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FAPI PET imaging value in radiotherapy planning and assessment in head and neck cancers

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Head and neck cancers (HNCs) represent a heterogeneous group of malignancies, predominantly composed of squamous cell carcinoma. Radiotherapy (RT), either alone or concurrently with chemotherapy, remains a central component of definitive and adjuvant treatment in HNCs. The success of radiotherapy depends on precise target volume delineation, which relies heavily on advanced imaging techniques. Positron emission tomography with fluorodeoxyglucose (FDG-PET) is well-established in RT planning workflows and endorsed by international guidelines. Recent advances in molecular imaging using fibroblast activation protein inhibitors (FAPI) targeting PET tracers offer improved tumor visualization and target delineation with early studies demonstrating more distinct tumor margins and improved diagnostic performance compared with FDG PET in HNCs. These advantages align with the critical need for highly reliable imaging in a disease site where complex anatomy complicates RT delivery. Early findings suggest a promising role for FAPI PET, in refining gross tumor volume (GTV) delineation and complementing current RT workflows. Despite the promising findings, current evidence is limited to small, primarily single-center cohorts, some with heterogeneous tumor subtypes, and the absence of prospective outcome-based validation. In addition, the utility of FAPI PET in post-RT response assessment and the optimal timing of imaging has yet to be clear defined. Rigorous, methodologically well-designed prospective studies are needed to establish the clinical value, prognostic significance, and impact of FAPI PET on radiotherapy outcomes in HNCs.

KEYWORDS FAPI, radiotherapy, head and neck cancer, PET/CT

Introduction

Head and neck cancers (HNCs) are the seventh most prevalent cancer worldwide, accounting for approximately 890,000 new cases and 450,000 deaths in 2022.[1] HNCs comprise a heterogeneous group of tumors, the majority of which are of epithelial origin, with squamous cell carcinomas (SCCs) accounting for more than 90% of

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cases. Various therapeutic options are available for HNCs, among which radiotherapy (RT) and chemoradiotherapy serve as cornerstone treatments, either as definitive or adjuvant approaches, depending on the primary tumor site and disease stage.[2,3] These therapeutic approaches have demonstrated significant improvements in local recurrence-free survival, progression-free survival, and overall survival.[2] Nevertheless, both acute and late radiation-related toxicities, are common and negatively impact quality of life (QoL).[4] Current efforts, both clinical and technological advances, are aimed to reduce radiation-related toxicities while preserving treatment efficacy, as maintaining good QoL is a key priority for patients with cancer.

Accurate tumor delineation is crucial in RT, as it directly influences both treatment efficacy and toxicity outcomes. Precise identification of tumor boundaries enables adequate dose delivery to malignant tissues while sparing adjacent healthy tissues, hereby contributing to higher tumor control and cure rates by ensuring adequate dose delivery to tumor, while minimizing damage to normal structures. Advances in imaging and contouring/segmentation technologies continue to enhance the accuracy and consistency of tumor delineation, resulting in safer and more effective RT planning.

This review aims to summarize and critically appraise current evidence regarding the role of fibroblast activation protein inhibitors (FAPI) positron emission tomography (PET) in RT planning and assessment in HNCs, with a particular focus on its performance compared to the current gold standard using F-18 fluorodeoxyglucose (FDG) PET and its potential clinical impact.

Radiotherapy planning in routine practice

RT planning in HNC is a complex, multidisciplinary process integrating clinical examination with anatomical and functional imaging to precisely delineate the tumor, aiming to achieve optimal tumor control while minimizing side effects. Over the past decades, RT techniques have evolved from volumetric-modulated arc therapy (VMAT) and intensity-modulated RT (IMRT) to the emerging intensity-modulated proton therapy (IMPT)[5]; allowing highly conformal dose distributions and reduced radiation-related toxicity. Image registration and fusion enable defining gross tumor volume (GTV), the generation of clinical target volume (CTV) (tumor plus a 5-10 mm margin of potential microscopic extension) and planning target volume (PTV) (CTV plus surrounding margins of 3-5 mm) according to international delineation guidelines.[5] This relies on accurately defining the primary tumor, the involved lymph nodes (LN) as well as the regional lymph nodes at risk of microscopic disease. In routine clinical practice, the GTV of the primary tumor is delineated using contrast-enhanced computed tomography (CT) as the reference imaging modality, often complemented by magnetic resonance imaging (MRI) and FDG PET for better soft-tissue contrast and metabolic characterization of the tumor respectively.[5]

Despite these technological advances, current RT planning is often hampered by the accuracy of tumor delineation. CT and MRI rely mainly on morphological criteria and may either underestimate the volume due to microscopic disease or overestimate volumes because of including regions with inflammatory or fibrotic changes. FDG PET is a valid technique for tumor delineation[6] and it is generally recommended for locally advanced tumors. Moreover, its accuracy is limited for smaller tumors (T1 and T2).[5–7] However, the nonspecificity of tracer uptake in inflamed or normal tissues is a major drawback, particularly in the oropharynx, larynx, and post-treatment settings. Furthermore, variability in image fusion, segmentation thresholds, and inter-observer contouring also contribute to inconsistencies in target definition.[8] These limitations underscore the need for further technical improvements or more specific molecular imaging techniques enabling better characterization of viable tumor tissue, hence improving the precision of RT planning in HNCs.

Emerging role of FAPI PET imaging in RT planning and assessment in head and neck cancer

Cancer-associated fibroblasts and FAPI PET imaging

Cancer-associated fibroblasts (CAFs) are a diverse cell population and the main constituents of the tumor stroma with critical effects on tumor evolution and patient prognosis.[9] In head and neck squamous cell carcinoma (HNSCC), the surrounding stroma contains an abundance of CAFs, which comprises up to 80% of the tumor mass in late-stage HNSCC.[10] Fibroblast activation protein (FAP) is highly expressed on CAFs and contributes to tumor growth, invasion, metastasis, and therapy resistance.[11] Over the last few years, FAP-targeted imaging using 68Ga and 18F-labeled FAP inhibitors (FAPI) has emerged as a novel pan-cancer imaging modality to visualize the tumor stroma rather than tumor metabolism.[12] In contrast to FDG PET, FAPI PET demonstrates negligible background activity in the head and neck region, including salivary glands, tonsils, and brain, thereby offering superior image contrast for lesion detection in HNCs.[13–15] Recently, the Society of Nuclear Medicine and Molecular Imaging (SNMMI) and the European Association of Nuclear Medicine (EANM) have published guidelines describing the methodologies, radiotracers, and procedural aspects of FAPI PET imaging.[16] From a procedural/practical point of view, FAPI PET offers several advantages over FDG PET related to patient preparation, as it obviates the need for fasting and allows image acquisition as early as 10 min post-injection, substantially reducing the examination time.[16,17]

Diagnostic performance of FAPI PET (TNM staging)

Multiple head-to-head studies have demonstrated that FAPI PET imaging achieves diagnostic performances comparable to or superior to FDG for primary tumor detection and lymph node metastases in HNC.

Jiang et al., prospectively studies 77 HNSCCs patients, reported a comparable sensitivity for FAPI and FDG PET for primary tumor detection and nodal metastases (100% and 86% respectively), but a superior specificity for patient-based nodal metastases (88% vs 13%, respectively).[18] In a small prospective study of 10 patients with oral squamous cell carcinoma (OSCC), FAPI PET identified all primary lesions with high tumor-to-background ratios (TBR), and outperformed MRI for nodal metastases detection (sensitivity 81% vs 50% and specificity 93% vs 61%).[13] Similarly, Promteangtrong et al. reported similar diagnostic performances for initial staging and recurrence in a mixed cohort of HNC patients with different disease states.[19] A summary of published prospective and retrospective studies comparing the diagnostic yield of FAPI and FDG PET in HNCs is provided in Table 1. In brief, all studies across different HNC types reported comparable performance for detecting the primary tumor with higher TBR on FAPI PET compared to FDG PET as well as superior accuracy for nodal metastases compared to FDG PET. Meta-analyses further substantiate these findings. Rizzo et al. pooled data from 14 studies ($n = 292$ pts) and reported a pooled sensitivity and specificity of 0.98 and 0.92, for primary tumor detection, and 0.91 and 0.84 for lymph node metastases, with comparable accuracy for primary lesion detection but superior performance to FDG PET for nodal assessment.[20] A recent meta-analysis of eight studies assessing the diagnostic performance of FAPI PET for lymph node evaluation in HNCs reported comparable sensitivity (89% vs. 91%) but higher specificity (93% vs. 50%) than FDG PET. [21]

These observations were corroborated in the most recent meta-analysis including 12 studies ($n = 386$ pts). Eventhough FDG PET showed slightly higher sensitivity than FAPI PET for detecting lymph node metastases (0.93 vs 0.82), FAPI outperformed FDG in terms of specificity (0.97 vs 0.36).[22]

Notably, in nasopharyngeal carcinoma (NPC), a primary site of complex anatomy, FAPI PET enabled more accurate tumor delineation at the skull base, parapharyngeal regions, and osseous extension compared to FDG PET, particularly in recurrent disease.[23,24]

Head and neck cancer of unknown primary (HNCUP) is defined as the presence of lymph node metastasis in the head and neck region without an identifiable primary tumor, even after a standardised diagnostic work-up. FDG PET is standard-of-care in this setting,[25] but the physiological FDG uptake in the oropharynx and more specific base of tongue makes primary tumor localization challenging, hence limits its sensitivity. In this setting, FAP-targeted PET with limited background activity in this region may complement FDG PET. The first study by Gu et al. in 18 HNCUP patients with negative FDG PET findings showed that FAPI PET was able to identify the primary tumor in 39% of cases, with lesions localized in the nasopharynx, palatine tonsil, submandibular gland and hypopharynx.[26] In a second prospective study, Gu et al. compared FAPI PET and FDG-PET in patients with squamous cell carcinoma cervical lymph node metastases and negative clinical examination, CT and MRI for a primary tumor detection. FAPI-PET/CT detected significantly more primary tumors than FDG PET (46 versus 17, $p < 0.001$), and led to treatment changes in 22 of 91 patients.[27] These preliminary data suggest that FAPI PET can improve primary tumor detection in HNCUP, particularly in cases where FDG PET is non-diagnostic. In conclusion, FAPI PET has practical advantages and comparable or superior diagnostic yield with higher TBR in primary lesions and superior accuracy for lymph node detection, than FDG PET, which may change or improve RT planning and management of patients.

Potential impact of FAPI PET on RT target volume delineation

The higher TBR of FAPI PET imaging is an advantage that could help to more accurately delineate primary tumor volume or to detect occult nodal metastases compared to current imaging techniques.

Various studies reporting the potential of FAPI PET imaging in RT planning are summarized in Table 2. Syed and colleagues evaluated FAPI PET guided GTV delineation in 14 patients with HNCs compared to conventional CT and/or MRI.[28] They developed an automated segmentation approach for FAPI-based GTV using TBR SUV ratios (three-, five-, seven-, or ten-fold increase in FAPI SUVmax in the tumor compared to the normal background). The authors reported that FAPI-based GTVs (generated using a 3-fold increase in SUVmax threshold) differed significantly from CT-based GTVs (median 68 mL vs 27 mL, respectively). Retrospective comparison of FAPI- and CT-derived volumes showed that FAPI uptake was present outside the planned dose coverage in several patients. An interdisciplinary consensus determined that a threshold of 3-fold higher tumor uptake than adjacent uptake in normal tissues was the most appropriate for target volume delineation.

In a pivotal study by Röhrich et al. in 12 patients, FAPI PET data altered the staging in 5/12 (42%) and led to significant modifications of GTV in adenoid cystic carcinoma, due to identification of perineural or skull base extension missed by MRI or CT alone.[29] The images were acquired at three time points (10 min, 1 h, 3 h), with the imaging at 1 h post-injection being the most optimal for better visualization of the tumor. Automated segmentation of GTV was based on a threshold of 25−35% of SUVmax. Since adenoid cystic carcinoma often shows little or no FDG uptake, the use of FAPI PET in this tumor type could offer significant advantages.

Wegen et al. performed a head-to-head comparison of FAPI and FDG PET in patients undergoing concomitant chemo-RT for HNSCC.[30] They reported higher tumor FAPI SUVmax (median 10.2 vs. 7.3, $p = 0.008$) and superior TBR. FAPI imaging resulted in upstaging and modification of

Table 1 FAPI vs FDG for TNM staging and potential advantages for RT planning.

Author	Design	Pts no.	Cancer Type	Sensitivity (FAPI/FDG)	Specificity (FAPI/FDG)	Key Findings	Advantage for RT Planning
Linz et al.,[13]	Prospective	10	Oral SCC	81.3% / 87.5% (nodal) MRI: 50%	93%/81% (nodal), MRI: 61%	Comparable sensitivity; higher specificity for nodal metastases	NA
Promteangtrong et al.,[19]	Prospective	40	HNSCC (mixed sites)	100% / 100% (primary)	50%/50% (primary)	High concordance and comparable diagnostic performance for initial staging and recurrence detection.	Clearer tumor boundaries, more confident GTV definition in complex anatomy. Higher primary tumour volume on FAPI.
Ding et al.,[47]	Prospective	28	NPC	100%/96% (primary), 92%/80% (nodal)	NA	Superior detection efficiency for primary tumour and nodal metastasis.	Enhanced skull base, intracranial and parapharyngeal margin definition for RT contouring.
Chen et al.,[48]	Prospective	26	Oral SCC	95%/100% (nodal)	100% / 29% (nodal)	FAPI improved primary tumor visualization and reduced false positives of LN metastasis. Higher specificity and accuracy for LN metastasis.	Improved margin delineation in post-inflammatory or post-surgical oral sites. Reduced false-positive nodal inclusion, improving RT targeting precision.
Wegen et al.,[30]	Retrospective	15	HNSCC	NA	—	Higher TBR with FAPI; detected 5 FAPI+/FDG− lesions. Significantly increased GTV size; target modification in ~33% of cases.	Increased GTV size and more accurate delineation.
Jiang et al.,[42]	Prospective	77	HNSCC	100%/100% (primary) 86%/ 86% (nodal, patient-based) 82%/ 82% (nodal, neck levels based)	88%/13% (nodal, patient-based) 97%/75% (nodal, neck levels based)	FAPI improved specificity and accuracy for N-staging; changed management in 16%.	Facilitated more selective nodal irradiation by reducing false-positive nodes. T staging upgrade due to additional visualization of skull-base and intracranial invasion.
Ji et al.,[49]	Retrospective	21	Tonsillar SCC	91%/41% (primary) and 87%/95% (nodal)	46%/11.5% (nodal)	Improved detection rate of primary tumour and superior diagnostic accuracy for metastatic LNs with FAPI PET.	Enabled precise delineation of primary and nodal targets with reduced false positives.
Gu et al.,[26]	Prospective	91	HNCUP	51%/25% (primary)	NA	FAPI outperformed FDG in detecting unknown primaries; changed management in 24%.	Guided more focused RT field definition and reduction of unnecessary mucosal irradiation.
Kuyumcu et al.,[50]	Retrospective	24	HNSCC	94%/88% (nodal)	86%/43% (nodal)	Superior specificity and similar sensitivity for nodal metastases.	Reduced false-positive nodal inclusion, improving RT targeting precision.
Xia et al.,[31]	Prospective	21	Laryngeal SCC	100%/ 86% (primary) and 50%/50% (nodal)	100%/91% (nodal)	Higher diagnostic efficacy for T staging (95.3% vs 57.1%), and downstaging of N-staging in 19% of the patients.	Provided clearer tumor boundaries in larynx; better alignment with CT-based volumes.

ACC; Adenoid cystic carcinoma, NPCa ; nasopharyngeal cancer, LSCC; laryngeal squamous cell carcinoma, CUP; cancer of unknown primary, FAPI; fibroblast activation protein inhibitor, RT; radiotherapy, FDG; fluorodeoxyglucose, GTV, gross tumor volume, SUVmax; maximum standardized uptake value, NA: not available.

Table 2 summary of studies showing the potential impact of FAPI PET on RT planning and gross tumor volume contouring methods.

Author (Year)	Design	No. of Pts	Cancer type	Tracer & imging modalities	Key findings for RT planning	Contouring threshold(s)	Impact on RT volumes
Syed et al., 2020[28]	Retrospective	14	HNC (mixed)	[^{68}Ga]FAPI PET/CT ± CE-CT/MRI	High TBR; FAPI-GTVs differed markedly from CT/MRI; FAPI volumes not fully covered by CT-PTV in several cases	Ratio to normal tissue × 3, × 5, × 7, × 10 SUVmax	Fusion/merge with CT reduced geographic miss; supports FAPI-guided contour refinement
Wegen et al., 2022[30]	Retrospective	15	HNCs	[^{68}Ga]FAPI-46 vs FDG PET/CT	Higher TBR with FAPI; FAPI-GTV (median 57.9 ml) > FDG-GTV (42.5 ml) > conventional (39.2 ml).	Not fixed; expert-driven	Final GTVs used for RT were significantly correlated with FAPI-GTV, the correlation of FAPI was higher than the correlation of FDG and conventional imaging
Röhrich et al., 2021[29]	Retrospective	12	ACC	[^{68}Ga]FAPI PET/CT vs CT/MRI	More accurate FAPI-GTVs than CT-GTVs on consensus read; clearer perineural/skull-base spread on FAPI PET; staging altered in 2/12	Threshold values of 25−35% of FAPI SUVmax	More accurate inclusion of infiltrative tracts; improved RT planning confidence
Qin et al., 2021[38]	Prospective	15	NPCa	[^{68}Ga]FAPI-04 PET/MR vs FDG PET/MR	Better delineation of skull-base/intracranial invasion; FAPI-TV and FDG-TV highly consistent with MRI-TV; staging changed in 6/15	FAPI 25% SUVmax FDG 20% SUVmax	More accurate inclusion of skull-base / intracranial disease in GTV/CTV
Zhao et al., 2021[23]	Retrospective	45	NPCa	[^{68}Ga]FAPI vs FDG PET/CT ± MRI	Higher uptake in primary/nodal/metastatic sites; TNM upstaging in 26% and management change in 18%; supplement to MRI for T-staging	40% SUVmax threshold for FAPI and FDG PET	Refined T-extent for contouring; potential dose-painting candidates
Zheng et al., 2022[32]	Prospective	47	NPCa	[^{68}Ga]FAPI-04 vs FDG PET/CT	Superiority of FAPI PET for cavernous sinus & bone invasion (T), inferiority to FDG for N staging; therapy changed in 8/47 patients	Not specified	Better T-staging → more appropriate skull-base/osseous coverage; caution for nodal fields

Table 2 (Continued)

Author (Year)	Design	No. of Pts	Cancer type	Tracer & imging modalities	Key findings for RT planning	Contouring threshold(s)	Impact on RT volumes
Xu et al., 2025[24]	Prospective	21	NPCa	[^{18}F]AlF-NOTA-FAPI-04 PET/CT vs MRI	GTV-FAPI 20−30% SUVmax ≈ MRI; superiority of FAPI PET for soft tissue & bone involvement in primary tumours	20−30% SUVmax (best match: 20%)	Higher precision in GTV; reduces under/over-coverage risk
Xia et al., 2025[31]	Prospective	21	LSCC	[^{18}F]FAPI-42 vs FDG PET/CT	FAPI better for primary detection and T-staging (95.3% vs 57.1%); N down-staged in 19% (pathology-consistent)	FAPI 40% SUVmax FDG 35% SUVmax	Clearer primary margins for laryngeal contours; fewer false-positive nodes included
Serfling et al., 2021[34]	Retrospective	8	CUP	[^{68}Ga]FAPI-04 vs FDG PET/CT	Higher TBR for primaries; inferior for very small nodes	Not applicable	Enables focused mucosal RT, potentially avoiding extensive bilateral irradiation

ACC; Adenoid cystic carcinoma, NPCa ; nasopharyngeal cancer, LSCC; laryngeal squamous cell carcinoma, CUP; cancer of unknown primary, FAPI; fibroblast activation protein inhibitor, RT; radiotherapy, FDG; fluorodeoxyglucose, GTV, gross tumor volume, SUVmax; maximum standardized uptake value, TBR; tumor-to-background ratio.

target volumes in approximately one-third of patients. Similar to other studies, FAPI-derived GTVs (median 57.9 mL) were significantly larger than those obtained with FDG PET (42.5 mL; $p < 0.05$) and those based on CT/MRI (37.7 mL; $p = 0.003$), and they showed a stronger correlation with the final expert-defined GTVs (rho = 0.72; $p = 0.004$). FAPI-based GTVs were incorporated into treatment planning in 10 patients (67%); among these, one patient experienced local progression within the irradiated region at 4.5 months, while five patients in the entire cohort developed out-of-field progression. Although these findings may reflect improvements in delineation of tumor boundaries by FAPI PET, the small sample size warrants cautious interpretation.

Further site-specific studies have echoed these observations. Xia et al. found that in laryngeal SCC, FAPI PET achieved better accuracy in T-staging (95% vs. 57% with FDG) and led to nodal downstaging with a change of staging in 19% of total patients. The authors proposed an SUV-based segmentation threshold (35% SUVmax on FDG PET−40% SUVmax on FAPI PET) for RT contouring, with volumes being highly consistent with CT-based tumour volumes. Even though volumes were similar, FAPI PET resulted in more accurate inclusion of skull base/intracranial disease in the GTV/CTV.[31]

In a study by Xu et al. in 21 patients with NPC, FAPI-based GTV was generated using 20-30% SUVmax thresholds, with GTV-FAPI volumes using 20% SUVmax threshold best approaching MRI-based GTV. The authors demonstrated that FAPI PET was superior to MRI in detecting soft and bone tissue involvement in primary tumors.[24] Two more studies on NPC comparing FAPI PET with FDG PET demonstrated that FAPI imaging might help refine the GTV of primary tumors, as it outperforms FDG PET in T staging.[23,32]

Cancer of unknown primary in the head and neck is not an uncommon presentation. FDG PET and p16 immunohistochemistry in conjunction with biopsy and/or tonsillectomy have increased the diagnostic yield for determining the primary site. Total mucosal irradiation with IMRT has been recommended in cases of HNCUP; however, the wide field of radiation is associated with important toxicity.[33] As mentioned previously, preliminary data have shown the superiority of FAPI PET over FDG PET in detecting primary tumors in HNCUP,[26,27,34] which may enable to better guide RT rather than irradiating blindly.

Beyond primary tumor delineation/detection, accurate evaluation of cervical lymph node involvement is fundamental for RT planning in HNCs, as the nodal status determines the extent of target volume delineation for RT.[35] Traditional imaging tools, including CT and MRI, mainly rely on morphological features such as nodal size and shape, which can miss small nodes with micrometastatic deposits. Similarly, although widely used for functional assessment, FDG PET may yield false-positive results in inflammatory nodes and false-negative findings in necrotic or low-metabolic nodes.[36] FAPI PET has the potential to overcome some of these limitations by identifying metastatic nodes with high specificity, thereby improving nodal staging and RT target definition (see Table 1 and the section on TNM staging). This may

translate into either expansion of the radiation fields to include additional malignant nodes or, conversely, avoidance of unnecessary nodal irradiation in cases of nodal downstaging.

The optimal method for tumor segmentation on FDG PET remains controversial, as no standardized or universally accepted approach has been validated for RT in HNCs.[37] FAPI PET imaging provides inherently higher image contrast, which may enable more accurate and inter-intraobserver reproducible target delineation. Some studies have evaluateds SUVmax-based tresholding strategies for defining GTVs on FAPI PET, reporting threshold values between 20% to 40% of the SUVmax,[24,28,29,31,38] Table 2. Experience from FDG-PET-based delineation suggests that lower thresholds tend to generate larger GTVs, potentially increasing the risk of overestimating the field and unnecessary irradiation of normal tissue, whereas higher thresholds may underestimate tumor extent and compromise target coverage. To establish a reliable and standardized segmentation method, large prospective studies are needed to compare FAPI-based delineation methods with conventional imaging approaches and to correlate volumetric parameters with clinically relevant endpoints such as local control, overall survival, and quality of life.

Current evidence suggests that FAPI PET can enhance GTV delineation in both primary and recurrent HNC as well as in cancers of unknown primary, offering complementary information to FDG PET and MRI.

From a technical perspective, the high TBR of FAPI PET may assist radiation oncologists in delineating primary and nodal target volumes with greater precision. However, early findings suggest that FAPI PET tends to yield larger GTVs than conventional techniques, and it remains unclear whether this reflects improved accuracy in defining tumor boundaries or an overestimation of tumor extent.

Role in response assessment

Beyond its potential in initial staging and RT planning, FAPI PET has shown promise for treatment response assessment and therapy outcome prediction across various cancer types.[39–41] However, no mature data are currently available regarding its role in evaluating the response to RT in HNCs. Preliminary findings from Jiang et al.[42] demonstrated that, in patients with oral SCC undergoing neoadjuvant chemoimmunotherapy, reductions in FAPI uptake strongly correlated with pathological response and outperformed FDG PET in early response prediction.

In NPC, Zhao et al. reported that FAPI PET was able to detect residual or recurrent disease following RT.[23] Among six patients imaged for suspected recurrence, FAPI PET correctly identified recurrence in 4 patients but produced false-positive results in 2 patients attributable to post RT fibrosis and inflammation. Importantly, the imaging interval after RT was not specified. Given that RT induces fibrotic changes and that FAPI PET targets fibroblasts, which may be abundant in the post-RT setting, distinguishing treatment related changes from true residual tumor can be challenging. Experience with FDG PET has shown that early imaging during chemoradiotherapy, so-called interim PET, is inferior to assessments performed at 2-4 months after treatment completion[43] In clinical practice, early response assessment could potentially guide adaptive strategies such as intensifying the current treatment or switching to other options with the aim to improve outcome while recuding unnecessary toxicity. Because of the lack of an imaging technique capable of reliably characterizing early post-RT changes, current guidelines recommend waiting at least 12 weeks post-RT or chemoradiotherapy before assessing response or residual disease.[44] This consideration is particularly important for FAPI PET imaging, as the optimal timing for post-RT imaging has not yet been defined and warrants comprehensive investigation.

Pitfalls and interpretative considerations during RT planning

Although FAPI imaging offers several notable advantages, it is not fully specific to malignant tissue. Increased uptake has been documented in benign conditions associated with fibroblast activation, such as arthritis, atherosclerosis, postoperative fibrosis, and inflammatory lymph nodes. Prior publications have highlighted these limitations of FAPI PET imaging across multiple anatomical regions, including the head and neck[45,46] Recognizing these uptake patterns is crucial when incorporating FAPI into RT planning, as misinterpretation may lead to overestimation of target volumes. Therefore, FAPI PET findings should always be interpreted in conjunction with morphological imaging and relevant clinical information.

Potential clinical impact and future perspectives

The integration of FAPI PET into RT workflows has the potential to substantially enhance biologically informed target delineation, post-treatment surveillance. Early clinical results suggest that integrating FAPI PET into RT planning may alter disease staging or therapeutic strategy in 20–40% of patients.[29,30] Prospective studies are now needed to determine whether these imaging-driven modifications translate into measurable improvements in clinical endpoints, particularly local tumor control and toxicity reduction.

Despite its excellent performance in primary tumor detection, the utility of FAPI PET for detecting lymph node metastasis remains less consistent.[19,32,34,38] Meta-analytic evidence indicates a pooled sensitivity of approximately 90% and specificity of 84%.[20] However, some studies have reported that FAPI PET detects fewer metastatic nodes than FDG PET, but most lacked histopathological confirmation. For example, Serfling et al. performed histopathological confirmation and demonstrated superior specificity (100%) and overall

accuracy (99%) for FAPI PET compared to FDG PET (91% and 90%), raising the possibility that a fraction of FDG-positive nodes represents false positives.[34] Given the high lesion specificity observed in other settings,[13] the diagnostic performance of FAPI PET for nodal assessment may currently be underestimated. Additional robust prospective trials with comprehensive histological validation are essential to clarify its accuracy in this setting, as nodal mapping is critical for defining nodal target volumes in RT. Prospective randomized investigations with medium- to long-term follow-up are required to determine whether FAPI-based planning translates into reduced radiation-related toxicity and improved clinical outcomes compared with conventional imaging approaches.

Although the high TBR characteristic of FAPI PET is theoretically advantageous for accurate tumor delineation, the optimal delineation strategy remains to be established. By analogy to FDG PET, gradient-based methods that leverage signal-to-background profiles may prove most suitable; however, current available data are insufficient to draw definitive conclusions.

Evidence for the role of FAPI PET in RT response assessment is presently scarce. All available imaging techniques—FDG PET, CT, and MRI—face well-recognized limitations for early response assessment. Whether FAPI PET can serve as a superior alternative, and what timing optimally balances specificity and interpretability after RT will require rigorous evaluation in well-designed prospective studies.

Conclusion

FAPI PET imaging represents a promising advancement in the TNM staging of HNCs, with the potential to substantially improve the precision for RT planning. Emerging evidence across multiple studies suggests a growing/compelling consensus that FAPI PET outperforms FDG PET in both TNM staging accuracy and GTV delineation. Nonetheless, these data remain preliminary, and the clinical utility of FAPI PET, whether as a complementary tool or potential alternative to FDG PET, must be confirmed through large-scale, rigorously well-designed prospective studies. Furthermore, early data indicate that FAPI PET may offer superior detection of local recurrence, however its role in RT response assessment in HNSCC remains insufficiently defined and warrants further investigation.

Declaration of competing interest

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All authors have no conflict of interest related to this work, to declare.

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CRediT authorship contribution statement

Qaid Ahmed Shagera: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Supervision, Writing – original draft, Investigation, Resources, Software, Validation, Visualization, Writing – review & editing. **Ayça Arçay Öztürk:** Conceptualization, Data curation, Validation, Writing – review & editing, Visualization. **Kim M. Pabst:** Conceptualization, Writing – review & editing, Validation. **Eléonore Longton:** Conceptualization, Writing – review & editing, Validation. **Jean-Pascal H. Machiels:** Conceptualization, Validation, Writing – review & editing. **Olivier Gheysens:** Conceptualization, Validation, Writing – review & editing. **Sandra Nuyts:** Conceptualization, Supervision, Validation, Writing – review & editing.

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