Research article

Prospective comparative study of MRI including diffusion-weighted images versus FDG PET-CT for the detection of recurrent head and neck squamous cell carcinomas after (chemo)radiotherapy

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ABSTRACT

Objective: This prospective study aims to test if MRI including diffusion weighted images can replace FDG PET-CT in the diagnosis of patients with suspicion of local recurrent head and neck squamous cell carcinomas after (chemo)radiation.

Methods: Seventy-five patients suspected of local recurrence underwent a MRI and a FDG PET-CT. Qualitative assessment of the images was performed. Reference standard was the results of biopsy or the absence of a recurrence during follow up.

Results: Seventy patients were included. Fifty percent had local recurrence. FDG PET-CT had accuracy of 71% compared to 73% for MRI. The sensitivity and specificity were 97% compared to 69% and 46% compared to 77% for FDG PET-CT and MRI respectively.

Conclusions: MRI showed similar diagnostic accuracy, superior specificity but inferior sensitivity compared to FDG PET-CT. Based on current results, we consider MRI including diffusion weighted sequences unable to replace FDG PET-CT as a single imaging modality when local recurrent disease of HNSCC after (C)RT is suspected.

1. Introduction

Patients with head and neck squamous cell carcinomas (HNSCC) are often treated with radiotherapy with or without chemotherapy ((C)RT). Depending on subsite and tumor stage, loco-regional recurrence rates vary from less than 5% up to 55% after (C)RT [1,2]. Early detection of local recurrences is one of the main objectives during follow-up as delayed detection reduces the chance of successful salvage surgery and may decrease survival rates. However, discrimination between local recurrence and post-radiation effects is known to be a difficult clinical problem [3]. Post-radiation effects such as fibrosis, edema and inflammation may mimic tumor recurrence.

In clinical practice, patients with suspicion of local recurrent pharyngeal or laryngeal carcinoma undergo examination under general anaesthesia with taking of biopsies. Actually, a negative biopsy does not exclude a local recurrence due to sampling error. Unnecessary biopsies in previously radiated areas are undesirable as they can lead to wound healing problems [4]. An accurate selection strategy that reduces the number of patients requiring a biopsy without compromising early detection of residual disease is therefore of great interest. Several studies have shown the value of fluorine ^{18}F-Fluorodeoxyglucose (FDG) PET-CT in the detection of local recurrence after (C)RT [5,6]. This technique is reported to have high negative predictive value, but is limited by false positive results due to FDG avidity in inflammation and tissue changes after radiation therapy [7,8].

A different imaging technique in head and neck cancer is diffusion-weighted magnetic resonance imaging (DW-MRI). DW-MRI is described to accurately discriminate malignant lesions from benign, [9,10] and

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DW-MRI might be superior to PET-CT in the detection of local recurrences [11–13]. The present prospective study aimed to investigate if MRI including DW-MRI could replace PET-CT for the detection of local recurrent HNSCC after (C)RT in patients with clinical suspicion of local residual or recurrence disease by comparing the diagnostic accuracy of (DW-)MRI and FDG PET-CT.

2. Methods

The institutional ethical committee approved this study and written informed consent was obtained from all participants. Prior to the inclusion of the first patient the prospective trial was registered in the Netherlands Trial Registry (http://www.trialregister.nl, NTR3172).

2.1. Patients

Seventy-five patients were consecutively and prospectively included in this study between April 2011 and November 2014. Patients clinically suspected of local recurrence after (C)RT for HNSCC underwent as standard procedure an FDG PET-CT and an additional investigational MRI with diffusion-weighted MRI. Inclusion criteria were patients with laryngeal, hypopharyngeal or oropharyngeal cancer with clinical suspicion of local recurrence between 3 months and 3 years after the end of primary (chemo)radiation with curative intent. Oropharyngeal tumors received 69 Gy in 33 fractions in 6 weeks. Small glottic tumors received 60 Gy in 25 fractions in 5 weeks. In all other cases a total dose of 70 Gy in 35 fractions in 7 weeks was given. In case of concurrent chemotherapy 100 mg/m^2 intravenous cisplatinum was added at day 1, 22 and 43. In case of contraindication for chemotherapy the radiation was combined with cetuximab. Clinical suspicion of local recurrence was defined by presentation with new, persistent or progressive symptoms, or suspicious findings during physical examination. Patients in whom, based on physical examination, local recurrence was so obvious that there was no reasonable doubt were not included in this study. Reporting was done in accordance to the STROBE statement [14].

2.2. Imaging

MRI was performed on a 3 T unit (Intera NT, Philips Medical Systems, Best, The Netherlands) using a dedicated head and neck coil. The conventional MRI included a transverse T1-weighted turbospin-echo (TSE) before and after gadolinium, a transverse and coronal T1-weighted spectral presaturation with inversion recovery (SPIR) after administration of gadolinium and a transverse and coronal proton density SPIR. Echo-planar DW-MRI was performed in the transverse plane. Four diffusion gradient b values (0, 100, 500 and 1000 s/mm^2) were applied in three orthogonal directions, minimizing the effects of diffusion anisotropy. See Table 1 for the imaging parameters.

The FDG PET-CTs were performed on a whole body PET-CT scanner (Biograph mCT, Siemens Medical Systems, Erlangen, Germany) approximately one hour after injection of 2.0 MBq/kg of ^{18}F -FDG after a 6-hour fasting period. First, dedicated head and neck imaging was performed with the arms placed beside the body to minimize artifacts in the head and neck area. Subsequently, a whole body scan was performed ranging from the shoulders to the upper thigh with the patient's arms placed above the head. PET acquisition was preceded by a low dose CT scan (40mAs, slice thickness 3 mm). CTs were non-contrast enhanced. PET images were acquired in 3D mode with Time of Flight for 4 min per bed position for the head and neck scan and 3 min per bed position for the whole body scan. High resolution PET reconstructions were made with FWHM of 5 mm (whole body scan) or FWHM 4 mm (head/neck scan), 4 iterations and 21 subsets.

2.3. Image assessment

The MRI including DW-MRI and the FDG PET-CT scan were

Table 1
Imaging parameters.

	ST (mm)	S	IG (mm)	TR (ms)	TE (ms)	FS	M	FOV (mm^2)
Transverse T1w TSE	4	33	0	653	16	–	268 × 211	240 × 218
Transverse PD TSE SPIR	4	33	0	2818	25	SPIR	240 × 183	240 × 200
Coronal PD TSE SPIR	3	30	0.3	2486	25	SPIR	220 × 171	220 × 196
Transverse T1w TSE Gd	5	43	0.8	653	16	–	240 × 209	240 × 220
Transverse T1w TSE SPIR Gd	4	33	0	703	16	SPIR	240 × 192	240 × 222
Coronal T1w TSE SPIR Gd	3	30	0.3	703	16	SPIR	220 × 175	220 × 196
Transverse DWI EPI SPIR	4	27	1	2588	68	SPIR	116 × 116	230266

ST: slice thickness, S: number of slices, IG: intersection gap, TR: repetition time, TE; echo time, FS: fat suppression, M: matrix, FOV: field of view, TSE: turbo spin echo, Gd: gadolinium, PD: proton density, SPIR: spectral presaturation with inversion recovery, DW: diffusion weighted, EPI: echo planar imaging, STIR: short tau inversion recovery.

independently reviewed. The FDG PET-CT scan was assessed by a nuclear medicine physician with 5 years of experience in head and neck PET-CT scanning (J.H.). The MRI was assessed in consensus by a radiologist, with more than 15 years of experience in head and neck imaging, and an ENT resident, with 4 years of experience in head and neck (DW-)MRI (F.A.P. and J.P.D.). MRI was interpreted by a combination of all available MRI images (conventional images, DW-MRI images and ADC map). Both DW-MRI and FDG PET-CT were assessed based on qualitative/visual analysis: measurement of apparent diffusion coefficient (ADC) or standard uptake value (SUV) was not performed. For the DW-MRI hyperintense signal on the heavily diffusion-weighted image with a b-value of 1000s/mm^2 with corresponding low signal in the ADC map was considered as local recurrence. A low signal was defined as visibly low diffusion coefficients compared to surrounding tissue. Absence of this low signal on the ADC map was considered as local control. Only the primary tumor site was evaluated, lymph nodes were not a subject of this study. Clinical information and all previous imaging, including pre-treatment imaging were available of the patients. Reviewers of the MRI were blinded to the FDG PET-CT scan and vice versa, all reviewers were blinded to the clinical outcome. Cases could be scored as local recurrence, local control or inconclusive. A conservative approach was adopted with 'inconclusive' scorings treated as 'local recurrence' for all following steps.

2.4. Added value

Adding the results of both modalities was done in two ways: 1 - An approach which will increase the sensitivity, where patients were considered to have a local recurrence on imaging if one or both of the modalities were positive; and 2 - an approach which will increase the specificity, where only patients who had a positive FDG PET-CT combined with a positive MRI were considered to have local recurrence.

2.5. Reference standard

The local outcome of the patients was determined as follows: If at least one of the imaging modalities was suspicious for a local recurrence, investigation under general anesthesia was performed with

biopsy of the primary tumor region. If this biopsy was negative, or if both imaging modalities were suggestive of local control, disease free follow-up of 6 months was considered reference standard for local control. During the 6 months follow-up patients had routine bimonthly examinations by their otolaryngologist including direct flexible laryngoscopy. If a renewed suspicion of recurrence arose, additional imaging was performed outside of study protocol. Recurrent disease was scored if patients had biopsy proven local recurrence within this follow-up of 6 months after initial imaging for suspicion of recurrent disease.

2.6. Sample size and statistical analysis

For the use of MRI to be clinically relevant, the positive and negative predictive value of the MRI should be comparable to the current results of FDG PET-CT. We expected 70% of the DW-MRI to be positive for local recurrence based on previous research [12]. To prove a positive predictive value of ≥ 70%, comparable to the current results of FDG PET-CT, with a precision of ~10% we needed to include 75 patients [6,15]. A conservative approach was adopted by treating 'inconclusive' scorings the same as a 'local recurrence' scoring.

Diagnostic accuracy, sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) were calculated for MRI with diffusion-weighted imaging and FDG PET-CT. Sensitivity and specificity were compared with the McNemar test. Data was processed using SPSS (SPSS Inc. v20.0, Chicago, IL, USA) and MedCalc (MedCalc Software v 12.5, Ostend, Belgium).

3. Results

3.1. Patients

Seventy-five patients were included in this study. Five patients were excluded after inclusion due to incomplete imaging or death of the patient without a biopsy or autopsy after imaging. The seventy remaining patients had clinical suspicion of local recurrence based on new or persistent symptoms (including pain, stridor, dysphonia or dysphagia) or findings at physical examination (e.g. edema, irregular mucosal surface or vocal cord impairment). Fifty-one patients were male (73%), the median age was 61 years (range 42–81). Thirty-four patients (49%) had laryngeal, 12 (17%) hypopharyngeal and 24 (34%) oropharyngeal cancer. Primary T stage ranged from 1 to 4b, N stage 0 to N2c. All patients were treated with primary fractionated radiotherapy: radiotherapy alone (n = 50, 71%), combined with cisplatin (n = 11, 16%) or combined with cetuximab (n = 9, 13%). Patients and tumor characteristics are presented in Table 2.

3.2. Histopathology

Thirty-five patients (50%) had local recurrence, of which 31 were histologically proven by the first biopsy after imaging. One patient had initially negative biopsy, but due to persistent clinical suspicion for recurrence within the follow-up of the study protocol, a second endoscopy with biopsy was performed after 4 weeks which confirmed recurrent disease. One patient with local control on FDG PET-CT and (DW-)MRI received an biopsy outside of the study protocol. Finally, one patient with a positive MRI and a positive FDG PET-CT refrained from biopsy. Within the follow-up of this study, this patient had clinical progressive local disease combined with progressive alterations seen on repeated imaging (CT and conventional MRI). Therefore, this patient was considered as having recurrent disease. The remaining thirty-five patients all completed the follow-up period and had no biopsy proven recurrence within 6 months after inclusion for this study. Twenty-one had negative biopsy, and fourteen of these patients had no biopsy, but all these patients had at least 6 months' disease free follow-up (Fig. 1).

Table 2
Baseline patient characteristics.

Variable	N	%
Age (y)[a]	61 (42–81)	
Sex		
female	19	27
male	51	73
Tumor site		
larynx	34	49
supraglottic	17	50[b]
glottic	16	47[b]
subglottic	1	3[b]
hypopharynx	12	17
oropharynx	24	34
AJCC tumor stage		
T1	12	17
T2	20	29
T3	23	33
T4a	14	20
T4b	1	1
Nodal stage		
N0	39	56
N1	7	10
N2a	2	3
N2b	12	17
N2c	10	14
Treatment		
Radiotherapy	50	71
Chemoradiotherapy	11	16
Radiotherapy + Cetuximab	9	13

[a] Median (range).
[b] Percentage within subsite, AJCC: American Joint Committee on Cancer 7th edition.

3.3. Imaging

Median time between MRI and FDG PET-CT was one day (0–31 days). All images were of sufficient quality to be evaluated. For the FDG PET-CT the plasma glucose of each patient was < 10 mmol/l, except for one who had a plasma glucose of 12.5 mmol/l. Seventy-three percent (51/70) of the FDG PET-CTs were positive for local recurrence compared to only 46% (32/70) of the MRI. Two FDG PET-CTs were inconclusive. For the calculation of the diagnostic accuracy, inconclusive imaging results were regarded as positive. FDG PET-CT had a similar diagnostic accuracy compared to MRI (71% for FDG PET CT versus 73% for MRI (p = 0.85)). The sensitivity of FDG PET-CT was significantly superior compared to MRI (97% versus 69%; p < 0.01). The specificity of FDG PET-CT was significantly inferior compared to MRI (46% versus 77%; p < 0.01 MRI had a false negative rate of 31% (11/35) compared to 3% for FDG PET-CT (1/35). See Tables 3 and 4 for the complete results. See Figs. 2 and 3 for examples of the images obtained from two of the included patients.

3.4. Added value

Combining both modalities and using the sensitive method resulted in a sensitivity of 100% and a specificity of 43%. Using the specific method resulted in a sensitivity of 66% and specificity of 80%. The accuracy of the combined tests was almost similar to the individual modalities. The complete results of this analysis are presented in Tables 3 and 4.

4. Discussion

The present study compares FDG PET-CT and MRI including diffusion weighted images regarding the detection of recurrence of oropharyngeal, hypopharyngeal or laryngeal cancer. It shows that MRI has a similar diagnostic accuracy as FDG PET-CT (73% compared to 71%; p = 0.85). MRI has superior specificity but inferior sensitivity
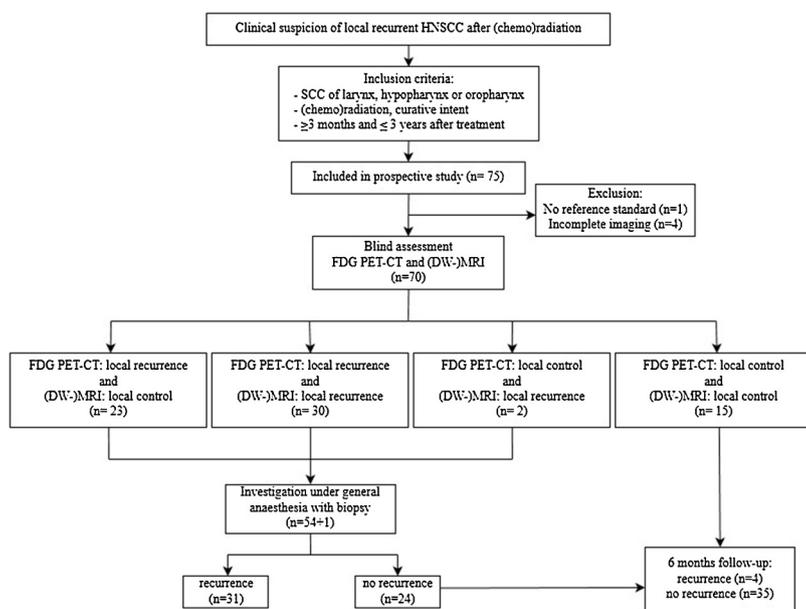
Fig. 1. Flow-chart of study design. Flow of patients. One patient with local control on FDG PET-CT and (DW-)MRI received an biopsy outside of the study protocol, one patient with positive imaging refrained from biopsy and 54 patients received the biopsy as per protocol. SCC: squamous cell carcinoma, DW-MRI: diffusion-weighted MRI.

Table 3
Results of DW-MRI and FDG PET-CT.

Imaging	Local recurrence	Local control
MRI positive	24	8
MRI negative	11	27
PET-CT positive	33	18
PET-CT negative	1	16
PET-CT inconclusive	1	1
Both modalities positive	23	7
MRI positive PET-CT negative	1	1
MRI negative PET-CT positive	11	12
Both modalities negative	0	15

MRI: MRI including diffusion weighted images, PET-CT: 18 F-fluorodeoxyglucose positron emission tomography-computed tomography, for the combination of modalities the inconclusive PET-CT scores are considered to be PET-CT positive.

compared to FDG PET-CT (specificity 77% versus 46%, sensitivity 69% versus 97%; p < 0.01). During follow-up after (chemo)radiation, early detection of residual or recurrent disease is one of the main objectives as salvage surgery might still be a curative option. In this scenario, a high sensitivity is the most important feature of an imaging modality. False negative results of a selection strategy can have tremendous effects; they will cause delay in detection of recurrences, which will potentially influence the chance of successful salvage surgery. Therefore, we consider FDG PET-CT to be superior to MRI including diffusion weighted sequences in the early diagnosis of recurrence of HNSCC after (C)RT.

The complementary effect of both modalities is limited. We found only a small difference in test characteristics between the combined test and the individual modalities. Combining all positive findings of FDG PET-CT and MRI improves the sensitivity for recurrences to 100% where FDG PET-CT alone missed one recurrence. Less desirable was that the same method scored 20 patients erroneously as having a local recurrence: one patient more than FDG PET-CT alone. It is debatable whether the difference in early detection of recurring disease in one patient at the cost of one extra patient with an unnecessary biopsy, justifies a combined use of FDG-PET and MRI.

Few studies report on the diagnostic accuracy of DW-MRI in HNSCC after (C)RT using a visual assessment method for the DW-MRI images. Those that do, show excellent results with accuracies up to 94% [12,16]. Compared to literature our results concerning DW-MRI are somewhat disappointing. This might be because we included patients based on 'clinical suspicion of local recurrence'. This is prone to subjectivity, which might be physician, institution and study dependent. Also the design of this study facilitates the inclusion of very early recurrences and therefore very small lesions which may be under or at the border of the detection limit. DW-MRI suffers from relative low spatial resolution, making it less suitable for detection of very small tumor residues. Partial volume effects will prevent diffusion restriction to stand out at the ADC map. Furthermore, forty-nine percent of the patients in our study had a laryngeal localization of their primary tumor. The larynx, compared to other regions of the head and neck is especially known for movement and susceptibility artefacts. FDG PET-CT, due to its faster acquisition of individual slices, will be more forgiving of movement artefacts such as swallowing and breathing. In addition, differences in methodology between our research and previous studies, such as the use of repeated imaging to detect recurrent or residual tumors by Tshering Vogel et al. [12] compared to our single acquisition
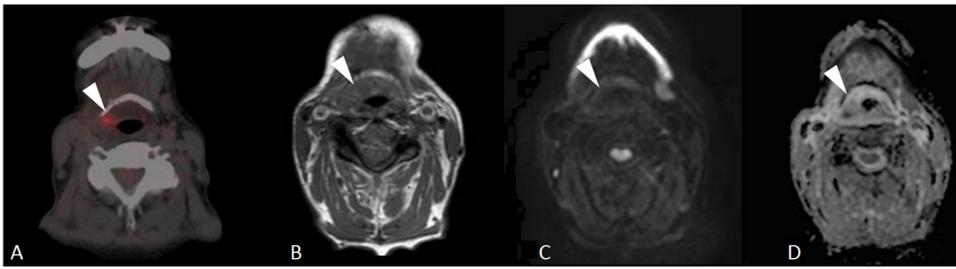
Table 4
Diagnostic accuracy of DW-MRI and FDG PET-CT.

| | FDG PET-CT (95% CI) | MRI (95% CI) | Both modalities combined | |
			Sensitive (95% CI)	Specific (95% CI)
Sensitivity	97% (85–100)	69% (51–83)	100% (90–100)	66% (48–81)
Specificity	46% (29–63)	77% (60–90)	43% (26–61)	80% (63–92)
Accuracy	72%	73%	71%	73%
Positive predictive value	64%	75%	64%	77%
Negative predictive value	94%	71%	100%	70%

DW-MRI: diffusion-weighted MRI, FDG PET-CT: 18 F-fluorodeoxyglucose positron emission tomography-computed tomography.

Fig. 2. (A–D) Example of an included patient. 42-year-old-man with T2N1M0 oropharyngeal carcinoma in the right vallecula. Seven months after radiotherapy he presented with asymmetry in the vallecula and an ulcer in the right vallecula. (**A**) FDG PET-CT shows metabolic activity at the primary site (arrow). This scan was considered as a recurrent carcinoma (**B**) T1w MRI shows swelling of the vallecula at the primary tumor site (arrow). (**C**) DW-MRI B1000 shows no increased signal intensity and no diffusion restriction on ADC therefore it was considered as a local control based on the DW-MRI (**D**, arrow). Histology confirmed recurrence of a squamous cell carcinoma.

approach, might explain the comparatively lower observed accuracy of (DW-)MRI of our study.

Several studies reported on the effectiveness of DW-MRI in detecting recurrences using quantitative measurements instead of visual review [13,17–19]. All report an ADC cutoff value for differentiating treatment induced tissue alterations from recurring tumors. Quantitative assessment yields accuracies of 90% and higher. This is similar to the accuracies reported by the studies were only visual review was used.

In our study, we chose visual e.g. qualitative assessment of DW-MRI instead of quantitative ADC measurements because it most closely resembles clinical practice. Radiologists usually visually score MRIs and base their final decision on the existence of recurrence on a combination of information given by all sequences, rather than based on one solitary measure of for example ADC. Also, quantitative ADC measurements is dependent on the placement of a region of interest within an ADC map, and therefore highly variable with low repeatability. Furthermore, using ADC as a discriminating tool for recurrence or benign lesions also comes with challenges and questions such as which ADC threshold to use and its reproducibility on other type of scanners and protocols [20]. Even though quantitative ADC measures are described to have significantly different mean values in benign compared to malignant lesions, there is extensive overlap between ADC values of malignant and benign lesions [11,21]. This limits its use on individual patients. Qualitative e.g. visual assessment has limitations as well; as it is subjective and might have a learning curve; however, our data of the diagnostic accuracy divided in three time-frames showed no time trends.

Although the high sensitivity of FDG PET-CT is arguably the most important test characteristics when trying to detect a tumor recurrence, the high specificity of DW-MRI could be important in reducing the amount of unnecessary examinations under general anesthesia in future patients. A possible use of DW-MRI is in direct combination with PET using PET/MRI scanners. This is shown by Becker et al. who found an excellent overall diagnostic accuracy using FDG PET/MRI in patients suspected of a local tumor recurrence [22].

One strength of this study is the design, in which biopsy and follow-up of six months served as the reference standard. The extra time frame of six months' disease free follow-up was incorporated to prevent sampling errors of negative biopsies. Indeed, there was one subject in which biopsy was negative at first but turned out positive after 4 weeks

during a second endoscopy because of persistent clinical suspicion of local disease. One could argue that 6 months might be too short, however it cannot be expected that these imaging modalities can detect subclinical recurrence which become manifest more than 6 months after imaging.

Our study has limitations. First, the diffusion-weighted MRI was evaluated in combination with the anatomical images of the conventional MRI. This resembles clinical practice, as the diffusion-weighted images suffer from low resolution and lack anatomical landmarks these images should always be viewed in context of other MRI sequences. Therefore, our results reflect MRI including DW-MRI, and does not study the added diagnostic value of diffusion weighted images to conventional MRI sequences. Secondly, pretreatment imaging of the primary tumor consisted of conventional CT, MRI and sometimes FDG PET-CT. None of the patients had diffusion-weighted MRI as pre-therapeutic imaging, neither was there any post therapeutic baseline imaging available. If these additional examinations had been available they possibly could have made the interpretation of the MRI or FDG PET-CT, at the time of a suspected recurrence, more accurate. Furthermore, the DW-MRI sequence used was echo-planar (EPI) DW-MRI. Image distortion, especially in the head and neck region, might occur with EPI DW-MRI. Other techniques with less image distortion might increase DW-MRI accuracy [23].

The FDG PET-CT protocol in the hospital where this study was performed did not contain intravenous contrast. Contrast enhanced CT images might increase the sensitivity or specificity of FDG PET-CT. Suenaga et al. [24] showed that the addition of a contrast-enhanced CT to a FDG PET-CT protocol has minimal added value in patients with recurring HNSCC. However in their study only 32% of patients received some form of radiotherapy as the initial treatment. It is possible that contrast enhanced FDG PET-CT might be more accurate in this patient group than non-contrast enhanced FDG PET-CT. Finally, not all patients had biopsy as a reference standard, since 14 patients were considered as local control based on negative DW-MRI and negative FDG PET-CT combined with 6 months disease free follow-up. Because of the high negative predictive value of FDG PET-CT we felt that it was ethically incorrect to expose these patients to unnecessary general anesthesia with biopsy.
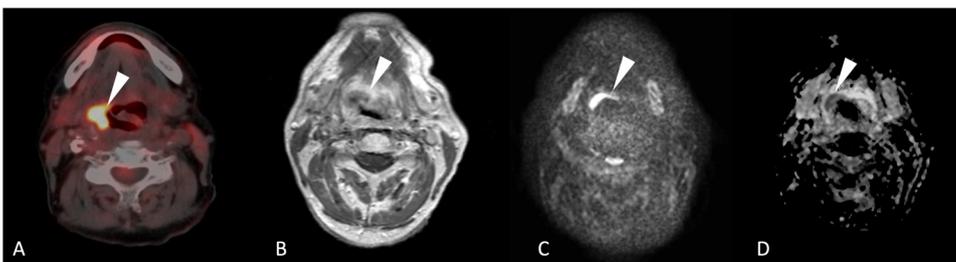

Fig. 3. (A–D) Example of an included patient. 81-year-old-man with T4aN2cM0 oropharyngeal carcinoma in the right base of tongue. Thirteen months after chemoradiotherapy with Cetuximab he presented with progressive otalgia. (**A**) FDG PET-CT shows metabolic activity at the primary site, and therefore it was considered a recurrent carcinoma (arrow). (**B**) T1w contrast-enhanced MRI shows an isointense region at the primary tumor site (arrow). (**C**) DW-MRI B1000 shows increased signal intensity with corresponding diffusion restriction on ADC, and was therefore also considered as a local recurrence based on DW-MRI (**D**, arrow). Histology confirmed recurrence of a squamous cell carcinoma.

5. Conclusion

In conclusion, non-contrast enhanced FDG PET-CT is superior to MRI including DW-MRI in the detection of local recurrent oropharyngeal, hypopharyngeal or laryngeal cancer in patients with suspicion of recurrence after (chemo)radiation. Though having similar accuracies, MRI suffers from more false negative results than FDG PET-CT. When early detection of recurrences is the main goal, false negatives lead to delayed detection and might lead to irresectability and decreased survival rates. The effect of combining FDG PET-CT and MRI is limited but might reduce false negative findings. Based on current results, we consider MRI including diffusion weighted sequences unable to replace FDG PET-CT as a single imaging modality when local recurrent disease of HNSCC after (C)RT is suspected.

Conflicts of interest

None.

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