[18F]FLT-PET and [18F]FDG-PET in the evaluation of radiotherapy for laryngeal cancer

Lukas B. Been a,b,1, Harald J. Hoekstra b,*, Albert J.H. Suurmeijer c, Pieter L. Jager a, Bernard F.A.M. van der Laan d, Philip H. Elsinga a

a Department of Nuclear Medicine and Molecular Imaging, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
b Department of Surgical Oncology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
c Department of Pathology and Laboratory Medicine, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
d Department of Otorhinolaryngology – Head and Neck Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands

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SUMMARY

The evaluation of response to radiotherapy in patients with laryngeal cancer is a challenge because of the difficulty to differentiate between post-therapy changes and recurrent or residual tumor. Positron emission tomography is a non-invasive imaging tool that may be helpful in this differentiation. In this study, [18F]-fluoro-3-deoxy-L-thymidine ([18F]FLT), a proliferation tracer is compared with 2-[18F]-fluoro-2-deoxy-D-glucose ([18F]FDG).

Patients with primary laryngeal cancer, scheduled to undergo radiotherapy were included in this study. Patients underwent both [18F]FLT-PET and [18F]FDG-PET shortly before radiotherapy. Ten patients underwent [18F]FLT-PET and [18F]FDG-PET 2–3 months after radiotherapy. Scans were analyzed visually for areas of increased tracer uptake. The standardized uptake value (SUV) was measured as a semi-quantitative value of tracer uptake.

Fourteen patients, all male, were included in this study. Both [18F]FLT-PET and [18F]FDG-PET showed increased tracer uptake in 12 out of 14 patients (86%). [18F]FDG uptake was significantly higher than [18F]FLT uptake (SUVmax: 4.5 vs. 2.4 (P = 0.002); SUVmean: 3.4 vs. 1.9 (P = 0.002)). After radiotherapy, 3 patients had histologically proven residual or recurrent laryngeal cancer. [18F]FDG was true positive in 2 out of 3 patients, whereas [18F]FLT showed increased tracer uptake in only one. Of the remaining 7 patients, [18F]FLT was true negative in all, whereas [18F]FDG showed increased uptake in one (false positive).

[18F]FLT-PET is feasible in visualizing laryngeal cancer and its evaluation of treatment. The overall uptake of this tracer is significantly lower as compared with [18F]FDG, but tumor to background ratios are comparable.

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Introduction

Laryngeal cancer is the most frequently diagnosed malignant tumor in the head and neck region and it comprises approximately 2% of all malignancies. Treatment strategies for this type of malignancy are surgery, radiotherapy or a combination of both. In some cases, CO2-laser evaporation or photodynamic therapy is an option, but this is limited to a small group of patients with superficial tumors.

Most small tumors (T1 and T2) can be curatively treated with radiotherapy alone, allowing for preservation of normal laryngeal function and voice, and subsequently good quality of life after treatment.

Evaluating the response to radiotherapy in patients with laryngeal cancer is a challenge because of the difficulty to differentiate between post-therapy changes and recurrent or residual tumor. Posttreatment surveillance consists of frequent physical examinations, laryngoscopy and, in case of clinical suspicion, conventional imaging (CT) and endoscopic examination with histological biopsies. Histological biopsies are the gold standard for diagnosing recurrent or residual disease, but false negative biopsies are reported because of submucosal tumor growth. Furthermore, repeated and deep biopsies are often needed, increasing the risk of radionecrosis or impaired voice.
Positron emission tomography is a functional imaging modality that uses radioactive tracers to visualize different metabolic processes in vivo. 2-[\(^{18}\)F]-fluoro-2-deoxy-D-glucose (\[^{18}\)FDG\]) is the most widely used PET tracer in oncology. In laryngeal cancer, however, there are only limited data available.\(^1\)\(^-\)\(^6\) Drawbacks of \[^{18}\)FDG\] are the physiological uptake in muscles of the larynx, uptake in inflammatory tissues and in reactive tissues (for example after radiotherapy).\(^8\)\(^,\)\(^9\)

In the search for other tracers, two amino acid tracers, \[^{11}\)C\]-methionine and \[^{11}\)C\]-tyrosine, have been subject to investigations in patients with laryngeal cancer.\(^10\)\(^-\)\(^12\) tracers show promising results, however, commercial distribution of these \[^{11}\)C\] radiotracers is limited owing to a relatively short half-life.

In 1998, \[^{18}\)F\]-fluoro-\(^3\)-deoxy-L-thymidine (\[^{18}\)FLT\]) was introduced as a proliferation tracer. \[^{18}\)FDG\] uses the salvage pathway of DNA synthesis for PET visualization. After entering the cell, \[^{18}\)FLT\] is phosphorylated by thymidine kinase 1 into \[^{18}\)FLT-monophosphate, after which it is trapped in the cell. Thymidine kinase 1 is a principle enzyme in the salvage pathway of DNA synthesis. Its activity is increased in proliferating cells.

The aim of the current study was to investigate the feasibility of \[^{18}\)FLT\] to visualize primary laryngeal cancer in comparison with \[^{18}\)FDG\]. Secondly, the evaluation of radiotherapy was performed using \[^{18}\)FLT\]-PET and \[^{18}\)FDG\]-PET.

**Materials and methods**

**Patients**

In this prospective study, fourteen patients with primary laryngeal carcinomas suitable for radiotherapy were included. All patients underwent physical examination of the head and neck, laryngoscopy under general anesthesia with histological biopsies of suspicious areas and CT imaging of the neck.

Patients underwent megavolt radiotherapy of the neck with a conventional fractionation schedule to a total absorbed dose of 70 Gy, in fraction of 2 Gy.

Patients visited the outpatient clinic regularly to undergo physical examinations and indirect laryngoscopy. In case of suspicion of residual or recurrent disease, additional CT and histological biopsy was performed.

This study protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen and all patients gave written informed consent.

**PET imaging**

Synthesis of \[^{18}\)FLT\] was performed according to the method of Machulla et al.\(^13\) \[^{18}\)FLT\] was produced by fluorination with \[^{18}\)F\]fluoride of the 4,4'-dimethoxytrityl protected anhydrothymidine, followed by a deprotection step. After purification by reversed phase HPLC, the product was made isotonic and passed through a 0.22 \(\mu\)m filter. \[^{18}\)FLT\] was produced with a radiochemical purity of >95% and specific activity of >10 T(Bq)/mmol. The radiochemical yield was 8.8 ± 3.7% (decay corrected).

\[^{18}\)FDG\] was produced according to the method of Hamacher et al. by an automated synthesis module.\(^14\) The radiochemical yield was 65.9 ± 7.1% (decay corrected).

Patients were scheduled for a separate \[^{18}\)FLT\]-PET and \[^{18}\)FDG\]-PET scan shortly before and 2–3 months after radiotherapy. For both scans, patients were instructed to fast for at least 6 h. Tracers were injected intravenously and after 60 or 90 min (for \[^{18}\)FLT\] or \[^{18}\)FDG\], respectively) scanning was performed on an ECAT EXACT HR + PET camera (Siemens/CTI Inc.). PET images were iteratively reconstructed (ordered subset expectation maximization).\(^15\)

**Data analysis**

Both \[^{18}\)FLT\]-PET and \[^{18}\)FDG\]-PET images were analyzed visually on a Leonardo workstation (Syngo Leonardo, Siemens AG, Berlin). Increased uptake of the tracer was considered as a ‘positive scan’. The absence of increased tracer uptake was considered as a ‘negative scan’.

Semi-quantitative analysis was performed using a volume of interest (VOI), consisting of a 70% isocountour of the maximum standardized uptake value (SUV). Within this VOI, the maximum and mean SUV were measured. In normal laryngeal tissue, the mean background SUV was measured to produce the tumor to non-tumor ratio (TNT).

\(\text{SUV}_{\text{max}}\), \(\text{SUV}_{\text{mean}}\) and \(\text{TNT}\) of \[^{18}\)FLT\] and \[^{18}\)FDG\] were compared using Wilcoxon signed rank test.

**Results**

**Patients**

Fourteen patients, all male, were included in this study. Ten patients underwent all four PET scans. In four patients, only the pre-therapy scans were performed; two patients refused post-therapy scans, one patient died shortly after radiotherapy and in one patient there were technical problems. All patients had primary laryngeal cancer. Five patients had a T1 tumor, another five patients had a T2 tumor and the remaining patients had a T3–T4 tumor. There were no patients with lymph node metastases (all patients N0). Patient and tumor characteristics are given in Table 1.

**Visualization of laryngeal cancer**

Both \[^{18}\)FLT\]-PET and \[^{18}\)FDG\]-PET showed uptake in 12 out of 14 tumors (86%). Two T1 tumors showed no increased tracer uptake.

Visual analysis of all scans revealed avid \[^{18}\)FDG\] uptake in most tumors, whereas \[^{18}\)FLT\] uptake was less avid. Mean \(\text{SUV}_{\text{max}}\) and mean \(\text{SUV}_{\text{mean}}\) for \[^{18}\)FDG\] were significantly higher than for \[^{18}\)FLT\] (\(\text{SUV}_{\text{max}}\): 4.5 vs. 2.4 \((P = 0.002)\); \(\text{SUV}_{\text{mean}}\): 3.4 vs. 1.9 \((P = 0.002)\)). Due to higher background activity of \[^{18}\)FDG\], TNT did not differ significantly between \[^{18}\)FDG\] and \[^{18}\)FLT\] (5.1 vs. 3.9 \((P = 0.158)\)).

**Additional findings**

In one patient (patient 4), \[^{18}\)FDG\]-PET showed increased uptake in the right lobe of the thyroid gland (Fig. 2), whereas \[^{18}\)FLT\]-PET showed no increased tracer uptake in this region. Fine needle aspiration revealed medullary thyroid cancer, for which this patient was treated by thyroidectomy. In another patient (patient 5), both \[^{18}\)FDG\]-PET and \[^{18}\)FLT\]-PET showed increased uptake in the thyroid region. Further analysis showed that this patient was suffering from Hashimoto’s thyroiditis. Therefore, both \[^{18}\)FLT\]-PET and \[^{18}\)FDG\]-PET were false positive (see Fig. 1).

**Evaluation of radiotherapy**

Ten out of 14 patients underwent posttreatment \[^{18}\)FDG\]-PET and \[^{18}\)FLT\]-PET. Three patients had histologically proven residual or recurrent disease at the time of the second PET scan. \[^{18}\)FDG\] was true positive in two patients and false negative in one. \[^{18}\)FLT\] was true positive in one patient and false negative in two (see Table 2).

Of the remaining 7 patients, \[^{18}\)FLT\] was negative in all patients. However, \[^{18}\)FDG\] was positive in one patient (Fig. 3).
Laryngoscopy under general anesthesia and histopathological biopsies showed no recurrent or residual disease. Therefore, this [18F]FDG-PET scan was considered false positive. In follow up, three years after diagnosis this patient did have recurrent laryngeal cancer and was treated with laryngectomy.

Discussion

In this study the feasibility of [18F]FLT to visualize primary laryngeal cancer was investigated in 14 patients. Furthermore, a side by side comparison between [18F]FLT and [18F]FDG was performed. Finally, in 10 patients, the effect of radiotherapy was evaluated with [18F]FLT-PET and [18F]FDG-PET.

Both [18F]FLT and [18F]FDG showed increased tracer uptake in 12 out of 14 tumors. This sensitivity of 86% is in accordance with the literature on.11,16,17 Although in this study [18F]FLT had the same sensitivity, overall [18F]FLT uptake was significantly lower than [18F]FDG uptake. In the recent literature, [18F]FLT has demonstrated lower tracer uptake than [18F]FDG in most tumor types.18 A possible explanation for this lower tracer uptake is the fact that tumors consist of malignant cells and inflammatory tissue. In fact, in laryngeal cancer, many tumors show ulceration with inflammation. [18F]FLT is probably taken up only by the malignant cells, whereas [18F]FDG is taken up by malignant cells and inflammatory tissues. Furthermore, [18F]FLT is in competition with native thymidine for the enzyme thymidine kinase 1. The affinity of [18F]FLT for this enzyme is 30% less, leading to preferable phosphorylation of native thymidine.19 Finally, tumors vary in the relative contribution of the salvage pathway of DNA synthesis. Some tumors rely solely on the ‘de novo’ pathway, leading to decreased [18F]FLT uptake and phosphorylation.20,21 [18F]FLT is expected to be a more cancer specific PET tracer, showing no uptake in inflammatory tissues. Van Waarde et al. demonstrated this in an acute inflammation model in rats.22 However, in this study we found that both [18F]FLT and [18F]FDG showed uptake in the thyroid gland of a patient suffering from Hashimoto’s thyroiditis, a chronic autoimmune inflammation of the thyroid gland. False positive [18F]FLT uptake has been demonstrated earlier in reactive lymph nodes.23 [18F]FDG demonstrated increased uptake in the right lobe of the thyroid gland of patient 4. Further analysis revealed a medullary carcinoma of the thyroid gland. [18F]FLT did not show uptake in this lesion.

After radiotherapy, the sensitivity for [18F]FDG to detect residual or recurrent tumor was higher as compared with [18F]FLT; [18F]FDG missed one out of three tumors, whereas [18F]FLT missed two out of three tumors. [18F]FDG images showed diffuse slightly increased tracer uptake, whereas [18F]FLT showed increased background tracer uptake (for example in the irradiated vertebral bodies). In one patient, [18F]FDG showed focal increased uptake, suspect for residual tumor. [18F]FLT and histopathological biopsies were negative at that time. Three years later, this patient did develop recurrent disease. We do not believe that [18F]FDG detected this lesion three years before it became clinically and histologically apparent. Therefore, [18F]FDG produced one false positive scan after radiotherapy.

### Table 1

<table>
<thead>
<tr>
<th>Pt/Age</th>
<th>Localization</th>
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<td></td>
<td>4.6</td>
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</table>

**Figure 1** Hashimoto’s disease on [18F]FDG-PET and [18F]FLT-PET. [18F]FDG-PET (left) and [18F]FLT-PET in patient 5 with a T2 laryngeal cancer. Both scans show diffuse increased tracer uptake in the thyroid region. Further analysis revealed Hashimoto’s thyroiditis. Both scans also showed uptake in the laryngeal cancer (not shown in this figure).

**Figure 2** Medullary thyroid cancer on [18F]FDG-PET. [18F]FDG-PET of patient 4 with a T1 laryngeal cancer. Uptake is seen in the right thyroid gland. Further analysis showed a medullary carcinoma of the thyroid, for which this patient received treatment. Both scans did not show increased uptake in the laryngeal cancer.
Table 2
Posttreatment PET results and follow up.

<table>
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<tr>
<th>Pt</th>
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<th>Follow up</th>
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<td>TNT</td>
<td>SUV_{max}</td>
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<td>2.4</td>
<td>1.9</td>
<td>n.a.</td>
</tr>
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<td>n.a.</td>
</tr>
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<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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<tr>
<td>9</td>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
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</table>

It remains unclear what the value of both tracers will be in the detection, staging and therapy evaluation of laryngeal cancer. Low overall [^{18}F]FLT uptake will probably result in lower sensitivity as compared with [^{18}F]FDG. In our population, there were no patients with lymph node metastases. In other tumor types, the sensitivity of [^{18}F]FLT to detect lymph node metastases has been poor.\(^{24,25}\) In primary head and neck cancer, Troost et al. reported high sensitivity for [^{18}F]FLT-PET. However, [^{18}F]FLT also showed uptake in many reactive lymph nodes, resulting in a specificity of only 17%. In evaluating the response to radiotherapy, our study population was small and only three patients had residual tumor directly after radiotherapy. Sensitivity for [^{18}F]FLT seems to be lower than for [^{18}F]FDG, but [^{18}F]FDG-PET produced a false positive scan. Larger studies are needed for more definite conclusions on this matter.

Conflicts of Interest Statement

None declared.

References


