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HEAD & NECK

FDG-PET/CT improves detection of residual disease and reduces the need for examination under anaesthesia in oropharyngeal cancer patients treated with (chemo-)radiation

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Abstract

Purpose Early detection of residual disease (RD) after (chemo)radiation for oropharyngeal (OPC) is crucial. Surveillance of neck nodes with FDG-PET/CT has been studied extensively, whereas its value for local RD remains less clear. We aim to evaluate the diagnostic value of post-treatment FDG-PET/CT in detecting local RD and the outcome of patients with local RD.

Methods A cohort ($n=352$) of consecutively treated OPC patients at our institute between 2010 and 2017 was evaluated. Patients that underwent FDG-PET/CT at 3 months post-treatment ($n=94$) were classified as having complete (CMR) or partial metabolic response (PMR). PMR was defined as visually detectable metabolic activity above the background of surrounding normal tissues. Primary endpoint was diagnostic accuracy in detecting local RD.

Results Local RD was seen in 19/352 patients (5%), all of them were HPV negative. The FDG-PET/CT had a sensitivity of 100% (8/8), specificity 85% (73/86), PPV 38% (8/21), NPV 100% (73/73), and accuracy 86%. Patients with local RD had significantly worse OS at 2 years, compared to those without (10 versus 88%, $P<0.001$). In multivariable analysis, local RD remained a significant predictive factor for death with a hazard ratio of 11.9 (95% CI 5.8–24.3). The number of patients that underwent PET/CT increased over time ($P<0.001$), whereas the number of patients that underwent EUA declined ($P=0.072$).

Conclusion FDG-PET/CT has excellent performance for the detection of RD, with the sensitivity and negative predictive value approaching 100%. Due to these excellent results is examination under anaesthesia today in the vast majority of the PET-negative cases not necessary anymore.

Keywords Radiotherapy · Head and neck · PET/CT · Chemoradiation · Recurrence · Oropharynx

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Introduction

Organ preservation by means of radiation therapy for head and neck squamous cell carcinoma (HNSCC) has become mainstay since publication of several practice changing trials [1–3]. Results have improved since the addition of cisplatin or cetuximab to radiation and since the introduction of altered fractionation schedules. Nonetheless, a not-negligible proportion of those patients responds inadequately to these treatment schedules and has residual disease (RD). This RD has a significant impact on overall survival (OS) of these patients. An earlier publication [4] showed that patients who underwent salvage treatment for local recurrence or RD had a significantly better OS at 2 years, compared to those where salvage surgery was not possible (70 versus 6%, $P < 0.001$).

Since RD might be successfully salvaged, accurate response evaluation is of utmost importance. The classical backbone of response evaluation is based on imaging combined with physical diagnostic examination, where imaging consists of dedicated contrast-enhanced magnetic resonance imaging (MRI) and/or contrast-enhanced computed tomography (CT). If RD is suspected, the evaluation is complemented with examination under general anaesthesia (EUA) and biopsy, in case of persistant suspicion.

The randomized controlled trial of Mehanna et al. [5] investigated the role of image-guided surveillance by means of PET/CT compared with planned neck dissection 12 weeks after chemoradiation for N2–3 HNSCC. The PET/CT-guided approach resulted in significantly fewer neck dissections compared to the planned dissection (54 versus 221) without jeopardizing outcome. The 2-year OS rates in the surveillance and the planned-surgery group were 84.9% and 81.5%, respectively. Since that study focused on the neck, the remaining pivotal question is whether the PET/CT-guided surveillance of the primary tumor is also reliable to timely and accurately detect RD after (chemo-)radiation.

The aim of this study was to retrospectively investigate the diagnostic value of PET/CT in detecting local RD after (chemo-)radiation for oropharyngeal cancer (OPC), the clinical outcome of patients with RD and to investigate the impact of the introduction of PET/CT on the reduction of the need for invasive diagnostic procedures such as EUA and biopsy.

Patients and methods

All consecutive patients with OPC that underwent (chemo-)radiation at The Netherlands Cancer Institute between 2010 and 2017 were collected.

Treatment

Patients were treated by external beam radiotherapy in supine, immobilized position. All patients underwent a contrast-enhanced CT scan and MRI scan in treatment position. The gross tumor volume (GTV) of the primary tumor and eventual pathological lymph nodes was delineated. The high-dose clinical target volume (CTV_{70Gy}) consists of GTV plus a margin of 1 cm. The low, elective CTV_{46Gy} consists of CTV_{70Gy} plus 5-mm margin. The low, elective CTV_{46Gy} of the neck inlcudes levels I–V in case of N + and level II–IV in case of N0. The planning target volume (PTV) was generated with an isotropic margin of 5 mm around all the CTVs. Since April 2015, 3-mm margin was used to expand the CTV to the PTV. Treatment was delivered using image-guided intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT). Prescribed dose was 70 Gy to the high-risk CTV and 46 Gy (or 54.25 Gy in case of an simultaneous integrated boost) to the low-dose CTVs. Patients with high-risk features (T3–T4, extranodal extension, $N2_c$–N3) received concomitant systemic therapy (cisplatin-based chemotherapy or cetuximab).

Imaging

MRI scan

MRI was performed 3 months after treatment for response evaluation. MRI scans were acquired at 1.5 or 3.0 T on a Philips MRI scanner. The imaging protocol included T1 turbo spin echo-weighted sequences before and after gadolinium injection (TR/TE: 538/10 ms, FA: 90 degrees, slice thickness: 3–4 mm with an 0.5 interslice gap), axial and coronal T2 SPIR-weighted sequences (TR/TE: 3554/90 ms, FA: 90 degrees, slice thickness 3 mm with a 0.3 interslice gap) and 3D Thrive (T1 weighted) sequences after gadolinium injection (TR/TE: 4595/10 ms, FA: 10 degrees, slice thickness: 0.9 mm).

For the primary tumor, the post-treatment MRI was compared to the pre-treatment MRI by a dedicated head and neck radiologist. The response was scored according to a 4-point grading system introduced by Ojiri et al. [6] *Ojiri 0* was scored if no detectable focal abnormalities other than post-radiation changes remained. *Ojiri 1* represented anatomical asymmetry or discrete mass ≤ 10 mm. *Ojiri 2a* meant the presence of a discrete mass > 10 mm and *Ojiri 2b* was scored when the greatest diameter reduced by less than 50%.

18-FDG-PET/CT

PET/CT was performed at 3 months post-treatment in case of a discrepancy between the clinical and radiological findings, because of physician discretion or patients' preference.

Images were acquired using a Philips Gemini TF PET/CT, at 60 +/− 10 min after intravenous administration of 190–240 MBq Fluor-18-FDG. Patients fasted for 6 h prior to the examination, serum glucose was required to be < 10 mmol/l, and during the biodistribution time patients rested in a dimly lit room. The voxel size in the head and neck area was 2 mm. The scanner fulfills the EARL accreditation criteria. Osirix version 7.0.3 was used for the PET analysis. We defined complete metabolic response (CMR) as the absence of visually detectable uptake of FDG at prior tumor locations, above the background of FDG uptake in surrounding normal tissues in the head–neck area. Those with any visually detectable residual metabolic activity inside the original tumor area above background of surrounding normal tissues were scored as partial metabolic response (PMR).

Statistics

Primary endpoint of the study was to investigate the accuracy of PET/CT to detect local RD. Local RD was defined as residual disease present at the site of the primary tumor within 6 months after (chemo-)radiation. Secondary endpoints were the oncological outcomes in terms of local failure (LF) beyond 6 months, overall survival (OS) and disease-free survival (DFS). The performance of Ojiri score and PET/CT to detect local RD was evaluated using Pearson chi-squared test. This was compared with the combination of both Ojiri score and PET/CT (a positive result consisted of patients with both Ojiri score 2a + b and PMR). Subsequently, the sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated.

Univariable and multivariable analyses were done by χ^2, Fisher's Exact test and Cox regression analysis. Significant factors in univariable analyses or clinical relevant factors were included in the multivariable analysis.

Kaplan–Meier survival estimate was used to investigate OS and DFS. For the comparision with regard to the presence or abscence of local RD (yes/no) and to the possibilities of having salvage surgery for local RD (yes/no), a log-rank test was used.

All *P* values were two sided using a significance threshold of 0.05. All analyses were done using SPSS statistics version 22, 2013.

Results

A total of 352 patients with OPC were treated in The Netherlands Cancer Institute with (chemo-)radiation with curative intent in the period of 2010–2017. Patient, tumor and treatment data were retrospectively collected and are shown in Table 1.

Response evaluation

All patients underwent post-treatment MRI and 94 patients underwent post-treatment PET/CT. Of the patients that underwent PET/CT, 73 had a CMR (78%) and 21 (22%) had a PMR. Of those without a PET/CT, MRI showed Ojiri score 0–1 in 225 patients (88%) and Ojiri score 2a–2b in 33 patients (13%). A flowchart of the diagnostic trajectory can be found in Fig. 1.

Table 1 Patient, tumor and treatment characteristics

Age		
Median	62	
Range	38–83	
Follow-up		
Median (months)	38	
Range (months)	4–102	
Sex		
Male	240	68%
Female	112	32%
Smoking status		
Smoker	269	76%
Non-smoker	83	24%
Treatment year		
2010–2011	82	23%
2012–2013	97	28%
2014–2015	90	26%
2016–2017	83	24%
T-stage		
T1–T2	209	59%
T3–T4	143	41%
N-stage		
N0	78	22%
N1–$N2_a$	80	23%
$N2_{b-c}$–N3	194	55%
HPV status		
HPV positive	169	48%
HPV negative	150	43%
Unknown	33	9%
ECE		
Present	68	19%
Absent	284	81%
Concurrent systemic treatment		
Platinum based	167	47%
Cetuximab	31	9%
No systemic treatment	154	44%

HPV human papilloma virus, *ECE* extra-capsular extension

In 80 patients, an EUA was performed, for suspicious local RD. The number of patients that underwent PET/CT increased over time ($P < 0.001$), where the number of patients that underwent EUA declined ($P = 0.072$) (Fig. 2).

In 19 patients (5%) RD at the primary site was found, 11 (4.3%) in the group without PET/CT and 8 (8.5%) in the group with PET/CT ($P = 0.119$). Characteristics of these patients can be found in Table 2. As expected, patients with local RD were all smokers, had

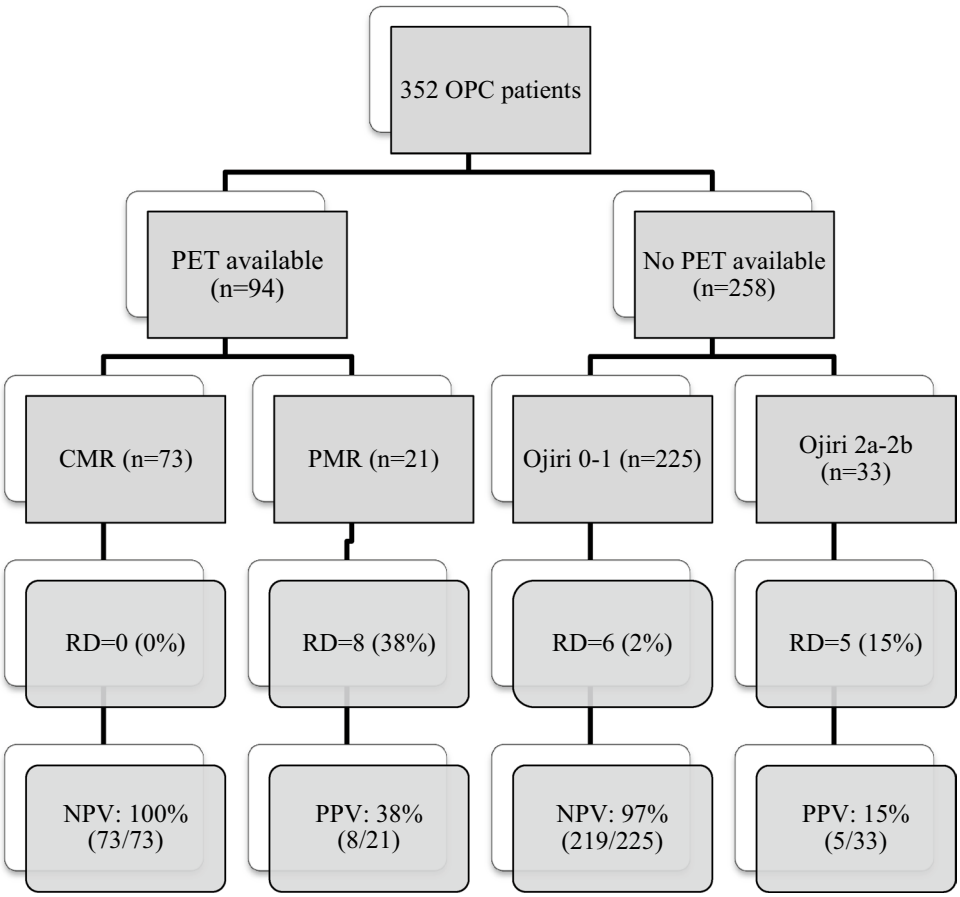

Fig. 1 Flow chart of included patients. *CMR* complete metabolic response, *PMR* partial metabolic response, *PPV* positive predictive value, *NPV* negative predictive value

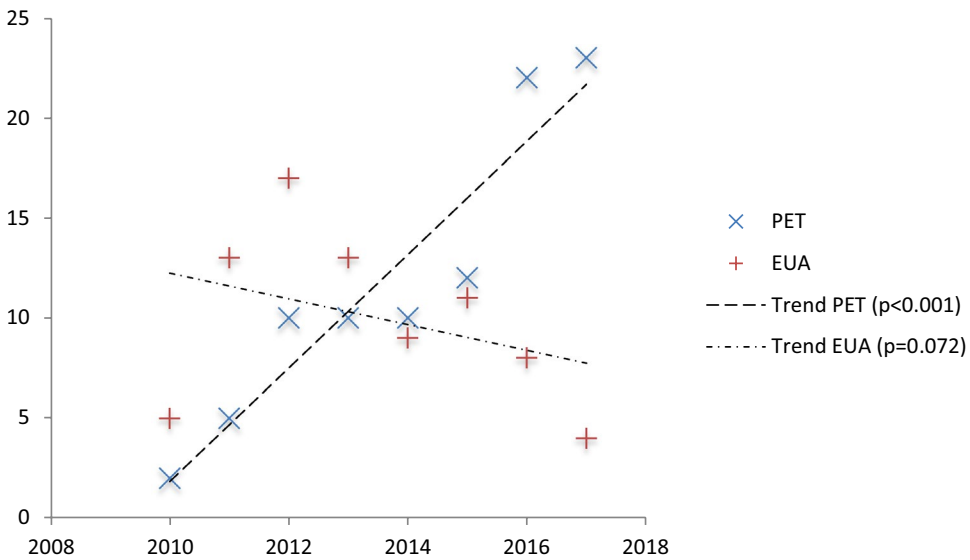

Fig. 2 Use of PET/CT and examination under anaesthesia (EUA) over time

Table 2 Characteristics of patients with local RD compared to patients without local RD

	With RD	Without RD	*P* value
Sex			
Male	10	230	0.203
Female	9	103	
Smoking status			
Smoker	19	250	0.01
Non-smoker	0	83	
HPV status			
Positive	0	169	< 0.001
Negative	18	132	
T-stage			
T1–T2	5	204	< 0.001
T3–T4	14	129	
Year of incidence			
2010–2011	5	77	0.929
2012–2013	4	93	
2014–2015	5	85	
2016–2017	5	78	

HPV-negative disease or frequently locally advanced OPC (T3 or T4). Six of the patients with local RD were able to undergo a salvage procedure [local excision (3), commando procedure (2), interstitial photo-dynamic therapy(1)]. Two of these patients are still alive at follow-up. Three died because of the OPC and one patient died of treatment-related complications. The other 13 patients with RD were not able to have salvage surgery because of simultaneous distant metastases ($n = 2$), inoperable bulky RD ($n = 8$), simultaneous inoperable regional failure ($n = 2$) or because of patient's request ($n = 1$). All the patients that did not underwent a salvage procedure died.

Predictive value of the imaging (Table 3)

The PET/CT detected 21 patients without a CMR, of those eight patients truly had RD (true positives). None of the patients with CMR had RD. Sensitivity of the PET/CT in detecting RD was 100% (8/8), specificity 85% (73/86), PPV 38% (8/21), NPV 100% (73/73), and accuracy 86%.

By means of the Ojiri score, the MRI was able to identify five patients with RD, but missed six patients. This resulted in a sensitivity of 45% (5/11), specificity of 88% (219/247), NPV of 97%(219/225), PPV of 15% (5/33), and accuracy of 86% .

Combining the MRI (Ojiri 2_a–2_b) and PET/CT (PMR) resulted in an accuracy of 89% (84/94).

Table 3 Diagnostic performance of MRI and PET/CT for local RD

	MRI	PET/CT
Sensitivity	63% (12/19)	100% (8/8)
Specificity	83% (278/333)	85% (73/86)
Accuracy	82% (290/352)	86% (81/94)
PPV	18% (12/67)	38% (8/21)
NPV	98% (278/285)	100% (73/73)

MRI magnetic resonance imaging, *PET* positron emission tomography,*PPV* positive predictive value, *NPV* negative predictive value

Long-term outcome

After a median follow-up of 38 months (range 4–102), the 2-year OS, DFS and local control beyond 6 months for the entire group were 84%, 76%, and 92%.

The HPV-positive patients had a significantly ($P < 0.001$) higher estimated 3-year OS of 95% versus 71% in the HPV-negative group. Patients with local RD had a significantly ($P < 0.001$) worse OS (median 8 months, with a 2-year OS of 10%) while patients without RD did not reach median OS in the follow-up and had a 2-year OS of 88% (Fig. 3). A total of 25 patients (7%) had a local failure (LF) beyond 6 months; 4 of those patients were HPV positive. Median time to LF was 15 months. 2-Year estimated OS of the patients with LF was 62%.

Patients with RD in which a salvage procedure was performed had a significant better OS compared to those in which salvage procedure was not performed (median 15 versus 7 months, $P = 0.009$).

Table 4 shows the univariable and multivariable Cox regression analyses for OS. Significant variables were local RD [HR 11.9 (95% CI: 5.8–24.3)], HPV-negativity [HR 4.7 (95% CI 2.5–9.1)] and extra-capsular extension of lymph node metastases [HR 2.0 (95% CI 1.2–3.3)].

Discussion

This paper describes the role of FDG-PET/CT in the early and accurate detection of RD and the clinical outcome of the patients with RD. The key findings of this retrospective cohort study are the high sensitivity of PET/CT in the detection of RD, the low incidence of local RD, especially in HPV-positive patients, and the increasing use of PET/CT in the response evaluation with subsequent reduction of the need for EUA.

The negative predictive value and the accuracy for the detection of local RD after (chemo)radiation were excellent (100% and 86%, respectively). You can interpret this as the PET/CT outperforming MRI in case of CMR.

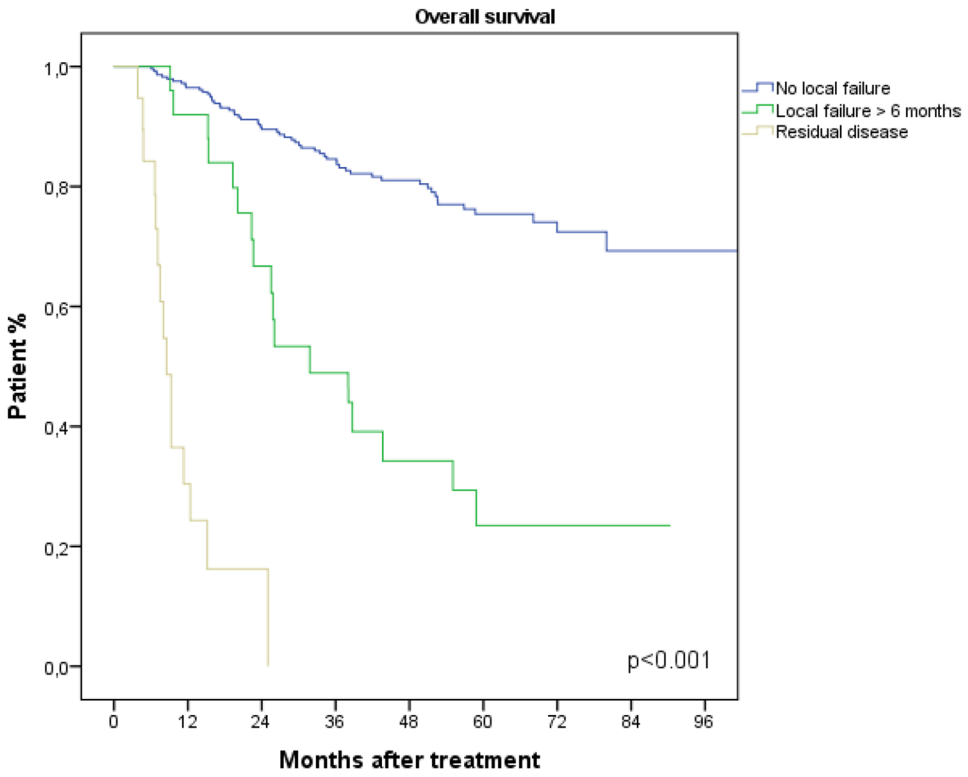

Fig. 3 Kaplan–Meier curve estimating overall survival of patients with residual disease, local failure beyond 6 months and without local failure after treatment

Table 4 Cox regression analyses for overall survival

	UVA		MVA	
	HR death (95% CI)	*P* value	HR death (95% CI)	*P* value
Sex (female[ref])	1.3 (0.8–2.1)	0.247		
Local RD (no RD[ref]))	27.0 (14.0–51.8)	< 0.001	11.9 (5.8–24.3)	< 0.001
HPV (positive[ref]))	7.1 (3.9–12.8)	< 0.001	4.7 (2.5–9.1)	< 0.001
ECE (negative[ref]))	1.2 (0.7–2.0)	0.433	2.0 (1.2–3.3)	0.013
Smoking (non[ref]))	5.2 (2.3–12.0)	< 0.001	2.0 (0.8–5.0)	0.113
Age (years)	1.04 (1.01–1.06)	0.01	1.01 (0.98–1.04)	0.483
T-stage (T1-2[ref]))	2.1 (1.4–3.3)	< 0.001	1.3 (0.8–2.1)	0.247
N-stage (N0[ref]))	1.5 (0.9–2.6)	0.15		

UVA univariable analysis, *MVA* multivariable analysis, *HR* hazard ratio, *HPV* human papilloma virus, *ECE* extra-capsular extension, *RD* residual disease

However, PMR of the PET/CT yields false positives, the combination of PET/CT and MR increased the accuracy in that case tot 89%.

Although only 5% of the whole group has local RD, the impact of local RD on OS was significant. Patients with local RD had a significantly worse OS, compared to those without and OS of patients with local RD without possibilities for salvage surgery was very poor with median survival of 7 months.

We also showed an increase in the use of PET/CT over time and a decrease in the need for EUA. This is a quite important step forward to reduce the need for invasive procedures such as biopsies in this vulnerable group of patients shortly after the (chemo-)radiation.

PET/CT performance

The PET/CT performance results are in line with the systematic review and meta-analysis (2,335 patients) by Gupta et al. [7] and different other retrospective cohort studies [8–14] on the role of PET/CT in response assessment of head and neck cancers. Pooled data on response at the primary site showed a high NPV of around 95% but moderate sensitivity and PPV. This might be explained by the fact that they

defined local failure as any failure at the primary site during follow-up, where we focused on RD (defined as cancer at the primary site < 6 months after the end of treatment) because we believe that the aim of response evaluation at 3 months post-treatment is to accurately identify patients with RD without distant metastasis. Our data show that LF is detrimental for prognosis, but the prognosis for patients with RD is even worse.

The lower specificity and PPV could be explained by the inflammatory response of normal tissue during radiation and in the early period thereafter, but this does not diminish the importance of NPV. This inflammatory response mimics RD in meanings of FDG-avidity. The radiation-induced inflammatory response is only temporary and most often disappeared within 8–10 weeks. Timing of the scan is, therefore, crucial to improve the performance of PET/CT as early scanning might reduce the accuracy of the detection of eventual RD [15].

The NPV reported in our study was higher than reported in other retrospective papers [8–14]. This might be explained by the fact that we mainly looked at RD and not at LR. McDermott et al. [16] found a NPV of 91% of PET/CT and stated that this was too low to rely fully on a single negative PET/CT finding and they proposed that two consecutive negative PET/CT results are enough (NPV 98%).

With regard to the head to head comparison of PET/CT with other diagnostic modalities, two papers [13, 14] used contrast-enhanced CT scans as comparison.

PET/CT-based approach and decline in EUA

Using PET/CT enables very reliable exclusion of RD. As a consequence, the need for EUA as well as MRI for response evaluation has become very low. This, together with the increased use of PET/CT led to a decline of the number of patients exposed to EUA with biopsy over time. EUA/biopsy of irradiated tissue increases the risk wound healing problems [17] especially in patients that persistently smoke cigarettes [18], but EUA/biopsy also increases the costs [19] and discomfort for the patient.

Risk factors and survival in RD

The incidence of local RD in the current study was around 5% and had a highly significant negative influence on OS. This finding has also been shown previously by others [10, 20]. Salvage of RD, if possible, results also in this cohort in a slight improvement in OS, although OS in case of salvaged local RD is still far lower than patients without RD.

The OS of patients with CMR on post-treatment PET/CT without local RD was good and for HPV-positive patients was excellent. These results are in line with the results from MD Anderson Cancer center published by Ng et al. [20] They showed that CMR on post-treatment PET/CT in HPV-positive OPC patients resulted in OS rates at 5 year of 89%. As expected, patients with local RD had significantly more "classical" risk factors for worse outcome compared to those that did not fail. More patients were active smokers, HPV negative and had a higher T-stage. The impact of these factors on outcome is well known and has already been established in the early 2000's [21]. This study showed that local RD is one of the factors explaining the worse outcome of the HPV-negative patients.

Limitations

The limitations of this study include the inevitable selection bias, based upon the retrospective character of this study. What is shown in the time trend analysis is that the use of PET/CT in response assessment increased over the years, making it more common nowadays in daily practice, but the role of selection cannot be ruled out. We did not find a significantly higher number of patients with RD in the group of patients with PET/CT, so the selection bias will be limited. However, these data need to be interpreted with some caution, despite that all available retrospective evidences point in the same direction. Similar to the findings of the randomized study of Mehanna et al. [5] on PET/CT-surveillance for neck response, we believe that patients with CMR at the primary tumor site on PET/CT at 3 months post-treatment are at very low risk of having local RD. In these patients, deintensified clinical surveillance, without MRI, can be safely discussed with the patients.

The most important advantage of using FDG-PET for the detection of RD is an non-invasive approach with high NPV. However, it is quite an expensive diagnostic tool with limited availability in different parts of the world. Furthermore, FDG-PET has low PPV.

Given our findings, different possibilities for the current clinical practice might exist. In PET-negative patients without any clinical suspicion, regular follow-up schedule will be advocated. In PET-negative patients with high clinical suspicion, biopsy from the suspected region is needed. In PET-positive patients, biopsy from the high-uptake region is needed, regardless of the presence or absence of clinical suspicion. This can be done under local anaesthesia or otherwise during EUA to confirm or exclude the diagnosis of RD and to evaluate the resectability of the possible RD. When FDG-PET not ready at hand, the combination of the clinical suspicion with the best available imaging (CT or MRI) might be the best option to identify RD. Gouw et al. [22] published on the high accuracy of combining clinical suspicion with the Ojiri score. In that study, clinical suspicion was defined as the presence of suspected mucosal lesion, persistent need of opiate analgesics or tube feeding

at the time of the response evaluation 3 months after the (chemo)radiation.

Conclusion

The current study showed excellent performance of PET/CT for the detection of local residual disease after (chemo-) radiation, as the sensitivity and negative predictive value approached 100% in the current study. Only 5% of all patients with oropharyngeal cancer have local residual disease after (chemo)radiation; all of these patients were HPV negative. The added value of PET/CT to MRI has likely contributed to the reduced need for examination under general anaesthesia over time. A PET/CT-based surveillance approach opens the discussion for deintensified surveillance in HPV-positive patients with CMR.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval This article does not contain any studies with human participants or animals performed by anyof the authors.

Informed consent The local IRB waived informed consent for this retrospective analysis of clinical data.

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