



[¹⁸F]F FDG PET/CT and [⁶⁸Ga]Ga-FAPI-4 PET/CT Imaging Following EGFR Targeted Erlotinib Treatment Toward Accurate Disease Status Evaluation in Metastatic or Advanced Head and Neck squamous Cell Carcinoma (HNSCC): A Complementary Role?

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Abstract

Head and neck squamous cell carcinoma (HNSCC) comprises a heterogeneous group of malignancies affecting the oral cavity, pharynx, and larynx, representing the seventh most common malignancy worldwide. Management of HNSCC with standard treatments remains inadequate in a substantial fraction of patients. Epidermal growth factor receptor (EGFR) is a novel treatment target, which is overexpressed in approximately 90% of HNSCC, making EGFR inhibitors such as erlotinib a promising therapeutic agent. [¹⁸F]F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) serves as the standard imaging modality for HNSCC management, while [⁶⁸Ga]Ga-fibroblast activation protein inhibitor-04 (FAPI-04) represents an emerging radiotracer showing superior performance in specific clinical scenarios. We herein present two HNSCC patients who underwent two imaging modalities ([¹⁸F]F-FDG PET/CT and [⁶⁸Ga]Ga-FAPI-04 PET/CT) following erlotinib treatment. In the first patient, [¹⁸F]F-FDG-PET/CT failed to identify metastatic cervical and mediastinal lymph nodes and skeletal lesions that were clearly visualized on [⁶⁸Ga]Ga-FAPI-04 PET/CT. In patient 2, post-erlotinib, [⁶⁸Ga]Ga-FAPI-04 PET/CT demonstrated reduced uptake in primary and lymph nodal lesions compared to [¹⁸F]F-FDG PET/CT. These findings suggest that both molecular imaging agents provide complementary information for accurate disease status evaluation and treatment response assessment in advanced HNSCC patients receiving erlotinib therapy.

Keywords

- ▶ head and neck squamous cell carcinoma (HNSCC)
- ▶ epidermal growth factor receptor (EGFR)
- ▶ erlotinib
- ▶ [¹⁸F] F FDG PET/CT
- ▶ [⁶⁸Ga]Ga FAPI-04 PET/CT
- ▶ treatment response
- ▶ complementary imaging

Introduction

Head and neck squamous cell carcinoma (HNSCC) represents a significant global health burden, being the seventh most

common cancer worldwide, accounting for approximately 947,211 new cases annually worldwide, with poor survival outcomes despite therapeutic advances.¹ Erlotinib, an epidermal growth factor receptor (EGFR) tyrosine kinase

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inhibitor, shows promise in HNSCC treatment.^{2,3} Traditional imaging modalities often provide incomplete assessment of disease extent and treatment response, hence the management of advanced HNSCC remains challenging.⁴ [¹⁸F]F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) has established utility in HNSCC evaluation. Because of several clinical scenarios in HNSCC evaluation, the utility of [¹⁸F]FDG-PET/CT has limitation particularly in posttreatment evaluation with inflammation, physiological uptake in lymphoid tissues of the neck region, and low spatial resolution for small lesions. These limitations become particularly problematic when assessing response to targeted therapies, where subtle changes in tumor biology may precede gross morphological alterations.⁴

Recent advances in molecular imaging have introduced [⁶⁸Ga]Ga-fibroblast activation protein inhibitor-04 (FAPI-04) PET/CT as a promising alternative, targeting cancer-associated fibroblasts (CAFs) within the tumor microenvironment.⁵ Preliminary studies suggest superior performance characteristics compared to [¹⁸F]F-FDG PET/CT, including higher tumor-to-background ratios and improved detection of small metastatic deposits.⁵ However, limited data exists regarding the comparative utility of these tracers in evaluating response to EGFR-targeted therapy.

The integration of molecular imaging with precision oncology approaches represents a critical frontier in personalized cancer care. Understanding how different imaging biomarkers respond to specific therapeutic interventions could optimize treatment selection and monitoring strategies. This report examines the complementary roles of [¹⁸F]F-FDG PET/CT and [⁶⁸Ga]Ga-FAPI-04 PET/CT in two patients receiving erlotinib therapy, addressing this important clinical question.

Case Report

Case 1: A 63-year-old female presented with a 3-month history of ulcer on the anterior part of the tongue. Physical examination revealed a 4-cm ulcerative lesion on the right lateral tongue border. Biopsy confirmed moderately differentiated squamous cell carcinoma (T2N2bM0, stage IVA). She underwent extended glossectomy with bilateral selective neck dissection (levels I–IV) followed by adjuvant local external beam radiotherapy (60 Gy in 30# to oral margins and 54 Gy in 30# to bilateral lymph nodes). Pathology revealed positive surgical margins and extracapsular extension in 3/15 right cervical lymph nodes. Twelve months posttreatment, routine follow-up CT showed evidence of distant metastases. Given the patient's EGFR overexpression (3+ by immunohistochemistry) and good performance status (Eastern Cooperative Oncology Group 1), erlotinib therapy was initiated at 150 mg daily. After 4 months of treatment, dual-tracer PET/CT imaging was performed to assess treatment response. [¹⁸F]F-FDG PET/CT scan (performed first), demonstrated low-grade metabolic activity in the right cervical nodal lesion and right femur lesion (maximum standardized uptake value [SUVmax]: 4.0) as seen in maximum intensity projection image (A) in ►Fig. 1. Axial fused image of the neck (B) and thoracic region (C) and sagittal image of the lumbar region (D) of [¹⁸F]F-FDG PET/CT scan showed no to low-grade metabolism in the right level II cervical lymph node (SUVmax: 3.2), mediastinal lymph node (SUVmax: 2.0), and lumbar vertebra L4 lesion, respectively. Subsequently, within a week, patient underwent [⁶⁸Ga]Ga FAPI-04 PET/CT scan, which showed (E–H) intense uptake of [⁶⁸Ga]Ga FAPI-04 in all previously identified lesions (SUVmax: 10.1 at L4). Additionally,

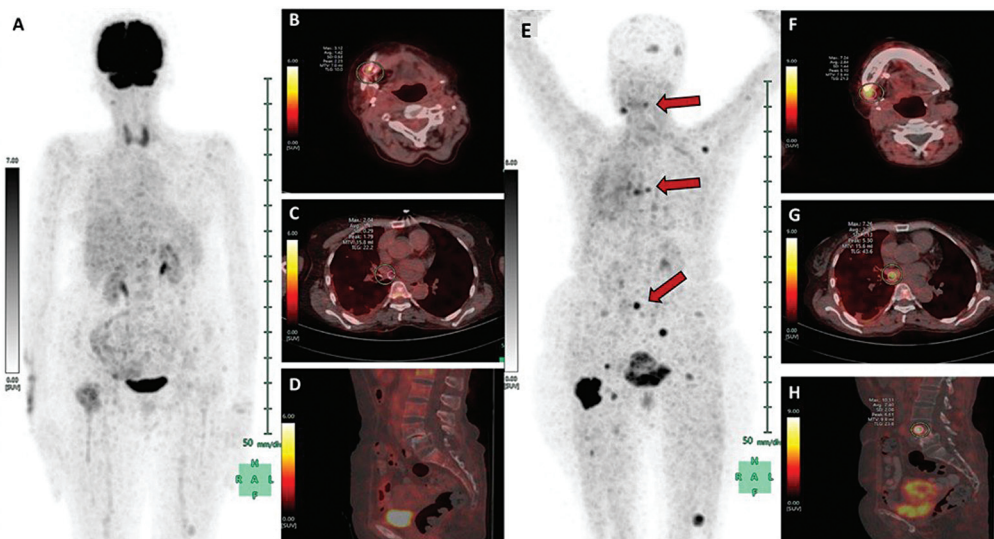


Fig. 1 [¹⁸F]F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan demonstrating low-grade metabolic activity in the right cervical nodal lesion and right femur lesion (maximum standardized uptake value [SUVmax]: 4.0) as seen in maximum intensity projection (MIP) image (A). The axial fused image of the neck (B) and thoracic region (C) and sagittal image of the lumbar region (D) of [¹⁸F]F-FDG PET/CT scan showing no to low-grade metabolism in right level II cervical lymph node (SUVmax: 3.2), mediastinal lymph node (SUVmax: 2.0), and lumbar vertebra L4 lesion, respectively. [⁶⁸Ga]Ga FAPI-04 PET/CT scan, which showed (E–H) intense uptake of [⁶⁸Ga]Ga FAPI-04 in all previously identified lesions (SUVmax: 10.1 at L4). Additionally, [⁶⁸Ga]Ga FAPI-04 PET/CT scan detected unrecognized cervical and mediastinal nodes (SUVmax: 7.2) and skeletal lesions (red arrows) as compared to [¹⁸F]F-FDG PET/CT.

[⁶⁸Ga]Ga FAPI-04 PET/CT scan detected unrecognized cervical and mediastinal nodes (SUVmax: 7.2) and skeletal lesions (red arrows) as compared to [¹⁸F]F-FDG PET/CT scan, leading to upstaging of disease extent as shown in ►Fig. 1.

Case 2: A 54-year-old male with a 30-year history of tobacco chewing presented with a painful ulcerative growth on the right lateral tongue border with progressive difficulty in swallowing and speech articulation for over 5 months. Physical examination revealed a 4.5-cm indurate mass with surface ulceration. Biopsy confirmed moderately differentiated squamous cell carcinoma of tongue. Staging imaging demonstrated locally advanced disease with bilateral cervical lymphadenopathy. The patient underwent comprehensive surgical management including right extended hemiglossectomy, right modified radical neck dissection, left extended supraomohyoid dissection, and tracheostomy due to anticipated postoperative airway compromise. Adjuvant cisplatin-based concurrent chemoradiotherapy was planned but discontinued after two cycles due to severe myelosuppression and hepatic toxicity. The patient then completed adjuvant external beam radiotherapy to the primary site and bilateral cervical regions.

Follow-up imaging revealed persistent/recurrent disease in the tongue and cervical lymph nodes. Given the treatment toxicities experienced with cytotoxic chemotherapy and documented EGFR overexpression in the tumor, erlotinib therapy was initiated at 150 mg daily and dual-tracer PET/CT was performed after 3 months for response evaluation. Post-erlotinib, [¹⁸F]F-FDG PET/CT scan demonstrated persistent intense metabolic activity in the tongue, cervical, and mediastinal lesions as seen in maximum intensity projection image (A) in ►Fig. 2. Coronal fused image of face (B) and axial fused image of neck (C) show hypermetabolic tongue lesion (SUVmax: 16.9) and cervical lymph nodes (SUVmax:

8.2), respectively. Subsequently, within a week, patient underwent [⁶⁸Ga]Ga FAPI-04 PET/CT scan, which revealed (D-F) low to mild-grade uptake of [⁶⁸Ga]Ga-FAPI in the tongue lesion, cervical (SUVmax: 3.7), and mediastinal lymph nodes (blue arrows) as compared to [¹⁸F]F-FDG PET/CT scan, as shown in ►Fig. 2, indicating treatment response that was not apparent on conventional [¹⁸F]F-FDG PET/CT scan.

Discussion

Treatment response assessment in advanced HNSCC remains challenging, particularly with targeted therapies like erlotinib where traditional imaging may not accurately reflect therapeutic efficacy. EGFR overexpression is seen in up to 90% of HNSCC cases and this provides a strong rationale for use of erlotinib therapy. Current imaging approaches in HNSCC often provide incomplete assessment of treatment response. We highlight the contrasting imaging patterns in two cases, this is because of fundamental differences in the biological targets and mechanism of action between [¹⁸F]F-FDG and [⁶⁸Ga]Ga FAPI-04 PET/CT, particularly in the context of EGFR-targeted therapy with erlotinib.

[¹⁸F]F-FDG accumulation reflects cellular glucose transporters (particularly GLUT 1) and hexokinase activity.⁴ EGFR signaling directly regulates glucose metabolism by enhancing glucose transporter expression and promoting glycolytic pathways. Erlotinib, as an EGFR tyrosine kinase inhibitor, disrupts this signaling cascade by blocking EGFR autophosphorylation and downstream AKT-mediated glucose uptake.

[⁶⁸Ga]Ga-FAPI targets fibroblast activation protein (FAP), a membrane-bound serine protease highly expressed on CAFs within the tumor stroma.⁵ Unlike [¹⁸F]F-FDG, which reflects cellular metabolism, [⁶⁸Ga]Ga-FAPI indicates stromal activity and fibroblastic proliferation independent of glucose

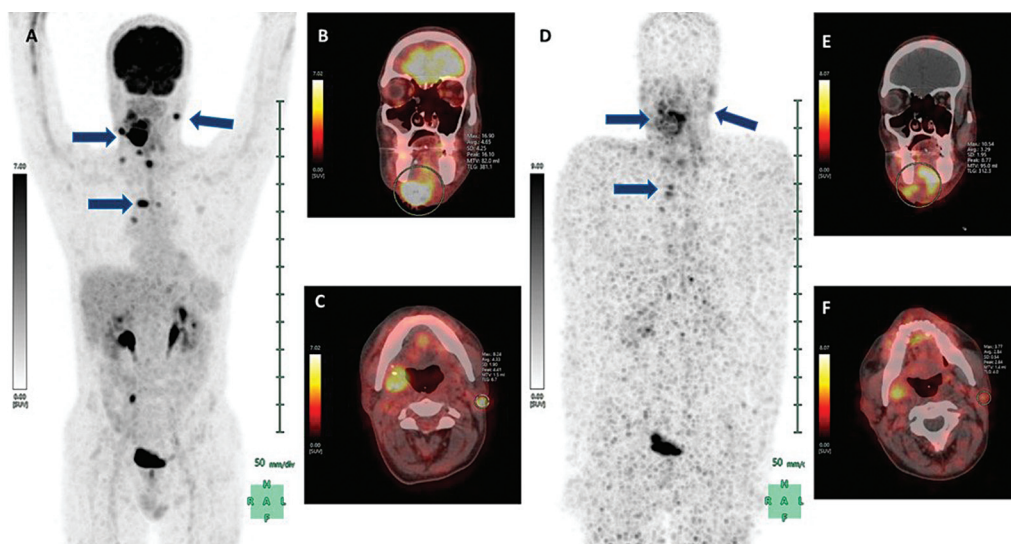


Fig. 2 [¹⁸F]F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan demonstrating persistent intense metabolic activity in the tongue, cervical, and mediastinal lesions as seen in maximum intensity projection image (A). Coronal fused image of face (B) and axial fused image of neck (C) show hypermetabolic tongue lesion (maximum standardized uptake value [SUVmax]: 16.9) and cervical lymph nodes (SUVmax: 8.2), respectively. Subsequently, within a week, patient underwent [⁶⁸Ga]Ga FAPI-04 PET/CT scan, which revealed (D-F) low to mild-grade uptake of [⁶⁸Ga]Ga-FAPI in the tongue lesion, cervical (SUVmax: 3.7), and mediastinal lymph nodes (blue arrows) as compared to [¹⁸F]F-FDG PET/CT.

metabolism. The differential [⁶⁸Ga]Ga FAPI patterns noted in our patients suggest distinct stromal responses to erlotinib therapy.

In case 1, the observed low [¹⁸F]F-FDG uptake post-erlotinib (SUVmax: 2–4) likely reflects successful metabolic suppression through EGFR pathway inhibition, resulting in decreased glucose transporter expression and glycolytic activity.^{2,5} However, this metabolic downregulation did not necessarily correlate with tumor viability or stromal activity, as demonstrated by the contrasting [⁶⁸Ga]Ga-FAPI findings.⁶

High [⁶⁸Ga]Ga-FAPI-04 uptake (SUVmax: 7.2–12.4) indicated active stromal component and viable CAFs, despite metabolic suppression evident on [¹⁸F]F-FDG imaging. This finding suggests that while erlotinib successfully inhibited tumor cell metabolism, the stromal microenvironment remained active, potentially harboring viable malignant cells.⁶

Conversely, case 2 demonstrated persistent high [¹⁸F]F-FDG uptake (SUVmax: 16.9) despite erlotinib treatment, suggesting either incomplete metabolic response, EGFR-independent glucose metabolism, or treatment resistance mechanisms.^{2,5} This pattern indicates that [¹⁸F]F-FDG may provide misleading information about treatment efficacy when metabolic suppression is incomplete or when alternative metabolic pathways are activated.⁵

Reduced [⁶⁸Ga]Ga-FAPI uptake (SUVmax: 3.7–5.8) compared to expected baseline values suggests successful stromal suppression and CAF deactivation following erlotinib treatment.⁶ This stromal response was not apparent on [¹⁸F]F-FDG imaging, indicating that FAPI-PET may be more sensitive for detecting treatment-induced changes in the tumor microenvironment.⁶

The observed discordances between tracers can be explained by their distinct biological targets and differential effects of erlotinib on tumor cells versus stromal components. The EGFR expression is predominantly found on epithelial tumor cells, while FAP expression is restricted to activated stromal fibroblasts. Erlotinib's direct effects on glucose metabolism may not proportionally affect stromal FAP expression, leading to discordant imaging patterns.⁶

Furthermore, the response of tumor microenvironment to targeted therapy may be heterogeneous, with some stromal components showing delayed or differential responses compared to tumor cells.⁷ This temporal and spatial heterogeneity explains why single-tracer imaging may provide incomplete assessment of treatment responses.

In our cases, complementary patterns suggest that single-tracer imaging may provide incomplete assessment of treatment responses in HNSCC patients receiving targeted therapy. The integration of both metabolic [¹⁸F]F-FDG and stromal [⁶⁸Ga]Ga-FAPI-04 imaging biomarkers offers a more comprehensive evaluation of therapeutic efficacy, potential-

ly optimizing treatment monitoring and clinical decision-making.⁷

Conclusion

Through the two illustrated case studies, we concluded that [¹⁸F]F-FDG-PET/CT and [⁶⁸Ga]Ga-FAPI-04 PET/CT imaging provide distinct but complementary information in HNSCC patients receiving erlotinib therapy. While [¹⁸F]F-FDG reflects metabolic treatment response through EGFR pathway modulation, [⁶⁸Ga]Ga-FAPI-04 offers superior lesion detection and stromal activity assessment. The observed discordances on PET/CT imaging highlight erlotinib's differential effects on tumor metabolism versus stromal microenvironment. These findings suggest that dual-tracer PET/CT imaging may optimize treatment response assessment in advanced HNSCC, potentially improving clinical outcomes through more accurate disease status evaluation. Future prospective studies are warranted to establish standardized protocols and interpretation criteria for dual-tracer PET/CT in patients receiving targeted therapy, with correlation to treatment outcomes and survival endpoints. The complementary use of dual-tracer PET/CT imaging represents a novel approach that may enhance therapeutic monitoring with targeted therapies and refine treatment decisions in the era of targeted cancer therapy.

Conflict of Interest

None declared.

References

- 1 Sun H, Yu M, An Z, et al. Global burden of head and neck cancer: Epidemiological transitions, inequities, and projections to 2050. *Front Oncol* 2025;15:1665019
- 2 Tsien CI, Nyati MK, Ahsan A, et al. The effect of erlotinib on EGFR and downstream signaling in oral cavity squamous cell carcinoma. *Head Neck* 2013;35(09):1323–1330
- 3 Song J, Chen C, Raben D. Emerging role of EGFR-targeted therapies and radiation in head and neck cancer. *Oncology (Williston Park)* 2004;18(14):1757–1767
- 4 Goel R, Moore W, Sumer B, Khan S, Sher D, Subramaniam RM. Clinical practice in PET/CT for the management of head and neck squamous cell cancer. *AJR Am J Roentgenol* 2017;209(02):289–303
- 5 Puré E, Blomberg R. Pro-tumorigenic roles of fibroblast activation protein in cancer: back to the basics. *Oncogene* 2018;37(32):4343–4357
- 6 Gu B, Yang Z, Du X, et al. Imaging of tumor stroma using ⁶⁸Ga-FAPI PET/CT to improve diagnostic accuracy of primary tumors in head and neck cancer of unknown primary: a comparative imaging trial. *J Nucl Med* 2024;65(03):365–371
- 7 Li R, Nan X, Li M, Rahhal O, Tang X, Chen Y. Fibroblast activation protein (FAP) as a prognostic biomarker in multiple tumors and its therapeutic potential in head and neck squamous cell carcinoma. *Oncol Res* 2024;32(08):1323–1334