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PET/MR in Head and Neck Cancer – An Update

Martin W. Huellner, MD

In academic centers, PET/MR has taken the road to clinical nuclear medicine in the past 6 years since the last review on its applications in head and neck cancer patients in this journal. Meanwhile, older sequential PET + MR machines have largely vanished from clinical sites, being replaced by integrated simultaneous PET/MR scanners.

Evidence from several studies suggests that PET/MR overall performs equally well as PET/CT in the staging and restaging of head and neck cancer and in radiation therapy planning. PET/MR appears to offer advantages in the characterization and prognostication of head and neck malignancies through multiparametric imaging, which demands an exact preparation and validation of imaging modalities, however. The majority of available clinical PET/MR studies today covers FDG imaging of squamous cell carcinoma arising from a broad spectrum of locations in the upper aerodigestive tract. In the future, specific PET/MR studies are desired that address specific histopathological tumor entities, nonepithelial malignancies, such as major salivary gland tumors, squamous cell carcinomas arising in specific locations, and malignancies imaged with non-FDG radiotracers.

With the advent of digital PET/CT scanners, PET/MR is expected to partake in future technical developments, such as novel iterative reconstruction techniques and deviceless motion correction for respiration and gross movement in the head and neck region. Owing to the still comparably high costs of PET/MR scanners and facility requirements on the one hand, and the concentration of multidisciplinary head and neck cancer treatment mainly at academic centers on the other hand, a more widespread use of this imaging modality outside major hospitals is currently limited.

PET/MR Protocols

In order to ensure acceptance of a positron emission tomography/magnetic resonance (PET/MR) examination both by patients and by referring physicians, its acquisition time should roughly not exceed the acquisition time of a full head and neck MR protocol. Such a fully diagnostic MR protocol is usually in the range of 30-40 minutes. Furthermore, the PET/MR acquisition time should fit within an examination slot allotted for positron emission tomography / computed tomography (PET/CT).[1-3] A diagnostic PET/MR scan in head and neck cancer patients consists of a regionalized MR scan covering the head and neck, and a whole-body PET/MR scan covering the area from the vertex of the skull to the mid-thighs.[4]

The head and neck MR scan should be acquired preferentially during the last minutes of the uptake phase in order to meet the patient's in-house time with a PET/CT examination. Whenever possible, the regionalized MR scan should be gadolinium contrast-enhanced, with the ulterior motive of providing highest diagnostic accuracy and saving the patient an additional separate MR examination. Examination time may be saved instead by refraining from diffusion-weighted pulse sequences and perfusion-weighted pulse sequences, whose diagnostic yield and clinical impact appear to be limited in the presence of PET data, although controversy exists on this matter.[3,5-7] Time may also be saved by limiting the usually fat-suppressed T2-weighted MR pulse sequences to only one single plane, typically axial, and the T1-weighted contrast-enhanced fat-suppressed MR

Address reprint requests to Martin W. Huellner, MD, Section Head PET/CT/MR Imaging, Department of Nuclear Medicine, University Hospital Zurich/University of Zurich, Raemistrasse 100, CH-8091, Zurich, Switzerland. E-mail: martin.huellner@usz.ch

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pulse sequences to the axial plane and another plane (coronal or sagittal, depending mainly on the location of the primary tumor). Hence, the minimum requirements consist of the following MR pulse sequences: T1-weighted non-enhanced (axial), T2-weighted fat-suppressed (axial), T1-weighted contrast-enhanced fat-suppressed (axial + coronal/sagittal). Specific protocols may vary depending on the exact clinical question, the location and extent of the primary tumor and regional metastases (eg, skull base tumors, sinonasal tumors, possible vessel infiltration).[2,3,8]

The whole-body PET/MR scan usually consists of several bins or body sections of a Dixon-type T1-weighted MR pulse sequence, such as Liver Acquisition with Volume Acceleration (LAVA)-flex, yielding different tissue contrasts, acquired in axial plane, and a T2-weighted MR pulse sequence with or without fat suppression, acquired in a different plane, typically coronal. Each two different MR pulse sequences per body section are acquired simultaneously with the PET scan and their acquisition time therefore not exceed the PET listening time per body section. Since the lung represents the most common site of distant metastases encountered in head and neck cancer patients, it should be addressed by a dedicated MR pulse sequence for lung tissue imaging. Such may be a motion-corrected, respiration-triggered T2-weighted MR pulse sequence using oblique k-space trajectories or periodically rotated overlapping parallel sampling (eg, PROPELLER, BLADE, MultiVane etc.), or MR sequences with ultrashort or zero time to echo.[9-13] If the first type of pulse sequence is obtained, the acquisition frame may be expanded slightly in order to cover the upper abdomen as well. If gadolinium contrast medium is used for the dedicated head and neck MR scan, a second identical axial Dixon-type T1-weighted MR pulse may be acquired after contrast administration, covering the whole-body (Fig. 1).

An overview of results of recent major studies on PET/MR in head and neck cancer is provided in Table 1. In this table, if not specified otherwise, the term "head and neck cancer" alludes to various malignant neoplasms, not limited to squamous cell etiology. If no specific radiotracer is mentioned, then FDG is implied.

T Staging

In the local staging of primary tumor extent and infiltration of adjacent structures, the vast majority of comparative studies reports a draw between PET/MR and PET/CT.[14-26] However, the median number of subjects (n = 35) in these studies is comparably low, ranging from 14 in the study by Partovi et al to 150 in the study by Kuhn et al.[18,24] The latter authors compared contrast-enhanced PET/CT, T2-weighted PET/MR and contrast-enhanced T1-weighted PET/MR of the head and neck. They report slight advantages of both PET/MR techniques over PET/CT for local tumor staging, and particular advantages of contrast-enhanced T1-weighted PET/MR with regard to infiltration of neighboring structures by tumors and perineural tumor spread.[24] Moreover, the assessment of tumors is differently affected by imaging artifacts, depending on their location: Tumors arising in the oral cavity and oropharynx are more affected by artifacts on PET/CT (mainly beam hardening artifacts from dental hardware), while tumors arising in the hypopharynx and larynx are more affected by artifacts on PET/MR (mainly motion artifacts from swallowing).[24]

In a cohort of 35 patients with nasopharyngeal carcinoma, Cheng et al also report superiority of T2-weighted and non-enhanced T1-weighted PET/MR over PET/CT in the local tumor staging.[25] They, however, do not provide data on contrast-enhanced PET/MR. Sekine et al specifically addressed resectability-defining factors, such as vessel encasement, prevertebral space invasion and bone invasion, and report equally favorable performance of contrast-enhanced PET/CT and PET/MR containing a fully diagnostic regional MR protocol.[15] However, the identification of prevertebral space

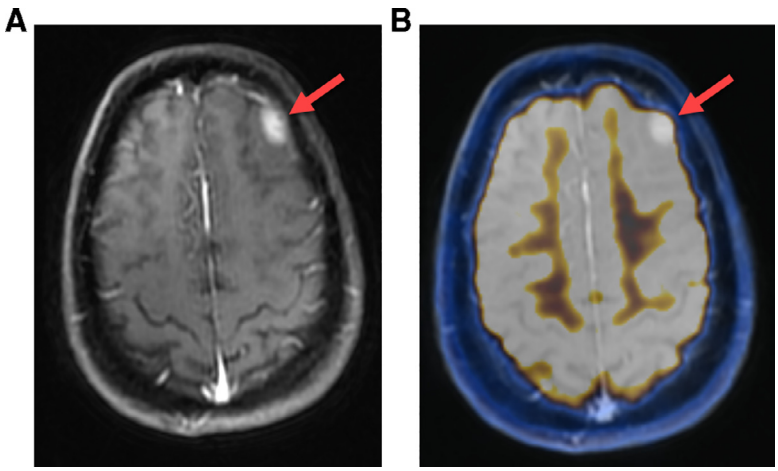

Figure 1 Incidental dural metastasis identified on a whole-body PET/MR scan. While the lesion (arrow) is well seen on the axial contrast-enhanced T1-weighted fat-suppressed MR image (A, LAVA-flex), it is not as easily appreciated on the fused PET/MR image (B, arrow) because its uptake is within the range of normal cortex. Acquisition of this MR pulse sequence takes only approximately 2:30 minutes for the whole body.

TABLE 1 Major Clinical PET/MR Studies on Head and Neck Cancer Since 2015 (Without Non-English Articles and Without Studies Covering Retrospective Fusion of PET and MR Image Datasets)

First Author, Year Published	Study Design	Number of Subjects	PET/MR System	Main Results
Covello et al, 2015[17]	Prospective	44	Biograph mMR, Siemens	High agreement on tumor ROI and PET measures among PET/MR and PET/CT.
Rasmussen et al, 2015[100]	Prospective	30	Biograph mMR, Siemens	FDG uptake parameters in PET/CT and PET/MR are highly reproducible
Schaarschmidt et al, 2016[16]	Retrospective	25	Biograph mMR, Siemens	PET/MR and PET/CT are equal in tumor staging and recurrence detection
Leibfarth et al, 2016[95]	Retrospective	15	Biograph mMR, Siemens	Multiparameteric PET/MR provides substantial different functional imaging data, which may be useful for cancer treatment adaptation
Surov et al, 2016[98]	Prospective	11	Biograph mMR, Siemens	DWI and PET parameters derived from PET/MR are correlated with different histopathological parameters, such as proliferation index and Ki 67 level.
Cavaliere et al, 2017[35]	Prospective	16	Biograph mMR, Siemens	Laryngeal carcinoma: • PET/MR is useful for staging and may help treatment planning. • Significant correlations of PET parameters, DWI-derived parameters and perfusion.
Sekine et al, 2017[14]	Prospective	27	Trimodality PET/CT+MR, GE	PET/MR and PET/CT are equal in whole-body staging of head and neck cancer.
Leifels et al, 2017[96]	Prospective	34	Biograph mMR, Siemens	Head and neck squamous cell carcinoma metabolism, diffusivity and perfusion depend on tumor grading.
Sekine et al, 2017[15]	Prospective	58	Trimodality PET/CT+MR, GE	Contrast-enhanced PET/MR and contrast-enhanced PET/CT are equal in defining local resectability of head and neck cancer.
Rasmussen et al, 2017[58]	Prospective	21	Biograph mMR, Siemens	Radiation therapy planning: • Gross tumor volumes derived by different PET/MR techniques (T2w, FDG-PET, DWI) are similar (82% overlap). • No correlation between FDG uptake and DWI.
Wang et al, 2017[59]	Prospective	11	Biograph mMR, Siemens	Radiation therapy planning: Gross tumor volumes derived by PET/MR and CT are similar.
Chan et al, 2018[22]	Prospective	113	Biograph mMR, Siemens	Nasopharyngeal carcinoma: • T staging: PET/MR «more accurate» than MR in 4/113 subjects (no *P* value reported). • N staging: Equal accuracy of PET/MR (99.3%), PET/CT (96.3%) and MR (98.2%) ($P = 0.87$). • M staging: Similar accuracy of PET/MR (98.9%), PET/CT (97.8%) and MR (97.6%) (no *P* value reported).
Becker et al, 2018[6]	Prospective	74	Ingenuity, Philips	Recurrent head and neck cancer: • PET/MR with DWI: High sensitivity (97.4%) and specificity (91.7%) for recurrence detection after radiochemotherapy. • Excellent agreement between imaging-based T-stage and pathological T-stage (kappa 0.84). • PET/DWI-MRI may facilitate salvage surgery planning in the irradiated neck.

TABLE 1 (*Continued*)

First Author, Year Published	Study Design	Number of Subjects	PET/MR System	Main Results
Kim et al, 2018[72]	Prospective	72	Biograph mMR, Siemens	Combined PET/MR parameters (metabolic volume corrected by cellularity derived from ADC) may predict tumor recurrence after surgery.
Jentzen et al, 2018[61]	Prospective	16	Biograph mMR, Siemens	Thyroid carcinoma: • Neck lesion quantification with ^{124}I-PET/MR is comparable to ^{124}I-PET/CT for activitiy concentrations above 1 kBq/mL.
Kirchner et al, 2019[68]	Retrospective	10	Biograph mMR, Siemens	Adenoid cystic carcinoma: • Higher diagnostic accuracy of PET/MR (91%) vs MR (84%), $P < 0.05$, for detecting locally recurrent adenoid cystic carcinoma. • High negative predictive value of PET/MR (93%) vs MR (73%) considered particularly useful in clinical setting.
Samołyk-Kogaczewska et al, 2019[60]	Prospective	10	Biograph mMR, Siemens	Radiation therapy planning: 30%-40% SUV_{max} works best for gross tumor volume delineation.
Olin et al, 2019[99]	Retrospective	11	Biograph mMR, Siemens	Multiparametric PET/MR imaging analysis of head and neck cancer requires proper preparation of imaging modalities.
Cheng et al, 2020[25]	Not mentioned	35	Trimodality PET/CT+MR, GE	Nasopharyngeal carcinoma: • PET/MR and PET/CT are roughly equal, with slight advantages for PET/MR in analyzing primary tumors and lymph nodes. • No association of PET parameters, DWI-derived parameters and IVIM-derived parameters.
Samołyk-Kogaczewska et al, 2020[29]	Not mentioned	38	Biograph mMR, Siemens	PET/MR superior to CT in T staging and N staging.
Pizzuto et al, 2020[32]	Retrospective	50	Signa PET/MR, GE	Sublingual glands (not mylohyoid muscles) yield highest FDG uptake in normal floor of the mouth.
Dang et al, 2020[97]	Prospective	23	Signa PET/MR, GE	Squamous cell carcinoma: Multiparametric PET/MR may allow prognosticating tumor grading.
Klain et al, 2020[74]	Prospective	40	Biograph mMR, Siemens	Thyroid carcinoma: • PET/MR and PET/CT are equal in following-up patients with elevated serum thyroglobulin levels after thyroidectomy and radioiodine therapy.
Huang et al, 2020[26]	Prospective	20	Signa PET/MR, GE	Hypopharyngeal carcinoma: • T staging: Equal accuracy of PET/MR (81.6%), PET/CT (63.6%) and MR (72.7%). • N staging: Equal sensitivity and specificity of PET/MR, PET/CT and MR.
Park et al, 2020[36]	Retrospective	73	Biograph mMR, Siemens	PET/MR is superior to MR and PET alone in lesion classification in head and neck cancer.

If no radiotracer is stated for a given study, FDG is implied.

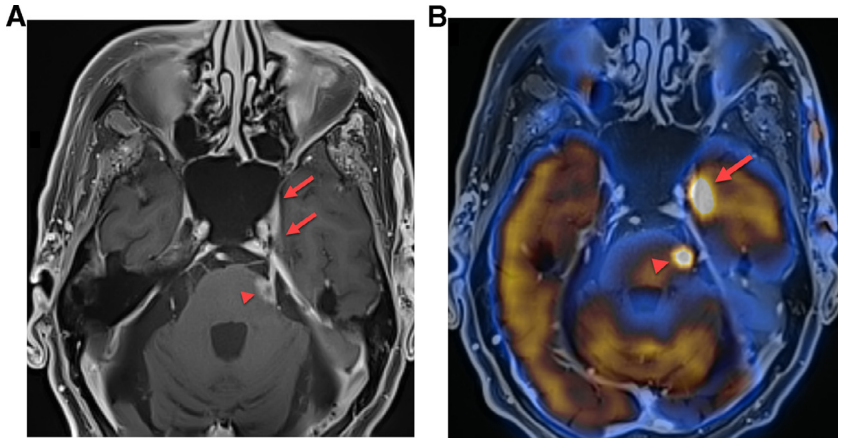

Figure 2 Perineural spread in PET/MR (contrast-enhanced T1-weighted fat-suppressed images). FDG-avid contrast-enhancing tumor extension is seen along the trigeminal nerve in the lateral wall of the cavernous sinus and in Meckel's cave (arrows on A and B), all the way to the thickened cisternal segment of the nerve and the root entry zone in the pons (arrowhead on A and B).

invasion and the differentiation of local tumor recurrence and postradiogenic osteonecrosis remains a challenging task for cross-sectional hybrid imaging, even if intravenous contrast is used.[27,28]

Most available PET/MR studies discuss rather heterogeneous cohorts of squamous cell carcinoma arising in the head and neck, and some studies include non-squamous cell malignancies as well. Data on specific tumor subsites in the head and neck is scarce, as well as specific data on non-squamous cell tumors. Also, some PET/MR studies lack comparative data on PET/CT, which still serves as a standard of reference for oncological cross-sectional hybrid imaging. Samołyk-Kogaczewska et al report superiority of PET/MR over CT imaging in the primary tumor staging of a cohort of mainly moderately differentiated (G2) squamous cell carcinomas of various origins.[29] In a large prospective study on nasopharyngeal carcinoma patients, Chan et al reported PET/MR to be "more accurate" than MR in 4 out of 113 subjects, however, without providing a *P* value.[22] Huang et al recently reported in 20 patients with hypopharyngeal carcinoma that PET/MR performs equally well as PET/CT and MR, with insignificant advantages for PET/MR (diagnostic accuracy: PET/MR 81.6%, PET/CT 63.6%, MR 72.7%).[26] In a small cohort of oral and oropharyngeal carcinoma patients (n = 11), all with histopathological standard of reference, Hayashi et al reported that separately acquired and retrospectively fused PET-MR images facilitate the assessment of mandible and medial pterygoid infiltration, both of which rendering such a tumor either T4 (p16-positive) or T4a (p16-negative).[30] They also report that PET-MR is easy to understand for non-radiologists, such as head and neck surgeons. However, retrospectively fused PET-MR images are known to have inferior registration accuracy compared to simultaneously acquired PET/MR image datasets in head and neck cancer patients.[31] Cavaliere et al in their study on 16 patients with laryngeal carcinoma report that PET/MR has "relevant clinical impact", mainly by assisting in treatment planning (9 of 16 subjects). Endoscopic findings were confirmed in 6 of 16 subjects, while the endoscopic staging of the primary tumor was modified only in one single subject.

The local assessment of head and neck tumors may be challenged by structures that physiologically exhibit 18F-fluorodeoxygluocse (FDG) uptake, such as muscles or salivary glands, and which may be closely related and exhibit similar density on CT. A recent study by Pizzuto et al using PET/MR confirmed that it is in fact the sublingual glands that show physiological high FDG uptake in the floor of the mouth, and not the mylohyoid muscles.[32-34]

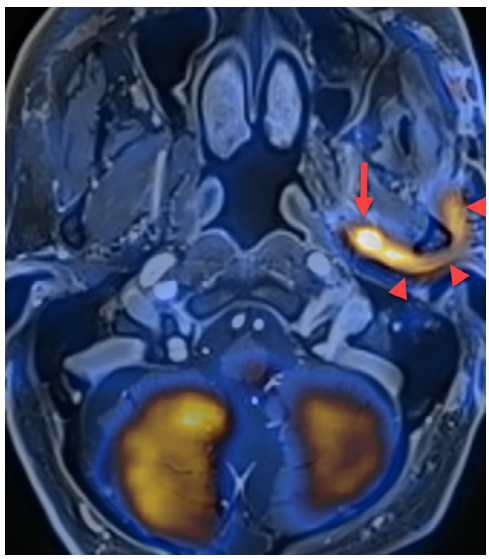

Figure 3 Perineural spread in PET/MR (same subject as in Fig. 2). FDG-avid tumor extension is seen within and below the foramen ovale along the mandibular nerve (arrow), which is the largest of the three major branches of the trigeminal nerve, and further behind the condylar neck of the mandible along the auriculotemporal nerve (arrowheads), which is the posterior and larger division of the mandibular nerve.

Perineural tumor extension refers to tumor growth along nerves and accompanying structures, in the head and neck mainly occurring along larger cranial nerves and their branches, sometimes unto the brain stem (Fig. 2). While the majority of adenoid cystic carcinomas exhibit such perineural spread, owing to their overall greater incidence, it is mainly seen with run-of-the-mill squamous cell carcinomas (Fig. 3). The presence of perineural spread implies a bad prognosis for patients, and may change or preclude a surgical approach and impact on the radiation therapy volume. Nevertheless, it is often overlooked, even in clinically symptomatic patients. Its detection therefore warrants scrutinizing of images. PET/MR generally is believed to surpass both MR and PET/CT in the assessment of perineural spread. However, so far, only a few studies reported on this topic. Kuhn et al state that perineural spread in their cohort of 150 patients with mainly T2 to T4 tumors was detected overall in 7% of subjects with PET, in 2% with MR, and in 1% with CT. They, however, do not provide a direct comparison of PET/MR and PET/CT.[24] Such was done in a study by Sekine et al, who reported perineural spread in 22% of locally advanced squamous cell carcinomas.[15] Here, PET/MR and PET/CT reach equal high accuracy (100% vs 98%, respectively).

N Staging

As with T staging, the majority of PET/MR studies covers mainly unselected cohorts of head and neck cancers. An overall equal performance in comparison with PET/CT is reported.[14,16,18,21,23,24] In nasopharyngeal carcinoma, Chan et al report an equal diagnostic accuracy of PET/MR (99.3%), PET/CT (96.3%), and MR (98.2%) ($P = 0.87$).[22] In the same tumor entity, Cheng et al report a slight advantage of T2-weighted PET/MR imaging over T1-weighted PET/MR imaging in nodal staging[25] (Fig. 4). Also in the nodal staging of hypopharyngeal carcinoma, a tumor entity that frequently exhibits regional lymph node metastases, evidence exists that PET/MR reaches equal sensitivity and specificity as PET/CT and MR.[26] In their study on laryngeal carcinomas, Cavaliere et al do not comment on the N staging, probably owing to the small cohort of only 3 nodal positive subjects out of a total of 16.[35] The larynx, particularly the glottic area with the true vocal cords, is known for its paucity of lymphatics. Not surprisingly, the studies by Park et al and Samołyk-Kogaczewska et al report superior performance of PET/MR compared to MR alone and CT alone in cohorts of squamous cell carcinomas of various origins.[29,36] In their large general head and neck cancer cohort, Kuhn et al claimed that PET/MR without contrast, which in their study performed equally well as contrast-enhanced PET/CT, might hence easily replace PET/CT in patients who cannot receive contrast medium.[24]

M Staging and Second Primary Tumors

Data is somewhat scarce concerning the M staging and the detection of second primary tumors in patients with head and neck cancer that underwent PET/MR. This finding might be due to the overall comparably low median number of study subjects on the one hand, and due to the only approximately 5%-10% of head and neck cancer patients exhibiting distant metastases or second primary tumors at their initial staging on the other hand.[37-39]

Within one year, approximately 10% of head and neck cancer patients develop metachronous distant metastases, increasing to approximately 20% by 5 years.[40] Approximately two thirds of distant metastases occur in the lung, followed by the bone and liver, if cervical soft tissue metastases are excluded.[41] While the lung initially was considered problematic for PET/MR, in oncological populations it actually turned out to work well.[42-44] Dedicated MR pulse sequences for lung imaging used in PET/MR can detect nodules of only 3 mm size on the one hand, while on the other hand nodules

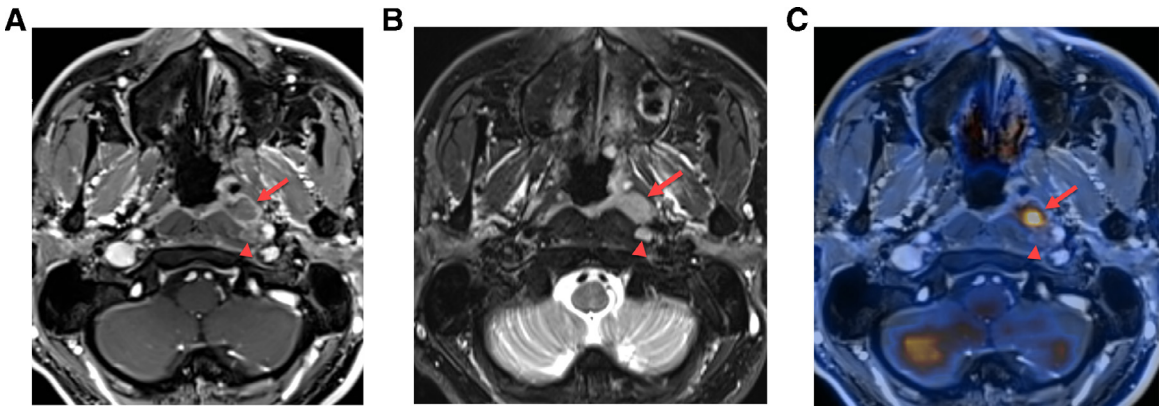

Figure 4 Nasopharyngeal carcinoma. The FDG-avid tumor (arrow) arises in the left-sided fossa of Rosenmüller, as seen on the axial contrast-enhanced T1-weighted fat-suppressed MR image (A), T2-weighted fat-suppressed MR image (B) and fused PET/MR image (C). No infiltration of the prevertebral space by the primary tumor is seen. However, a T2w-hyperintense, FDG-negative lateral retropharyngeal lymph node metastasis (arrowhead) is seen adjacent to the prevertebral muscles, rendering the patient ineligible for surgery.

missed on PET/MR do not grow in 97%, and FDG-*negative* sub-centimeter nodules are benign in >98%.[14,45-47] Novel MR pulse sequence with zero time to echo (ZTE) are becoming available in PET/MR and show promising results for the assessment of lung parenchyma.[11]

A large recent meta-analysis covering more than 450,000 head and neck cancer patients showed that 5% of patients have synchronous second primary tumors, and 13% of patients will have metachronous primary tumors within 2 years' time.[38] The majority of second primary tumors occur in the upper aerodigestive tract, followed by the lung.[38]

Hence, PET/MR might proof valuable in the detection of distant metastases and second primary tumors. Sekine et al had only one single patient with distant metastasis in their cohort of patients referred for initial staging.[14] Partovi et al had a total of 38 distant metastases in their cohort of 14 patients referred mainly for restaging, and report a similar performance of PET/MR and PET/CT in assessing these lesions, but do not specifically comment on staging.[18] Chan et al report similar diagnostic accuracy of PET/MR (98.9%), PET/CT (97.8%), and MR (97.6%) in 113 nasopharyngeal carcinoma patients with a total of 30 distant metastases.

Specific PET/MR data on second primaries in head and neck cancer patients is currently lacking. There is, however, evidence that PET/MR might surpass PET/CT in the detection of hitherto occult primaries particularly in the head and neck region, indicating that PET/MR might also perform well in the incidental detection of second primaries.[48,49]

Radiation Therapy Planning

PET-based radiation therapy planning offers several advantages over conventional morphological radiation therapy planning in head and neck cancer patients.[50-52] The probably most important advantage lies in the more holistic identification of disease extent – not only in the head and neck region but also with regard to distant sites.[52] Using FDG as radiotracer, PET-based radiation therapy planning reduces the risk of geographical miss of radiation delivery to the gross tumor volume in head and neck cancers.[52,53] The use of other radiotracers, such as 18F-fluoromisonidazole (F-MISO) or 18F-fluoroazomycin (FAZA) that serve as biomarkers for hypoxia, may characterize the biological behavior of tumors, identifying tissues that deserve modulated or escalated radiation therapy approaches.[52,54] Other biomarkers important for radiation therapy planning may also be derived from MR imaging, such as the vascularity and permeability of tissues using perfusion-weighted imaging (PWI) or the cellularity using diffusion-weighted imaging (DWI).[6,52] Increasing attention has been paid in the last years to MR-guided radiation therapy systems, which can image and treat cancer patients simultaneously, and first technical studies have recently been published showing the feasibility in head and neck cancer patients.[55-57] For these reasons, PET/MR-based radiation therapy planning appears to be an appealing option in head and neck cancer patients.[6]

However, data on PET/MR-based radiation therapy planning is somewhat scarce. Three prospective studies targeted this topic, with results in radiation therapy planning available in 10-12 patients per study, all examined with FDG.[58-60] Rasmussen et al examined different PET/MR-derived tumor delineation techniques (T2w, FDG-PET, DWI) and reported a similar performance of methods, with 82% overlap of gross tumor volumes.[58] Wang et al state that PET/MR-derived gross tumor volumes also match CT-derived gross tumor volumes, achieving similar radiation doses.[59] Samołyk-Kogaczewska et al focused on which volume threshold of the maximum standardized uptake value (SUV_{max}) serves best for primary tumor delineation and nodal gross tumor volume, reporting best results for 30% SUV_{max} and 30-40% SUV_{max}, respectively.[60]

PET/MR-based radiation therapy planning of the head and neck region in clinical routine requires positioning devices, such as masks and a flat tabletop for the PET/MR gantry, which impedes with the rather narrow gantry gauge of PET/MR scanners. The latter represents still an unsolved issue, limiting the clinical usage of PET/MR for radiation therapy planning of head and neck cancer.

For radioiodine therapy planning, Jentzen et al showed that neck lesion quantification with 124I-PET/MR is comparable to 124I-PET/CT for activity concentrations above 1 kBq/mL.[61] Hence, PET/MR may be used for pre-therapy dosimetry painting in patients with differentiated thyroid carcinoma.[61]

Treatment Response Assessment and Recurrence Detection

The detection of tumor persistence or recurrence within tissues altered by surgery and/or radiotherapy is a challenging task, both for clinicians and for radiologists. Owing to the high intrinsic soft tissue contrast, MR is superior to CT for this task.[62,63] PET/CT in the other hand is believed to be superior to both CT and MR, mainly owing to its high negative predictive value, although familiarity with false-positive findings, such as postradiogenic inflammation or muscle tonicity, is required.[32,64-66] PET/MR, combining the aforementioned advantages of PET and MR, hence may represent an optimal approach to tackle this issue.[67]

Queiroz et al in their study on 87 patients found that PET/MR and PET/CT overall perform equally well in local recurrence detection, but explicitly mention that PET/MR specifies focal FDG uptake better than PET/CT, thereby decreasing false-positive results.[20] Both Sekine et al and Schaarschmidt et al also report similar performance of both modalities in the restaging of head and neck cancer patients.[14,16] Becker et al in 74 patient with recurrent head and neck cancer report high sensitivity (97%) and specificity (92%) for recurrence detection after radiochemotherapy using PET/MR including DWI, and an excellent agreement between the T stage

derived by PET/MR imaging and the one derived by pathology (kappa 0.84).[6]

In a small but selected cohort of patients (n = 10, with a total of 32 examinations) with locally recurrent adenoid cystic carcinoma, Kirchner et al reported higher diagnostic accuracy of PET/MR compared to MR (91% vs 84%, respectively).[68] They claimed that particularly the high negative predictive value of PET/MR compared to MR (90% vs 73%, respectively) may be beneficial in clinical routine. This finding is not surprising, since adenoid cystic carcinoma usually exhibits comparably low but visible FDG uptake on the one hand and frequently comes with small regional lymph node metastases on the other hand.[69-71] Hence, PET/MR may be an optimal approach in this setting. The authors, however, did not address extracervical recurrence, and adenoid cystic carcinoma is notorious for developing slowly growing lung metastases within 2-5 years' time. Hence, a side-by-side comparison with PET/CT would be desirable to properly assess the value of PET/MR for this type of tumor.

In a prospective study analyzing 72 patients before treatment, Kim et al identified several PET/MR-derived biomarkers as predictors of recurrence after surgery, among them the metabolic tumor volume, the ratio of metabolic tumor volume and mean apparent diffusion coefficient (ADC_{mean}), and the ratio of total lesion glycolysis and ADC_{mean}.[72] Another recent study used retrospective PET-MR fusion and found combined FDG-PET/MR parameters (volumes derived from DWI and FDG-PET) to predict clinical outcome in rhabdomyosarcoma patients.[73] Hence, combined PET/MR parameters may have prognostic capability in head and neck cancer patients.

Thyroid cancer, orphan tumors, and non-FDG radiotracers

FDG-PET/CT represents the most accurate imaging modality in the staging and restaging of patients with differentiated thyroid carcinoma of an aggressive histology, with radioiodine-negative malignant lesions, or in patients with increased thyroglobulin serum concentration in the absence of pathologic imaging findings.[74] A recent study by Klain et al in 40 patients proved equal performance of PET/MR and PET/CT in following-up 40 subjects with differentiated thyroid cancer and elevated thyroglobulin levels.[74] Jentzen et al covered the potential of pre-therapeutic dosimetry painting in patients with differentiated thyroid carcinoma using 124I-PET/MR (for details, please see above).[61]

Specific PET/MR studies on major salivary gland tumors are currently lacking. It is expected that PET/MR might be useful for the work-up of such lesions, owing to the large variety of tumor entities arising in this location and their heterogeneous MR signal characteristics and uptake characteristics (Fig. 5).

Pourmehdi Lahiji et al reported that the overlap of hypermetabolism plus restricted diffusion predict unfavorable outcome in pediatric and adolescent patients with rhabdomyosarcoma of the neck.[73] These authors, however, used separately acquired PET and MR image datasets that were retrospectively fused by software. To date, no data on PET/MR using FDG, DOTA-peptides or 18F-dihydroxyphenylalanine in paragangliomas of the head and neck exist. However, a single case of a retroperitoneal pheochromocytoma imaged with FDG-PET/MR was reported in a study on succinate dehydrogenase mutation-related pediatric pheochromocytomas and paragangliomas.[75] The generally lower radiation exposure with PET/MR compared to PET/CT is another indisputable advantage, particularly in the pediatric and adolescent population.

A favorable performance of 18F-choline PET/MR has been reported in patients with primary hyperparathyroidism and hitherto occult parathyroid adenomas or hyperplasia.[76-78] No data currently exists on 18F-choline PET/MR in parathyroid malignancies (Fig. 6).

Technical Issues

Motion Correction in PET/MR in Head and Neck Cancer Patients

In head and neck cancers patients, motion affects image quality most often in two ways: First, repetitive, predictable and unidimensional movement of the chest and upper abdomen due to respiration, and second, non-repetitive, unpredictable and multidimensional bulk movement in the head and neck. Both types of motion impact on PET and MR data.

Since the lung represents an important distant site in head and neck cancer patients with regard to metastases and

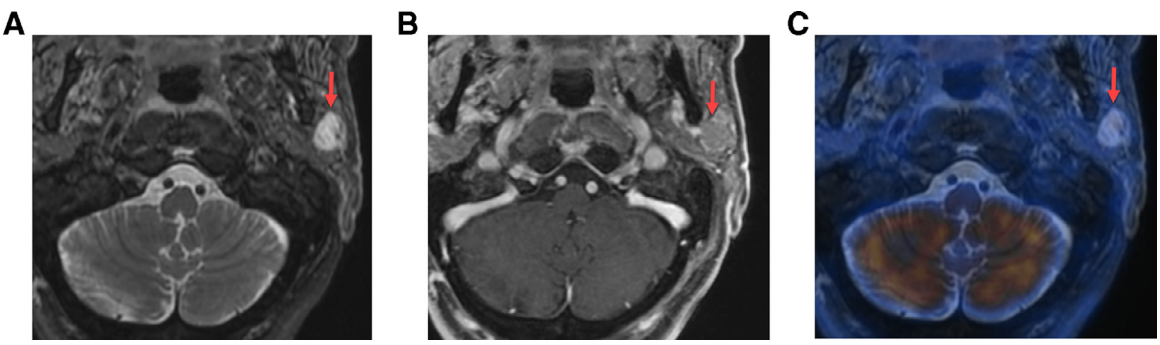

Figure 5 Acinic cell carcinoma of the parotid gland. The well-defined tumor (arrow) is T2w-hyperintense (A), enhances only little contrast medium if any (B) and is FDG-negative (C).

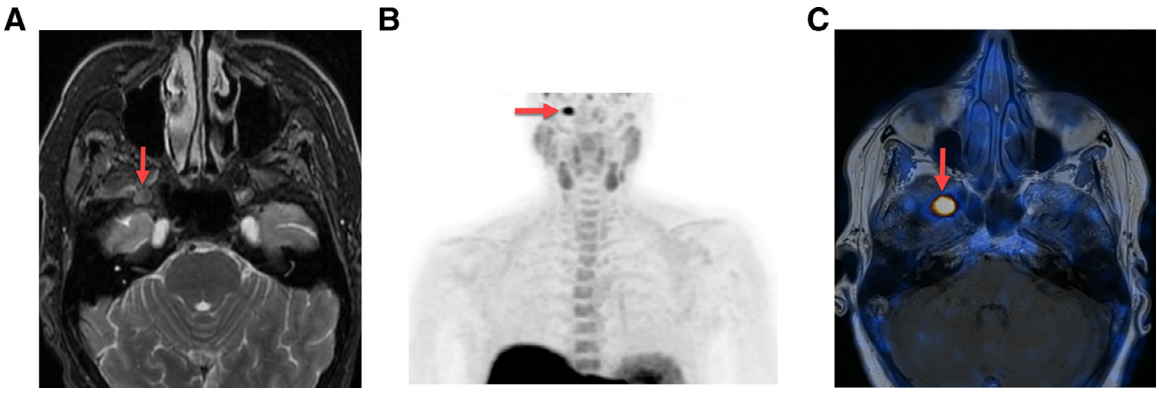

Figure 6 Parathyroid carcinoma metastasis in a patient with relapsing parathyroid hormone increase five years after parathyroidectomy. A well-defined roundish T2w-hyperintense (A) lesion (arrow) is seen in the right-sided skull base, exhibiting intense 18F-choline uptake on the coronal maximum intensity projection (B) and on the retrospectively fused axial nonenhanced T1-weighted nonenhanced PET/MR image (C). The lesion was resected and confirmed by histopathology.

second primary tumors, a proper consideration of motion is desired here. Since the acquisition of images covering the whole chest (approximately 6 minutes) exceeds patients' breathhold capability, all clinical MR pulse sequences for lung imaging (eg, T2-weighted propeller, ZTE) use gating devices that recognize the respiratory cycle and allow image acquisition during the quiescent phase.[9,10,42,45] Such devices are typically external ones placed on the patient, such as bellows, but image-based tracking has been used as well.[18,79,80] External gating devices have also been used for motion correction of PET, either bellows or reflecting markers and infrared cameras. Beyond being time consuming and somewhat uncomfortable for patients, this technique has several drawbacks. Most importantly, motion can only be corrected for in one single bed position, which must be prescribed before the scan. Also, technical failure may spoil the whole acquisition. In recent years, novel deviceless gating techniques were developed that rely solely on PET data.[81,82] These techniques outperform external gating methods.[81] In brief, PET coincidence data is broken down into dynamic sinograms. A principal component analyses then decomposes these sinograms into a set of components with the maximum variation in data over time. Finally, a Fourier transformation of these components identifies respiratory motion, generating waveforms and triggers. If significant motion is detected, it is automatically corrected.[83] This software-based method today is only available with PET/CT scanners, but is expected to be implemented in PET/MR scanners as well.

Things are more complicated with bulk motion of the head and neck, which is typically nonrepetitive, unpredictable and may occur in more than one direction. Software-based solutions for PET are expected to solve this problem in the future.[84,85] Unlike PET, MR acquisition is typically repeated if it is spoiled by bulk motion, but correction methods exist as well.[84] The combination of PET and MR bulk motion correction techniques might amend the known swallowing-related shortcomings of PET/MR compared to PET/CT that are encountered in the larynx and hypopharynx.[24]

Dental Artifacts

Artifacts elicited by dentures and other metallic dental work are known to impact on PET/MR image quality, both by distorting the MR-based attenuation correction of PET emission data, and by spoiling MR image quality. Ladefoged et al showed in 148 PET/MR patients that dental hardware leads to severe MR signal voids, and that the resulting PET/MR artifacts exceed the volume of dental hardware.[86] This causes severe bias in PET data in and near to the signal voids, affecting the conspicuity of lesions in the jawbone.[86] Gunzinger et al in a study with 25 subjects have shown that MR pulse sequences with multiacquisition variable-resonance image combination might be useful for the reduction of artifacts elicited by dental implants in PET/MR, potentially improving the diagnostic accuracy in patients with oral and oropharyngeal carcinoma.[87]

MR-based Attenuation Correction in the Head and Neck

In the same study, Gunzinger et al have also shown that relative errors in SUV calculation through MR-based attenuation correction are negligible for simulated artifacts of 0.5 cm size, but become substantial (relative error -33%) if the artifact size is increased to 5.2 cm.[87] Ladefoged et al report an MR-based volume of susceptibility-induced signal voids on the MR-AC attenuation maps to range between 1.6 and 520.8 mL.[86] They also report significant underestimation of SUV that is correlated with the volume of the susceptibility artifact on the MR attenuation map, decreasing with the distance to the signal void.[86] Both of these studies used Dixon-type MR pulse sequences for MR-based attenuation correction. Wiesinger et al used ZTE-based pseudo-CT image conversion in the whole head for this purpose.[88] They report this method to be accurate, robust and fast.[88]

PET Image Reconstruction Techniques

A novel PET image reconstruction technique relies on a Bayesian penalized likelihood reconstruction algorithm (block sequential regularized expectation maximization [BSREM]).[89,90] It yields reportedly higher signal-to-noise ratio and higher SUV compared to conventional ordered subset expectation maximization in mediastinal lymph node assessment, but does not improve the accuracy of N staging.[91] Another study showed that artificial intelligence using deep learning yields better results in lung nodule assessment with BSREM compared to ordered subset expectation maximization.[92] While BSREM is used on many digital PET/CT scanners, it is also increasingly available on PET/MR scanners.[93] To date, no results have been published concerning the use of BSREM in PET/MR in head and neck cancer patients.

Functional MR Techniques and Multiparametric PET/MR

In a clinical setting, Queiroz et al have shown that the addition of DWI does not provide additional value for the staging of 70 head and neck cancer patients with PET/MR, while Becker et al pointed out that DWI might be particularly useful to detect local tumor recurrence.[5,6]

Most research questions about multiparametric PET/MR using different functional MR techniques in conjunction with PET revolve around the additive value of such techniques and their use as surrogate markers – alone or in combination – for different endpoints, such as biological characteristics and behavior of tumor, its responsiveness to therapy, as well as the disease-specific survival of patients. Hitherto published PET/MR studies in head and neck cancer cover DWI, perfusion-weighted imaging and intravoxel incoherent motion. These studies report different and partly contradicting results.

Varoquaux et al and Leibfarth et al found no association of PET parameters and DWI-derived parameters in primary tumors; both techniques might therefore be complementary.[94,95] Leifels et al reported different correlations of PET parameters with DWI parameters and PWI parameters in 34 patients with head and neck cancer, which are related to tumor grading.[96] Dang et al reported a correlation of PET parameters with PWI parameters, but not with DWI parameters in 23 patients, stating multiparametric PET/MR might predict tumor grading.[97] Surov et al in a study with 11 subjects stated that primary tumor PET parameters and DWI parameters from PET/MR are correlated with different histopathological parameters, such as the proliferation index and the Ki 67 level.[98] Kim et al reported that a combination of PET parameters and ADC may predict treatment failure (see above).[72]

Caution is warranted when interpreting the results of these studies. Beyond the rather small median number of subjects which might limit the significance of results, comparability of data might also be affected by the lack of inter-scanner harmonization, different acquisition and reconstruction techniques, and different preparation methods or the omission of such. Olin et al showed that incorporating point spread function modelling into PET image reconstruction affects tumor quantification (10%-20% increase in SUV).[99] DWI geometric distortion can be reduced by correction methods. Both parameters sets are influenced differently: While the PET reconstruction technique (point spread function) has little influence on spatial correlation with DWI, distortion correction of DWI significantly affects the spatial correlation with PET.[99] Hence, in order to properly conduct, analyze and interpret multiparametric PET/MR studies of head and neck cancer, an appropriate preparation of the imaging modalities is essential.[99]

Summary

PET/MR is a valid and clinically accepted imaging tool in the head and neck. Overall, it provides at least equal diagnostic accuracy as PET/CT, offering advantages over PET/CT in specific clinical situations, besides the generally lower radiation burden. In the future, specific PET/MR studies are desired addressing specific histopathological tumor entities and specific anatomical subsites in the head and neck, as well as malignancies imaged with non-FDG radiotracers.

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