Original Article

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Diagnostic Value of ^{68}Ga-FAPI PET/CT Versus ^{18}F-FDG PET/CT in Laryngeal Cancer Staging

Laringeal Kanser Evrelemesinde ^{68}Ga-FAPI PET/BT ile ^{18}F-FDG PET/BT'nin Karşılaştırılması

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Abstract

Objectives: To investigate whether gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography ^{68}Ga-FAPI PET/CT is superior to ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG) PET/CT in the staging of patients with laryngeal cancer (LC).

Methods: A total of 14 patients diagnosed with LC were retrospectively included in the study, of whom 13 were male and 1 female, with a mean age of 65 years. All participants were initially referred to our department for staging with ^{18}F-FDG PET/CT. Subsequently, each patient underwent a ^{68}Ga-FAPI PET/CT scan three days following the ^{18}F-FDG PET/CT. Both sets of imaging studies were independently evaluated by two experienced nuclear medicine physicians, and the findings were systematically compared to assess potential differences in diagnostic performance.

Results: The median maximum standard uptake values (SUV_{max}) of primary tumors was significantly higher in ^{68}Ga-FAPI PET/CT 10.95; range: 3.5-19.2) compared to ^{18}F-FDG PET/CT (4.85; range: 2.2-10.9). Lymph node involvement was observed on FDG scans in 3 patients, in ipsilateral levels 2 and/or 3, with a median SUV_{max} of 3.7 (range: 2.4-4.1). FAPI PET/CT also detected lymph node involvement at the same levels in 3 patients, with a notably higher SUV_{max} of 7.9 (range: 6.8-10.4).

Conclusion: In this study, our results suggest that ^{68}Ga-FAPI PET/CT demonstrates superior radiotracer uptake in both primary tumors and lymph nodes, which may enhance detection sensitivity for LC staging compared with ^{18}F-FDG PET/CT. Nevertheless, further prospective studies with larger patient populations are warranted to validate these preliminary observations and determine the clinical value of this emerging imaging modality.

Keywords: Laryngeal cancer, ^{68}Ga-FAPI PET/CT, ^{18}F-FDG PET/CT

Öz

Amaç: Bu çalışmanın amacı, galyum-68 fibroblast aktivasyon protein inhibitörü pozitron emisyon tomografisi/bilgisayarlı tomografi (^{68}Ga-FAPI PET/BT) yönteminin, ^{18}F-florodeoksiglukoz pozitron emisyon tomografisi (^{18}F-FDG) PET/BT ile karşılaştırıldığında larinks kanseri (LC) hastalarının evrelendirilmesinde üstün olup olmadığını araştırmaktır.

Yöntem: Çalışmaya, LC tanısı almış 14 hasta retrospektif olarak dahil edilmiştir. Hastaların 13'ü erkek, 1'i kadın olup ortalama yaş 65 olarak bulunmuştur. Tüm katılımcılar başlangıçta bölümümüze ^{18}F-FDG PET/BT ile evreleme amacıyla yönlendirilmiştir. Daha sonra her hastaya ^{18}F-FDG PET/BT çekiminden üç gün sonra ^{68}Ga-FAPI PET/BT görüntülemesi uygulanmıştır. Her iki görüntüleme yöntemi iki deneyimli nükleer tıp uzmanı tarafından bağımsız olarak değerlendirilmiş ve tanısal performanstaki olası farklılıkları belirlemek amacıyla bulgular sistematik olarak karşılaştırılmıştır.

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Bulgular: Primer tümörlerin medyan maksimum standart tutulum değeri (SUV_{maks}), ^{68}Ga-FAPI PET/BT'de (10,95; aralık: 3,5-19,2), ^{18}F-FDG PET/BT'ye göre (4,85; aralık: 2,2-10,9) anlamlı derecede daha yüksek bulunmuştur. Lenf nodu tutulumu FDG görüntülemelerinde 3 hastada, ipsilateral seviye 2 ve/veya 3'te gözlenmiş olup medyan SUV_{maks} 3,7 (aralık: 2,4-4,1) olarak saptanmıştır. FAPI PET/BT'de aynı seviyelerde 3 hastada lenf nodu tutulumu göstermiş, ancak SUV_{maks} değeri belirgin şekilde daha yüksek (7,9; aralık: 6,8-10,4) bulunmuştur.

Sonuç: Bu çalışmanın sonuçları, ^{68}Ga-FAPI PET/BT'nin hem primer tümörlerde hem de lenf nodlarında daha yüksek radyotracer tutulumu gösterdiğini, bunun da larinks kanseri evrelemesinde ^{18}F-FDG PET/BT'ye kıyasla saptama duyarlılığını artırabileceğini düşündürmektedir. Bununla birlikte, bu ön bulguların doğrulanması ve bu yeni görüntüleme yönteminin klinik değerinin belirlenmesi için daha geniş hasta popülasyonlarını içeren ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Laringeal kanser, ^{68}Ga-FAPI PET/BT, ^{18}F-FDG PET/BT

Introduction

Laryngeal cancer (LC) constitutes a significant proportion of head and neck malignancies, accounting for approximately 25% of all cases (1). The predominant histological subtype is squamous cell carcinoma (SCC), which comprises nearly 90% of LC cases and can arise in any region of the larynx. The disease exhibits a marked male predominance in incidence rates. Precise staging of LC is critical for guiding treatment decisions and estimating prognosis. Imaging techniques are indispensable in this context. Conventional modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are routinely utilized for staging; however, their sensitivity in differentiating metastatic from non-metastatic lymph nodes remains suboptimal (2,3). In contrast ^{18}F-fluorodeoxyglucose positron emission tomography/CT (^{18}F-FDG PET/CT) offers added value in initial staging, restaging, evaluation of therapeutic response, and the detection of locoregional and distant metastases during follow-up (3,4).

Fibroblast activation protein (FAP), primarily expressed by cancer-associated fibroblasts (CAFs), plays an instrumental role in tumor development and progression. Its upregulation across various tumor types has made it an attractive target for novel molecular imaging strategies. Gallium-68-labeled FAP inhibitors (^{68}Ga FAPI), used in PET/CT imaging, have shown promising results, particularly in malignancies where ^{18}F-FDG PET/CT demonstrates limited efficacy. The aim of the present study is to investigate the potential superiority of ^{68}Ga-FAPI PET/CT over ^{18}F-FDG PET/CT in staging patients with LC. To our knowledge, no previous studies have directly compared these two modalities in this specific clinical context. Therefore, this research may serve as a novel and foundational contribution to the existing body of literature.

Materials and Methods

This retrospective study was approved by the Clinical Research Ethics Committee of Gaziantep University (approval no: 2025/173, date: 06.08.2025). All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments. A total of 14 patients diagnosed with LC were retrospectively included in the study, of whom 13 were male and 1 female, with a mean age of 65 years (range: 43-75). In all cases, the diagnosis of SCC was confirmed by histopathological analysis. All participants were initially referred to our department for staging with ^{18}F-FDG PET/CT. Subsequently, each patient underwent a ^{68}Ga-FAPI PET/CT scan three days following the ^{18}F-FDG PET/CT. All participants signed informed consent forms before undergoing either procedure. Both sets of imaging studies were independently evaluated by two experienced nuclear medicine physicians, and the findings were systematically compared to assess potential differences in diagnostic performance.

Patient Preparation and Imaging Protocol

Prior to ^{18}F-FDG PET/CT imaging, all patients were instructed to fast for a minimum of six hours and to discontinue any intravenous glucose infusions during this period to minimize non-specific uptake. Blood glucose levels were measured via finger-prick testing immediately before tracer administration and were required to be ≤150 mg/dL for the scan to proceed. Following this, ^{18}F-FDG was administered intravenously at a dose ranging from 3.5 to 5.5 MBq/kg of body weight. For the ^{68}Ga-FAPI PET/CT scan, the radiotracer was injected intravenously at a dose of 2 MBq/kg. Both PET/CT scans were acquired using a Discovery IQ PET/CT system (GE Healthcare, Milwaukee, WI, USA), equipped with five detector rings and a transaxial field of view of 20 cm. Image acquisition began approximately 60 minutes post-injection for both tracers. Whole-body PET/CT imaging was performed from the vertex of the skull to the mid-thigh in the supine position. The CT component was used for attenuation correction and anatomical localization and was acquired using the following parameters: 120 kVp, 80 mAs per slice, a scan field of view of 700 mm, no interslice gap, 64 × 0.625-mm

collimation, and a 3.3-mm slice thickness. PET images were acquired in three-dimensional mode, maintaining the same patient positioning as the CT scan. The acquisition time per bed position was 2.5 minutes, ensuring adequate coverage and image quality. All images were reconstructed and analyzed using the system's dedicated software platform.

Image-Analysis

All PET/CT images were independently interpreted by two board-certified nuclear medicine physicians, each blinded to the other's assessment to minimize observer bias. Image evaluation included multiplanar reconstructions (axial, coronal, and sagittal) of the PET, CT, and fused datasets to ensure comprehensive lesion localization and characterization. Semi-quantitative analysis was performed using dedicated image-processing software (AW VolumeShare; GE Healthcare). Radiotracer uptake was assessed using the maximum standard uptake value (SUV_{max}) for both ^{18}F-FDG and ^{68}Ga-FAPI scans. For each lesion, volumes of interest were manually delineated on three orthogonal planes to ensure accurate measurement and avoid partial volume effects SUV_{max} values were recorded for all detectable primary tumors as well as regional and distant metastatic lesions. These values served as the primary metrics for comparing the metabolic activity and diagnostic performance of the two radiotracers.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 27, IBM Corp., Armonk, NY, USA). Descriptive statistics were presented as mean, median, minimum, and maximum values for continuous variables, and as frequencies (percentages) for categorical variables. The Wilcoxon signed-rank test was used to compare paired non-parametric SUV_{max} values between FDG and FAPI PET/CT scans. Spearman's rank correlation coefficient (ρ) was used to evaluate the strength and direction of associations between SUV_{max} values and clinical parameters such as age, primary tumor localization, and lymph node involvement. A p-value of <0.05 was considered statistically significant.

Results

A summary of patient demographics and imaging findings is shown in Table 1. A total of 14 patients [13 males (92.9%) and 1 female (7.1%)] with a mean age of 65 years (range: 43-75) were included in the study. The mean duration of smoking among the patients was 35.1 years (range: 25-50). All patients were histopathologically diagnosed with SCC. The most common tumor localization was glottic (64.3%), followed by supraglottic (28.6%) and subglottic (7.1%). The median SUV_{max} of primary tumors was significantly higher on ^{68}Ga-FAPI PET/CT (10.95; range: 3.5-19.2) than on ^{18}F-FDG PET/CT (4.85; range: 2.2-10.9) (Figure 1). Lymph node involvement was observed in 3 patients on FDG scans, located in ipsilateral level 2 and/or level 3, with a median SUV_{max} of 3.7 (range: 2.4-4.1). ^{68}Ga-FAPI PET/CT also detected lymph node involvement at the same levels in 3 patients, with a notably higher SUV_{max} of 7.9 (range: 6.8-10.4). No distant metastases were identified with either imaging modality (Table 1).

No statistically significant differences in SUV_{max} values across tumor localizations were observed for either FDG or FAPI (p>0.05).

Correlation analysis between SUV_{max} and the variables is shown in Table 2. A moderate positive correlation (r=0.46) was observed between FDG and FAPI SUV_{max} values; however, it was not statistically significant at the 0.05 level (p=0.098). The correlation between age and FDG SUV_{max} was weakly negative (r=-0.035, p=0.905),

Table 1. Summary of patient demographics and imaging findings (n=14)

Variable	Median (min-max), n (%)
Age (years)	65 (43-75)
Gender	
Male	13 (92.9%)
Female	1 (7.1%)
Smoking history	35.1 (25-50)
Pathology subtype	
SCC	14 (100.0%)
Primary tumor localization	
Glottic	9 (64.3%)
Subglottic	1 (7.1%)
Supraglottic	4 (28.6%)
FDG primary SUV	4.85 (2.2-10.9)
FAPI primary SUV	10.95 (3.5-19.2)
Lymph node FDG (location)	
Level 2	1 (7.14%)
Level 2 and 3	2 (14.28%)
Lymph node FDG (SUV)	3.7 (2.4-4.1)
Lymph node FAPI (SUV)	7.9 (6.8-10.4)
Lymph node FAPI (location)	
Level 2 and 3	2 (14.28%)
Level 2, 3, and 4	1 (7.14%)
Metastasis FDG	0
Metastasis FAPI	0

SCC: Squamous cell carcinoma, FDG: Fluorodeoxyglucose, SUV: Standard uptake value, FAPI: FAP inhibitor

while the correlation between age and FAPI SUV_{max} was nearly negligible and weakly positive (r=0.009, p=0.976). The correlation between age and FDG SUV_{max} was weakly negative (r=-0.04, p=0.905), while that between age and FAPI SUV_{max} was very weakly positive (r=0.01, p=0.976). A strong and statistically significant positive correlation was found between lymph node FDG SUV and FDG SUV_{max} (r=0.76, p=0.002), as well as between lymph node FDG SUV and FAPI SUV_{max} (r=0.59, p=0.015). Additionally, a statistically significant, moderate-to-strong correlation was observed between lymph node FAPI SUV and both FDG SUV_{max} (r=0.52, p=0.018) and FAPI SUV_{max} (r=0.63, p=0.008) (Table 2).

Table 2. Correlation analysis of between SUV_{max} and variables

Variables	FDG SUV_{max}	FAPI SUV_{max}
FDG SUV_{max} (p-value)	-	0.098
Correlation coefficient (r)	-	0.46
Age (p-value)	0.905	0.976
Correlation coefficient (r)	-0.04	0.01
Lymph node FDG (SUV) (p-value)	0.002	0.015
Correlation coefficient (r)	0.76	0.59
Lymph node FAPI (SUV) (p-value)	0.018	0.008
Correlation coefficient (r)	0.52	0.63

FDG: Fluorodeoxyglucose, FAPI: FAP inhibitor SUV_{max}: Maximum standard uptake value

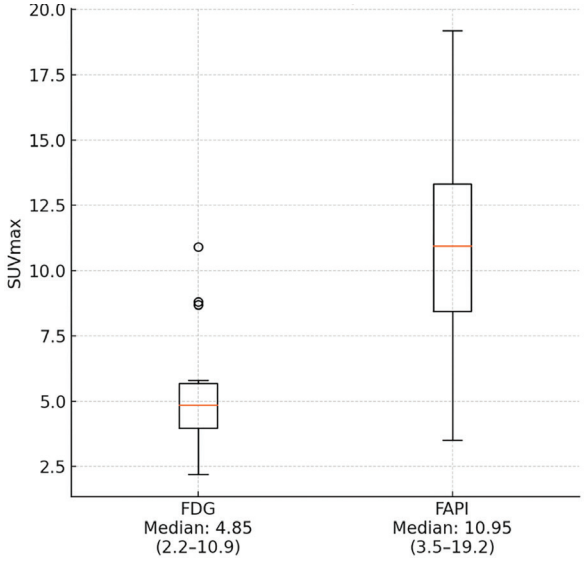

Figure 1. Comparison of FDG and FAPI SUV_{max} values with median and range in primary laryngeal tumors
SUV_{max}: Maximum standard uptake values, FDG: fluorodeoxyglucose, FAPI: FAP inhibitors

Discussion

LC is a relatively common malignancy of the respiratory tract and represents a significant subset of head and neck cancers (5). SCC is the predominant histological subtype and can arise from any anatomical region of the larynx. In contrast, rare histological variants, such as sarcomas, malignant melanomas, lymphomas, and minor salivary gland carcinomas, are infrequently encountered (6). Approximately 98% of LC originate in the glottic or supraglottic regions, with glottic tumors occurring nearly three times as often as supraglottic tumors. Subglottic cancers are rare, accounting for only about 2% of cases (7). Our findings are similar. The disease shows a clear male predominance, with a male-to-female ratio of approximately 3:1, and its incidence increases with advancing age. The pathogenesis of LC is multifactorial, with tobacco use and alcohol consumption recognized as the most significant risk factors. Smoking, in particular, shows a linear dose-response relationship with LC development and increases the risk 10-15-fold compared with non-smokers (8,9).

Management of LC is complex because of the larynx's essential roles in respiration, phonation, and swallowing. Treatment goals include complete tumor eradication, prevention of recurrence, and preservation of laryngeal function. The choice of treatment is primarily guided by the tumor's stage and anatomical subsite, as outcomes vary by location. Glottic tumors typically yield the highest success rates, followed by supraglottic and subglottic tumors (10). However, approximately 60% of patients are diagnosed at an advanced stage (11), often with deep tissue invasion and cartilage involvement (12). Early lymphatic dissemination is a defining feature of supraglottic carcinomas, with clinical nodal metastases identified in approximately 55% of patients at the time of diagnosis. Contralateral nodal involvement is observed in approximately 16% of cases. Cervical lymph node levels II, III, and IV are most frequently implicated (13).

Treatment modalities include surgery, radiotherapy, chemotherapy, or a combination thereof, with emerging interest in targeted therapies. Accurate staging is fundamental for selecting optimal treatment strategies and estimating prognosis. Understanding the specific patterns of tumor spread is equally critical, as it directly influences therapeutic planning. Detailed anatomical and pathological evaluation allows for maximal oncologic control while preserving organ function. The diagnostic workup for LC begins with a comprehensive clinical history and physical examination, followed by direct laryngoscopy to visualize the lesion and obtain biopsy samples for histological confirmation. These steps are essential for accurate staging and subsequent management. Imaging modalities serve as

crucial adjuncts to physical and endoscopic examination, enabling evaluation of local invasion, nodal involvement, and distant metastases (14,15).

CT, MRI, and PET are the primary imaging tools utilized in LC assessment (14). While CT and MRI are both integral to staging, MRI has demonstrated superior ability to detect cartilage invasion, perineural invasion and marrow involvement, and extracapsular spread (14,15,16,17). However, both modalities are frequently used complementarily, as they offer distinct advantages in delineating tumor extent and guiding therapeutic decisions. Despite their utility, conventional imaging (CI) often falls short in differentiating metastatic from benign lymphadenopathy (2,3). In this context, ^{18}F-FDG PET/CT has become an indispensable imaging modality for staging, response assessment, and long-term follow-up in LC patients (3,4). It also facilitates the detection of nodal metastases, distant lesions, and synchronous primary tumors (18). Notably, a retrospective study reported that PET/CT findings altered clinical management in approximately 31% of LC cases (18). While several studies have indicated that ^{18}F-FDG PET/CT and CI provide comparable diagnostic accuracy in LC (3,4,19,20), PET/CT offers superior sensitivity in detecting distant metastases due to whole-body coverage. However, its limited spatial resolution may hinder precise delineation of the primary tumor and T-staging (21). Recent advances have introduced hybrid PET/MRI as a promising modality, combining the functional benefits of PET with the superior soft-tissue contrast of MRI (22).

FAP, a serine protease selectively overexpressed in CAFs, is implicated in various oncogenic processes, including tumor proliferation, immune evasion, angiogenesis, extracellular matrix remodeling, and metastasis (23). Due to its minimal expression in normal tissues, FAP has emerged as a highly promising molecular target for both imaging and therapeutic applications (24,25,26). FAP-targeted radiotracers exhibit favorable pharmacokinetics, high tumor-to-background ratios, and broad applicability across various solid tumors (25). ^{68}Ga-FAPI have recently attracted attention as a novel class of radiotracers that may be superior to ^{18}F-FDG for oncologic imaging. Numerous studies have demonstrated enhanced sensitivity of ^{68}Ga-FAPI PET/CT for detecting both primary and metastatic lesions across a range of malignancies, including hepatocellular carcinoma, lung adenocarcinoma, gastrointestinal stromal tumors, gastric signet-ring cell carcinoma, and other metastatic malignancies (25,26,27,28,29,30).

In a study by Gu et al. (31), ^{68}Ga-FAPI PET/CT demonstrated improved detection rates of primary tumors in patients with head and neck cancers of unknown primary origin, particularly when ^{18}F-FDG PET/CT was negative. Similarly, Bhat et al. (32) reported a high diagnostic accuracy for ^{68}Ga-FAPI PET/CT, with a sensitivity of 88.3% and a specificity of 95.8% in a cohort of 41 patients with head and neck malignancies, including eight cases of LC.

Study Limitations

In our study, the small total number of patients and small subgroup sizes limited our ability to conduct reliable statistical analyses. Therefore, further prospective case-control studies with larger sample sizes and standardized methods are needed.

Conclusion

In this study, our results suggested that ^{68}Ga-FAPI PET/CT demonstrated superior radiotracer uptake in both primary tumors and lymph nodes, which may enhance detection sensitivity for LC staging compared with ^{18}F-FDG PET/CT (Figure 2). Nevertheless, further prospective studies with larger patient populations are warranted to validate these

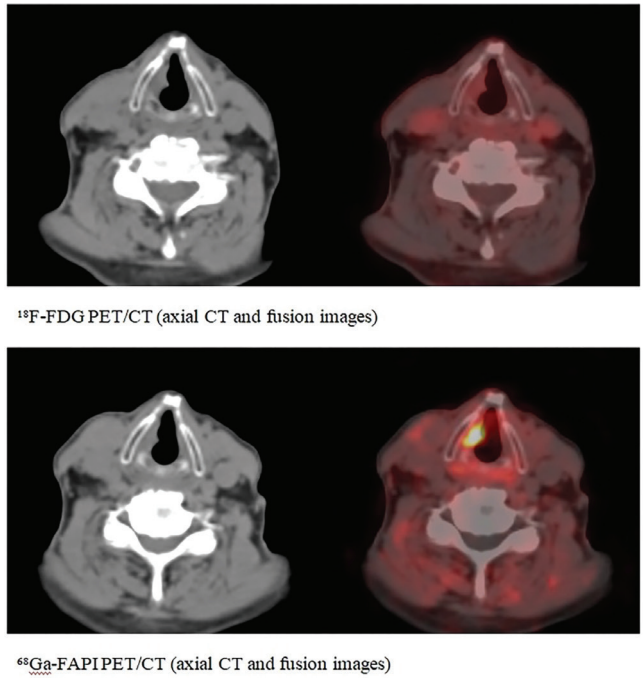

Figure 2. A 69-year-old man was diagnosed with glottic squamous cell carcinoma of the larynx. While the primary lesion in the right glottic region demonstrated low ^{18}F-FDG uptake (SUV_{max}: 2.2), it exhibited significantly increased uptake of ^{68}Ga-FAPI (SUV_{max}: 13.9), which is of particular note

^{68}Ga-FAPI PET/CT: Gallium-68 fibroblast activation protein inhibitor positron emission tomography/computed tomography, SUV_{max}: Maximum standard uptake value, FAPI: FAP inhibitors, ^{18}F-FDG: ^{18}F-fluorodeoxyglucose

preliminary observations and determine the clinical value of this emerging imaging modality.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Clinical Research Ethics Committee of Gaziantep University (approval no: 2025/173, date: 06.08.2025). All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments.

Informed Consent: This is retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: U.E., Concept: B.E., E.Ş., Design: U.E., Data Collection or Processing: E.E.Y., E.Ş., Analysis or Interpretation: B.E., Literature Search: E.K., Writing: E.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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