Clinical value of $^{18}$FDG PET/CT in screening for distant metastases in head and neck squamous cell carcinoma

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Objectives: The detection of distant metastases is of major importance in management of head and neck squamous cell carcinoma patients.

Design: All patients underwent $^{18}$FDG PET/CT for the detection of distant metastases.

Setting: Retrospective single-centre study.

Participants: Head and neck squamous cell carcinoma patients with high-risk factors for distant metastases.

Main outcome measures: Accuracy of $^{18}$FDG PET/CT for the detection of distant metastases using clinical development of distant metastases and a minimal follow-up of twelve months as reference standard. Comparison of overall survival between patients diagnosed with distant metastases during initial screening and patients diagnosed with distant metastases during follow-up.

Results: In 23 (12%) of the 190 patients, $^{18}$FDG PET/CT detected distant metastases at screening. Sensitivity and negative predictive value were 46.2% (95% CI 32.6-59.7) and 82.6% (95% CI 76.8-88.5). No difference in median overall survival from the time of distant metastases detection was found between patients diagnosed with DM during work-up or during follow-up.

Conclusions: In head and neck squamous cell carcinoma patients with high-risk factors, $^{18}$FDG PET/CT has a high negative predictive value for the detection of distant metastases and should be used in daily clinical practice, although the sensitivity is limited when long-term follow-up is used as reference standard.

INTRODUCTION

Distant metastases are major determinants in both management and prognosis of head and neck squamous cell carcinoma (HNSCC) patients. Patients diagnosed with distant metastases are generally considered incurable and will undergo palliative treatment. Thus, futile extensive curative treatment can be prevented with careful screening for distant metastases during initial work-up. The time of diagnosis of distant metastasis (during pre-treatment diagnostic work-up or follow-up) may be important for overall survival.

The reported prevalence of distant metastases detected during pre-treatment diagnostic work-up in HNSCC patients varies from 2% to 26%, depending on the selected group of patients (eg stage of disease, locoregional control). Due to the relatively low prevalence of distant metastases, it is important to identify patients who are most at risk of developing distant metastases and screen these patients with the best diagnostic techniques. High-risk factors have been identified (Table 1). The most frequent sites of distant metastases are the lungs, followed by the skeletal system and the liver.
The combination of whole-body 18FDG PET and contrast-enhanced PET is able to detect distant metastases not detected by chest CT.

18FDG PET/CT has taken a major role in screening for distant metastases in head and neck cancer, as it combines functional (metabolic) and integrated PET/CT imaging (MRI) of the head and neck. If considered indicated, ultrasonography and/or magnetic resonance imaging (MRI) of the head and neck. If considered indicated, ultrasound guided) fine needle aspiration of cervical lymph nodes was performed. Post-treatment follow-up was performed by regular visits to the outpatient clinic (every 6-8 weeks in the first year, with increasing intervals in following years). No routine imaging was planned to screen for distant metastases, but additional examination was performed when suspicion arose based on patient history or physical examination (e.g., weight loss, lesions/complaints suspicious of recurrence).

2.2 Combined 18FDG-PET/CT imaging

During our study period, both the Gemini TF-64 and Ingenuity TF-integrated PET/CT systems (Philips Medical Systems, Best, The Netherlands) were used to perform whole-body (from mid-thighs to skull vertex) 18FDG PET/CT scans. The CT scans were low-dose non-contrast made for attenuation correction and anatomical correlation of PET, as well as CE-CT of the chest during the same session. Patients fasted for at least 6 hours prior to scanning, which started...
approximately 60 minutes after intravenous $^{18}$FDG administration. The dose administered was 2.5 MBq/kg body weight ($\pm$10%). Glucose levels were measured prior to $^{18}$FDG administration. Image acquisition and reconstruction were performed according to the EANM 1.0 procedure guidelines.22

The $^{18}$FDG PET/CT images were interpreted by experienced nuclear medicine physicians and radiologists who had access to all relevant clinical information, according to common clinical practice. We scored what suspicion arose from the $^{18}$FDG PET/CT using the written report of each scan. Most lesions suspicious of being malignant on $^{18}$FDG PET/CT were confirmed using additional (follow-up) imaging, endoscopic work-up and/or biopsy, using a rational approach. In some cases, findings of $^{18}$FDG PET/CT were considered equivocal proof of distant metastases and consensus was reached not to perform additional work-up by the multidisciplinary team (giving the patient the benefit of the doubt). If tissue of both the primary process and the suspicious lesion outside of the head and neck region was obtained, and consisted of identical cell types, preferably a loss of heterozygosity analysis was performed.

2.3 Statistical analysis

The reference (gold) standard used was follow-up of 12 months. Sensitivity, specificity, positive and negative predictive values of the $^{18}$FDG PET/CT for detection of distant metastases were calculated. $^{18}$FDG PET/CT findings suspicious of being metastases were considered positive. Equivocal findings were scored as negative because patients with equivocal findings cannot be withheld from curative treatment. As in clinical practice, these patients were treated with curative intent. If no suspicious lesion or lesions suspicious of being either benign or second primary tumours were found, the scan was considered negative. The $^{18}$FDG PET/CT findings were compared to the findings of further initial work-up and findings during follow-up. We considered negative findings on $^{18}$FDG PET/CT in patients who developed distant metastases during follow-up as being false negative, assuming these metastases were (subclinically) present at time of screening. In a separate analysis, these results were corrected for locoregional recurrence, as no distinction can be made between growth of subclinical metastases already present at the time of screening and reseeding of a locoregional recurrence after initial screening.

Overall survival (OS) was estimated using the Kaplan-Meier method and compared between groups using the log-rank test. The OS was measured from the time of initial $^{18}$FDG PET/CT screening as well as from the time of detection of distant metastases during follow-up until the date of death. We compared the survival of the following groups: patients without distant metastases vs those with distant metastases and patients diagnosed with distant metastases during initial work-up vs those diagnosed with distant metastases during follow-up.

Patients with second primary tumours outside the head and neck region, which were found during screening, were described separately. Significance was attributed to a P-value less than .05 ($P < .05$). All calculations were performed using spss 22.0 for Windows.

### RESULTS

A total of 190 patients who underwent an $^{18}$FDG PET/CT between 2009 and 2014 were included. Patient and tumour characteristics are summarised in Table 2. Median follow-up was 21 months (range: 0-62 months), in which every patient not succumbing to distant metastases had a follow-up exceeding 12 months.

3.1 Accuracy of $^{18}$FDG PET/CT

Table 3 quantifies the suspicion based on the $^{18}$FDG PET/CT scan and the conclusion after initial diagnostic work-up and follow-up. In total, 51 of 190 patients (26.8%) were diagnosed with distant metastases.

During pre-treatment screening, $^{18}$FDG PET/CT identified 29 patients (15.3%) with at least one lesion suspicious of distant metastasis. Further work-up confirmed the presence of distant metastases in 23 (12.1%) of these patients. In one patient, a second primary tumour was diagnosed. In the remaining five patients, work-up of the suspicious lesion and follow-up showed no evidence of

| **TABLE 2** Patient population (n = 190) |
|----------------------------------------|
| Characteristics                       | No. of patients | Percentage (%) |
| **Age:** years mean±SD                | 61.0 ± 9.2      | (30.2 – 87.0)  |
| **Gender:** male/female               | 137/53          | 72/28          |
| **Tumour location**                   |                |                |
| Oral cavity                          | 32              | 16.8           |
| Oropharynx                           | 78              | 41.1           |
| Hypopharynx                          | 31              | 16.3           |
| Larynx                               | 29              | 15.3           |
| Unknown primary                      | 12              | 6.3            |
| Cervical oesophagus                  | 8               | 4.2            |
| **T-classification**                  |                |                |
| T1                                    | 25              | 13.2           |
| T2                                    | 54              | 28.4           |
| T3                                    | 34              | 17.9           |
| T4a                                   | 49              | 25.8           |
| T4b                                   | 16              | 8.4            |
| Tx                                    | 12              | 6.3            |

| **TABLE 3** Accuracy of the $^{18}$FDG PET/CT in screening for distant metastases |
|----------------------------------------|
| Metastases | No metastases | Total |
|------------|--------------|-------|
| $^{18}$FDG PET/CT positive | 23 ± 1* | 5 | 29 |
| $^{18}$FDG PET/CT negative | 28 | 133 | 161 |
| **Total** | 51 ± 1* | 138 | 190 |

* $^{18}$FDG PET/CT could not differentiate between second primary lung cancer and DM, considered true positive.
malignancy. Twenty-eight patients with a negative $^{18}$FDG PET/CT screening were diagnosed with distant metastases during follow-up. Based on these numbers, the sensitivity of $^{18}$FDG PET/CT in detecting distant metastases in this high-risk patient cohort was 46.2% (95% CI 32.6-59.7%), at a specificity of 96.4% (95% CI 93.3-99.5%), corresponding with positive and negative predictive values of 82.8% (95% CI 69.0-96.5%) and 82.6% (95% CI 76.8-88.5%), respectively (Table 3). In the 123 patients achieving locoregional control, sensitivity, specificity, positive and negative predictive values were 48.4% (95% CI 30.8-66.0%), 94.6% (95% CI 89.9-99.2%), 75.0% (95% CI 56.0-94.0%) and 84.5% (95% CI 77.7-91.5%), respectively.

3.2 | Survival

Median OS in patients with distant metastases was significantly worse compared to patients without distant metastases ($P < .001$) (Figure 1). OS from time of detection of patients in whom distant metastases were found during follow-up (median 6 months, 95% CI 0.5-11.5) when compared to patients diagnosed with distant metastases during screening (median 7 months, 95% CI 5.2-8.8) was not significantly different ($P = .8$). Median delay of diagnosis in the former group was 7 months (range 1-47 months). When comparing the OS from the time of initial screening, the patients diagnosed with distant metastases at initial screening (7 months, 95% CI 5.2-8.8) have a significantly worse expected survival ($P = .001$) compared to the group diagnosed during follow-up (16 months, 95% CI 11.9-20.1).

3.3 | Second primary tumours

In twenty-four patients (12.6%), the initial $^{18}$FDG PET/CT was suspicious for second primary tumours outside of the head and neck region. In ten patients, the detected lesions were suspicious of being either distant metastases or second primary tumours. Five of these lesions proved to be distant metastases through further work-up and were classified as true positive in Table 3. Of the remaining 19 patients (all classified as true negative for distant metastases), work-up revealed 11 lesions (57.9%) to be second primary tumours, whereas in the other cases further work-up of the lesion showed no signs of malignancy. Table 4 depicts the number of lesions found in each organ (system).

4 | DISCUSSION

4.1 | Prevalence

In our cohort, 51 of 190 patients (26.8%) developed distant metastases, which is at the high end of the percentages found in previous studies. This can be explained by our definition of the high-risk patient and our follow-up duration. We included also patients with a previous malignancy of the head and neck region and/or recurrent disease, whereas other studies included only patients with previously untreated head and neck cancer. The prevalence of distant metastases found by Haerle et al and Kim et al is lower compared to our findings, 19.7% and 7.4%, respectively. Haerle et al specified the inclusion criteria to high-risk patients with clinically advanced HNSCC (T3/4 and/or N2/3), whereas Kim et al included all patients with head and neck cancer. Recurrent disease is a previously identified important risk factor for development of distant metastases.

4.2 | $^{18}$FDG PET/CT

At first glance, the sensitivity of PET/CT to detect distant metastases in our study seems to be considerably lower than in other studies (Table 3). This difference can partly be explained by the duration of follow-up: we considered all distant metastases identified during follow-up and negative on initial $^{18}$FDG PET/CT, as false negative. Thus, in the present study, long-term follow-up was used as reference standard. Moreover, in this study, the findings were corrected
for locoregional recurrence in a separate analysis, as no distinction can be made between growth of subclinical metastases already present at the time of screening and reseeding of a locoregional recurrence after initial screening in patients with locoregional recurrence.

We applied this approach to the large studies published by Haerle et al. and Kim et al., which contain information on long-term follow-up and locoregional control. Haerle et al. considered all cases of distant metastases detected only within six months of follow-up (metachronous) as being true negative, but provided further follow-up data on later development of distant metastases. Kim et al. considered all distant metastases found during follow-up using the 18FDG PET/CT true positive. Using the published data of both studies, we calculated the accuracy of the 18FDG PET/CT in which all distant metastases found after negative initial screening were interpreted as false negative. This approach resulted in similar findings when compared to our found accuracy (Table 5). The sensitivity is close to 50%, and the specificity remained high in all three studies. The notable decrease in positive predictive value in Kim et al. is caused by 17 cases originally interpreted as true positive (distant metastases detected during follow-up using the 18FDG PET/CT, but not detected during pre-treatment screening), which in our approach are considered false negative. Cho et al. found several adverse prognostic factors in HNSCC patients with newly diagnosed distant metastases who underwent 18FDG PET/CT in their series in 94 (4.1%) patients, distant metastases were detected during initial diagnostic work-up (including 18FDG PET/CT) and in 118 (5.3%) patients during follow-up, resulting in a sensitivity of 44.8%.

Regarding the limited sensitivity of 18FDG PET/CT to detect distant metastases, there is room for improvement and development of new techniques. New diagnostic tests in detection of distant metastases in head and neck cancer are being investigated. The development of whole-body MR imaging including diffusion-weighted imaging with background-body-signal suppression (DWIBS) has made MRI an interesting modality in screening for distant metastases.

### 4.4 Limitations

In the present study, we did not analyse the tumour burden of distant metastases. The role of performing aggressive treatment of distant sites of disease was arguably more controversial given its questionable therapeutic benefit. However, the concept of treating oligometastases, successful for some other neoplasms, has recently been reintroduced in HNSCC and may change the treatment paradigm. If locoregional disease (if still present) is controlled, or
resected, and the distant sites are ablated (surgically or with radiation), a prolonged disease-free interval, and possible cure, may be achieved. More research is needed to develop a new protocol for screening for distant metastases after implementation of the concept of treating oligometastases in HNSCC.

Another limitation of this study is potential bias in comparing survival of patients with distant metastases diagnosed at initial screening and follow-up due to different treatment regimens in these groups of patients. However, overall survival of patients with distant metastases detected during follow-up suggests that initial locoregional treatment with curative intent may be worthwhile in these patients with negative screening by PT/CT at initial work-up.

5 CONCLUSION

Head and neck squamous cell carcinoma patients with low jugular lymph node metastases or regional recurrence have the highest risk of distant metastases. Patients diagnosed with distant metastases at initial screening have a significantly worse expected survival (from time of initial screening) compared to the group diagnosed during follow-up. In HNSCC patients with high-risk factors, 18FDG PET/CT (including chest CE-CT) has a high negative predictive value for the detection of distant metastasis and should be part of the initial diagnostic work-up, although the sensitivity is limited when long-term follow-up is used as reference standard.

CONFLICT OF INTEREST

The authors have nothing to disclose.

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