Head-to-Head Comparison of Chest X-Ray/Head and Neck MRI, Chest CT/Head and Neck MRI, and ^{18}F-FDG PET/CT for Detection of Distant Metastases and Synchronous Cancer in Oral, Pharyngeal, and Laryngeal Cancer

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The purpose of this study was to determine the detection rate of distant metastasis and synchronous cancer, comparing clinically used imaging strategies based on chest x-ray + head and neck MRI (CXR/MRI) and chest CT + head and neck MRI (CHCT/MRI) with ^{18}F-FDG PET/CT upfront in the diagnostic workup of patients with oral, pharyngeal, or laryngeal cancer. **Methods:** This was a prospective cohort study based on paired data. Consecutive patients with histologically verified primary head and squamous cell carcinoma at Odense University Hospital from September 2013 to March 2016 were considered for the study. Included patients underwent CXR/MRI and CHCT/MRI as well as PET/CT on the same day and before biopsy. Scans were read masked by separate teams of experienced nuclear physicians or radiologists. The true detection rate of distant metastasis and synchronous cancer was assessed for CXR/MRI, CHCT/MRI, and PET/CT. **Results:** A total of 307 patients were included. CXR/MRI correctly detected 3 (1%) patients with distant metastasis, CHCT/MRI detected 11 (4%) patients, and PET/CT detected 18 (6%) patients. The absolute differences of 5% and 2%, respectively, were statistically significant in favor of PET/CT. Also, PET/CT correctly detected 25 (8%) synchronous cancers, which was significantly more than CXR/MRI (3 patients, 1%) and CHCT/MRI (6 patients, 2%). The true detection rate of distant metastasis or synchronous cancer with PET/CT was 13% (40 patients), which was significantly higher than 2% (6 patients) for CXR/MRI and 6% (17 patients) for CHCT/MRI. **Conclusion:** A clinical imaging strategy based on PET/CT demonstrated a significantly higher detection rate of distant metastasis or synchronous cancer than strategies in current clinical imaging guidelines, of which European ones primarily recommend CXR/MRI, whereas U.S. guidelines preferably point to CHCT/MRI in patients with head and neck squamous cell carcinoma.

Key Words: detection rate; distant metastases; HNSCC; MRI; PET/CT; synchronous cancer

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Distant metastases and synchronous cancers at the time of diagnosis are serious occurrences that have a significant impact on treatment decisions in otherwise good-prognosis patients with oral, pharyngeal, or laryngeal squamous cell carcinoma (*1,2*). The incidence of distant metastasis and synchronous cancer in head and neck squamous cell carcinoma (HNSCC) patients has been reported around 10%–18% depending on the primary tumor site (i.e., oral cavity, pharynx, or larynx), stage, and the applied diagnostic imaging modalities (*3–9*).

Distant metastases rarely occur at the time of diagnosis of HNSCC, but will in most cases lead to a palliative treatment strategy (*10,11*). Synchronous cancers, on the other hand, are found even in patients with early-stage HNSCC (*12*). Precise diagnostic assessment of tumor extension is, therefore, important in any incident case or suspicion of HNSCC to determine the most relevant treatment approach.

With the purpose to reduce waiting time for diagnosis and treatment, a head and neck cancer fast-track program was introduced in Denmark in 2007 (*13*) and it is now implemented nationally. The program includes a clinical imaging strategy (performed before biopsy) with chest x-ray + head and neck MRI (CXR/MRI) for suspected oral, pharyngeal, or laryngeal cancer (*14*). The European guidelines from the European Head & Neck Society and the European Society for Medical Oncology also recommend standard CXR/MRI and consideration of chest CT + head and neck MRI (CHCT/MRI) to rule out distant metastasis and synchronous cancer (*15*). CXR is thus routinely used for tumor assessment outside the head and neck region in many European head and neck cancer centers, whereas ^{18}F-FDG PET/CT is recommended only for evaluating patients with malignant cervical adenopathy from an

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unknown primary tumor. The U.S. National Comprehensive Cancer Network guidelines recommend CHCT/MRI for oral, pharyngeal, or laryngeal cancer, and to consider PET/CT for clinical stage 3–4 patients (*16*). However, recent studies have demonstrated PET/CT as a more sensitive imaging modality (*4,17–19*).

The objective of this study was to determine the detection rate of distant metastasis and synchronous cancer comparing clinical imaging strategies based on CXR/MRI and CHCT/MRI with PET/CT upfront in the diagnostic workup of patients with oral, pharyngeal, or laryngeal cancer.

MATERIALS AND METHODS

A masked prospective cohort study based on paired data was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology statement (*20*).

Setting and Participants

Consecutive patients with suspected primary oral, pharyngeal, or laryngeal carcinoma who were referred to the Head and Neck Cancer Center, Odense University Hospital, from September 2013 to March 2016 were considered for the study. At the initial contact, a clinical head and neck examination, including nasopharyngo laryngoscopy and ultrasound of the neck, was performed by an experienced head and neck cancer specialist. If the suspicion of HNSCC was confirmed, the patient was offered inclusion in the study.

Exclusion criteria were allergy or intolerance to contrast, treatment with high doses of systemic steroids (>50 mg/d), reduced kidney function (defined as elevated serum creatinine or diagnosed kidney disease), or being considered unable to cooperate.

Patients underwent CXR/MRI, CHCT/MRI, and PET/CT on the same day, and upfront (i.e., before biopsy and histologic evaluation). To minimize irradiation, the CHCT was derived from the PET/CT examinations, which were performed as full diagnostic CTs (not attenuation-correction scans). Patients with histologically verified HNSCC constituted the study population and were used for analysis regarding detection of distant metastasis or synchronous cancer.

Imaging Techniques

PET/CT data were acquired on a hybrid PET/CT scanner (Discovery 690, 710, VCT, or RX; GE Healthcare).

^{18}F-FDG (4 MBq/kg) was injected intravenously after a fasting period of at least 4 h. The PET scan was obtained using a standard whole-body acquisition protocol extending the vertex to the thigh, and an acquisition time of 2.5 min per bed position. PET data were reconstructed into transaxial slices with a matrix size of 128 × 128 (pixel size, 5.47 mm) or 256 × 256 (pixel size, 2.73 mm) and a slice thickness of 3.27 mm using iterative 3-dimensional ordered-subset expectation maximization. Multislice, diagnostic-quality CT scans with intravenous contrast medium (Ultravist [Bayer]; 370 mg/mL) were acquired after the PET scan. The CT scan was obtained with continuous shallow breathing. Data were reconstructed with a standard filter into transaxial slices with a field of view of 50 cm, matrix size of 512 × 512 (pixel size, 0.98 mm), and a slice thickness of 3.75 mm. The scan field of view was 70 cm for both PET and CT scans. PET/CT was analyzed on an Advantage Workstation (version 4.4 or 4.3; GE Healthcare) or AW Server (version 3.1 or 3.2; GE Healthcare).

MRI was performed using Achieva, Achieva dStream, or Ingenia 1.5T (Philips) hardware with 20-channel (dStream) head–neck coil. The examination protocol was kept unchanged for the duration of the study and consisted of short tau inversion recovery (STIR), turbo spin echo (TSE)-T2, and TSE-T1 with and without contrast enhancement, in axial or coronal planes with coverage from skull base to aortic arch using 5-mm slices. Diffusion-weighted imaging with spectral fat saturation and apparent diffusion coefficient maps derived from b values 0 and 1,000 mm^2/s were done in axial 6-mm slices. Images were read on a Centricity RA1000 PACS workstation (GE Healthcare). The acquisition parameters of the MRI sequences are displayed in Supplemental Table 1 (supplemental materials are available at http://jnm.snmjournals.org).

CXR was performed to departmental standards in full inspiration anteroposterior and lateral projections with 130–145 kV and automatic exposure control. FD-X hardware systems (Siemens Healthineers) were used, and studies were read using a Centricity RA1000 PACS workstation (GE Healthcare) with dual 3MP medical-grade monitors.

Image Interpretation

The 3 applied imaging modalities were evaluated separately. The MRIs and the CXRs were evaluated by 2 experienced head and neck radiologists. The chest CTs were all evaluated by 1 radiologist. PET/CT was evaluated by a team consisting of 2 experienced radiologists and 2 nuclear physicians. Standard forms including variables concerning distant metastasis or synchronous cancers were filled out by each team during imaging evaluation. The same referral text was used for each of the evaluation sessions and the teams were masked to one another (Fig. 1).

The interpretation of distant metastases and synchronous cancers relied on pattern recognition of anatomic information (i.e., morphologic changes, altered signal intensity, contrast enhancement, changes in diffusivity) and metabolic information regarding ^{18}F-FDG avidity for PET. Malignant lesions were suspected when considered more likely than benign lesions.

For lymph nodes, the following characteristics were considered: enlargement, round shape, absence of fatty hilum, necrosis, dense center, topography of node distribution, and ^{18}F-FDG avidity for PET.

For CT, lung lesions were considered distant metastases if one or more nodules were present. Small subpleural nodules (especially when calcified) were not considered metastases on CT unless multiple were present. By PET/CT, ^{18}F-FDG avidity of the nodules assisted in the determination of malignancy or not. Lung lesions in the field of view of the MRI were considered suggestive, when the configuration was nodulary or spiculary and not consistent with infectious pattern. Distant metastases were suspected on CXR, when opacification was not consistent with infectious pattern.

For PET/CT, bone lesions were regarded as metastases, when ^{18}F-FDG–avid osteolytic (or osteosclerotic) lesions were present. Significantly increased ^{18}F-FDG uptake in the bone marrow even without the lytic or sclerotic changes was also regarded as metastases. Lesions close to the joints were rarely considered metastases. Regarding MRI, focal signal changes on T2 and STIR and presence of enhancement were observed, but as these may vary, only lesions appearing with low signal of T1 were considered suggestive of metastasis. Osteolytic or osteosclerotic changes on CXR were considered suggestive of bone metastasis.

For PET/CT, liver metastases and malignant pleural effusion were suspected only in lesions with significantly increased ^{18}F-FDG uptake as compared with the surroundings. Muscle metastases were suspected in patients with randomly distributed focal areas of increased ^{18}F-FDG uptake in the muscles and corresponding morphologic changes. Longitudinal muscular ^{18}F-FDG uptake was considered to be physiologic.

Synchronous cancers were suspected if tumors were present in organs, atypical of nesting metastases. Other parameters were also weighted, for instance, the size and the ^{18}F-FDG intensity (i.e., for PET) of the primary compared with the suspected synchronous tumor. Likewise, the pattern of spread and possible gaps between lymph node stations were taken into consideration. Regarding lung lesions, the presence of spicules and hilar lymph nodes by CT helped determine whether these represented a metastasis or a synchronous cancer.

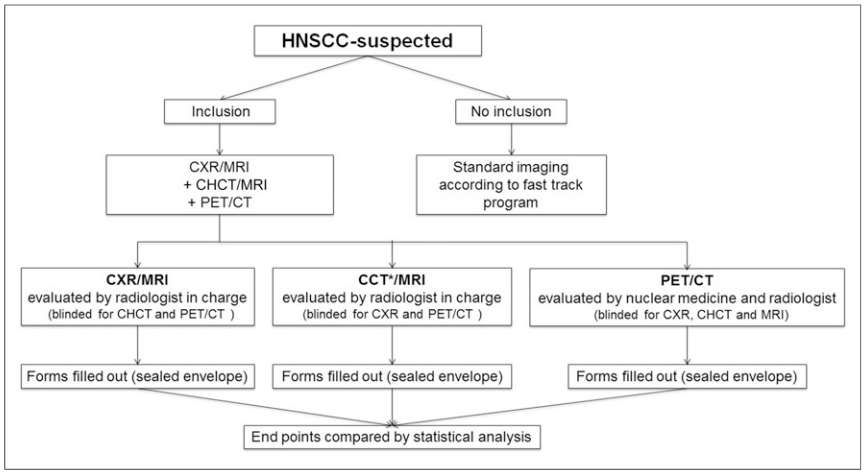

FIGURE 1. Diagram of patient inclusion and image interpretation. *Extracted from PET/CT.

Reference Standard

Verification of metastatic disease or synchronous cancer (i.e., true detection rate [TDR]) was confirmed by histology, cytology, or follow-up imaging (within 6 mo) as reference standard. When only imaging was available as a validator, we applied the RECIST for measurable lesions and progression (*21*). Only lesions fulfilling the RECIST for progression were characterized as metastatic disease or synchronous cancer.

Sample Size

We assumed a detection rate of distant metastasis or synchronous cancer of only 4%–8%, as we also included patients with a low risk of distant metastasis (e.g., small glottic cancers). Furthermore, we anticipated a drop-out rate of 20% and that 2% of cases would be detected by both CXR/MRI and PET/CT. This resulted in an estimated sample size of 366 patients. However, a predetermined interim analysis of 149 patients demonstrated a detection rate of 13% for PET/CT and only 1% for CXR/MRI, and a drop-out rate of less than 5%; thus, an adequate sample size was obtained.

Outcomes and Variables

The outcome measure was TDR of distant metastasis and synchronous cancer at the time of diagnosis. TDR was calculated as the proportion of individuals correctly identified as having distant HNSCC metastasis or synchronous cancer (i.e., true-positives). Tables (2×2) containing true-positive CXR/MRI versus PET/CT and CHCT/MRI versus PET/CT were produced to match TDR of distant metastasis or synchronous cancer.

Statistical Analysis

Continuous variables are presented by means and SD (normally distributed variables) or medians and ranges. The McNemar test was performed on differences in paired proportions, and the absolute difference in TDR along with a 95% confidence interval was assessed. *P* values below 0.05 were considered significant. A comparison of TDR for CXR/MRI versus PET/CT and CHCT/MRI versus PET/CT was performed for all subgroups (oral cavity, pharynx, larynx) and presented in forest plots. Moreover, a subgroup analysis for identification of distant metastasis or synchronous cancer in stage 1–2 and stage 3–4, and N0 neck and N+ neck patients, based on clinical examination was performed.

All analyses were performed with Stata/IC 14 (StataCorp LP).

Ethics and Disclosures

This study was conducted in accordance with good clinical practice and the Declaration of Helsinki. Permission was granted from the local ethics committee (project ID S_20120217), and informed consent was obtained from all included patients. The project was implemented without the involvement of private organizations or companies.

TABLE 1
Basic Clinical Characteristics of HNSCC Patients ($n = 307$)

Clinical characteristic	Patient	%
Median age (y)	64 (range, 22–89)	
Sex		
Men	227	74
Women	80	26
Tumor site		
Oral cavity	147	48
Pharynx	103	34
Larynx	57	18
Clinical TNM classification*		
Stage 1–2/3–4	166/141	54/46
N0/N+	183/124	60/40
p16 status		
Negative/positive	242/65	79/21

*Based on clinical head and neck examination including only nasopharyngo laryngoscopy and ultrasound of neck.

RESULTS

A total of 307 patients were included in the study, with basic clinical characteristics as outlined in Table 1. A flowchart of patient selection is presented in Figure 2.

CXR/MRI correctly detected 3 (1%) patients with distant metastasis, CHCT/MRI detected 11 (4%) patients, and PET/CT detected 18 (6%) patients. The differences of 5% and 2%, respectively, were statistically significant in favor of PET/CT (Tables 2 and 3). PET/CT also correctly detected 25 (8%) synchronous cancers, which was significantly more than CXR/MRI (3 patients, 1%) and CHCT/MRI (6 patients, 2%). The TDR of distant metastasis or synchronous cancer with PET/CT was thus 13% (40 patients), which was significantly higher than the 2% (6 patients) for CXR/MRI and 6% (17 patients) for CHCT/MRI. The results are illustrated graphically in forest plots in Supplemental Figures 1 and 2.

For patients with clinical stage 1–2, CXR/MRI correctly detected 1% (1 patient) with distant metastasis or synchronous cancer, CHCT/MRI detected 4% (7 patients), and PET/CT detected 10% (17 patients). The differences of 10% and 6%, respectively, were statistically significant in favor of PET/CT (Supplemental Tables 2 and 3). Also, in patients with clinical stage 3–4, PET/CT correctly detected 23 (16%) distant metastasis or synchronous

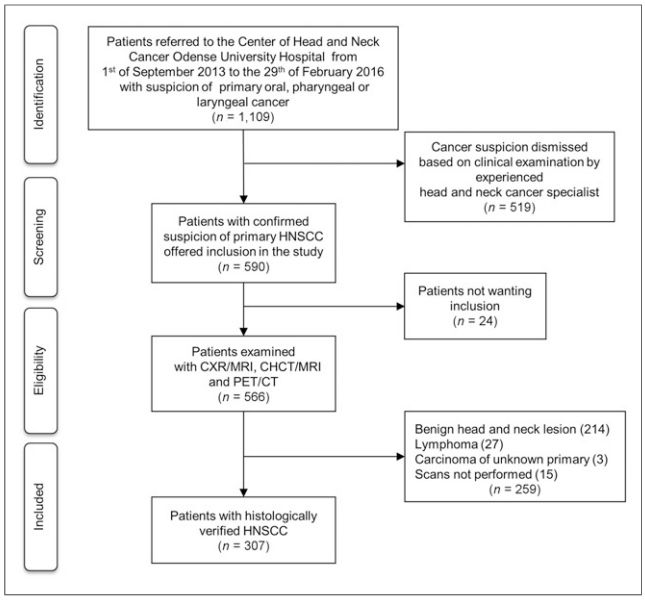

FIGURE 2. Flowchart of patient selection.

cancers, which was significantly greater than with CXR/MRI (5 patients, 4%) and CHCT/MRI (10 patients, 7%).

The TDR of distant metastasis or synchronous cancer in patients with N0 neck with PET/CT was 16% (21 patients), which was significantly more than the 1% (1 patient) with CXR/MRI and 4% (7 patients) with CHCT/MRI. Last, in patients with clinical N+ neck, PET/CT correctly detected 15% (19 patients) with distant metastasis or synchronous cancer, which was significantly higher than 4% (5 patients) with CXR/MRI and 8% (10 patients) with CHCT/MRI.

All of the 18 patients with metastatic disease had involvement of the thoracic region, with the lungs (72%) as the primary metastatic site, followed by mediastinal lymph nodes (28%), bone (22%), liver (11%), pleura (6%), and muscles (6%) (Supplemental Table 4).

Supplemental Table 4 shows the sites of the 25 detected synchronous cancers. The most frequent sites were head and neck (20%), lung (16%), and lymph nodes (malignant lymphoma) (12%).

The reference standards applied for verification of distant metastasis and synchronous cancer are shown in Supplemental Table 6. In patients with distant metastases, 84% of cases were confirmed with follow-up imaging, 8% with histology, and 8% with cytology. All of the synchronous cancers were confirmed by histology.

DISCUSSION

This masked prospective cohort study evaluated upfront imaging for detection of distant metastasis and synchronous cancer in HNSCC patients in a fast-track diagnostic program. We found significantly higher TDRs of distant metastasis or synchronous cancer with an imaging strategy based on PET/CT compared with strategies with CXR/MRI or CHCT/MRI. PET/CT was especially valuable in patients with squamous cell carcinoma of the oral cavity and pharynx, whereas the trend was less clear in patients with laryngeal cancer, likely due to the lower metastatic potential of this disease as well as a relatively low number of cases compared with the other groups.

In line with our results, Kim et al. (*22*) demonstrated a PET/CT detection rate of 7% for distant metastasis in patients with newly diagnosed primary HNSCC. Concerning synchronous cancers, Strobel et al. (*23*) showed a detection rate with PET/CT of 9%. In both studies, biopsy and histologic evaluation of the head and neck cancer were performed before the PET/CT scan.

Synchronous cancers may affect treatment decisions in patients with localized HNSCC (*24,25*), and the use of PET/CT may improve patient survival because of a higher detection rate of early-stage synchronous cancer. Furthermore, we found that more than half of the synchronous cancers detected by PET/CT were located

TABLE 2
TDR of Distant Metastasis and Synchronous Cancer for CXR/MRI of Head and Neck Versus ^{18}F-FDG PET/CT in 307 HNSCC Patients

HNSCC patients (n = 307)	PET/CT	CXR/MRI	Absolute difference in %	P
Distant metastasis	18 (6%)	3 (1%)	5% (2%–8%)	<0.001
Oral cavity (n = 147)	8 (5%)	1 (1%)	5% (1%–9%)	0.02
Pharynx (n = 103)	7 (7%)	1 (1%)	6% (0.1%–11%)	0.03
Larynx (n = 57)	3 (5%)	1 (2%)	4% (−3%–10%)	0.50
Synchronous cancer	25 (8%)	3 (1%)	7% (4%–10%)	<0.001
Oral cavity (n = 147)	13 (9%)	1 (1%)	8% (3%–13%)	<0.001
Pharynx (n = 103)	8 (8%)	2 (2%)	6% (0.1%–11%)	0.03
Larynx (n = 57)	4 (7%)	0 (0%)	7% (−1%–15%)	0.13
Distant metastasis or synchronous cancer	40 (13%)	6 (2%)	11% (7%–15%)	<0.001
Oral cavity (n = 147)	20 (14%)	2 (1%)	12% (6%–18%)	<0.001
Pharynx (n = 103)	14 (14%)	3 (3%)	11% (4%–18%)	0.001
Larynx (n = 57)	6 (11%)	1 (2%)	9% (−0.1%–18%)	0.06

Data in parentheses are 95% confidence intervals.

TABLE 3
TDR of Distant Metastasis and Synchronous Cancer for CHCT/MRI of Head and Neck Versus ^{18}F-FDG PET/CT in 307 Patients with HNSCC

HNSCC patients (n = 307)	PET/CT	CHCT/MRI	Absolute difference in %	P
Distant metastasis	18 (6%)	11 (4%)	2% (0.1%–4%)	0.02
Oral cavity (n = 147)	8 (5%)	5 (3%)	2% (−1%–5%)	0.25
Pharynx (n = 103)	7 (7%)	4 (4%)	3% (−1%–7%)	0.25
Larynx (n = 57)	3 (5%)	2 (4%)	2% (−3%–7%)	1.00
Synchronous cancer	25 (8%)	6 (2%)	6% (3%–9%)	<0.001
Oral cavity (n = 147)	13 (9%)	2 (1%)	7% (3%–12%)	0.001
Pharynx (n = 103)	8 (8%)	3 (3%)	5% (−1%–11%)	0.13
Larynx (n = 57)	4 (7%)	1 (2%)	5% (−2%–13%)	0.25
Distant metastasis or synchronous cancer	40 (13%)	17 (6%)	7% (4%–11%)	<0.001
Oral cavity (n = 147)	20 (14%)	7 (5%)	9% (4%–14%)	<0.001
Pharynx (n = 103)	14 (14%)	7 (7%)	7% (0%–13%)	0.04
Larynx (n = 57)	6 (11%)	3 (5%)	5% (−2%–13%)	0.25

Data in parentheses are 95% confidence intervals.

outside the thoracic region and were thus not identified by CXR/MRI or CHCT/MRI, emphasizing the need for a sensitive, whole-body screening imaging modality.

The National Comprehensive Cancer Network guidelines recommend CHCT/MRI for all HNSCC patients, and to consider PET/CT for clinical stage 3–4 patients (*16*). Various contemporary European guidelines, including those from the European Head & Neck Society, the European Society for Medical Oncology, and the Danish Head and Neck Cancer Group, all recommend routine CXR/MRI and consideration of CHCT/MRI to rule out distant metastasis and synchronous cancer (*14,15*). However, in terms of detecting distant metastasis and synchronous cancer, our results clearly show that PET/CT is preferable for all clinical HNSCC stages and regardless of clinical evidence of nodal metastases.

Distant metastases reduce the survival of HNSCC patients (*11,22*). Enhanced assessment of metastatic disease would thus allow more appropriate decisions regarding the optimal treatment strategy. This would be expected to improve the clinical management of a large proportion of patients and to provide more accurate assessment of prognosis. Because similar advantages have been demonstrated in several other cancers (*26*), it is also relevant for health-care providers and policy-makers to consider PET/CT as a possibly more cost-effective approach than conventional imaging modalities.

The strengths of our study include the prospective design, consecutive patients over a 2.5-y period, each patient acting as his or her own control with respect to the imaging modalities, the imaging modalities being performed on the same day with up-to-date technology, assessments by experienced experts masked to the results of the other imaging modalities, and high-quality reference standards. The strengths and validity of paired diagnostic studies versus randomized (controlled) studies have been well described (*27–30*). In a paired-data design, the risk of confounding along with the derived need for stratification analysis are minimized. Other advantages of a paired design are the dependence of the sample size on the agreement rate between the modalities, the multiple aims of diagnostic accuracy studies, and the possibility of early unmasking of results at the individual level. For this reason, we deliberately chose a paired-data design rather than a randomized one.

Comparing PET/CT, which is a whole-body scan, with regional radiologic imaging modalities may seem unfair. However, this study aimed at identifying the detection rate of distant metastasis and synchronous cancer for PET/CT compared with the contemporary clinical imaging strategies used in most head and neck cancer centers. Although all 18 patients were identified by PET/CT as having true-positive distant metastasis metastatic spread to the thorax, PET/CT showed a significantly higher detection rate than CXR/MRI and CHCT/MRI, and neither CXR/MRI nor CHCT/MRI detected malignancies in patients who were PET-negative. Our study design did not, therefore, provide information on patients with a negative PET/CT result (i.e., true-negatives and false-negatives). If false-negative was to be calculated, false-negative for PET/CT would be zero, leading to a sensitivity for PET/CT of 100%. Consequently, it was not possible to assess the true false-negative patients for PET/CT and to calculate the derived accuracy involving sensitivity, specificity, and negative predictive value.

A limitation of our study was that the CT scan was obtained with continuous shallow breathing. Standard CHCT is performed at breath-hold, which is known to be more sensitive, particularly for lung nodules near the base. Furthermore, our study was performed at a single institution, thus restricting the generalizability of the results. Patients suspected of having oral cavity cancer were referred from the entire Region of Southern Denmark, whereas patients with suspected laryngeal and pharyngeal cancer were referred from the smaller region of Funen. Our study population was thus overrepresented by patients with oral cavity cancer.

In the Danish head and neck cancer fast-track program, imaging is performed before biopsy to improve the quality of staging and diagnostic interpretation. Upfront imaging also provides the

opportunity for guided biopsies. The drawback of this approach is that a considerable proportion of patients undergo imaging without having a malignant disease. Therefore, a substantial clinical suspicion of cancer must be present to reduce unnecessary imaging and to ensure relevant inclusion of patients into the program.

CONCLUSION

A clinical imaging strategy based on PET/CT demonstrated a significantly higher detection rate of distant metastasis or synchronous cancer than strategies in current clinical imaging guidelines, of which European ones primarily recommend CXR/MRI, whereas U.S. guidelines preferably point to CHCT/MRI in patients with HNSCC.

DISCLOSURE

We are grateful for the doctoral research grants given by the University of Southern Denmark, the Danish Cancer Society, and the Region of Southern Denmark. No other potential conflict of interest relevant to this article was reported.

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