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Emerging Opportunities for Digital PET/CT to Advance Locoregional Therapy in Head and Neck Cancer

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The purpose of this article is to present the recent imaging advancements enabled by digital photon counting positron emission tomography detector technology and discuss its potential applications in the clinical management of head and neck cancer (HNC) and nodal metastases. ^{18}F-fluorodeoxyglucose positron-emission tomography is a clinically useful biomarker for the detection, targeted biopsy, treatment planning, and therapeutic response assessment of HNC. This article highlights the current state of ^{18}F-fluorodeoxyglucose positron-emission tomography imaging in HNC management as well as the emerging capabilities of the recently introduced digital photon counting positron emission tomography/computed tomography platform for more effective molecular and functional HNC imaging.
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Introduction

At present, conventional analog photomultiplier tube-based PET (cPET) detectors are routinely used with X-ray computed tomography (CT) for the detection of suspected/occult malignancy, initial staging, treatment monitoring during therapy, restaging after completion of therapy, and the detection of suspected recurrent malignancy and metastatic disease. The most commonly used FDA-approved PET radiotracer in clinical oncology is ^{18}F-fluorodeoxyglucose (FDG), which is a radiolabeled glucose derivative. FDG is administered intravenously and is then taken up by several cancer histologies like squamous cell carcinoma, which is the most common HNC. Conventional PET/CT imaging is used to detect and generate 3D image datasets of the biodistrubtion of FDG inside the body for precisely localizing tumors and metastatic lesions.

Although FDG-PET/CT is used routinely today for the clinical management of HNC patients, there remain several unmet clinical needs for PET/CT imaging like the improved detection of subcentimeter metastatic lesions, improved characterization of indeterminate lesions on PET/CT, and further PET biomarker validation for response assessment during a radiation therapy course and emerging therapies. It is critical for nuclear medicine physicians, radiologists, and radiation oncologists to be diagnostically confident and accurate in the description of a patient's disease burden in order to decide which therapeutic modality is most appropriate for the patient's outcomes. The authors have performed more than 150 intraindividual comparison studies between dPET/CT and cPET/CT systems in oncology patients (NCT02283125). This article will highlight some of those initial experiences with dPET/CT in HNC patients as

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Abbreviations: cPET, conventional positron emission tomography; CRT, chemoradiation therapy; CT, computed tomography; dDPP, digital Dynamic PET Perfusion; DPC, digital photon counting; dPET, digital positron emission tomography; FDG, Fluorine-18-fluorodeoxyglucose; HD, high definition; HNC, head & neck cancer; HPV, human papillomavirus; IJV, internal jugular vein; MRI, magnetic resonance imaging; MTV, metabolic tumor volume; PET, positron-emission tomography; RT, radiation therapy; SD, standard definition; SUV, standardized uptake value; TLG, total lesion glycolysis; ToF, time of flight; UHD, ultra-high definition

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well as emerging opportunities enabled by this new dPET detector technology.

Current State for FDG PET/CT in HNC Management

Initial Staging and Treatment Planning

PET/CT is important for accurately diagnosing and staging locally advanced HNC. FDG PET/CT offers a distinct advantage over other conventional imaging modalities such as contrast-enhanced CT and MRI, because FDG PET provides functional insights into tumor biology and tissue metabolism. A recent meta-analysis showed PET/CT to have a higher diagnostic accuracy than standard conventional imaging with a pooled sensitivity of 89.3% vs 71.6% and a pooled specificity of 89.5% vs 78%, respectively.[1] The main advantage of PET/CT applies to clinically node positive HNC. In a study comparing preoperative imaging and final pathologic stage, PET/CT was significantly more reliable at identifying positive neck disease (ipsilateral and contralateral) when compared to CT and/or MRI ($P = 0.005$). The sensitivity of PET/CT compared to CT and/or MRI to detect nodal metastases was 95% vs 79%, with similar specificity of 90%.[2] It should be noted that PET/CT has a higher false negative rate for detecting nodal involvement in the setting of a clinically N0 neck. A meta-analysis of 11 studies showed that the sensitivity and specificity of PET in cN0 patients was 66% and 87%, respectively, which was not significantly different from nonfunctional imaging modalities.[3] A large prospective study (N = 233) found that PET results led to a change in the therapeutic plan in 13.7% of cases.[4] Incorporating PET imaging data into radiation therapy (RT) planning allows for accurately delineating metabolic gross tumor volumes (GTV_{PET}). Studies have generally found that GTV_{PET} are smaller than GTV guided by CT alone.[5] National Comprehensive Center Network clinical practice guidelines currently recommend pretreatment ^{18}FDG PET/CT imaging for most stage III and IV HNC.

Restaging

The clinical utilization of FDG PET/CT in post-treatment/restaging evaluation of HNC is also well established. The timing of the restaging FDG PET/CT after radiation therapy is critical to minimize false positive findings due to radiation therapy-induced inflammatory changes that contribute to increased FDG uptake in benign tissues. Increased FDG PET uptake in recently irradiated tissues can persist for 12-16 weeks, which limits the ability to discern residual malignant/metastatic disease from benign inflammation using FDG PET.[6] National Comprehensive Center Network guidelines currently recommend waiting approximately 12 weeks before obtaining a restaging FDG PET/CT. In a recent meta-analysis (20 studies, N = 1293) assessing the diagnostic value of FDG PET/CT in detecting nodal disease within 6 months after treatment, the pooled estimates of sensitivity, specificity, positive, and negative predictive values were 85%, 93%, 58%, and 98%, respectively.[7] There is agreement in the literature that FDG PET/CT performed 8-16 weeks after completion of chemoradiation is useful to assess treatment response and to provide prognostic information because it correlates with local control, regional control, and survival.[8] Several studies examined the predictive value of PET for treatment response assessment and found that negative PET/CT results are indicative of a low likelihood of residual disease and thus, can eliminate the need for additional work up or interventions. On the other hand, there is a relatively low positive predictive value for primary and nodal tumors in the post-treatment setting, which is likely influenced (in part) by the lack of specificity of FDG for tumor cells as well as the heterogeneous nature of different HNC.[3] When restaging FDG PET is suggestive of residual tumor, salvage surgery is indicated. Therefore, differentiating residual tumor from postradiation therapy inflammation with high diagnostic confidence is critically important to reduce morbidity from additional unnecessary procedures.

The Impact of HPV-Status in the Management of HNC

HPV-positive (HPV+) tumors respond more favorably to treatment than HPV-negative (HPV−) tumors. Due to differences in tumor biology, the criteria used to evaluate treatment response may need to differ for HPV+ vs HPV− disease. This principle was suggested in the meta-analysis by Helsen et al[7] where post-treatment evaluation of HPV+ tumors was associated with lower sensitivity (75% vs 89%; $P = 0.01$) and specificity (87% vs 95%; $P < 0.005$). Authors suggest that this can be accounted for by the longer duration of time needed to detect the repopulation of a relatively low number of remaining radio-resistant tumor cells, and the increase in cytotoxic T-cell based immune response leading to a slower regression of inflamed nodes associated with HPV + tumors. Huang et al[9] compared 257 HPV-positive (HPV+) and 236 HPV-negative (HPV−) HNC patients with N2-N3 nodal disease treated with RT/chemo-RT. The actuarial LN resolution was similar in the HPV+ and HPV− groups at 12 weeks (42% vs. 43%), but it was higher in the HPV+ group than in the HPV− group at 36 weeks (90% vs 77%, $P < 0.01$). The 3-year recurrence rate was higher in the HPV− complete response (CR) cases vs. non-CR cases (92% vs 63%, $P < 0.01$) but was not different in the HPV+ CR cases vs non-CR cases (98% vs 92%, $P = 0.14$). The authors conclude that HPV+ LNs involute more quickly than HPV− LNs but undergo a more prolonged process to eventual CR beyond the time of initial assessment at 8-12 weeks after treatment. Postradiation neck dissection is advisable for all non-CR HPV−/non-CR N3 HPV+ cases, but it may be avoided for selected non-CR N2 HPV+ cases with a significant LN involution if they can undergo continued imaging follow-up. FDG PET was not routinely available in this study and CT/MRI was most commonly used for follow-up imaging. Further investigation of follow-up FDG PET imaging for HPV+ HNC and how it may differ from HPV− tumors is still needed.

Despite the need to further characterize how to best use PET to monitor HPV+ HNC after treatment, there is evidence that

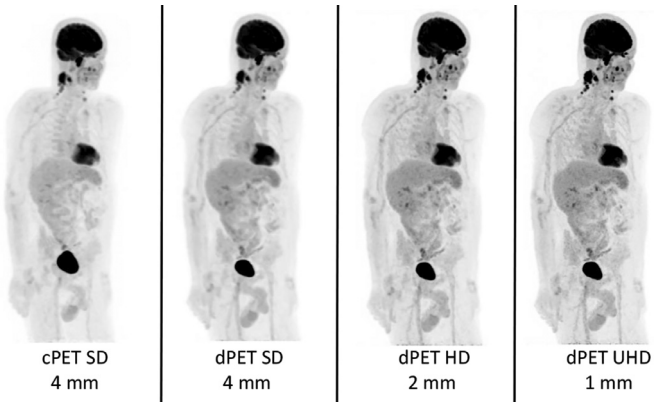

Figure 1 Intraindividual comparison in a HNC patient imaged using a conventional photomultiplier-tube based PET/CT (cPET) (Gemini 64 ToF, Philips) system and a precommercial release digital photon counting PET/CT (dPET) (Vereos, Philips) system with different reconstruction matrix/voxel volume sizes. The patient was intravenously administered a standard dose of 498 MBq of FDG and then underwent imaging on the dPET/CT system at 63 minutes and the cPET/CT system at 86 minutes post injection. Both cPET and dPET emission scans were acquired with 90 seconds per bed position. Although there is a large FDG-avid mass noted in the nasopharynx on both cPET and dPET images, there are subcentimeter nodes in the bilateral cervical regions which are visually more apparent on dPET images and becomes more conspicuous (and more suspicious) with higher definition image reconstructions. Left to right: Maximum intensity projection images from standard definition cPET (SD, matrix size = 144 × 144, voxel length = 4 mm, voxel volume = 4 × 4 × 4 mm^3), standard definition dPET (SD, matrix size = 144 × 144, voxel length = 4 mm, voxel volume = 4 × 4 × 4 mm^3), high definition dPET (HD, 288 × 288, 2 mm, 2 × 2 × 2 mm^3), and ultra-high definition dPET (UHD, 576 × 576, 1 mm, 1 × 1 × 1 mm^3). This case illustrates the capability of higher definition dPET technology to improve lesion detectability especially for subcentimeter nodal lesions without significant impact on background tissue activity.

FDG PET can help to inform decision-making regarding salvage surgery for patients with residual lymphadenopathy. A prospective, randomized controlled trial evaluated the role of FDG PET/CT-guided active surveillance as compared with planned neck dissection in the treatment of patients with squamous cell HNC who have advanced nodal disease (stage N2 or N3) after completion of chemoradiation.[10] This study recruited 564 patients (282 in the planned-surgery group and 282 in the surveillance group) in which 84% of the patients had oropharyngeal cancer, and 75% had tumor specimens that stained positive for the p16 protein (surrogate for HPV+ disease). At a median follow-up of 3 years, PET-CT–guided surveillance resulted in fewer neck dissections than did planned dissection surgery (54 vs 221). The overall survival rate at 2 years was 84.9% in the surveillance group and 81.5% in the planned-surgery group. The hazard ratio for death met the study's prespecified definition of noninferiority ($P = 0.004$) and actually slightly favored PET-CT–guided surveillance (hazard ratio = 0.92). There was no significant difference between the groups with respect to p16 expression. Active surveillance guided by FDG PET/CT resulted in considerably fewer operations and it was more cost-effective.

New PET Technologies, Disruptive Innovations, and Emerging Concepts

The practice of nuclear medicine is intimately associated with imaging technology. Recently, a technical innovation led to the replacement of the conventional analog photomultiplier tube-based PET detectors with solid-state, digital photon counting (DPC) PET detectors.[11,12] As with any technical innovation, improved performance, and potentially disruptive changes can occur when first using these new DPC dPET detectors in a PET/CT system, such as the detection and visualization of a small radiotracer-avid node using the new dPET detector technology that is not clearly visualized with current cPET technology. Another example of disruptive innovation is better delineation of true physiologic radiotracer distribution in small tissue structures like the adrenal and pituitary glands may be erroneously interpreted as discrete malignant/metastatic lesions (ie, pseudolesions). Such disruptive technical innovations in medical imaging require assessment, optimization, clinical translation, clinical validation, and clinical adoption.[13] With regards to disruptive innovations with PET imaging, these are not just limited to new detectors and hardware modifications, but also new PET image acquisition approaches, image reconstruction methodologies and software, and new cancer-specific PET radiotracers. At present, there is a paradigm shift in PET imaging to replace existing cPET detector technologies with next-generation dPET technologies in order to address the unmet clinical needs for oncologic PET imaging.

Lesion Detectability and Higher Definition PET Imaging

The detection of small metastatic lesions (ie, less than 15 mm) is a challenge for radiologists and nuclear medicine physicians

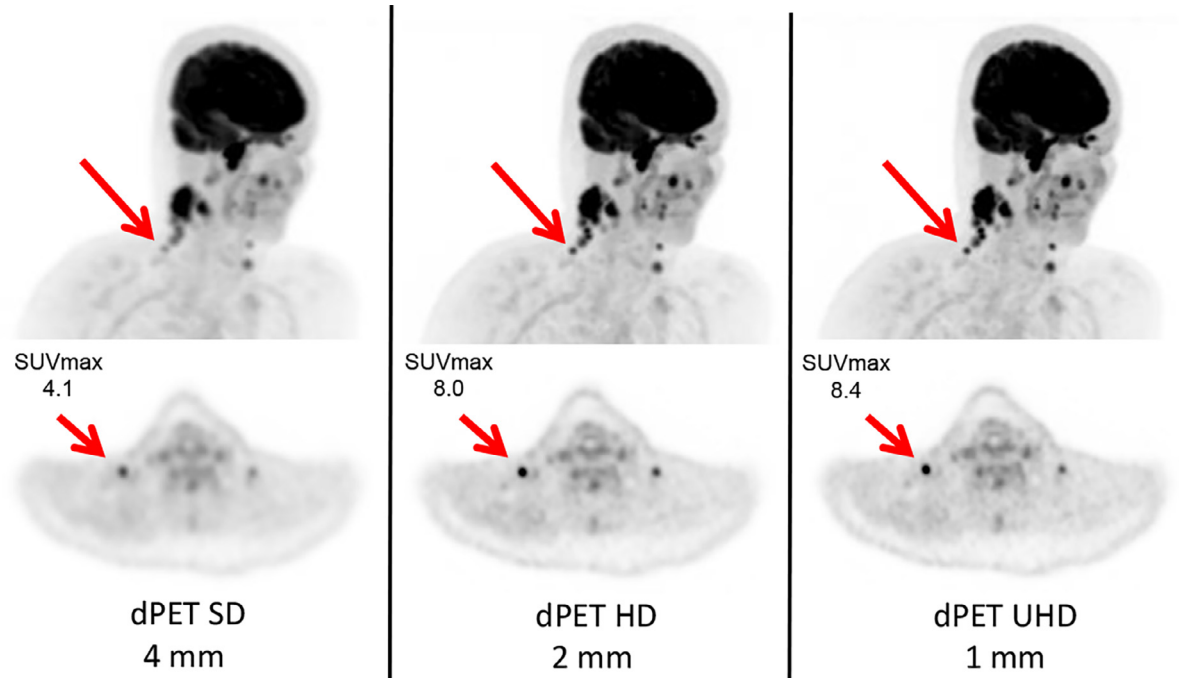

Figure 2 Intraindividual comparison in a HNC patient imaged using a precommercial release dPET/CT (Vereos, Philips) system with different reconstruction matrix/voxel volume sizes. The patient was intravenously administered a standard dose of 498 MBq of FDG and then underwent imaging on the dPET/CT system at 63 minutes post injection. The dPET emission scans were acquired with 90 seconds per bed position. Left to right: Maximum intensity projection images from SD dPET, HD dPET, and UHD dPET. Top: Maximum intensity projection images from the skull vertex through the level of the mid thorax. Bottom: Axial images taken at the level of a subcentimeter lymph node in the right inferior cervical region (red arrows) with associated SUVmax value. Again, there is a large FDG-avid mass noted in the nasopharynx on both dPET images. In addition, there are subcentimeter nodes in the right inferior cervical (red arrow) and bilateral cervical regions which are visually more apparent on dPET images and becomes more conspicuous (and more suspicious) with higher definition image reconstructions. The reduction in partial volume effects with higher definition dPET reconstructions enables more precise localization of FDG activity within subcentimeter lesions contribute to the increased conspicuity of the lesions. Likewise, higher definition dPET reconstructions enable more precise measurement of SUVmax in these subcentimeter lesions.

who interpret FDG PET/CT. Several factors can influence the detectability of a lesion. The FDG-avidity of the underlying tumor biology and the size of the lesion are 2 biological factors that influence lesion detectability. High-grade tumors are usually more FDG-avid than low-grade tumors. Smaller FDG-avid lesions are more susceptible to partial volume effects than larger lesions, which make smaller lesions harder to distinguish from background radiotracer activity. Some technical factors that can affect lesion detectability, include the amount of radiotracer dose administered, the time between radiotracer administration and PET imaging, image acquisition approaches, and image reconstruction methodologies.

At present, most cPET systems reconstruct images using standard definition voxel lengths of 3-4 mm (ie, matrix sizes of 144-200). The new dPET technology has the capability to reconstruct images with smaller voxel lengths of 1-2 mm (ie, larger matrix sizes greater than 200-400) which enable high definition and ultra-high definition PET imaging.[13] The use of these higher definition reconstructions (ie, smaller voxel lengths/larger matrix sizes) decreases the overall voxel volume, substantially reduces partial volume effects, and improves the visual conspicuity of radiotracer-avid lesions (Fig. 1). This is especially true for small radiotracer-avid lesions (Fig. 2). Our team has demonstrated the feasibility of these higher definition dPET approaches (without changing the total PET acquisition time), but these approaches require optimized reconstruction methodologies.[14] Clinically, these optimized higher definition dPET reconstructions not only contribute to better lesion detectability and image quality for subsequent tissue biopsy or radiation therapy planning, but also more precisely quantify FDG activity within metabolically active lesions.

Lesion Characterization and Digital Dynamic PET Perfusion

Although dPET technology can improve lesion detectability with optimized higher definition PET reconstructions, the more precise quantification of radiotracer activity within malignant and metastatic lesions by dPET can also enable better lesion characterization. Another existing challenge for radiologists and nuclear medicine physicians who interpret FDG cPET/CT is the indeterminate lesion or lymph node detected on the anatomic CT images. In some instances,

Table 1 Hopkins 5-Point Qualitative Therapy Response Interpretation Criteria for FDG PET/CT in Patients With HNC

Visual Assessment	FDG Uptake at the Primary Site and Nodes Less Than IJV	Focal FDG Uptake at the Primary Site and Nodes Greater Than IJV But Less Than Liver	Diffuse FDG Uptake at the Primary Site or Nodes is Greater Than IJV or Liver	Focal FDG Uptake at the Primary Site or Nodes Greater Than Liver	Focal and Intense FDG Uptake at the Primary Site or Nodes
Score	1	2	3	4	5
Response Category	Complete metabolic response	Likely complete metabolic response	Likely post-radiation inflammation	Likely residual tumor	Residual tumor

FDG PET can further characterize this indeterminate lesion as either malignant or benign based on its visual FDG avidity. In other instances, such lesions have FDG uptake that is not clearly malignant nor benign (ie, indeterminate on FDG cPET and CT). To this end, the Hopkins 5-point qualitative therapy response interpretation criteria were recently proposed for FDG cPET/CT in HNC (Table 1).[15] FDG cPET/CT studies of HNC patients from a single institution were retrospectively reviewed and interpreted according to the proposed 5-point scoring system. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy of the 5-point scoring assessment were 68%, 92%, 71%, 91%, and 87%, respectively. HPV status and FDG cPET/CT interpretation were the only factors associated with progression free survival and overall survival. Subsequent validation of the 5-point Hopkins criteria demonstrated excellent inter-reader agreement and prediction of progression free survival in HNC patients.[16]

The capability of dPET/CT imaging with higher definition reconstructions can also aid in the evaluation of indeterminate lesions by more precisely localizing FDG activity within smaller voxel volumes, reducing partial volume effects and more precisely quantifying radiotracer activity within a lesion or lymph node on CT imaging.[13] For small metastatic lesions, this reduction in partial volume effects may contribute to visually more conspicuous FDG-avid lesions and higher quantitative PET metrics. For larger heterogeneous lesions (Fig. 3), higher definition dPET may potentially identify areas of high-grade vs low-grade histology within a lesion.

Furthermore, quantitative PET assessment of FDG activity has been traditionally used to compliment the qualitative detection of FDG-avid lesions and provide objective metrics for subsequent comparison of lesions within and between patients. The most widely utilized quantitative FDG PET parameters include maximum standard uptake value (SUVmax), metabolic tumor volume (MTV), and tumor lesion glycolysis (TLG). MTV is defined as the sum of the volume of voxels with an SUV surpassing a threshold value in a tumor; and TLG is the MTV multiplied by the mean SUV. In a large meta-analysis (45 studies, N = 2928) evaluating the clinical value of FDG PET, SUVmax, MTV, and TLG were correlated with overall survival and disease-free survival.[17] MTV/TLG had a higher predictive value than SUVmax. MTV and TLG may be more representative of overall tumor heterogeneity and therefore serve as a more robust means of correlating FDG PET findings with clinical outcomes.

A novel approach for improved lesion characterization enabled by dPET detector technology is digital Dynamic PET Perfusion Imaging (dDPPI).[18] In the dDPPI approach, the patient is first placed on the imaging table within the dPET/CT gantry with the indeterminate target lesion centered in the dPET field-of-view. Continuous dynamic PET image acquisition is then started just prior to the patient's intravenous FDG administration. The dDPP approach allows for the continuous visualization of FDG activity in a specified lesion from the moment of injection to any specified later

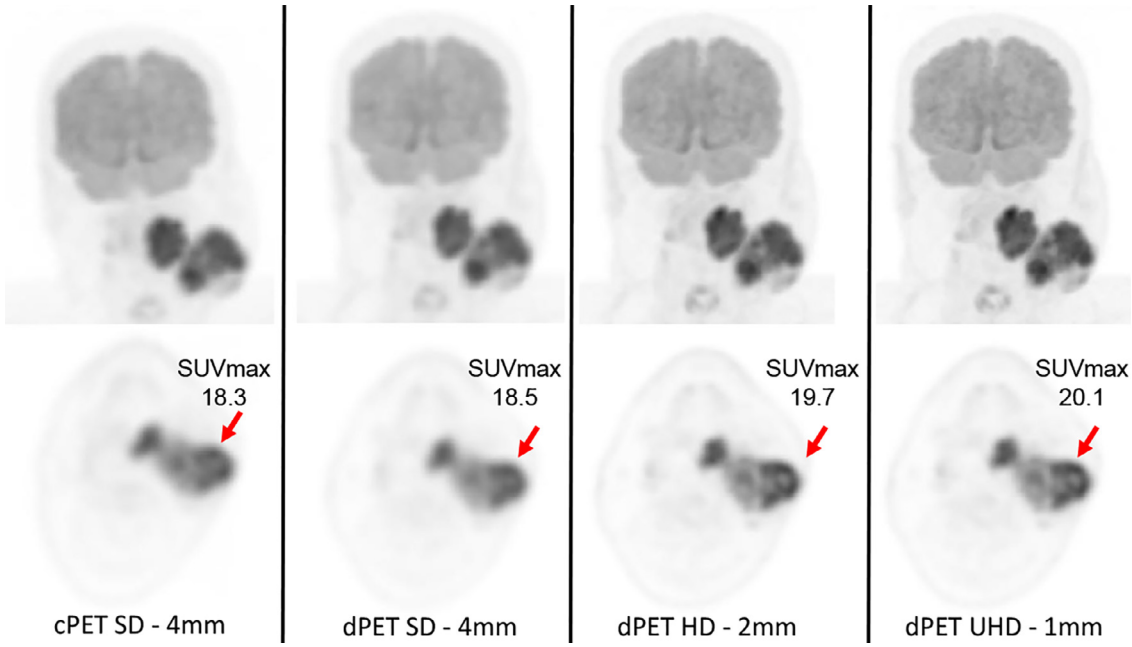

Figure 3 Intraindividual comparison in a HNC patient imaged using cPET/CT (Gemini 64 ToF, Philips) system and a precommercial release dPET/CT (Vereos, Philips) system with different reconstruction matrix/voxel volume sizes. The patient was intravenously administered a standard dose of 474 MBq of FDG and then underwent imaging on the dPET/CT system at 53 minutes and the cPET/CT system at 80 minutes post injection. Both cPET and dPET emission scans were again acquired with 90 seconds per bed position. Left to right: Images from SD cPET, SD dPET, HD dPET, and UHD dPET. Top: Maximum intensity projection images from the vertex of the skull through the level of the larynx. Bottom: Axial images taken at the level of the left cervical lymph node conglomeration with associated SUVmax assessment. There is a discrete FDG-avid mass in the left tonsillar region as well as a large heterogeneous left cervical lymph node conglomeration on both cPET and dPET images. The heterogeneous distribution of FDG activity within the left tonsillar mass and left cervical nodal conglomeration become visually more conspicuous and better delineated with higher definition dPET reconstructions. Again, the reduction in partial volume effects with higher definition dPET reconstructions enables more precise localization of FDG activity within these large heterogeneous lesions as well as more precise SUVmax measurements for FDG-avid components such large lesions.

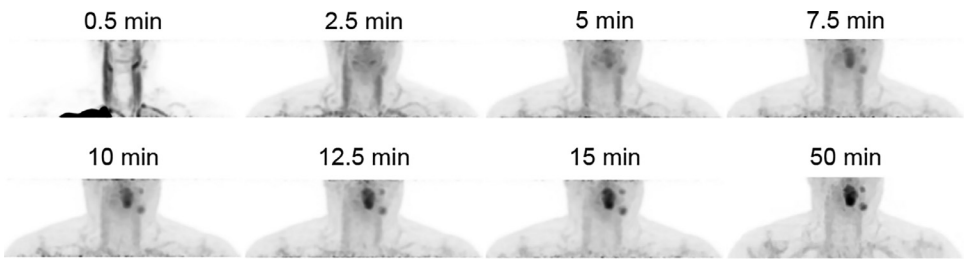

Figure 4 Digital dynamic PET perfusion imaging (dDPPI) in a HNC patient imaged using a precommercial release dPET/CT (Vereos, Philips) system. With the patient on the dPET/CT imaging table and the patient's known left tonsillar mass within the dPET imaging field-of-view, immediate dynamic dPET imaging was started as the patient was intravenously administered a standard dose of 450 MBq of FDG. This limited field-of-view (ie, single bed position) dDPPI was performed continuously for 15 minutes following FDG administration. The patient then underwent whole-body imaging on the dPET/CT system at 50 minutes post injection. The whole-body dPET emission scans were then acquired with 90 seconds per bed position. Maximum intensity projection images from dDPPI acquisition reconstructed into 30 seconds frames using HD dPET reconstructions. Bottom right: Corresponding maximum intensity projection image from the whole-body dPET acquisition at 50 minutes post injection and reconstructed using HD dPET. The dDPPI demonstrates a left tonsillar mass with 2 adjacent left cervical lymph nodes. The lower left cervical lymph node demonstrated early increased perfusion activity at 0.5 minutes post FDG injection. The left tonsillar mass and an upper left cervical lymph node demonstrate increased FDG uptake by 5 minutes post FDG injection. This case illustrates the capability of dPET technology to generate HD dynamic dPET image data sets for the assessment of early perfusion and FDG uptake kinetics which may aid in further characterizing and differentiating target lesions.

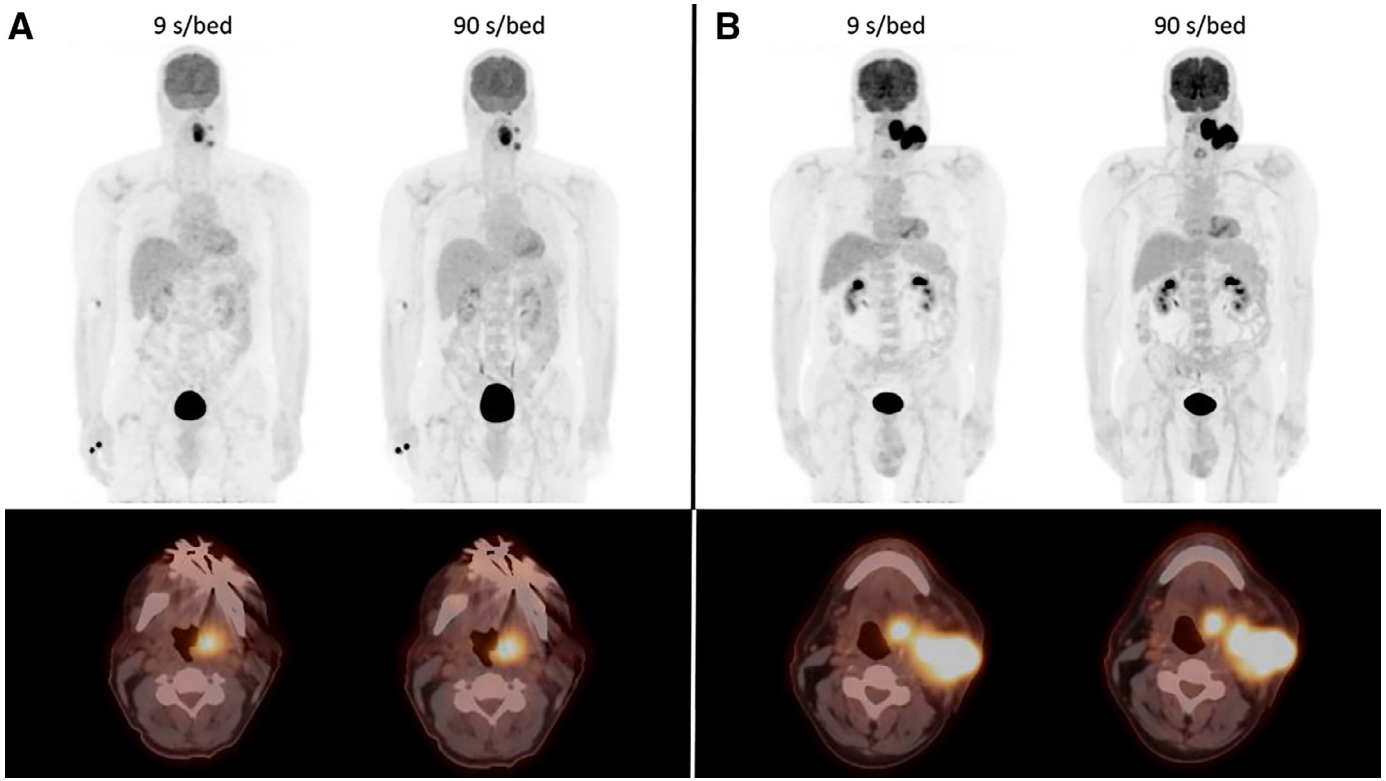

Figure 5 Intraindividual comparison in 2 patients with HNC imaged using a precommercial release dPET/CT (Vereos, Philips) system and acquired with different dPET image acquisition times (ie, standard = 90 seconds per bed position, and ultra-fast = 9 seconds per bed position). (A) The patient was intravenously administered a standard dose of 450 MBq of FDG and then underwent ultra-fast imaging (9 seconds per bed—total acquisition <2 minutes) on the dPET/CT system at 46 minutes post injection followed by standard imaging (90 seconds per bed—total acquisition ~16 minutes) at 50 minutes post injection. (B) The patient was intravenously administered a standard dose of 474 MBq of FDG and then underwent ultra-fast imaging (9 seconds per bed—total acquisition <2 minutes) on the dPET/CT system at 50 minutes post injection followed by standard imaging (90 seconds per bed—total acquisition ~16 minutes) at 53 minutes post injection. Top: Maximum intensity projection images from SD dPET using optimized reconstruction methodologies. Bottom: Axial images from SD dPET taken at the level of the FDG avid left tonsillar lesion for each patient. In both cases, the ultra-fast whole body dPET image acquisition generated visually comparable images that demonstrate the same FDG-avid left tonsillar mass and left cervical nodal metastases when compared with the standard whole-body dPET image acquisition. Furthermore, the background FDG activity is visually similar on the ultra-fast and standard dPET acquisitions. These cases illustrate the capability of dPET technology to markedly reduce dPET image acquisition times for HNC patients while generating visually comparable image quality.

time point (eg, from injection to 15 minutes post injection). The patient would then undergo routine static whole-body dPET/CT imaging at 50-70 minutes post FDG injection in accordance with institutional standard of care. In conjunction with the static whole-body dPET/CT images, the early dynamic dPET time series of the target lesion allows for the detailed assessment of both lesion perfusion and radiotracer uptake kinetics (Fig. 4). In the future, the dDPPI approach may be helpful in characterizing tumor perfusion (ie, hyperperfused vs hypoperfused), tumor differentiation (ie, well-differentiated vs poorly differentiated), and distinguishing between residual malignant disease from postradiation therapy inflammatory change. Such dPET-enabled approaches using higher definition reconstructions and dDPPI for improved lesion characterization will enhance diagnostic confidence and more precisely localize the patient's disease burden.

Opportunities for dPET Radiotracer Dose Reduction and Faster dPET Imaging

The dPET/CT platform is also capable whole-body dPET imaging at significantly lower FDG doses without affecting overall image quality or quantification when compared with cPET/CT. As such, oncology patients undergoing serial dPET/CT evaluations throughout an extended treatment course may appreciate significant overall PET radiotracer dose reductions. Another capability of this new dPET/CT platform is faster whole-body dPET imaging at standard FDG doses or even slightly lower FDG doses with no significant impact on overall image quality or quantification (Fig. 5). Our team has demonstrated the feasibility of (1) FDG dose reductions or (2) dPET image acquisition times by more than 50% without affecting dPET image quality and quantification but these new approaches again require optimized reconstruction methodologies.[19] In general, faster whole-body dPET imaging can help to minimize PET/CT misregistration artifacts from patient motion and maximize patient comfort while lying motionless on the PET/CT imaging table.

Opportunities for Interim dPET Assessment During Radiation Therapy

A number of studies have evaluated the potential role of FDG PET/CT during RT with the goal of discerning favorable or unfavorable metabolic changes in the target lesions earlier in the treatment process. Reliable, early detection may make adaptive strategies to intensify or de-escalate radiation therapy even more feasible (eg, changes in systemic therapy, adapting radiation dose, earlier intervention with salvage surgery). In a recent meta-analysis by Garibaldi et al, the correlation of interim PET findings during CRT with clinical outcomes as well as the predictive value of FDG PET was demonstrated in 5 studies whereas the others did not find any significant correlation.[8] Given that no definite conclusions about the utility of interim FDG PET in HNC management can be drawn from the existing literature, this interim PET strategy has not been introduced into clinical practice. The current challenge of surmising the value of interim PET from the existing literature is the variability in the PET metrics used across studies (including median SUVmax, mean SUVmax, SUVmax reduction ratio, complete PET response, MTV, and TLG), as well as the inconsistency in the time point during radiation therapy in which the interim PET study is performed. Likewise, other challenges in multicenter cancer clinical trials are the variability in PET image acquisition, image reconstruction, image quality, and PET activity quantification that results from PET scanners that utilize different technologies and software. In the future, interim biomarker trials utilizing cPET and dPET platforms will necessitate more consistent image timing, image acquisition and image reconstruction for serial PET assessments. In addition, the incorporation of early dDPPI CT assessmen/CT assessment of HNC patients at initial staging, interim treatment monitoring during RT/CRT, and restaging after RT/CRT may be beneficial in further differentiating treatment responders from nonresponders.

Conclusion

The diagnosis, treatment and management of HNC is complex and requires the collective insights and efforts of several specialties including otolaryngology, radiology, nuclear medicine, pathology, medical oncology, and radiation oncology. This article highlights that FDG cPET is clinically useful in the routine assessment, treatment planning, and management of HNC, but several unmet clinical needs remain to be addressed. In particular, the recent clinical introduction of DPC-based dPET/CT represents a new transformative technology platform to address the needs for improved HNC lesion detectability with higher definition dPET reconstructions, improved lesion characterization with dDPPI, improved quantitative accuracy, faster patient PET imaging, reduced PET radiotracer dose levels, and more effective interim PET assessment strategies that can drive biologically adaptive radiation. Future clinical trials and biomarker validation studies incorporating these new and emerging dPET/CT approaches will likely advance locoregional therapy, response assessment for novel drugs, and overall clinical management strategies for patient with HNC.

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