The Journal of Laryngology & Otology

cambridge.org/jlo

A retrospective analysis: follow up with ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in oro- and hypopharyngeal squamous cell carcinoma patients

Joke Van Nuffel[1], Katia Verbruggen[1], Mia Voordeckers[2], Yannick De Brucker[3], Nele Platteaux[2], Ina Foulon[1] and Olaf Michel[1]

[1]Department of Otorhinolaryngology, Head and Neck Surgery, University Hospital of the Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Jette, Belgium, [2]Department of Radiotherapy, University Hospital of the Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Jette, Belgium and [3]Department of Radiology, University Hospital of the Vrije Universiteit Brussel, Laarbeeklaan 101, 1090 Jette, Belgium

Abstract

Objective. This study evaluated the significance of positron emission tomography/computed tomography (PET/CT) in detecting recurrences or other primary malignancies in patients treated for oro- and hypopharyngeal squamous cell carcinoma.

Method. A retrospective analysis of the follow up of 132 patients was performed and 370 PET/CT scans were assessed for their accuracy.

Results. All asymptomatic clinical occult recurrences were detected by PET/CT and accounted for 28 per cent of recurrences. Asymptomatic patients with metastases detected by PET/CT had a significant survival benefit compared to patients diagnosed in a symptomatic stage. For locoregional recurrence, no significant difference in overall survival could be demonstrated. In total, 33 primary malignancies were discovered, of which 48 per cent were first detected by PET/CT. The specificity and negative predictive value of the PET/CT scans had ranges of 85–100 and 83–100 per cent, respectively.

Conclusion. The role of PET/CT scans in detecting primary malignancies, clinical occult recurrences and especially asymptomatic metastases was observed.

Introduction

Treatment response after primary curative therapy for head and neck cancer should be evaluated and monitored during follow up.[1] Local, regional (cervical nodes) or distant (metastasis) recurrence, which may occur in up to 50 per cent of patients with locally advanced (stages III and IV) squamous cell carcinoma (SCC), should be ruled out or at least detected at the earliest stage possible. Most relapses emerge within the first two years post-treatment.[2]

Another impediment for lasting salvage is the occurrence of secondary primary malignancies.[1] Secondary primary malignancies are subdivided into three categories based on the time interval between diagnoses of the primary and secondary malignancy: simultaneous (less than one month), synchronous (one to six months) and metachronous (more than six months). Besides the head and neck region itself, the most common locations for secondary primary malignancies are the lungs and esophagus.[3–5]

Surveillance imaging aims to detect recurrence and secondary primary malignancies at an early stage.[1] In patients with head and neck cancer, recurrence influences overall survival to a strong degree.[6] Functional (positron emission tomography (PET)) and whole-body anatomical (computed tomography (CT)) images combine metabolic and morphologic imaging within an integrated procedure. Since its introduction in 1998, PET/CT has gained increasing significance, particularly in the follow up of head and neck cancer patients. Recent meta-analyses have demonstrated the high sensitivity and specificity for detection of recurrence, which supports the value of PET/CT in long-term follow up.[7,8] It detects particularly small and more concealed carcinogenic hypermetabolic spots more concisely than other conventional anatomic imaging techniques such as magnetic resonance imaging (MRI) or CT alone.[9]

Follow-up protocols, including PET/CT imaging, differ widely among institutions. The National Comprehensive Cancer Network endorses post-treatment baseline imaging within six months to guide decisions for neck dissection in patients with advanced SCC after chemoradiation. They support further imaging for surveillance based on symptoms and prognostic factors, and for areas inaccessible to clinical examination.[10] However, it is uncertain whether detection of recurrence by strict surveillance imaging results in an improved salvage outcome and quality of life for the asymptomatic patient.[1] So far, there

Main Article

Joke Van Nuffel takes responsibility for the integrity of the content of the paper

Cite this article: Van Nuffel J, Verbruggen K, Voordeckers M, De Brucker Y, Platteaux N, Foulon I, Michel O. A retrospective analysis: follow up with ^{18}F-fluoro-2-deoxy-D-glucose-positron emission tomography/computed tomography in oro- and hypopharyngeal squamous cell carcinoma patients. *J Laryngol Otol* 2024;1–8. https://doi.org/10.1017/S0022215123001214

Received: 19 February 2023
Revised: 1 May 2023
Accepted: 31 May 2023

Keywords:
Head and neck cancer;
oropharyngeal squamous cell carcinoma;
hypopharyngeal squamous cell carcinoma;
positron emission tomography computed tomography; follow-up studies

Corresponding author:
Joke Van Nuffel;
Email: v.nuffel@gmail.com

is little evidence to support long-term active surveillance imaging for asymptomatic patients with a negative clinical examination after six months.[10–15] In the light of a growing discussion about the cost-effectiveness of PET/CT, there is a need for more data and research.[16]

The present study aimed to evaluate the role of PET/CT in revealing recurrent disease or synchronous and metachronous primary malignancies in patients curatively treated for oropharyngeal and hypopharyngeal SCC by a retrospective chart analysis.

Material and methods

Data collection part 1: Detection of recurrence and other primary malignancies

A total of 217 patients who were treated for primary oropharyngeal and hypopharyngeal cancer between 1 January 2005 and 31 December 2017 were identified using a database from the tumour board of the hospital (multidisciplinary oncological consultations). Histopathological results other than SCC were excluded, leaving 198 cases. Primary treatment had to be intended curatively and in line with the University Hospital of the Vrije Universiteit Brussel Oncology Guidelines.[17] Only patients evaluated free of residual disease after primary therapy were included. Patients treated for metachronous primary head and neck cancers or for metastases from other regions, patients treated or monitored in other hospitals for malignancies as well as patients who refused surveillance with PET/CT were excluded. According to these criteria, 132 patients remained for retrospective analysis.

Until 2018, the follow-up schedule at the University Hospital of the Vrije Universiteit Brussel included surveillance scans up to five years after treatment. A PET/CT was performed 4 and 12 months post-treatment and repeated annually for 4 years thereafter. Before 2008, patients were also scanned eight months post-treatment. Other imaging techniques (e.g. echo, MRI) were used when more information was needed for unclear findings.

Information about tumour characteristics, reports on surveillance imaging and outcome were drawn from the electronic medical data system and anonymised for further evaluation for each patient included in the analysis. Staging of the primary tumour was performed according to the seventh edition of the IUCC Classification of Malignant Tumors.[18] The date of histopathological confirmation or, if not obtainable, the date of the first imaging with evidence for recurrent tumour was taken as time of relapse. The clinical symptoms at time of diagnosis and the corresponding physical and fibre-optic findings were collected from medical records of follow up. For each patient, a timeline was reconstructed to determine how the recurrence was detected.

Statistical analysis part 1

A Kaplan–Meier curve was used to visualise the incidence of recurrence or secondary primary malignancy in relation to time after treatment. Here, 'relapse-free survival' indicates the time between completion of treatment and diagnosis of recurrence (local, regional or distant), with patients who died from other causes being censored. The time between diagnosis of recurrence and death from any cause was termed 'overall survival after recurrence'. The influence of detection by PET/CT versus clinical examination on overall survival after recurrence was examined using Kaplan–Meier analysis and log-rank (Mantel–Cox) tests. Statistical calculations were performed with Statistical Program in Social Sciences for Windows, version 23. p values less than 0.05 were considered statistically significant.

Data collection part 2: Accuracy of routine positron emission tomography/computed tomography scans

A separate second analysis was done to determine the accuracy of PET/CT scans in relation to the time period after treatment. The notation PET/CT is used to include all PET scans performed with or without CT. The second analysis started with the collection of all surveillance PET/CT scans. For each patient included in the first analysis, all PET/CT scans performed as routine follow up were collected from the electronic medical data system. If recurrence was confirmed or a secondary primary malignancy was detected, subsequent scans were not included for evaluation. As a result, 396 PET/CT scans were collected. Subsequently, it was determined which PET/CT scans should be included in the second analysis. Scans were included if information about outcome (recurrence or not) was available in the electronic medical data system for six months after the PET/CT scan was performed. If this was not the case, the scan was not included in the second analysis.

^{18}F-fluoro-2-deoxy-D-glucose was used as the radiotracer for PET scans. Patients were administered 250, 275 or 300 MBq of ^{18}F-fluoro-2-deoxy-D-glucose depending on weight. Whole-body PET scans were carried out 60 minutes after administration. All PET images were acquired on a Philips Gemini TF6 PET/CT scanner, which is a Lutetium-yttrium oxyorthosilicate-based PET scanner with time-of-flight capability and 18 cm (axial) and 70 cm (transaxial) fields of view. PET images were reconstructed to 144×144 pixels (4-mm isotropic pixels) with 4-mm slice thickness using the vendor's standard Binary Large Object - Object Storage - Time of Flight reconstruction. All CT images were performed prior to the PET study. CT scans were acquired using a slice thickness of 5 mm at 120 kV and 50 mAs for a low-dose CT and 2 mm at 120 kV and 250 mAs for a diagnostic CT. Intravenous iodine contrast agent was used when contraindications were absent.

Follow-up PET/CT scans were analysed by experienced radiologists and nuclear medicine physicians, and related to previous scans when possible. The maximum standardised uptake value (SUV_{max}) was calculated to guide evaluation. Cut-off values were not used to define a positive scan. For each scan, a score for local, regional and distant recurrences was determined based on the radiological findings. When no relapse-suspected lesion was detected, the scan was rated 'negative'. When an intensified ^{18}F-fluoro-2-deoxy-D-glucose tracer signal was found, resulting in a follow-up consultation out of schedule or additional diagnostic tests, the PET/CT scan was assessed as 'equivocal'. Finally, PET/CT scans with abnormal ^{18}F-fluoro-2-deoxy-D-glucose accumulation were scored 'positive'. In case of ambiguity, scans were anonymously re-evaluated by an otorhinolaryngologist who specialised in head and neck cancer.

The outcome for local, regional and distant recurrence was scrutinised to assess the accuracy of the PET/CT scans. The initial score of the scan was rated as 'true' or 'false' after a surveillance interval of six months. For example, a PET/CT scan was classified 'true negative' when no relapse could be found for all subsites within a period of six months after the scan was performed. On the other hand, a scan was classified as 'true positive' if recurrence was detected by further

https://doi.org/10.1017/S0022215123001214 Published online by Cambridge University Press

investigation in a previously 'positive' or 'equivocal' scored site. Tumour recurrence could be confirmed by either histopathology or proven progression on subsequent imaging, resulting in the decision to start (palliative) therapy.

Statistical analysis part 2

PET/CT scans were categorised according to their time interval after finishing primary treatment. Their accuracy was evaluated with descriptive statistics using crosstabs to calculate sensitivity, specificity, positive predictive value and negative predictive value for each time interval. Although trends of accuracy were described in an explorative phase, this was not confirmed by a Fisher analysis of variance (ANOVA) or Scheffée ANOVA because of the different and small cohort sizes for each time interval, the lack of homogeneity of variances and partially paired test results for different time frames (scans of same patient). Statistical calculations were performed with Statistical Program in Social Sciences for Windows, version 23.

A schematic representation of the study algorithm can be found in the supplementary material.

Results

Cohort

A total of 132 patients were included. In 93 patients oropharyngeal SCC (70 per cent) was diagnosed and in 39 patients hypopharyngeal SCC (30 per cent) was diagnosed. Patient and tumour characteristics are shown in Table 1. An advanced stage of head and neck cancer (stages III and IV) was present in 86 per cent of patients at the time of diagnosis (81 per cent of oropharyngeal SCCs and all of the hypopharyngeal SCCs). Sixty-eight per cent of the patients were treated with multimodal therapy. The administered chemotherapy consisted of cisplatin and two patients received neoadjuvant therapy. The radiation dose at the site of the primary tumour varied (60, 66, 70 or 70.5 Gy) depending on the type of multimodal treatment administered. Four patients did not complete their radiation regimen as a result of treatment-related adverse effects, but were still included in the study.

Table 1. Cohort demographics

Characteristic	Value
Age (years)	
Median	59
Mean	59
Range	41–79
Sex (*n* (%))	
Female	43 (32.6)
Male	89 (67.4)
Primary site (*n* (%))	
Oropharynx	93 (70.5)
Hypopharynx	39 (29.5)
Grade of differentiation (*n* (%))	
G1	28 (21.2)
G2	61 (46.2)
G3	27 (20.5)
G4	16 (12.1)
Curative treatment (*n* (%))	
Surgery	6 (4.5)
RT	35 (26.5)
Surgery + RT	10 (7.6)
CRT	70 (53.0)
Surgery + CRT	10 (7.6)
Chemotherapy	1 (0.8)
Stage (*n* (%))	
I	6 (4.5)
II	12 (9.1)
III	36 (27.3)
IVA	60 (45.5)
IVA/B*	14 (10.6)
IVB	4 (3.0)

*IVA/B means category A or B could not be determined from the file data. G = histopathological grade; RT = radiotherapy; CRT = chemoradiation.

Recurrence

The median follow-up period was 2.67 years (range, 22 days to 12 years) and the median time of follow up for surviving patients was 4.25 years. In total, 61 patients (46 per cent) were diagnosed with recurrent disease. The median time to develop recurrence was 0.81 years (range, 0.13–8.02 years). In Figure 1, a Kaplan–Meier curve shows relapse-free survival after completion of primary therapy. The estimated 10-year relapse-free survival was 41 per cent. Figure 2 depicts the incidence of recurrence after completion of therapy. According to this analysis, 80 per cent of the recurrences occurred before 2.5 years and 90 per cent before 5 years post-treatment. Relapse occurred in 43 per cent of patients locally and in 33 per cent regionally. Metastases were present in 49 per cent of patients at the time of diagnosis of recurrence. In total 70 per cent of patients developed metastases, of which 50 per cent were found in the lungs. Recurrent disease was first detected by surveillance imaging in 39 patients (64 per cent). For 28 out of 39 patients neither clinical nor fibre-optic examination could detect malignant lesions. However, 11 of these patients with clinical occult relapse did report new symptoms, most likely related to the recurrence (e.g. newly developed referred otalgia). The remaining 17 out of 39 patients did not report extra symptoms in addition to the already known treatment morbidity. These 17 asymptomatic and clinical silent recurrences, representing 28 per cent of all recurrences, were all detected by PET/CT. Fourteen out of 17 patients were diagnosed within 3 years post-treatment, but 3 out of 17 recurrences were discovered later during follow-up. One of these patients had already had five prior negative assessed PET/CT scans.

Overall survival after recurrence

The three-year overall survival after diagnosis of recurrence was investigated using Kaplan–Meier analysis. Survival was 23 per cent after salvage treatment and 0 per cent for the palliative supported patient group (Figure 3). Of the 61 diagnosed recurrences, 40 cases consisted of locoregional relapse, with or without associated metastases. In this group, 17 cases were first suspected by clinical examination, 20 by PET/CT and 1 by MRI. For the two remaining cases, no sufficient information

https://doi.org/10.1017/S0022215123001214 Published online by Cambridge University Press

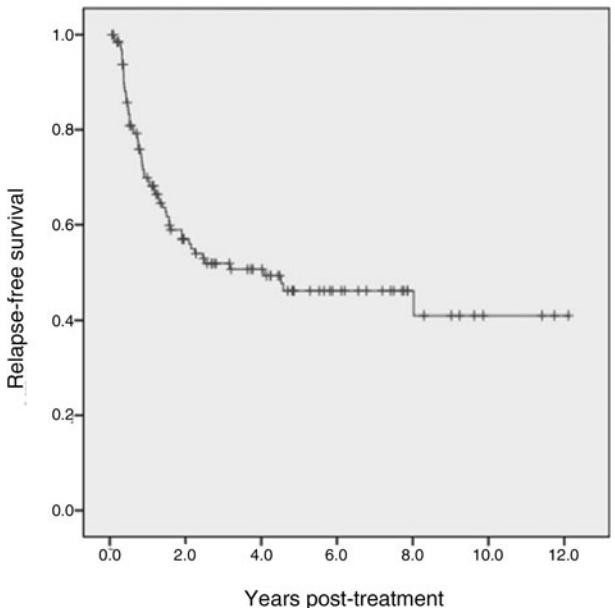


Figure 1. Kaplan–Meier estimation of relapse-free survival after completion of primary therapy.

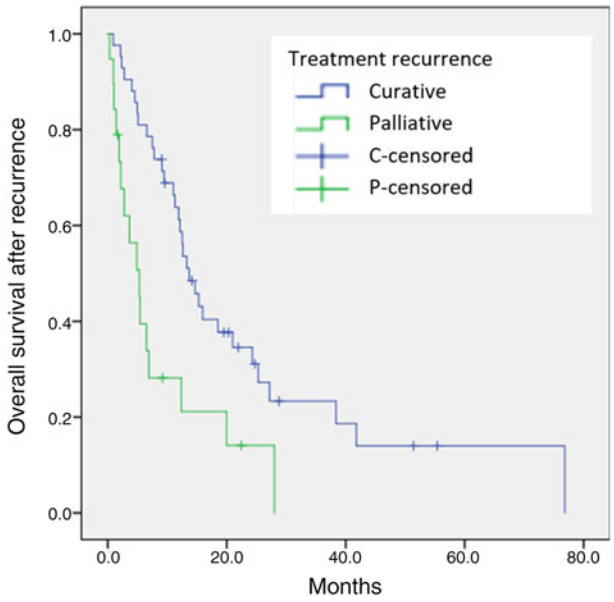


Figure 3. Kaplan–Meier estimation of overall survival after diagnosis of recurrence, stratified for curative or palliative treatment. C-censored = curative treated censored case; P-censored = palliative treated censored case.

was available. Based on Kaplan–Meier analysis (Figure 4a), survival after diagnosis of locoregional recurrence was compared between the cases detected by clinical examination and those detected by PET/CT. The median survival times were 25.3 and 9.1 months, respectively. The overall comparison with the log-rank (Mantel–Cox) test could not demonstrate a significant difference ($p > 0.05$).

A total of 21 out of 61 patients were found to have one or more metastases, without suspicion of locoregional recurrence. In this group, 17 metastases were initially found by PET/CT, of which only 1 could be detected by the subsequent physical examination. These 17 distant recurrences were stratified for symptomatology and their survival was estimated (Figure 4b). Only 1 of the 11 asymptomatic patients was no longer treated curatively. For the six symptomatic patients, palliative therapy was started. Median survival was 18.5 months for the asymptomatic patients and 4.9 months for the symptomatic patients with metastases. Overall comparison with the log-rank (Mantel–Cox) test demonstrated a significant difference ($p < 0.05$) in survival rate in favour of patients with asymptomatic distant recurrence.

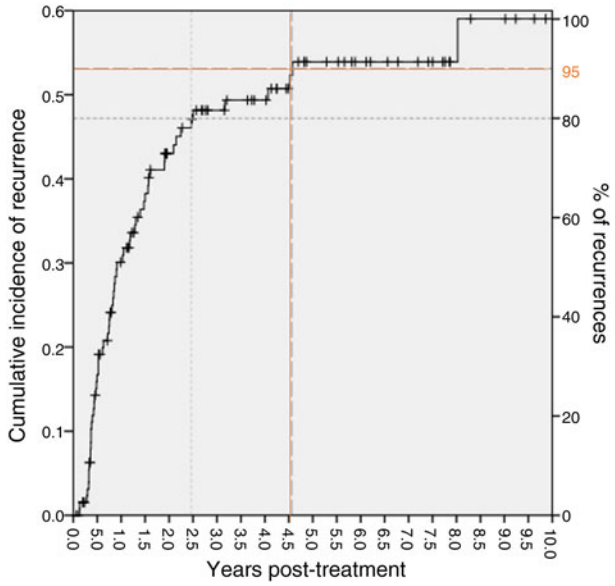


Figure 2. Kaplan–Meier estimation of the cumulative incidence of recurrence after completion of primary therapy.

Secondary primary malignancies

In total, 24 out of 132 patients developed a secondary primary malignancy after the diagnosis of a primary head and neck cancer. Among these patients, eight were also diagnosed with a tertiary primary malignancy and one with a fourth primary malignancy. Figure 5 shows the Kaplan–Meier estimation of the cumulative incidence of secondary primary malignancies discovered after completion of primary therapy. During the first eight years of follow up, the curve nearly approximates a linear function, with an increase in incidence of secondary primary malignancies of about 5 per cent a year.

For further descriptive analysis, the term primary malignancies includes second, third and fourth neoplasms. In total, 33 primary malignancies were discovered after diagnosis of the head and neck cancer primary. Six of these primary malignancies had already been discovered by pre-treatment PET/CT. They were classified as simultaneous malignancies, found at the level of the prostate, the colon (two), the mouth and the lungs (two). The other 27 primary malignancies were detected later during follow up. Thirteen of the 33 primary malignancies (48 per cent) were first discovered by PET/CT and 8 (30 per cent) were discovered by clinical examination, including fibre-optic endoscopy. The anatomical locations of the primary malignancies are listed in Table 2. At the time of detection, 30 per cent of the primary malignancies at the level of head and neck were symptomatic. Similar results were found for the primary malignancies located on other sites (32 per cent).

The accuracy of positron emission tomography/computed tomography surveillance imaging

For all 132 included patients, a total of 396 PET/CT scans were carried out during the observation period as part of routine

https://doi.org/10.1017/S0022215123001214 Published online by Cambridge University Press

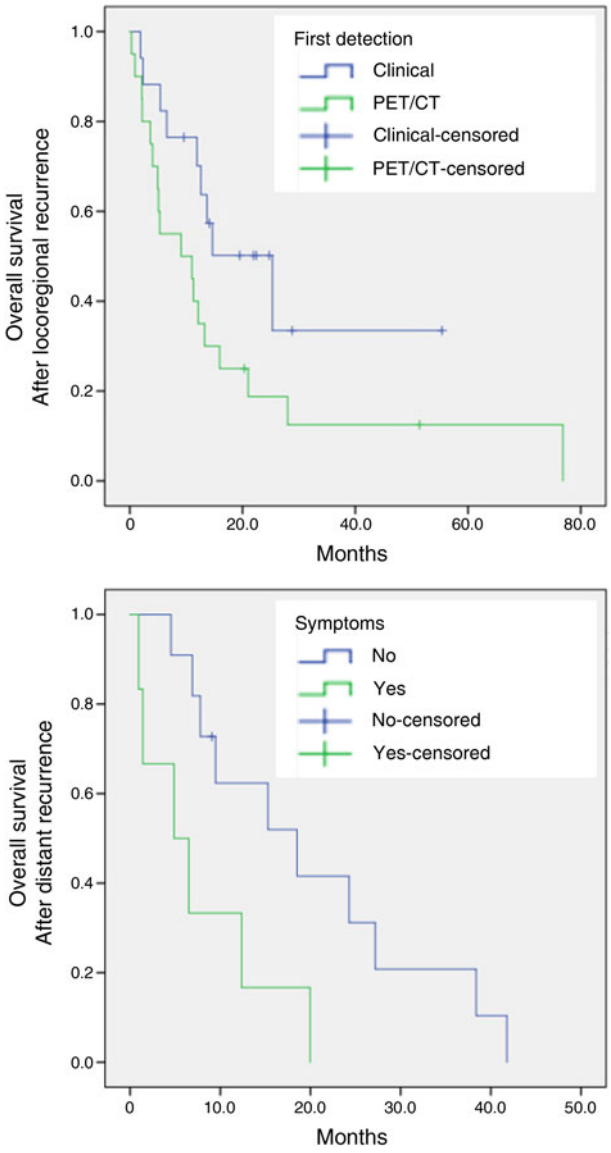


Figure 4. (a) Kaplan–Meier estimation of overall survival after diagnosis of locoregional recurrence, stratified for detection modality. (b) Kaplan–Meier estimation of overall survival after diagnosis of distant recurrence, stratified for symptomatology. CE = clinical examination; PET/CT = positron emission tomography/computed tomography; Clinical-censored = clinical detected recurrence censored; PET/CT-censored = PET-CT detected recurrence censored; Yes-censored = symptomatic recurrence censored; No-censored = asymptomatic recurrence censored.

follow up. No scans were included after diagnosis of recurrence or a second head and neck cancer. The outcome was evaluated based on a surveillance interval of six months after the scan. The scans were divided into time intervals as shown in Table 3. Overall, 111 scans were performed at 4 months after the end of treatment and 70 scans were performed at 12 months after the end of treatment. This number decreased to 13 scans at 5 years after the end of treatment. An additional 60 scans were performed around 8 months post-treatment, according to the Oncology Guidelines of the University Hospital of the Vrije Universiteit Brussel. The number of the PET/CT scans that were simultaneously performed with a CT scan to merge images was 349 (94 per cent). Iodine-containing contrast was used in addition to ^{18}F-fluoro-2-deoxy-D-glucose for 112 scans (30 per cent).

The numbers of PET/CT scans assessed as positive, equivocal and negative for each time interval are shown in Figure 6a. The proportions of equivocal scans at 4, 8 and 12 months post-treatment were 12, 11 and 10 per cent, and these

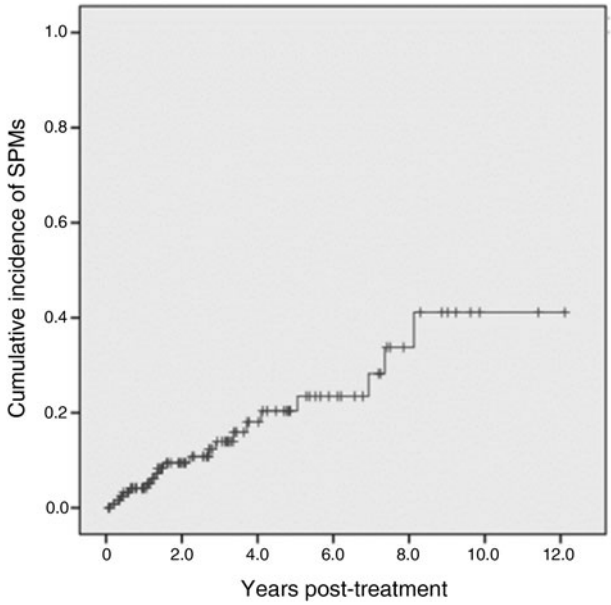


Figure 5. Kaplan–Meier estimation of cumulative incidence of secondary primary malignancies after completion of primary therapy. SPM = secondary primary malignancy.

proportions decreased to 5 per cent and 6 per cent for the 3- and 4-year PET/CT scans. Thereafter no scans were assessed as equivocal.

The specificity and negative predictive value for detection of recurrence had ranges of 85–100 and 83–100 per cent, respectively. Calculations for sensitivity and positive predictive value were more heterogeneously distributed, with ranges of

Table 2. Detection of other primary malignancies

Time of detection	Means of detection and location of malignancy
Pre-treatment	Six discovered by PET/CT
	– Lungs (two)
	– Colon (two)
	– Oral cavity
	– Prostate
Post-treatment	13 discovered by PET/CT
	– Two HNC
	– 11 non-HNC
	Lungs (five)
	Cervix
	Breast
	Bile duct
	Liver
	Pancreas
	Rectum
Post-treatment	Eight discovered by clinical examination
	– Six HNC
	– Two non-HNC
	Inguinal lymph node (Hogkin lymphoma)
	Skin (melanoma)

PET/CT = positron emission tomography/computed tomography; HNC = head and neck cancer.

https://doi.org/10.1017/S0022215123001214 Published online by Cambridge University Press

Table 3. Number of total and included PET and PET/CT scans for each time interval

Follow-up scans	Time interval*	Median time	Total scans	Included scans	PET	PET/CT	PET/CTce
4 months	2–6 months	3.97 months	111	109	10	65	34
8 months	6–10 months	8.08 months	60	56	3	36	17
1 year	10–18 months	13.25 months	70	67	2	44	21
2 years	1.5–2.5 years	2.07 years	69	66	4	37	25
3 years	2.5–3.5 years	3.00 years	39	36	1	24	11
4 years	3.5–4.5 years	4.07 years	34	24	1	20	3
5 years	4.5–5.5 years	5.06 years	13	12	1	10	1
All Follow-up scans	**2 months to 5.5 years**		**396**	**370**	**22**	**236**	**112**

*Time interval post-treatment after ending primary therapy, noted as the half open interval [x, y[. For example, a 4 month follow-up scan was performed from 2 months up to 6 months. From 6 months the scan was included in the next interval. PET = positron emission tomography; CT = computed tomography; ce = contrast enhanced. In bold: the sum of the above rows

56–100 and 20–100 per cent, respectively. After 3.5 years, all four PET/CT characteristics reached an accuracy of 100 per cent. Figure 6b shows the proportion of false-positive scans decreasing over time and Figure 7 shows the PET/CT characteristics for each time interval after completion of primary treatment.

Discussion

This retrospective analysis evaluates the role of PET/CT in revealing recurrent disease or synchronous and metachronous primary malignancies in patients curatively treated for oropharyngeal and hypopharyngeal SCC.

Compared to previous studies, a higher recurrence rate was found in this cohort, which can be related to the high number of advanced-stage head and neck cancers at the time of diagnosis (86 per cent at stages III and IV) and the ratio of 30 per cent hypopharyngeal SCC, which is known to have a worse prognosis than oropharyngeal SCC.[19,20] The long median time of follow up and frequent surveillance with different modalities may also favour the detection of recurrences. Most of the recurrences in this study occurred within the first five years of follow up, whereas other studies have report a shorter time interval of two years.[2,21,22] Recurrence of human papillomavirus (HPV) positive oropharyngeal SCC is known to occur later compared to the HPV-negative group, but there are no data concerning the attributable fraction of HPV or p16-immunopositive SCC in this study.[23–25]

The incidence of secondary primary malignancies was relatively consistent and within the range of other studies.[5,26] However, the number of secondary primary malignancies was possibly slightly underestimated, since most SCCs of the lungs were suspected to be a metastasis of the head and neck cancer, although no difference can be made histopathologically. The premise for classification as metastases is strongly supported by the literature, as recent molecular techniques demonstrate that most solitary lung nodules in association with head and neck SCC are metastases.[27]

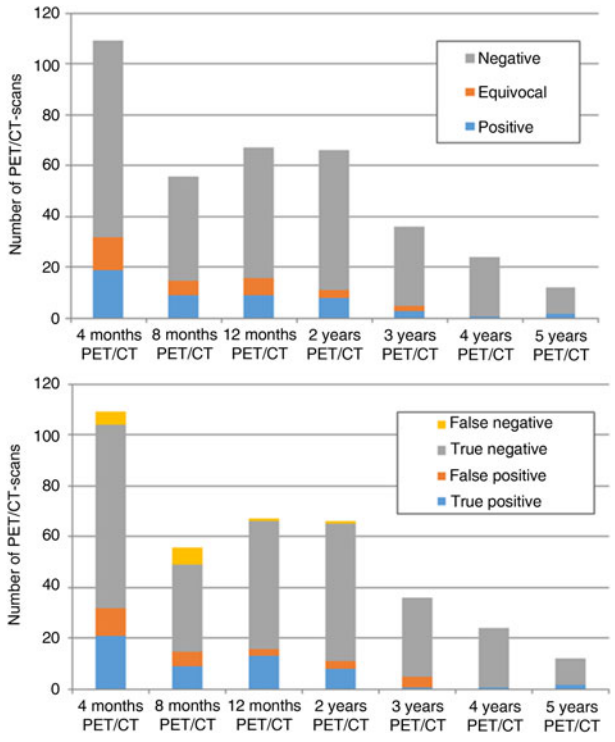


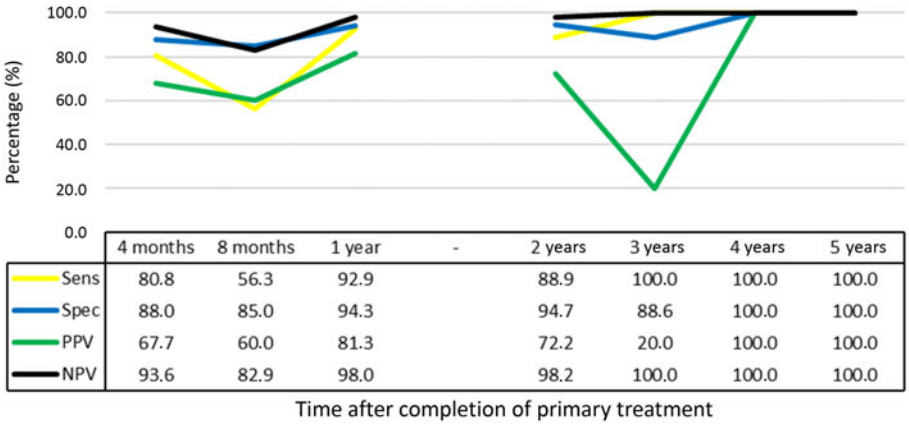
Figure 6. (a) Proportion of positron emission tomography/computed tomography (PET/CT) scans assessed as positive, equivocal and negative for each time interval post-treatment. (b) Proportion of true-positive, false-positive, true-negative and false-negative PET/CT scans for each time interval post-treatment. PET = positron emission tomography; CT = computed tomography.

Surveillance positron emission tomography/computed tomography

One of the main advantages of PET/CT is its ability to detect not only locoregional recurrences, but also distant metastases or secondary malignancies because a full-body scan is carried out for detection of hypermetabolic spots. In addition, smaller and more concealed carcinogenic sources are more easily detected by PET/CT scan compared to other imaging techniques, such as CT or MRI depicting straight anatomy.[9] Several meta-analyses have demonstrated the high sensitivity and specificity for detection of recurrence by PET/CT, which favours its use in long-term follow up.[7,8] Although performing PET/CT scans during follow up has become the norm, evidence-based recommendations on the number and duration of scans are lacking, and schedules of PET/CT imaging differ widely among institutions.[10–15,28]

This study confirms that surveillance PET/CT has a high specificity and negative predictive value for all time intervals.[7,8] In contrast, the sensitivity and positive predictive value varied considerably. However, to be a suitable screening test during follow up of asymptomatic patients, a high sensitivity to detect recurrence is crucial. In early post-therapeutic assessment, diagnostic accuracy of functional imaging mostly depended on the time interval between the end of treatment and the imaging examination.[7,8]

https://doi.org/10.1017/S0022215123001214 Published online by Cambridge University Press



	4 months	8 months	1 year	-	2 years	3 years	4 years	5 years
Sens	80.8	56.3	92.9		88.9	100.0	100.0	100.0
Spec	88.0	85.0	94.3		94.7	88.6	100.0	100.0
PPV	67.7	60.0	81.3		72.2	20.0	100.0	100.0
NPV	93.6	82.9	98.0		98.2	100.0	100.0	100.0

Figure 7. Positron emission tomography/computed tomography characteristics for overall detection of recurrence for each time interval post-treatment. Sens = sensitivity; Spec = specificity; PPV = positive predictive value; NPV = negative predictive value.

As shown in meta-analyses by Isles *et al.* and Sheikhbahaei *et al.*, the sensitivity of PET/CT is significantly lower in the two and a half to three months after completion of treatment.[7,8]

In line with other studies, outcome was assessed after six months. This (arbitrarily chosen) surveillance interval has a significant impact on the calculated PET/CT characteristics.[7,8,29] For example, a longer time interval to assess outcome would reduce the negative predictive value of PET/CT scans. For this reason, it would be beneficial to evaluate negative predictive value based on the outcome after five years, the time span in which the majority of recurrences occur. Furthermore, it would be interesting to analyse the cumulative overall negative predictive value of two or more negative scans, which was not within the scope of this study.

Survival benefit

A potential benefit in the form of survival rate is one of the most important arguments for continued scanning.

The estimated three-year overall survival (23 per cent) after salvage therapy for recurrence was in line with percentages found in the literature. According to a meta-analysis from 2016, the pooled three-year overall survival for recurrent oropharyngeal cancer after salvage therapy is 26 per cent.[30]

For locoregional recurrence, no difference in survival rates could be demonstrated between detection by PET/CT or diagnosis by clinical examination. This result supports the findings of Ho *et al.*[14]

On the other hand, distant recurrences were regularly detected by imaging techniques. With regard to the debate on active surveillance imaging of asymptomatic patients, the survival of this group was compared with that of patients who were already symptomatic at the time of diagnosis of metastatic disease. For distant recurrences detected by PET/CT, a significant survival benefit could be found for patients who had been diagnosed in an asymptomatic stage ($p < 0.05$). This observation supports continued surveillance imaging by PET/CT for asymptomatic patients.

The different survival times in the symptomatic and asymptomatic groups may be due to the fact that no curative treatment was initiated in the symptomatic patient group. However, no account was taken of possible lead-time bias, which may have wrongfully favoured the asymptomatic group. It also should be noted that because of the relatively limited cohort size in a single institution, the overall survival after recurrence is compared between small patient groups and therefore has less statistical power.

New perspectives supporting long-term active surveillance imaging

The prominent role of PET/CT in follow up is corroborated by the observation that all of the asymptomatic and clinical silent occurrences, accounting for 28 per cent of all recurrences, were detected by PET/CT. A possible significant survival benefit for asymptomatic distant recurrences needs to be further investigated, but may favour continued scanning. Between two and a half and five years post-treatment, only 72 PET/CT scans were needed to detect four relapses, of which three were clinically occult and asymptomatic. In addition, secondary primary malignancies occurred with an estimated incidence of 5 per cent for each year after the end of treatment, of which almost half were detected by PET/CT.

Recent articles request further research on risk-stratified follow-up protocols, based on pre-treatment characteristics and baseline PET/CT findings, to identify subgroups of head and neck cancer patients who may benefit from routine surveillance imaging.[1,10,12,16,23] Such research might lead to more targeted surveillance with PET/CT.

- This retrospective analysis brings new insight to the role of positron emission tomography/computed tomography (PET/CT) scans during the follow up of head and neck squamous cell carcinoma
- Overall, 28% of the recurrences were asymptomatic and clinical occult, and were all detected by PET/CT
- Asymptomatic patients with metastases detected by PET/CT had a significant survival benefit compared to patients diagnosed in a symptomatic stage
- Secondary primary malignancies occurred with an estimated incidence of 5% for each year after the end of treatment, of which almost half were detected by PET/CT

Conclusion

This retrospective analysis, carried out at a single institution, adds new insights to the current debate on the role of PET/CT scans during the follow up of head and neck SCC. The importance in detection of clinical occult recurrences and secondary primary malignancies was confirmed. In addition, PET/CT showed high specificity and negative predictive value for all time intervals. However, sensitivity varied considerably and no benefit for survival could be demonstrated for locoregional recurrence.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S0022215123001214.

Data availability statement. Only anonymous data were processed. All data and materials as well as software applications support the published claims and comply with field standards.

https://doi.org/10.1017/S0022215123001214 Published online by Cambridge University Press

Competing interests. None declared

References

1 Denaro N, Merlano MC, Russi EG. Follow-up in head and neck cancer: do more does it mean do better? A systematic review and our proposal based on our experience. *Clin Exp Otorhinolaryngol* 2016;**9**:287–97
2 Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet* 2008;**371**:1695–709
3 Rafferty MA, O'Dwyer TP. Secondary primary malignancies in head and neck squamous cell carcinoma. *J Laryngol Otol* 2001;**115**:988–91
4 Panosetti E, Luboinski B, Mamelle G, Richard JM. Multiple synchronous and metachronous cancers of the upper aerodigestive tract: a nine-year study. *Laryngoscope* 1989;**99**:1267–73
5 Vikram B. Changing patterns of failure in advanced head and neck cancer. *Arch Otolaryngol* 1984;**110**:564–5
6 Zafereo ME, Hanasono MM, Rosenthal DI, Sturgis EM, Lewin JS, Roberts DB *et al.* The role of salvage surgery in patients with recurrent squamous cell carcinoma of the oropharynx. *Cancer* 2009;**115**:5723–33
7 Sheikhbahaei S, Taghipour M, Ahmad R, Fakhry C, Kiess AP, Chung CH *et al.* Diagnostic accuracy of follow-up FDG PET or PET/CT in patients with head and neck cancer after definitive treatment: a systematic review and meta-analysis. *AJR Am J Roentgenol* 2015;**205**:629–39
8 Isles MG, McConkey C, Mehanna HM. A systematic review and meta-analysis of the role of positron emission tomography in the follow up of head and neck squamous cell carcinoma following radiotherapy or chemoradiotherapy. *Clin Otolaryngol* 2008;**33**:210–22
9 Abouzied MM, Fathala A, Alsugair A, Muhaideb AIA, Qahtani MHA. Role of fluorodeoxyglucose-positron emission tomography/computed tomography in the evaluation of head and neck carcinoma. *World J Nucl Med* 2017;**16**:257–65
10 National Comprehensive Cancer Network. Head and Neck Cancer Guidelines, version 2.2022. https://www.nccn.org/guidelines
11 Spector ME, Chinn SB, Rosko AJ, Worden FP, Ward PD, Divi V *et al.* Diagnostic modalities for distant metastasis in head and neck squamous cell carcinoma: are we changing life expectancy? *Laryngoscope* 2012;**122**:1507–11
12 Roman BR, Goldenberg D, Givi B, Education Committee of American Head and Neck Society. AHNS Series – Do you know your guidelines? Guideline recommended follow-up and surveillance of head and neck cancer survivors. *Head Neck* 2016;**38**:168–74
13 Heineman TE, Kuan EC, St John MA. When should surveillance imaging be performed after treatment for head and neck cancer? *Laryngoscope* 2017;**127**:533–4
14 Ho AS, Tsao GJ, Chen FW, Shen T, Kaplan MJ, Colevas AD *et al.* Impact of positron emission tomography/computed tomography surveillance at 12 and 24 months for detecting head and neck cancer recurrence. *Cancer* 2013;**119**:1349–56
15 Zätterström U, Boysen M, Evensen JF. Significance of self-reported symptoms as part of follow-up routines in patients treated for oral squamous cell carcinoma. *Anticancer Res* 2014;**34**:6593–9
16 Smith AF, Hall PS, Hulme CT, Dunn JA, McConkey CC, Rahman JK *et al.* Cost-effectiveness analysis of PET-CT-guided management for locally advanced head and neck cancer. *Eur J Cancer* 2017;**85**:6–14
17 Oncologische Centrum UZB. Oncologisch Handboek: Hoofd- en Halstumoren, *Iprova UZbrussel* Version 2015;1–18
18 Sobin L, Gospodarowicz M, Wittekind C. *TNM Classification of Malignant Tumours*, 7th edn. Union for International Cancer Control. Wiley-Blackwell, 2009
19 Hauswald H, Simon C, Hecht S, Debus J, Lindel K. Long-term outcome and patterns of failure in patients with advanced head and neck cancer. *Radiat Oncol* 2011;**6**:70
20 Hall SF, Groome PA, Irish J, O'Sullivan B. The natural history of patients with squamous cell carcinoma of the hypopharynx. *Laryngoscope* 2008;**118**:1362–71
21 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;**68**:7–30
22 Leemans CR, Tiwari R, Nauta JJ, van der Waal I, Snow GB. Recurrence at the primary site in head and neck cancer and the significance of neck lymph node metastases as a prognostic factor. *Cancer* 1994;**73**:187–90
23 Su W, Miles BA, Posner M, Som P, Kostakoglu L, Gupta V *et al.* Surveillance imaging in HPV-related oropharyngeal cancer. *Anticancer Res* 2018;**38**:1525–9
24 Nauta IH, Rietbergen MM, van Bokhoven AAJD, Bloemena E, Witte BI, Heideman DAM *et al.* Evaluation of the 8th TNM classification on p16-positive oropharyngeal squamous cell carcinomas in the Netherlands, and the importance of additional HPV DNA-testing. *Ann Oncol* 2018;**29**:1273–9
25 Subramaniam RM, Alluri KC, Tahari AK, Aygun N, Quon H. PET/CT imaging and human papilloma virus-positive oropharyngeal squamous cell cancer: evolving clinical imaging paradigm. *J Nucl Med* 2014;**55**:431–8
26 Khuri FR, Lee JJ, Lippman SM, Kim ES, Cooper JS, Benner SE *et al.* Randomized phase III trial of low-dose isotretinoin for prevention of second primary tumors in stage I and II head and neck cancer patients. *J Natl Cancer Inst* 2006;**98**:441–50
27 Ha PK, Califano JA. The molecular biology of mucosal field cancerization of the head and neck. *Crit Rev Oral Biol Med* 2003;**14**:363–9
28 Kytö E, Haapio E, Minn H, Irjala H. Critical review of the follow-up protocol for head and neck cancer patients. *J Laryngol Otol* 2019;**133**:424–9
29 Senft A, Yildirim G, Hoekstra OS, Castelijns JA, René Leemans C, de Bree R. The adverse impact of surveillance intervals on the sensitivity of FDG-PET/CT for the detection of distant metastases in head and neck cancer patients. *Eur Arch Otorhinolaryngol* 2017;**274**:1113–20
30 Jayaram SC, Muzaffar SJ, Ahmed I, Dhanda J, Paleri V, Mehanna H. Efficacy, outcomes, and complication rates of different surgical and non-surgical treatment modalities for recurrent/residual oropharyngeal carcinoma: A systematic review and meta-analysis. *Head Neck* 2016;**38**:1855–61