studies have been conducted. Menda showed a steep decline in SUV of FLT in eight patients after 10 Gy [31]. In Troost's study, ten patients with oropharyngeal cancer underwent FLT PET/CT before and twice during treatment. The SUV FLT declined already after 1 week of radiotherapy, while the gross tumor volume on CT declined after 4 weeks [32]. FLT and [^{18}F]-FDG-PET have been performed shortly before and 10 weeks after radiotherapy in ten patients with laryngeal cancer. The sensitivity for [^{18}F]-FDG to detect residual tumor was higher when compared with FLT. [^{18}F]-FDG missed one out of three residual tumors, whereas FLT missed two of the three residual tumors [27]. These results are not promising.

Choline

Choline is a precursor for the biosynthesis of phospholipids, which are essential components of all cell membranes. Biosynthesis of the cell membrane is enhanced in malignancies. In theory, choline could be an excellent radiopharmaceutical to visualize tumor proliferation. Choline has been successfully linked to ^{11}C and, more recently, to methyl ^{18}F. Due to its reduced renal excretion and up regulation of choline kinase in prostate cancer, [^{11}C]-choline is becoming more and more the first choice in molecular imaging of prostate cancer; Pubmed shows 141 publications dealing with prostate cancer. There are only two publications concerning head and neck cancer. These studies show that the sensitivity and specificity rates of [^{11}C]-choline are similar or slightly worse compared to those obtained with [^{18}F]-FDG in a heterogeneous head and neck population [33, 34]. In theory, [^{11}C]-choline could be an alternative to [^{18}F]-FDG in the early post-radiation phase because [^{11}C]-choline differentiates well between radiation induced tissue changes and local tumor recurrence. However, clinical data on head and neck tumors have been lacking so far.

Hypoxia-specific tracers

Patients with hypoxic head and neck tumors have a higher risk of local recurrences and distant metastases. Moreover, hypoxic tumors are more resistant to radiation and chemotherapy [35, 36]. Consequently, visualizing hypoxic areas within tumors may enable application of increased radiation doses to these areas, thus increasing the possibility of a successful outcome. (Pre)clinical studies showed that PET can visualize hypoxia in vivo. Several hypoxia tracers have been tested, including ^{18}F-fluoromisonidazole ([^{18}F]-FMISO), [^{18}F]-fluoroazomycin arabinoside ([^{18}F]-FAZA), ^{60}Cu-labeled methylthiosemicarbazone (^{60}Cu-ATSM), ^{18}F-2-(2-nitro-1H-imidazol-1-yl)-N- (2,2,3,3,3-pentafluoropropyl)-acetamide (^{18}F-EF5) and the single photon (SPECT) tracers 123I-iodoazomycin arabinoside (^{123}I-IAZA) and ^{99}Tcm-labeled dioximes (^{99}Tcm-HL91).

[^{18}F]-FMISO

[^{18}F]-FMISO has been used most frequently to visualize tumor hypoxia in head and neck cancer patients. [^{18}F]-FMISO is a 2-nitroimidazole molecule. Imidazole derivates are trapped in hypoxic cells. A relatively large study by Rajendran et al. [37] found that [^{18}F]-FMISO-PET scanning was effective in quantifying regional hypoxia in a series of 73 head and neck cancer patients. A study by Eschmann et al. [38] concluded also that [^{18}F]-FMISO-PET has the potential to predict response to radiotherapy. Another clinical study by the same research group showed the value of correlated [^{18}F]-fluorodeoxyglucose ([^{18}F]-FDG) and [^{18}F]-FMISO-PET scanning in predicting treatment response in head and neck cancer patients [39]. The clinical application of the most frequently applied tracer, [^{18}F]-FMISO is, however, hampered due to high lipophilicity and slow clearance from normoxic tissues, which leads to a low target-to-background ratio.

[^{18}F]-FAZA

[^{18}F]-FAZA, a relatively new imidazole radiopharmaceutical, shows faster clearance from blood and non-target tissues and is by some, therefore, considered to be a better tracer for the detection of hypoxia. Although [^{18}F]-FAZA PET clinical studies have been released, there are few clinical studies in head and neck cancer research. In a pilot study, Souvatzoglou et al. evaluated the feasibility of [^{18}F]-FAZA PET in 11 untreated head and neck cancer patients. The other purpose of the study was to determine the proper time of clinical imaging. This study acquired good quality [^{18}F]-FAZA PET images, suitable for clinical purposes. The authors suggested further studies for analyzing intratumoral differences in [^{18}F]-FAZA kinetics [40]. Postema et al. in a phase I/II study showed in five of the nine head and neck cancer patients clear [^{18}F]-FAZA uptake in the primary tumor, in two of those patients additional uptake in the cervical metastases, and in one patient uptake in a neck metastasis but not at the primary site. Based on their data, the authors concluded that, based on the good imaging properties, [^{18}F]-FAZA is a very promising tracer for assessing tumor hypoxia [41]. In conclusion, theoretically hypoxia markers have great potential for targeted therapy of hypoxic tumors either by applying hypoxia sensitizers or by increasing radiation dose using specific intensity modulated radiotherapy techniques. However, clinical data are limited at the time of writing, especially for the head and neck cancers.

Monoclonal antibodies

Advances in molecular and cellular biology have facilitated the discovery of novel molecular targets on tumor cells, for example, key molecules involved in proliferation, differentiation, cell death and apoptosis, angiogenesis, invasion, and metastasis. Monoclonal antibodies can be bound to these molecules, and by linking monoclonal antibodies to a positron emitting radionuclide, molecular targets can be visualized by PET. However, the development of radiolabeled monoclonal antibodies (MAbs) has been limited, due to several requirements

that need to be fulfilled. The emitter should allow facile, efficient, and stable coupling to the MAb. The physical half-life (t1/2) should be compatible with pharmacokinetics of the monoclonal antibody. In practice, to obtain sufficient binding, the half-life should be several days. Consequently, the half-life of ^{11}C and shorter lived isotopes are too short to allow labeling of MAbs, even as fragments. The binding time of MAb fragments are shorter. The half-life of 18F could be sufficient in case of MAb fragments. Unfortunately, however, the weakness of the bond between the ^{18}F-labeled MAb fragment and the target hampers their development. To our knowledge, no clinical studies have been published showing a stable ^{18}F-labeled MAb fragment so far. More suitable are long-lived positron emitters like 124I, 64Cu and 89Zr. The literature only shows seven head and neck studies [42–48]. Niu labeled panitumumab, a MAb against EGFR, with ^{64}Cu, and tested it in nude mice bearing human head and neck carcinoma cell lines. The results were disappointing: tumors with the lowest EGFR protein expression showed the highest ^{64}Cu-DOTA-panitumumab accumulation, whereas SQB20 tumors with the highest EGFR expression showed the lowest ^{64}Cu-DOTApanitumumab accumulation. An explanation could be the poor penetration of the antibody through perivascular tissues resulting in a low accumulation of ^{64}Cu-DOTA-panitumumab in SQB20 tumors [43]. Eiblmaier labeled cetuximab and showed a positive correlation between ^{64}Cu-DOTA-cetuximab and EGFR expression in five head and neck cell lines [44]. Verel et al. [49] showed that an injected head and neck tumor cell line could be visualized by ^{124}I-L19-SIP in eight nude mice. L19-SIP is an antibody fragment directed against the ED-B domain of fibronectin an excellent marker for tumor angiogenesis and has been successfully labeled to ^{124}I. The same group published a study in which nine head and neck tumor cell lines were injected in six nude mice. At the time of imaging, the volume of the tumors was less than 50 mm3. All tumors could be visualized by ^{124}I-L19-SIP [48]. Perk et al. visualized the anti-MET MAbs DN30. The MET oncogene encodes the tyrosine kinase receptor for hepatocyte growth factor (HGF). On his turn, HGF controls genetic programs leading to cell growth, invasion, metastasis, and protection from apoptosis. DN30 was linked to ^{89}Zr. An excellent correlation was found between PET imaged ^{89}Zr tumor uptake and ex vivo-assessed ^{89}Zr tumor uptake. A feasibility study with ^{89}Zr-labeled c-mAb U36, a monoclonal antibody against CD44, showed that all primary tumors and 18 of 25 positive neck levels could be visualized by immuno PET [45]. In another study with ^{89}Zrlabeled c-mAb U36, CD44 was found to be homogeneous in 96 % of all primary HNSCC and lymph node metastases[42]. Borjesson et al. showed in 20 HNSCC patients scheduled for surgery, an increasing uptake in time of ^{89}Zrlabeled antibody-MAb U36 in metastatic lymph nodes. The results were comparable with those obtained with CT and MRI [42]. It is an exciting thought that specific tumor characteristics can be visualized, not only in samples but also in vivo by dynamic imaging of the whole tumor. However, the application of monoclonal antibody tracers on a larger scale is hampered by the hard and labor intensive production of these radiopharmaceuticals. Therefore, the number of publications is still small at this time, and it is difficult to forecast what the actual value of PET imaging of monoclonal antibodies will be in the near future.

Conclusions and future perspectives

This review shows that other tracers than [^{18}F]-FDG have only been used on a small scale and have not become part of routine procedures in head and neck cancer. The data so far show that amino acid-based radiopharmaceuticals have no additional value to [^{18}F]-FDG as part of the dissemination work up, in the search for unknown primaries or in delining the gross tumor volume. However, amino acid-based radiopharmaceuticals may play a role in therapy evaluation after (chemo-)radiation, especially in the early post-radiation period, because [^{18}F]-FDG has problems in differentiating radiotherapy sequels from residual disease, resulting in high sensitivity, but lower specificity, rates. Amino acid based radiopharmaceuticals may present better specificity rates in this situation, although this is only documented on a very small scale and only for FET and TYR in vivo. The ^{11}C- amino acid tracers, like methionine, show both excellent sensitivity and specificity. However, the relative short half-life of the carbon isotope hampers further introduction as it requires an on-site cyclotron. Therefore, ^{18}F-labeled amino acid analogs will undoubtedly be further developed and investigated. Based on our literature search, we could not find any additional value for using FLT and choline in the head and neck area. Hypoxia tracers and labeled monoclonal antibodies can visualize specific characteristics of a tumor. Tumor hypoxia can be assessed in vivo with a number of available radiopharmaceuticals. Its role will be to optimize (chemo-) radiation strategies in the future. However, more research is necessary to warrant a clinical introduction. The tracking and quantification of monoclonal antibodies with long-lived PET-isotopes are an exciting novel option to improve diagnostic imaging and to guide MAb based therapy. Here again further research will be needed, before a wider introduction into clinical practice can be warranted.

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5

Visualization of small glottic laryngeal cancer using methyl-labeled 11C-Methionine Positron emission tomography

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Abstract

Despite abundant literature on the use of PET in head and neck cancer, little is known about the visualization of small laryngeal cancer. Moreover, most literature deals with the radiopharmaceutical ^{18}F-fludeoxyglucose (FDG), whereas only a few papers address the use of ^{11}C labelled amino acids. This study was performed to evaluate the feasibility of ^{11}C-labelled methionine in visualizing small laryngeal cancer.

Methods
Ten patients with a *de novo* small laryngeal cancer (7 T1, 3 T2) underwent a MET PET at least 3 weeks after biopsy but prior to further treatment. Static scans were made in 'whole body' mode, covering the head from the external auditory meatus downwards to the whole thorax. The resulting images were judged by experienced specialists in nuclear medicine, who assessed the relative visibility of each tumour on a 3-point scale.

Results
Nine tumours were visualized (5 clearly, 4 moderately). One (T1) was not visualized.

Conclusion
Small laryngeal cancer can be visualized with ^{11}C-methionine PET.

Keywords
Laryngeal cancer, ^{11}C-methionine, Positron emission tomography

Introduction

Positron Emission Tomography (PET) has an established role in the diagnosis and staging of various malignancies. PET can be used to differentiate between benign and malignant pathology [1, 2]. It is playing an increasingly prominent role in the staging process of unknown primary tumours and locally advanced head and neck squamous cell carcinoma (HNSCC) [1, 2]. Finally, it is becoming increasingly important in target volume definition for radiation therapy. ^{18}F-fludeoxyglucose (FDG) is the most frequently used and most validated radiopharmaceutical for many malignancies, including HNSCC. Literature reports sensitivity rates of 85 to 95% and specificity rates of 80 to 90% in visualizing head and neck carcinomas [3–9]. However, despite its established role, FDG also has some disadvantages. In particular, its specificity is hampered by the uptake of FDG in inflammatory tissues, especially in macrophages. In contrast to FDG, radiopharmaceuticals based on amino acids, such as ^{11}C-methionine (MET), accumulate more in malignancies and less in inflammatory tissues [1, 10–12].

A number of authors have reported on the use of ^{11}C-methionine (MET) in HNSCC with results at least as good as those obtained with FDG [13–17]. Though populations are small in most of these studies, a variety of head and neck tumour sites were included, particularly at advanced stages. The last ten years have seen more advanced radiation delivery techniques become available, enabling a high conformity of the high dose area around the target volume for radiation therapy, for which accurate delineation and thus accurate tumour visualization is crucial. One of the main problems of early glottic cancers is that they are hard to visualize with conventional diagnostic imaging techniques because of their low volume, movement artefacts and pooling of saliva.

Therefore, the main purpose of this pilot study was to assess whether the radiopharmaceutical ^{11}C-methionine (MET) would be suitable for imaging small laryngeal cancers.

Material and Methods

All patients had been referred by an ENT specialist to our tertiary referral hospital with a previously untreated histologically proven de novo T1 or small T2 glottic laryngeal squamous cell carcinoma. Only incisional biopsies were taken. Patients planned for surgery and/or radiotherapy for other disorders in the head and neck region were excluded.

MET PET was performed at least 3 weeks after the last biopsy was taken in order to avoid uptake induced by a wound-healing reaction. The day after the PET scan a microlaryngoscopy

was performed and the video/photos were recorded digitally. The size of the tumours was determined from these data.

^{11}C-methionine was prepared in our laboratory by ^{11}C-methylation of L-homocysteine thiolactone using a Zymark robotic system. To this end, a solution of L-homocysteine thiolactone in a NaOH/ethanol mixture was put into a C-18 cartridge followed by the passage of ^{11}C-methyl iodide. When the radioactivity on the cartridge was maximal, ^{11}C-methionine was eluted with a phosphate buffer through a second C-18 cartridge and a sterile filter to a sterile vial containing saline. This end product was ready for injection and meets the following radiopharmaceutical criteria – radiochemical purity > 95%, specific activity > 10000 GBq/mmol, sterile and pyrogen free, pH 4.5–8.5, ethanol < 3.5%, D/L ratio > 90%, osmolarity 200-800 mosmol/kg. We achieved successful MET production in > 95% of syntheses.

Each patient fasted from midnight. All scans were made in the morning hours. Two hundred MBq of MET were injected intravenously. After a waiting period of 20 to 30 minutes the scan was performed, ranging from the external acoustic meatus downwards over the neck and the thorax, which in general amounted to four or five bed positions. Each bed position had a duration of 5 minutes. Immediately after emission scanning, a transmission scan was performed over the same bed positions (2 minutes each) in order to correct for attenuation. The total scanning time was approximately 30 minutes and the whole procedure took approximately 1 hour per patient. The camera used was a Siemens/CTI ECAT Exact HR+ (Siemens, Knoxville, Tennessee), a BGO-based camera with an axial field of view (FOV) of 16 cm and a resolution of 4 to 5 mm in the centre of the FOV. All the PET scan images were assessed by experienced nuclear physicians on a computer screen using standard ECAT software. The presence of a lesion on the images was rated as follows: 0 = no visualization, 1 = moderate visualization, 2= clear visualization of the tumour. The study was approved by the Ethical Committee of the University Medical Center Groningen.

Results

Ten patients with ten tumours were included in this prospective pilot study, including eight male and two female patients, with a mean age of 70, ranging from 50 to 83. Three tumours were clinically staged as T2 by direct laryngoscopy under general anaesthesia, and seven as T1a. One T2 and four T1 were highly differentiated squamous cell carcinoma. Two T2 and three T1 were staged as moderately differentiated. The tumour volumes at the time of the PET scanning ranged between 16 mm^3 and 25 mm^3. There were no multifocal lesions and none of the patients had regional lymph node metastases present at the time of assessment. The final treatment consisted of laser excision or radiotherapy.

All the PET images were of good quality and could be readily assessed. Normal uptake was present in the salivary glands. No artefacts were present (Figure 1).

Figure1. T1 glottic laryngeal cancer clearly visualized.

With MET PET, nine of the ten glottic cancers could be visualized, five clearly and four moderately (Figure 2). Two of the clearly visualized tumours were highly differentiated and two moderately.

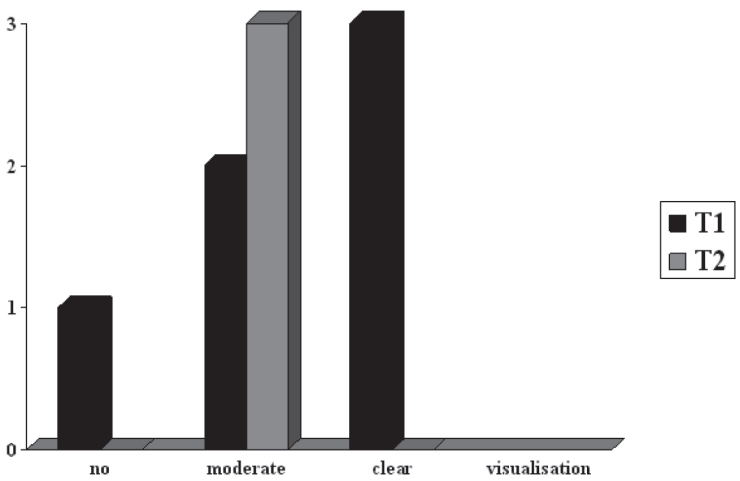

Figure2. Visualization of small laryngeal cancers. Black T1, Grey T2

One highly differentiated T1a tumour was not visualized with MET PET. This tumour was growing exophytically at the anterior third of the vocal cord and was well differentiated. The tumour was visualized well with laryngoscopy and the tumour volume was 20 mm^3.

No other malignancies, and in particular no regional or pulmonary metastases, were identified. During the one year follow-up period, one patient was laryngectomized because of residual disease after radiotherapy. During this period no regional or pulmonary metastases were demonstrated.

Discussion

The main purpose of this prospective pilot study was to assess whether small laryngeal cancers could be visualized by ^{11}C-labeled methionine. The results indicate that the vast majority of T1a and T2 laryngeal cancers can be visualized with methionine, while in general these cancers are often hard to visualize with conventional imaging techniques such as CT and MRI because of their small sizes [3, 4].

MET is used widely to visualize intracranial tumours [18, 19]. MET has never been used on a large scale for head and neck carcinomas, although the rare literature available shows excellent visualization rates of at least 80%[15, 16]. The study populations have been small and include several sub-sites and stages. Consequently, most findings in the literature cannot be extrapolated to the situation of patients with early laryngeal cancer. Therefore, the feasibility of incorporating PET into the clinical work-up of patients with laryngeal cancer still needs to be explored further.

With the development of an increasing number of different tracers, one of the most important questions to be addressed is which radiopharmaceutical should be used in which situation. As early glottic cancer is generally easily accessible via a direct endoscopy, we do not believe that diagnosing the primary tumour will be the target of molecular imaging. Radiation oncologists are increasingly interested in imaging modalities that enable accurate tumour visualization to define the gross tumour volume (GTV), in particular when more advanced radiation delivery techniques are used, such as intensity modulated radiotherapy (IMRT) or stereotactic irradiation. Since 90% of the cases in the current study could be visualized clearly with MET PET, this tracer could be usefully applied in the radiotherapy treatment planning process. Geets et al. described an overly large delineation of the tumour in eight laryngeal cancers of stage II or higher with MET PET compared to FDG PET [20]. The uptake of MET in salivary glands caused discrimination problems between malignancy and healthy mucosa. We believe that this can be countered by defining higher minimum uptake limits.

One of the problems in current practice is distinguishing local recurrence from radiation induced changes after primary radiotherapy for laryngeal cancer. FDG can visualize residual laryngeal cancer after radiotherapy [3, 21, 22]. However, amino acids may be better suited for that purpose as residual disease after radiotherapy is scattered and embedded in inflammatory tissues resulting in false positive findings with FDG. In *in vitro* studies, amino acid based radiopharmaceuticals permit better differentiation between cancer and inflammation than FDG [1, 2, 23, 24]. These results indicate that small tumours and possibly small recurrences after radiotherapy can also be visualized with MET, opening up new perspectives for early detection of tumour recurrence after radiation treatment. Our results confirm earlier data from our institution using L-[1-^{11}C]-tyrosine (TYR) [25, 26]. TYR was chosen because it is better suited for quantitative analyses, such as calculating protein synthesis rates. However, we demonstrated that quantitative analyses appear to have no clinical relevance in the head and neck region [25]. Given that the production of TYR is laborious, alternative amino acids have been explored. Although MET cannot be used for quantitative analyses, the radiochemical synthesis route is relatively simple and high yields can be achieved [27].

To conclude, the results of the current study show that MET PET can visualize small laryngeal cancer with high reliability, and confirms the results obtained with TYR in the past. This opens opportunities for better target volume definition for high-dose conformal radiation delivery techniques and the detection of residual disease after radiotherapy in an early stage.

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6

Is C-11 Methionine PET an alternative to 18-F FDG PET for identifying recurrent laryngeal cancer after radiotherapy?

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Keywords
Methionine; FDG; PET; Post radiation; Recurrence; Laryngeal cancer

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Abstract

Objective

18F FDG PET is superior to other imaging techniques in revealing residual laryngeal cancer after radiotherapy. Unfortunately, its positive predictive value is low, due to FDG uptake in inflammation and in anaerobic conditions. PET imaging with the amino acid-based radiopharmaceutical C11-methionine (MET) should be less influenced by post-radiation conditions. The aim of this study was to investigate the potential of MET in diagnosing recurrent laryngeal cancer after radiotherapy as compared to 18F-FDG.

Methods

Forty-eight patients with a clinical suspicion of local residual disease at least three months after completion of radiotherapy or chemoradiotherapy for a T2-4 laryngeal carcinoma, along with an indication for direct laryngoscopy, were included. They received MET PET and FDG PET prior to the direct laryngoscopy. One senior nuclear medicine physician assessed both the FDG PET and MET PET images visually for the degree of abnormal uptake. The gold standard was a biopsy-proven recurrence 12 months after PET. The nuclear physician had no access to the medical charts and was blinded to the results of the other PET. Sensitivity, specificity, and positive and negative predictive value were calculated.

Results

The sensitivity of FDG was 77.3% and the specificity 56.0% after the conservative reading, with these values equaling 54.5% and 76.0 % for MET. The positive predictive value of FDG was 60.7% and the negative predictive value 73.7%. The PPV of MET was 66.7%, and the NPV was 65.5%.

Introduction

In the Netherlands, more than 80% of laryngeal cancers are primarily irradiated. Salvage surgery is performed in case of residual disease, but detection of residual or recurrent disease can be difficult after radiotherapy. In the first half year after radiotherapy, residual or recurrent disease especially can have a scattered and sub-mucosal growth pattern, embedded in edema and inflammatory tissue (figure 1).[1] In some patients, these features will persist over the ensuing years.

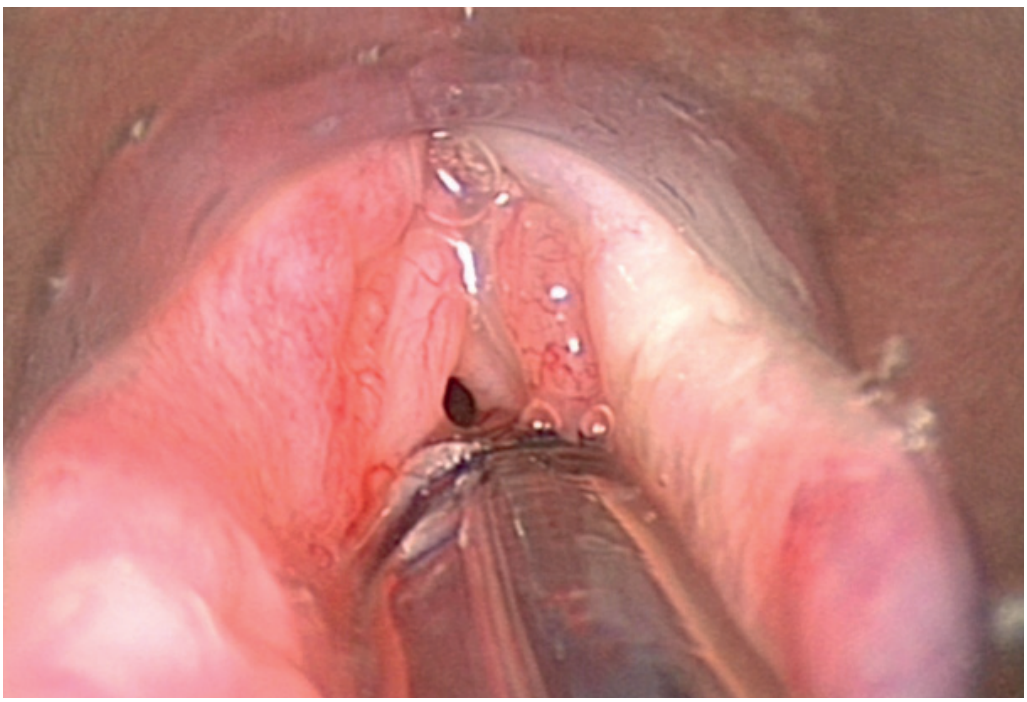

Figure1. Direct laryngoscopy patient 26. Originally T1N2aM0 supraglottic laryngeal cancer Treatment 70Gy radiotherapy. Clinical suspicion recurrent disease due to deterioration quality of voice 2 years after finishing radiotherapy. The second biopsy showed squamous cell carcinoma.

A positive biopsy, by means of endoscopy, is the gold standard for confirming residual or recurrent disease, but a negative biopsy does not necessarily exclude residual or recurrent disease. Several direct laryngoscopies may be necessary to prove the presence of residual or recurrent disease.[2-4] In addition, the tissue damage caused by biopsies may exacerbate the already existing inflammation, edema, and fibrosis.[5] Conventional imaging techniques to detect recurrent laryngeal carcinoma after radiotherapy include CT and MRI. The

sensitivity of both imaging techniques ranges from 58% to 72%.[6,7] In clinical practice, these figures may indicate that one needs to perform a direct laryngoscopy, despite negative CT or MRI findings. FDG-PET appeared to be helpful for select patients with clinical suspicion of recurrent laryngeal carcinoma after radiotherapy, when direct laryngoscopies under general anesthesia with biopsies were indicated.[8] A systematic review by Brouwer and colleagues shows that FDG PET can help to reveal residual disease after radiotherapy, with a sensitivity of 89% and a specificity of 74%.[3] An explanation for the relatively low specificity could be the uptake of FDG in activated macrophages. As in tumor cells, activated macrophages have an abundance of GLUT-1 receptors and will therefore have a high uptake of FDG.[9,10] The conditions after radiotherapy are characterized by non-vital tumor cells and macrophages dominating the former tumor site, regardless of the presence of residual disease or not.[11]

The uptake of amino acids – methionine, for example – is high in tumor cells but low in inflammatory tissues and could therefore be a good alternative to FDG.[12] C-11 MET is an established radiopharmaceutical and has been widely used to visualize intracranial lesions.[13] Methionine (MET) has also been successfully used in visualizing primary head and neck cancer.[14-18] In addition to preclinical studies validating MET in the evaluation of radiotherapy/chemoradiotherapy, preclinical studies also showed a fast decline for MET in the post-radiation phase.[19,20] Autoradiography shows that MET uptake is predominantly located in viable tumor cells, with low uptake in macrophages and nonviable tumor cells.[21] In this study, we hypothesize that MET PET is better than FDG PET in detecting recurrent disease in patients with clinical suspicion of recurrent laryngeal carcinoma after radiotherapy.

Methods

Patients

Forty-eight patients with a clinical suspicion – although no obvious local residual, recurrent disease, or second primary at least three months after completing radiotherapy/chemoradiotherapy with curative intent for a resectable T2-4 laryngeal squamous cell carcinoma – who had a clinical indication for direct laryngoscopy and biopsy under general anesthesia were included. Suspicion of recurrent disease was raised by the patient's complaints and changes on physical examination that included fiber-optic laryngoscopy. Exclusion criteria were no younger than 18 years, a clinically evident recurrence, and pregnancy. One patient had to be excluded because parts of the PET scan registration were lost. The patient received MET-PET and FDG-PET prior to direct laryngoscopy. The maximum allowed timeframe between scans and laryngoscopy was 1 month.

Ethical considerations

The protocol was approved by the ethics committee as required in the Netherlands under the Medical Research Involving Human Subjects Act. All patients provided written informed consent. Two university hospitals recruited patients for the study.

Procedures

C11-methionine was prepared in our laboratory by 11C -methylation of L-homocysteine thiolactone using a Zymark robotic system. To this end, a solution of L-homocysteine thiolactone in a NaOH/ethanol mixture was put into a C18 cartridge followed by the passage of C11 -methyl iodide. When the radioactivity on the cartridge was maximal, C11 -methionine was eluted with a phosphate buffer through a second C18 cartridge and a sterile filter to a sterile vial containing saline. This end product was ready for injection and met the following radiopharmaceutical criteria – radiochemical purity > 95%, specific activity > 10000 GBq/mmol, sterile and pyrogen free, pH 4.5–8.5, ethanol < 3.5%, D/L ratio > 90%, osmolarity 200-800 mosmol/kg. We achieved successful C11-methionine production in > 95% of syntheses.

F18-FDG was produced according to the method of Hamacher and colleagues, using an automated synthesis module.[14] The radiochemical yield was 65.9 ± 7.1% (decay corrected).

The patients were scheduled for separate C11-MET PET only and F18-FDG PET only scans, shortly before the direct laryngoscopy. For both scans, patients were instructed to fast for at least 6 hours. A 5 MBq/kg C11-MET or 5 MBq/kg F18-FDG was injected intravenously and again after 20 or 60 minutes (for C11-MET or F18-FDG, respectively). The scanning was performed on an ECAT EXACT HR + PET camera (Siemens/CTI Inc.) at both institutions, according to the Netherlands protocol for standardization and quantification of FDG whole body PET studies in multi-centre trials[22]. The scanned trajectory included skull base to the pelvis (figures 1 and 2). PET images were iteratively reconstructed (ordered subset expectation maximization). Both MET PET and FDG PET images were analyzed visually on a Leonardo workstation (Syngo Leonardo, Siemens AG, Berlin).

Assessment of the PET images was performed visually for both FDG PET and MET PET by one senior nuclear-medicine physician two years after inclusion was finished. He had no access to the medical charts and was blinded to the result of the paired scan. First all methionine PET images were assessed and in other session the FDG images. The larynx was assessed by the degree of abnormal uptake and side, and summarized in a three-point scale: negative, equivocal, or positive for local recurrent disease (figure 2,3). The PET report also included information on lymph node involvement and distant metastases in the field of view.

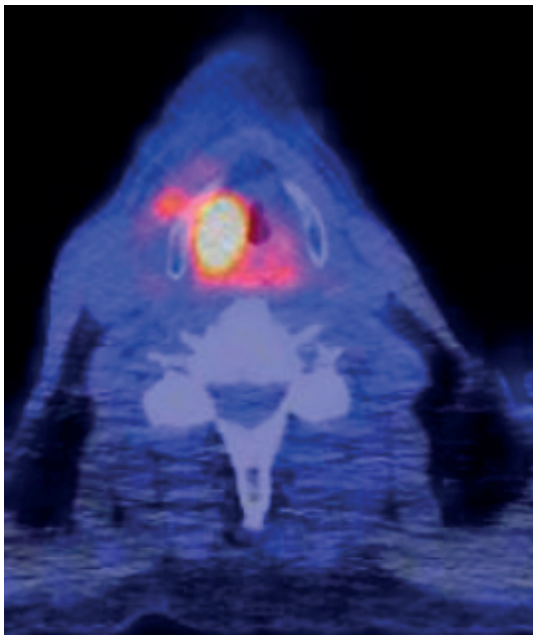

Figure 2. Positive FDG PET patient 26.

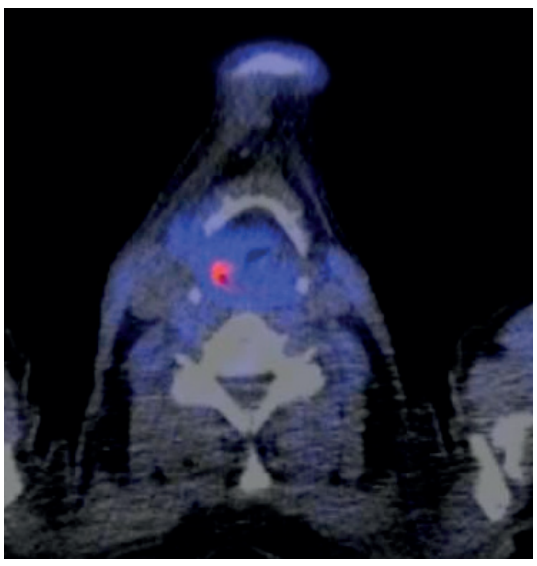

Figure 3. Equivocal MET PET patient 26.

All but two patients underwent direct laryngoscopy under general anesthesia, combined with biopsies when indicated during laryngoscopy at the discretion of the attending head and neck surgeon. After a negative direct laryngoscopy, the procedure was repeated within two weeks if there was still a suspicion of residual disease. If not, the head and neck surgeon evaluated the patient every eight weeks, for a minimum period of 24 months. Two patients did not undergo a direct laryngoscopy because of the combination of poor general condition and a low level of suspicion. These two patients did not develop residual disease within 24 months after PET scanning.

Outpatient clinic visits, hospital admission, operative procedures, additional imaging and histological recurrence of tumor, the results of any surgical procedure, and death were documented during the follow-up period.

Data were collected by the first author, and he was responsible for the completeness and accuracy of the reported data and analyses.

PET scans were evaluated both conservatively and sensitively. Equivocal or positive were considered positive, and negative as negative, when evaluating the test characteristics sensitively. Positive was considered positive, and negative and equivocal as negative, when evaluating the test characteristics conservatively. In an attempt to reduce false positive findings, MET PET scans were also sensitively evaluated after excluding negative sensitive evaluated FDG PET registrations. Histologically proven squamous cell carcinoma of the larynx within 12 months after the MET PET registration was considered the positive gold standard.

Sensitivity, specificity, positive and negative predictive value and corresponding exact binomial 95% CIs were calculated using STATA (StataCorp. 2015. *Stata Statistical Software: Release 14.0*, College Station, TX: StataCorp LP.).

This study was powered to detect a difference of 10% in the paired proportion of the sensitivity/specificity of FDG-PET and MET-PET using the McNemar chi-square test (power 80%; significance level <0.05). For this purpose 48 patients had to be included.

Results

Between November 1, 2008, and November 1, 2012, 48 patients were included, one of whom had to be excluded due to loss of PET data, which left 47 patients for analysis. Thirty-eight of the patients were male and nine female. The average age was 61 years

with a standard deviation of 6.7 years. Twenty patients had glottic, 24 supraglottic, and 3 transglottic carcinoma. Twenty-seven patients had T2, 17 patients T3, and 3 patients T4 primary tumors before primary radiotherapy. Initially, ten patients had positive lymph nodes, while none of the patients had distant metastases. Three patients received chemoradiation and the other 44 radiation therapy only. Details are listed in Table 1.

Table 1. Baseline characteristics of the patients

Variable	**47**
Male	39 (82%)
Female	8 (16%)
Age	
Mean (SD) — yr	62 (9)
< 65 yr — no. (%)	29 (62%)
≥ 65 yr — no. (%)	18 (38%)
Primary tumor site — %	
Supraglottic	24 (51%)
Glottic	20 (43%)
Transglottic	3 (6%)
Primary tumor stage — %	
T2	26 (55%)
T3	17 (36%)
T4	4 (9%)
Primary node stage — %	
N0	37 (81%)
N1	4 (9%)
N2a	1(2%)
N2b	2 (4%)
N2c	3(5%)
N3	
Previous treatment — %	
Radiotherapy	44 (94%)
Chemoradiotherapy	3 (6%)

Thirty patients experienced a deterioration of their voice, 16 in their swallowing function, 12 had a loss of weight, and 24 experienced an increase in pain. In 22 patients, the suspicion of a recurrence was moderate and in 25 patients severe, although not evident, as assessed by their treating physician. The median time from completion of radiotherapy to the MET PET was 14 months, with a minimum of 3 months, and a maximum of 13 years and 3 months. In 29 direct laryngoscopies a biopsy was taken. Four patients underwent more than one direct laryngoscopy; only in one patient were all (repeated) biopsies negative. Two residual cancers were not revealed by either FDG PET or MET PET, and one was revealed by FDG PET and not by MET PET. One residual disease was discovered after three consecutive direct laryngoscopies with biopsy taken, and the other two after two consecutive direct

laryngoscopies. After 12 months, a total of 25 (53%) patients had not developed recurrent disease, and after 24 months 20 patients. Ten patients died of the disease, while six patients died of other causes. However, of the patients who died of other causes, two patients were already known to have incurable residual disease. Fourteen patients received a laryngectomy. Six of the patients died of the disease after laryngectomy. The remaining eight patients who received a laryngectomy were still alive without evidence of disease 24 months after inclusion.

The ten patients with initially positive lymph nodes did worse, only three of them are still alive without disease. In four patients, the FDG PET and MET PET showed distant metastases. In three patients, the metastases were located in the lung, and in one patient bone metastases were visible. Although visible on both PET scans, the FDG PET signal was clearer.

Using a conservative reading, the sensitivity of FDG PET was 77.3% **(**95% CI = 54.6-92.2) and the specificity 56.0%. (95% CI = 34.9-75.6) The sensitivity of MET PET was 54.5 (95% CI = 32.2 – 75.6) and the specificity 76.0% (95% CI = 54.9 – 90.6). FDG showed a positive predictive value of 60.7% and a negative predictive value of 73.7%. The positive predictive value of MET was 66.7 % and the negative predictive value 65.5%. The McNemar test within diseased (sensitivity comparison) shows a p-value of 0.125 and the McNemar test within non-diseased (specificity comparison) shows a p-value of 0.180.

Using the sensitive approach, the sensitivity of FDG PET was 95.5% (95% CI = 77.2 – 99.9) and the specificity 24.0% (95% CI = 9.4-45.1). The sensitivity of MET PET was 86.4% (95% CI = 65.1 – 97.1) and the specificity 32.0 % (95% CI = 14.9 – 53.5). FDG showed a positive predictive value of 52.5% and a negative predictive value of 85.7%. The positive predictive value of MET was 52.8%, and the negative predictive value was 72.7%. The McNemar test within diseased (sensitivity comparison) shows a p-value of 0.500 and the McNemar test within non-diseased (specificity comparison) shows a p-value of 0.625 (table 2).

Table 2b. Overview of sensitivity, specificity, PPV (positive predictive value), NPV (negative predictive value) and false positive and false negative results

	Conservative approach		Sensitive approach	
	FDGPET Negative and equivocal combined	**METPET Negative and equivocal combined**	**FDGPET Positive and equivocal combined**	**METPET Positive and equivocal combined**
Sensitivity	77.3% 54.6-92.2	54.5% 32.2-75.6	95.5% 77.2-99.9	86.4% 65.1-97.1
Specificity	56% 34.9-75.6	76.0% 54.9-90.6	24.0% 9.4-45.1	32.0% 14.9-53.5
PPV	60.7% 40.6-78.5	66.7% 41.0-86.7	52.5.% 36.1-68.5	52.8% 35.5-69.6
NPV	73.7% 48.8-90.9	65.5% 45.7-82.1	85.7% 42.1-99.6	72.7% 39.0-94.0

The combined approach using the FDG PET followed by the sensitive MET PET, only if the FDG PET was positive or equivocal (N=40), led to a conversion of positive/equivocal evaluation to a negative evaluation five times. Three of these five were negative upon biopsy and therefore correctly classified as negative, while two were positive upon direct biopsy, so these would have been missed using this approach as compared to using FDG PET alone. The addition of MET PET therefore reduces the sensitivity, while only slightly reducing the number of unnecessary biopsies. Values for the test characteristics of this combined approach equaled: 86.4% sensitivity (95% CI: 65.1-97.1), 36% specificity (95% CI: 18.0-57.5), 54.3% PPV (95% CI: 36.8-71.2) and 75% NPV (95%CI: 42.8-94.5).

The patient who was included more than five years after finishing radiotherapy had a false positive FDG and METPET.

Seventeen patients were included between one and five years after finishing radiotherapy. Using the conservative reading, the sensitivity of FDG PET was 80.0% (95% CI = 0.6– 1.0.), the specificity 60.1% (95% CI = 0.09 – 1.00), the PPV 65.6%, and the NPV 78.1%. Twenty-six patients were included between three and twelve months after finishing radiotherapy. Using the conservative reading, the sensitivity of FDG PET was 75.3% (95% CI = 0.61 – 0.89), the specificity 53.3% (95% CI = 0.05 – 1.00), the PPV 61.5%, and the NPV 73.2%.

Using the conservative reading, the sensitivity of METPET in the group of patients who were included between one and five years was 57.4% (95% CI = 0.37 – 0.77), the specificity 80.4% (95% CI = 0.32 – 1.00), the PPV 70.80%, and the NPV 69.30%.

The sensitivity in the group of patients who were included between three and twelve months after finishing radiotherapy was 52.8% (95% CI = 0.21 – 0.83), the specificity 76.0% (95% CI = 0.36 – 1.00), the PPV 65.4%, and the NPV 63.3%.

Discussion

Because the majority of recurrent laryngeal cancers after radiotherapy can be salvaged if detected in a timely fashion, early detection of recurrent disease is of importance.[23] However, it may be difficult to differentiate between recurrence and post-radiation changes.[5] In the present study, FDG PET was able to detect recurrent laryngeal cancer after radiotherapy, with results worse than those results obtained in other studies.[6,8,24,25] This can be explained by the selection of our population. In most of the studies patients with obvious residual/recurrent disease were included, while we excluded these patients.

Three recurrent diseases were not demonstrated by PET after the conservative reading: two were not demonstrated by MET PET, and one not by either FDG PET or MET PET. These recurrent diseases were also not diagnosed by a direct laryngoscopy with taking of biopsies. Two or more direct laryngoscopies were necessary to diagnose the residual cancer. This shows that a false negative PET had no more influence on the time of laryngectomy than a traditional work up. These findings are in agreement with the literature.[5,26]

In addition to reliable detection of residual or recurrent laryngeal carcinoma after radiotherapy, PET is able to detect distant metastases.[27-29] Although the metastases were revealed both by FDG and MET PET, they were more clearly visualized by FDG PET. FDG PET is our preference for detecting distant metastases.

To make a reliable selection for direct laryngoscopy, a combination of high sensitivity and high negative predictive value is mandatory. The sensitive reading of the FDG results meets these demands. Unfortunately, the positive predictive value is much lower. This could result in a considerable number of unnecessary direct laryngoscopies, if PET were used to select patients for this procedure.

To avoid unnecessary direct laryngoscopies under general anesthesia, a higher positive predictive value is needed. The search for an alternative to FDG was mainly driven by a desire to improve the positive predictive value. The main goal of this study – an improvement in the positive predictive value without reducing the negative predictive value – was not achieved. The positive predictive value of MET for the conservative reading was slightly higher, though not significant, than the positive predictive value obtained with FDG. The

negative predictive of 65.5% was too low, which implies that MET PET cannot be used to select patients for a direct laryngoscopy.

It would be interesting to know whether MET PET is able to distinguish false-positive FDG PET scans from true-positive FDG PET scans. The combined approach using sensitive MET PET only for FDG PET positive/equivocal scans shows that the number of unnecessary biopsies is slightly reduced at the cost of missing positive cases. These findings show that MET selects better, although not well enough to reduce the number of unnecessary direct laryngoscopies significantly and safely.

We have no explanation for these disappointing results. It is known that recurrent disease after radiotherapy is usually scattered and embedded in inflammatory tissue. This is why we conducted this pilot study. This small study did show that even early laryngeal cancers (T1-2 glottic) were excellently visualized with MET.[14] Since the major part of this study was carried out using an older generation PET camera, one would expect that the results in this study might have been better due to the improved sensitivity of the new generation of PET cameras. The limited size of recurrent disease found should therefore not be an important reason for the low sensitivity observed.

In contrast to FDG, MET visualizes more than a single pathway. MET has a considerable non-protein synthesis part, which makes MET unsuitable for quantitative analyzes.[12] However the non-protein synthesis pathways are more strongly activated by malignancies than inflammation. The negative effects of non-protein pathways on the visualization of recurrent disease should therefore be limited. Although high salivary gland activity is demonstrated by MET PET, it is unlikely that this hampered interpretation of PET, because the larynx is out of the field of the submandibular and parotid glands.

A more likely explanation could be the tumor-to-background ratio. The tumor-to-background ratio of FDG is higher than the ratio obtained with MET.[12] Although the uptake of FDG in inflammatory tissues is thought to be higher than the uptake of MET, recurrent disease is probably better detected due to the absolutely stronger uptake of FDG in a malignancy (figures 2 and 3.).

Most malignancies show, in addition to an increased glucose metabolism, an increased metabolism of amino acids, nucleosides, and phospholipids. Parts of malignancies may be hypoxic and may have molecular targets on their cells.

Several amino acids, the nucleoside Thymidine, the precursor for the biosynthesis of phospholipids choline, hypoxia tracers, and labeled monoclonal antibodies are incorporated

in radiopharmaceuticals, which could be alternatives to FDG. The literature shows only a few studies in which an alternative to FDG is used to visualize recurrent head and neck carcinoma after radiotherapy. These studies have their limitations because none of the studies include more than 20 patients, and they frequently deal with more than one subsite. These studies show that 11C-choline and FLT visualize primary and recurrent head and neck cancer slightly worse than FDG does[28,29,30]. The amino acid tyrosine (TYR) and O-(2-[18F] fluor ethyl)-L-tyrosine (FET) are the only radiopharmaceuticals that show results that are equal or better than those obtained with FDG for visualizing recurrent or residual head and neck carcinomas. Unfortunately the laborious production processes are a serious limitation to using TYR and FET on a larger scale[31,32,33].
To answer the question of whether other radiopharmaceuticals are more suitable for revealing recurrent laryngeal disease after radiotherapy, studies designed like ours need to be conducted.

Conclusion

MET PET is not superior to FDG PET for identifying recurrent laryngeal cancer after radiotherapy.

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7

Summary and Discussion

Preservation of the larynx is an important goal in the treatment of laryngeal cancer. Early-stage laryngeal cancer is treated with radiotherapy alone, whereas in higher stages concomitant chemotherapy can be added to radiotherapy or radiotherapy can be accelerated. The recurrence rate is on an average 30% for stage III and higher after these intensive organ-preserving treatment protocols. The tumor may recur after radiation therapy in multicentric foci without necessarily involving the surface epithelium[1]. The differentiation between radiation reactions such as edema, fibrosis as well as soft tissue and cartilage necrosis, on the one hand, and recurrent carcinoma on the other hand, is a difficult clinical and imaging problem[2-6]. Conventional imaging modalities like CT and MRI have limited accuracy for the detection of recurrent carcinoma after (chemo)radiation and biopsies remain necessary[7-11]. Consequently, the current clinical practice to confirm a recurrence consists of direct laryngoscopy with biopsy under general anesthesia with all its negative consequences for the patient [12-15]. Depending on the initial T-stage, 1.7 to 4.9 direct laryngoscopy procedures are required to detect one recurrence within a time the period of 6 months after suspicion was the first considered[10]. For each direct laryngeal endoscopy general anesthesia is required, which in itself can be harmful to our patients who in general are not in a good condition. Biopsies cause scarring and even more so in the post-radiation larynx, which will have a negative influence on the function[16]. During the last decades, several studies have been published which indicate that [^{18}F]-FDG-PET may detect recurrent laryngeal cancer. These studies show an excellent negative predictive value, which implies that a negative [^{18}F]-FDG-PET excludes recurrent laryngeal cancer[17-21]. However, at the same time, it is difficult to validate these studies in daily practice because they include different subsites, different stages of the disease and a small number of patients.

To test the hypothesis, that [^{18}F]-FDG-PET will reduce the number of unnecessary laryngoscopies in case of suspected recurrent laryngeal cancer after radiotherapy, a randomized controlled multicenter clinical trial has been performed and discussed in chapter 2. The RELAPS study (REcurrent LAryngeal carcinoma PET Study) is designed to evaluate the efficacy of [^{18}F]-FDG-PET as a first-line diagnostic investigation for the selection of patients with suspected recurrent laryngeal carcinoma after radiotherapy for direct laryngoscopy (including biopsies) under general anesthesia. Hundred-fifty patients have been randomized to either direct laryngoscopy (conventional strategy), or to [^{18}F]-FDG-PET, only to be followed by laryngoscopy in case of positive or equivocal findings. If laryngoscopy does not reveal a recurrent tumor, an office-based flexible laryngoscopy is repeated within 6 weeks unless clinical signs and symptoms have diminished. In the PET-based strategy patients with a negative PET are not subject to additional investigations for at least 3 months, unless progression of symptoms. Of all the patients have been included, forty-five patients (30%) had biopsy-proven recurrence within 6 months after randomization. In the conventional strategy, the indication for direct laryngoscopy has appeared to be

unnecessary afterwards in 53 out of 74 patients (72%), compared to 22 out of 76 (29%) in the PET-based strategy. Thirty PET scans are true-negative and 1 is false-negative. Safety of the PET-based strategy has been confirmed; we have found no adverse effects on the operability of a recurrence or surgical margins of the salvage laryngectomy in the PET-based group. This trial shows that in patients suspected of having a recurrent laryngeal carcinoma after radiotherapy [^{18}F]-FDG-PET can act as the first diagnostic procedure and reduces the need for direct laryngoscopy by more than 50% of patients without endangering the quality of treatment.

In chapter 3 a cost-effectiveness analysis has been performed. The potential health benefits and cost consequences of introducing [^{18}F]-FDG-PET in the diagnostic work-up of patients suspected of having recurrent laryngeal carcinoma after radiotherapy are explored. The average total costs per patient within 6- and 12-months follow-up are compared between the two diagnostic strategies of the RELAPS study from chapter 2. A micro-costing method has been used, based on a detailed inventory and measurement of all resources consumed. Medical costs have been calculated. The diagnostic, treatment and follow-up phases are analyzed separately in subgroup analyses. After 6 months of follow-up, the mean total costs per patient in the conventional strategy are 11,784 euros, compared to 11,302 euros in the PET-based strategy, resulting in cost savings of 482 euros per patient with a PET-based strategy. The results of the same analyses for a 12 months follow-up period are comparable, with total costs savings of 1105 euros per patient in favor of the PET-based strategy. Sensitivity analyses confirm the robustness of the results. Therefore, the introduction of [^{18}F]-FDG-PET is favorable from both a clinical and an economic perspective. Despite the favorable results from these earlier studies the relatively low positive predictive value still causes a high number of unnecessary direct laryngoscopies. The cause has probably to be sought in the relatively low positive predictive value[22-25], as unfortunately residual laryngeal cancer after radiotherapy is usually embedded in inflammatory tissue that is also known to yield a high signal. Therefore, alternatives to [^{18}F]-FDG have been looked for. The ideal radiopharmaceutical has to result in PET registrations with a more favorable positive predictive value without reducing the excellent negative predictive value of [^{18}F]-FDG-PET/CT.

In chapter 4 we describe a comprehensive overview of alternatives to [^{18}F]-FDG that can be used in identifying head and neck cancer. The potential advantages and disadvantages of these radiopharmaceuticals are discussed. Our review shows that alternatives to [^{18}F]-FDG have only been used on a small scale and have not become part of routine PET procedures for revealing malignancies in the head and neck region.

Our literature search shows no additional value to FDG of a DNA precursor based radiopharmaceutical [^{18}F]fluoro-L-thymidine ([^{18}F]-FLT), neither for [^{18}F]- or [^{11}C]-choline, a (false) precursor for the biosynthesis of phospholipids, which are essential components of all cell membranes. Tumor hypoxia can be assessed in vivo with a number of available radiopharmaceuticals of which [^{18}F]-fluoromisonidazole ([^{18}F]-FMISO), [^{18}F]-fluoroazomycin arabinoside ([^{18}F]-FAZA) are by far the best known. Hypoxic tumors are more resistant to radiation- and chemotherapy. In the future, it can become a tool to optimize (chemo-) radiation strategies, however far more research is necessary to warrant a clinical introduction.

The tracking and quantification of monoclonal antibodies (MAb) with long-lived PET-isotopes are an exciting novel option to improve diagnostic imaging and to guide MAb-based therapy. Epidermal growth factor receptor (EGFR) inhibitors like the monoclonal antibody cetuximab have become part of treatment strategies for head and neck cancer. In vitro studies have been conducted to visualize the epidermal growth factor receptor with EGFR-specific antibody radiolabeled with [^{89}Zr]. The purpose is to select patients who will eventually benefit from treatment with a monoclonal antibody. In breast cancer in vivo studies have already been performed. These studies show that a [^{89}Zr]-MAb PET/CT can contribute to a better selection of patients who might benefit from targeted therapy. Introduction to clinical practice can be warranted.

The literature shows so far no additional value over [^{18}F]-FDG-PET/CT for amino acid-based radiopharmaceuticals as part of the diagnostic work-up of primary head and neck cancer. However, they may have a role in therapy evaluation after (chemo-)radiation, especially in the early post-radiation period as theoretically amino acid-based radiopharmaceuticals have to be more appropriate to discriminate residual disease from inflammation. The number of false-positive PET registrations have to be consequently less than obtained with [^{18}F]-FDG. This has been documented on a small scale and to our knowledge only for O-(2-[^{18}F]-Fluor ethyl)-L-tyrosine (FET) and TYR L-1-[^{11}C]-Tyrosine in vivo after radiotherapy.

Because amino acid-based radiopharmaceuticals can be an alternative to FDG in revealing recurrent disease after (chemo-)radiation, we have decided to explore an amino-acid based radiopharmaceutical. The amino acid methionine can be labeled with carbon-11 in the carboxyl group or in the methyl group. Carboxyl-labeled methionine can be used for assessing the protein synthesis rate. However, the molecule is more difficult to synthesize than the chemically identical methyl-labeled methionine. Consequently, the literature focuses on methyl-labeled [^{11}C]-labeled methionine. However, the methyl group is also donated to other chemical processes in the cell, predominantly DNA synthesis. As a result, methyl-labeled methionine cannot be used for quantitative analyses. A number of authors

have reported results on the use of [^{11}C]-methionine (MET) in HNSCC with results at least as good as those obtained with [^{18}F]-FDG[26-30]. For these reasons, we have chosen [^{11}C] labeled methyl labeled methionine for the subsequent studies[31].

The main purpose of the prospective pilot in chapter 5 study is to assess whether a small volume of cancer like T1-2 glottic cancer can be visualized by [^{11}C]-MET-PET/CT. Early glottic cancers are hard to visualize because of their low volume, movement artifacts and pooling of saliva. Ten patients with *de novo* small laryngeal cancer (7 T1, 3 T2) have undergone a [^{11}C]-MET-PET at least 3 weeks after the biopsy but prior to further treatment. Eight tumors are visualized. Six scans show strong and 2 moderate accumulation. One T1 and 1 T2 tumor are not visualized. The calculated sensitivity is 80%. These results show that [^{11}C]-MET-PET has the potential to visualize small laryngeal cancer, which opens opportunities to use the radiopharmaceutical in the follow-up of patients after radiotherapy, as a residual disease after radiotherapy often consists of dispersed small fields of the tumor.

In chapter 6 we investigate the potential of [^{11}C]-MET in diagnosing recurrent laryngeal cancer after radiotherapy compared to [^{18}F]-FDG. Forty-eight patients with a clinical suspicion of local residual disease at least three months after completed (chemo) radiotherapy for a T2-4 laryngeal carcinoma have been included. All patients have an indication for direct laryngoscopy. A [^{11}C]-MET-PET and an [^{18}F]-FDG-PET have been carried out prior to direct laryngoscopy. Both PET registrations have not been used for clinical purposes. One senior nuclear medicine physician has assessed the degree of abnormal uptake visually of both the [^{18}F]-FDG-PET and [^{11}C]-MET-PET images. The nuclear physician has no access to the medical charts and has been blinded to the results of the other PET. The gold standard is a biopsy-proven recurrence within 12 months after PET registration. Sensitivity, specificity and positive and negative predictive values have been calculated. The sensitivity of [^{18}F]-FDG is 77.3% and the specificity 56.0% after conservative reading, while these values are equaled 54.5% and 76.0 % for [^{11}C]-MET. [^{18}F]-FDG shows a positive predictive value of 60.7% and a negative predictive value of 73.7%. The PPV of [^{11}C]-MET is 66.7% and the NPV is 65.5%. The conclusion is that [^{11}C]-MET-PET is not superior to [^{18}F]-FDG-PET for identifying recurrent laryngeal cancer.

Discussion

Numerous studies show that the quality of life of patients is better after primary radiation than after laryngectomy[32-37]. However, severe post-radiation side effects, namely edema, chondro necrosis, and fibrosis have as a consequence loss of function of the larynx and swallowing problems, resulting in a long-term tracheotomy, difficult to treat pain, and/or

gastrostomy tube feeding [38-42]. Recent studies show that the quality of life in patients who still have their larynx but are dependent on tube feeding or need a tracheotomy is less than the patients who underwent a laryngectomy[43-47]. In our opinion, the main goal of non-surgical treatment has to be the preservation of function rather than organ preservation. As a consequence, one can sustain from repeating extensive diagnostic procedures in case of a non- functional larynx, in order to use the available resources more effectively. However, more robust studies are necessary before we can assert this as clinical practice.

In the case of a functional larynx, diagnostic procedures should not result in impaired functioning of the organ. The main goal of the post-radiation PET/CT scan is exactly that: to avoid unnecessary direct laryngoscopies with biopsy taking[10]. Literature shows that [^{18}F]-FDG-PET has great clinical value and is cost-effective in revealing residual disease after radiotherapy for laryngeal cancer and other subsites of the head and neck region[48-53]. This has already changed our routines. At the UMCG a CT or MRI scan is made routinely 2 months after finishing radiotherapy. In the past, endoscopy with biopsy taking, or in case of regional residual disease a neck dissection was performed when the CT or MRI showed signs of residual disease. Nowadays an [^{18}F]-FDG-PET is performed instead. Due to the excellent negative predictive value, one waives from biopsy taking or neck dissection, in case of a negative [^{18}F]-FDG-PET. However, due to the relatively low positive predictive value of the [^{18}F]-FDG-PET, a considerable number of unnecessary direct laryngoscopies with biopsy taking are still being performed. An alternative to [^{18}F]-FDG has to have a better positive predictive value(PPV), but with preservation of the excellent negative predictive value(NPV). Another condition has to be a relatively easy production process. In our prospective study, the results obtained with [^{11}C]-Methionine are slightly worse than the results obtained with [^{18}F]-FDG in revealing residual disease after radiotherapy. Especially, the negative predictive value of [^{11}C]-MET proves to be lower than the NPV obtained with [^{18}F]-FDG. Therefore [^{11}C]-MET cannot be an alternative to FDG, despite a roughly equal positive predictive value. Even combining [^{11}C]-MET-PET and [^{18}F]-FDG-PET hardly reduces the number of false-positive PET registrations.

An alternative to [^{18}F]-FDG-PET, can be diffusion weighted-MRI (DW-MRI). DW-MRI measures the displacement of water molecules in tissues. The degree of diffusion is represented by the apparent diffusion coefficient (ADC). In the case of an increased number or enlargement of cells, tissues will contain less extracellular water and will show a decreased ADC. Malignancies are characterized by a relatively high number of (enlarged) cells and therefore malignancies may have a lower ADC than the surrounding tissues. DW-MRI is more and more used in oncology, especially in primary staging of high cellularity tumors, like lymphoma, long cancer, and ovarian cancer. The advantage of DW-MRI over [^{18}F]-FDG-PET is the ability to visualize intracranial abnormalities[54]. However, DW-MRI has

more or less similar cons as [^{18}F]-FDG-PET/CT, in the sense that a number of benign lesions, and e.g. inflammation can exhibit restricted diffusion on images, thus mimicking malignant lesions[55].

DW-MRI has shown promising results in staging nodal metastasis, the detection of recurrent disease and the assessment of tumor response and prognosis after chemo-radiotherapy for HNSCC. The sensitivity and specificity rates obtained are more or less similar to those obtained with [^{18}F]-FDG-PET[56-66]. Unfortunately, the majority of these studies contain too few patients and included different sites. An exception is a recent study by Driesen et al. who included 149 patients with laryngeal carcinoma. A DW-MRI and [^{18}F]-FDG-PET were performed in case of suspected residual or recurrent disease after (chemo)radiation. MRI DWI shows similar diagnostic accuracy, superior specificity but inferior sensitivity compared to FDG-PET-CT. MRI DWI is therefore very comparable to the results we have obtained with [^{11}C]-MET-PET and as a consequence, we deem it unable to replace FDG-PET as a single imaging modality when local recurrent disease after (chemo)radiation is suspected[64].

Conclusion and future perspectives

More advanced PET scans, new ways to develop radiopharmaceuticals and combining the results of several imaging modalities in a systematic way will improve the follow up of laryngeal cancer after radiotherapy.

The first promising new development is the total-body PET. Over the course of the last 60 years, coincidence detection of positron-emitting radionuclides has evolved from single pairs of detectors for planar imaging to current PET scanners with rings of detector elements covering a maximum of approx. 22 cm, in axial length[67]. A total-body PET can cover the whole body by extension of the number of rings. As a consequence, the sensitivity of the system goes up with a factor of at least 40, enabling either a reduction of scan time to 1/40th (which results in a PET scanning time of half a minute!), or a reduction of the administered dose. On the downside, very powerful computers are needed to reconstruct images from the massive amount of data. At this moment one total-body PET scanner, the EXPLORER, has been built. The EXPLORER Consortium included teams from the University of Pennsylvania and Lawrence Berkeley National Laboratory as well as representatives from industry and several prominent imaging physician-scientists. The EXPLORER contains 10 rings and covers an axial length of 2 m[68].

The detection of small, low-density tumor deposits is an area to exploit total-body-PET's increased sensitivity. The minimum volume of a tumor that can be detected by a traditional CT FDG-PET is 5 mm. A total-body PET is able to decline the minimum volume further, which makes it easier to detect residual disease.

Pharmacokinetic studies usually use radiolabeled drugs with long live radiotracers. A PET needs a long registration time. Because the total body is scanned in a glance, a total body PET is able to discriminate small differences in radiotracer uptake. This is as well an important improvement for studies that use slow-clearing macromolecule radiotracers, for example, antibodies labeled with longer-life radionuclides such as [^{89}Zr].

On the basis of current levels of administered radioactivity, the radiotracer dynamic range will be extended from 3 to 4 to 7 to 9 radioactive half-lives. This is an important improvement when imaging small-molecule radiotracers labeled with short-lived radionuclides such as ^{11}C.

New radiopharmaceuticals are developed, although none of them have yet proven to be able to become an alternative to [^{18}F]-FDG. More and more PET scans are conducted with Gallium-68 labeled radiopharmaceuticals. These radiopharmaceuticals are used to reveal one characteristic of a disorder. An example is [^{68}Ga]-DOTATATE, which reveals somatostatin receptor expression in neuroendocrine tumor or [^{68}Ga]-labeled PSMA for identifying prostate cancer[69].

The development of new radiopharmaceuticals is a time-consuming, high-cost and empirical process. Universities have to collaborate with other partners to obtain the necessary facilities and financial resources. The developments of radiopharmaceuticals are much like drug development itself. Therefore more and more radiopharmaceuticals will be developed by project-specific collaborations between universities and pharmaceutical companies in order to generate new PET imaging agents, especially for imaging drugable biological targets[70].

New labeling techniques will make it easier to incorporate a [^{11}C] or [^{18}F] group in a pharmaceutical. This should lead to the development of new radiopharmarceuticals[71].
Radiomics is becoming more and more important as PET images are combined with other imaging modalities. Radiomics is defined as a method that extracts large amounts of features from (radiographic) medical images using algorithms. It uses a set of quantitative image features describing the geometrical structure, intensity distribution and texture of a region of interest (ROI) that are used by statistical or machine learning classifiers in order to identify abnormal tissues. Different imaging modalities (e.g., MRI, CT, PET, ultrasound)

are used to deliver these features and these features can be combined with all kinds of data. Finally, a mathematical model is built and its value for prognosis or prediction of the outcome of interest is assessed. Improved imaging capabilities, standardization of protocol and large amounts of data, will contribute to a fast improvement of radiomic strategies. Given the potentially very large number of features compared to the usually limited number of patients, machine (deep) learning(ML) is today a crucial part of the methodological toolbox used for radiomics analyses. Machine learning uses algorithms to analyze data, learn from that data, and make informed decisions based on what it has learned. Deep learning structures algorithms in layers to create an "artificial neural network" that can learn and make intelligent decisions on its own[72]. Some of the most dramatic developments have been in the area of medical imaging, where reports have shown that computer vision techniques built on deep learning algorithms can perform many tasks that have been thought to require human interpretive skills[73]. These applications are still in their earliest stages of technical development but may lead to improved imaging diagnoses with fewer inter-observer variability.[74]. Alongside these fascinating applications, there has been steady progress using similar artificial intelligence methods to improve the quality of medical imaging [75]. The aim of these technologies is to create better quality images, often starting from sub-optimal or low-dose scans. The image-quality enhancement algorithms rely on the power of deep convolutional neural networks. Rather than predicting diagnoses, these networks predict images[76]. Because the suboptimal images will now meet the requirements, fewer demands can be made on the quality of images. Finally, this will result in a reduction of tracer dose and scanning time.

More and more publications show that radiomics can provide strategies for risk assessment of tumor failure in head-and-neck cancer[77-81]. PET is one of the major contributors to the necessary data[82,83]. We hope radiomics will, in the near future, help us to select patients with laryngeal cancer who will develop recurrent disease after radiotherapy and to diagnose recurrent disease.

In the near future the follow up of post-radiation laryngeal cancer will definitely be improved. New radiopharmaceuticals will be developed visualized by the next generation of PET scans. The features of the PET scans will be combined with the features of other imaging modalities, including light images[84]. The localization of the residual disease can be pointed out with great accuracy. Only a small biopsy will be necessary. The biopsy can be done office based with a flexible laryngoscope, avoiding general anesthesia and with minimal damage to the vulnerable mucosa.

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8

Discussie / Samenvatting

Het behoud van het strottenhoofd is een belangrijk doel bij de behandeling van strottenhoofdkanker. Strottenhoofdkanker wordt daarom vaak bestraald. De kans dat de tumor na bestraling terug komt, is ongeveer 30%. De hoeveelheid bestraling op het strottenhoofd is zo hoog dat de kans op bestralingsschade navenant groot is. Bestralingsschade zoals oedeem, fibrose en kraakbeen necrose zijn lastig te onderscheiden van een recidief, daarbij komt dat een recidief in tegenstelling tot de oorspronkelijke tumor vaak in losse velden onder het slijmvlies ligt. Beeldvorming zoals CT en MRI kunnen een primair strottenhoofdkanker goed weergeven. Helaas kunnen ze lastig bestralingsschade van een recidief na bestraling onderscheiden. Een onderzoek onder narcose met het nemen van biopten zal daarom nodig blijven als er een verdenking op een recidief bestaat, met alle negatieve gevolgen voor de patiënt. Gemiddeld zijn er 2,3 onderzoeken onder narcose nodig om een recidief te ontdekken. Voor elk onderzoek onder narcose is volledige anesthesie nodig. Complete anesthesie op zich kan al schadelijk zijn voor onze patiënten, die over het algemeen niet in goede conditie zijn. Bovendien veroorzaken biopsieën vaak blijvende schade aan het strottenhoofd wanneer deze bestraald is geweest. In de afgelopen decennia zijn er verschillende onderzoeken gepubliceerd die aangeven dat [^{18}F]-FDG-PET een recidief strottenhoofdkanker na bestraling kan aantonen. Deze onderzoeken laten zien dat PET een uitstekende negatieve voorspellende waarde heeft. Dit betekent dat wanneer de [^{18}F]-FDG-PET geen tumor laat zien, de kans dat er toch nog een recidief is minimaal is. De positief voorspellende waarde is echter aanzienlijk lager. Wanneer een PET scan tumor laat zien is de kans aanzienlijk dat dit onterecht is.

In hoofdstuk 2 wordt de volgende hypothese getest. [^{18}F]-DG-PET vermindert het aantal onnodige onderzoeken onder narcose wanneer er een verdenking is op een recidief strottenhoofdkanker na radiotherapie. Om dit doel te bereiken werd de RELAPS (REcurrent LAryngeal cancer Pet Study) uitgevoerd. Een beleid waarbij patiënten een PET ondergingen, indien er een verdenking op een recidief was, werd afgezet tegen een beleid waarbij patienten een CT of MRI ondergingen gevolgd door een onderzoek onder narcose. Honderdvijftig patiënten uit diverse klinieken werden gerandomiseerd. Wanneer de [^{18}F]-FDG-PET niet negatief was werd er een onderzoek onder narcose uitgevoerd. Zowel de patiënten die een negatieve PET hadden als de patiënten die een negatief onderzoek onder narcose hadden, werden poliklinisch vervolgd. Van alle geïncludeerde patiënten hadden 45 patiënten (30%) binnen 6 maanden een biopsie bewezen recidief. In de groep die direct een onderzoek onder narcose ondergingen bleek de indicatie voor het onderzoek onder narcose achteraf onnodig te zijn geweest bij 53 van de 74 patiënten (72%), vergeleken met 22 van de 76 (29%) in de PET groep. Dertig PET-scans waren waar-negatief en 1 was vals-negatief. Deze vals negatieve bevinding had geen nadelig effect op de operabiliteit of de chirurgische marges. Deze studie toonde aan dat bij patiënten die worden verdacht van een recidief strottenhoofdkanker na radiotherapie [^{18}F]-FDG-PET kan fungeren als de eerste diagnostische procedure.

In hoofdstuk 3 wordt een kosten-batenanalyse uitgevoerd. De mogelijke gezondheidsvoordelen en kosten worden onderzocht die de introductie van de [^{18}F]-FDG-PET heeft in de diagnostische work-up. De gemiddelde totale kosten per patiënt binnen een follow-up van 6 en 12 maanden worden vergeleken tussen de twee diagnostische strategieën van de RELAPS-studie uit hoofdstuk 2. Na 6 maanden follow-up zijn de gemiddelde totale kosten per patiënt in de conventionele strategie groep 11.784 euro, vergeleken met 11.302 euro in de op PET-gebaseerde strategie groep. Een op PET-gebaseerde strategie resulteert in een kostenbesparingen van 482 euro per patiënt. Na 12 maanden is de kostenbesparing zelfs 1105 euro.

Helaas is het aantal onnodige [^{18}F]-FDG-PET scans behoorlijk hoog. De oorzaak moet worden gezocht in een relatief lage positieve voorspellende waarde. Waarschijnlijk is de door radiotherapie veroorzaakte ontstekingsreactie de oorzaak. Zowel ontstekingen, als een carcinoom laten een verhoogde opname van [^{18}F]-FDG zien. Het metabolisme van tumoren is op vele fronten verhoogd en beperkt zich niet tot een verhoogde suiker opname. Aminozuren en bouwstenen voor DNA etc. kunnen cf. het suikerderivaat [^{18}F]-FDG in een radiofarmacon worden in gebouwd. Het ideale radiofarmacon zou moeten leiden tot een hogere positief voorspellende waarde zonder de uitstekende negatief voorspellende waarde van [^{18}F]-FDG-PET / CT te verminderen.

In hoofdstuk 4 beschrijven we een uitgebreid overzicht van alternatieven voor [^{18}F]-FDG die kunnen worden gebruikt bij het identificeren van hoofd- en halskanker. De potentiële voor- en nadelen van deze radiofarmaca worden besproken. Het blijkt dat alternatieven voor [^{18}F]-FDG vaak lastig zijn te produceren, alleen op kleine schaal zijn gebruikt en geen onderdeel zijn geworden van routinematige PET-procedures voor het aan het licht brengen van maligniteiten in het hoofd-halsgebied. Een radiofarmacon op basis van een aminozuur zou een alternatief voor[^{18}F]-FDG kunnen zijn, omdat maligniteiten een verhoogd aminozuur opname hebben, terwijl de opname in ontstekingsweefsel achter blijft. Het aminozuur methionine kan relatief gemakkelijk aan methyl [^{11}C] worden. Enkele onderzoeken lieten zien dat [^{11}C] methionine (MET) hoofd-halstumoren goed zichtbaar konden maken met resultaten die minstens zo goed zijn als die verkregen met [^{18}F]-FDG. Daarom hebben we gekozen voor [^{11}C] methyl gelabeld methionine.

Het belangrijkste doel van de verkennende studie die in hoofdstuk 5 wordt besproken is om aan te tonen of tumoren met een klein volume zoals T1-2 stembandkanker zichtbaar gemaakt kunnen worden m.b.v. [^{11}C]-MET-PET/CT. Deze tumoren zijn lastig zichtbaar te maken door hun kleine volume en bewegingsartefacten. Tien patiënten met een klein strottenhoofdkanker (7 T1, 3 T2) ondergingen een [^{11}C]-MET-PET minstens 3 weken na een biopt en voor de uiteindelijke behandeling. Acht tumoren waren zichtbaar. Een T1 en 1 T2 tumor

waren niet zichtbaar. Deze resultaten lieten zien dat [^{11}C]-MET PET kleine strottenhoofdtumoren zichtbaar maakt. Dit opent mogelijkheden om [^{11}C]-MET PET te gebruiken om een recidief strottenhoofdkanker vast te stellen na bestraling. Namelijk een recidief bestaat vaak uit kleine velden tumor.

In hoofdstuk 6 worden bij patiënten met een verdenking op een recidief T2-4 strottenhoofdkanker na radiotherapie zowel een [^{11}C]-MET als [^{18}F]-FDG-PET verricht. Achtenveertig patiënten, met een verdenking op een recidief strottenhoofdkanker, minstens 3 maanden na de laatste bestraling en met een indicatie voor een onderzoek onder narcose werden geïncludeerd. De PET-scans werden niet voor klinische doeleinden gebruikt. Een ervaren nucleair geneeskundige beoordeelde de PET beelden. Hij had daarbij geen toegang tot de patiënten gegevens en de resultaten van de andere PET. De gouden standaard was een d.m.v. biopt aangetoond recidief binnen 12 maanden na de PET. De positief en negatief voorspellende waardes werden berekend. [^{18}F]-FDG liet een positief voorspellende waarde van 60.7% en een negatieve van 73.7% zien. De positief voorspellende waarde van [^{11}C]-MET was 66.7% en de negatieve 65.5%. De conclusie kon getrokken worden dat de betere positief voorspellende waarde van [^{11}C]-MET ten koste ging van de negatief voorspellende waarde. De conclusie was daarom dat [^{11}C]-MET-PET geen alternatief kan zijn voor [^{18}F]-FDG-PET om een recidief strottenhoofdkanker vast te stellen.

In Hoofdstuk 7 geven we een samenvatting en gaan we in de discussie in op toekomstige ontwikkelingen die in de nabije toekomst de non invasieve diagnostiek naar het recidief strottenhoofdkanker na bestraling kunnen verbeteren.

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CURRICULUM VITEA

Jan Wedman werd geboren op 10 juni 1963 in Heerenveen. Na het afronden van het VWO in 1983 ging hij Geneeskunde studeren aan de Vrije Universiteit te Amsterdam. Het doctoraal examen werd in 1987 behaald. Daarna liep hij coschappen van 1987 tot 1991, wat werd afgesloten met het artsexamen. Hij combineerde de coschappen met een loopbaan als semiprofessioneel marathonschaatser bij de VGZ ploeg.

De militaire dienstplicht vervulde hij als luchtmacht arts met als standplaats Gilze-Rijen. Al tijdens de dienstplicht startte hij als eerste hulp arts in het West-Fries Gasthuis te Hoorn. Daarna heeft hij 1 jaar gewerkt als arts assistent chirurgie in het Diaconessen Ziekenhuis locatie Heemstede en vervolgens 1 jaar als arts assistent in het Antoni van Leeuwenhoek Ziekenhuis te Amsterdam.

Zijn opleiding tot Kno-arts had hij in Noorwegen genoten van 1995 tot 2000. De perifere stages werden gelopen in Stavanger en in Skien. Het academische deel vond plaats in Bergen (N) onder leiding van Jan Olofsson. Als staflid legde hij zich toe op traumatologie, neusbijholte en cosmetische chirurgie.

In 2001 begon hij als algemeen KNO-arts op de afdeling Kno in het UMCG. In 2002 startte hij het fellowship hoofd-halschirurgie. Zijn opleiders waren B.F.A.M. van der Laan en A.A. Annyas. Stages van elk een half jaar heeft hij gelopen in het Antoni van Leeuwenhoek Ziekenhuis (opleider A.J.M. Balm) en het VUmc (opleider R.C. Leemans).

Vanaf 2004 is hij werkzaam als KNO-arts hoofd-halschirurg in het UMCG. Hij is toen ook gestart met het promotie traject

Hij is getrouwd met Brecht Kolhoff. Zij hebben 4 kinderen. Bente, Sanne, Silke en Rik.

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