

Distant metastases and synchronous malignancies on FDG-PET/CT in patients with head and neck cancer: a retrospective study

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Abstract

Background: Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) has been proven to be a good method to detect distant spread of head and neck cancer (HNC). However, most prior studies are based on Asian populations and may not be directly transferable to western populations.

Purpose: To investigate the frequency and distribution of distant metastases and synchronous malignancies detected by PET/CT in HNC in a northern Swedish population.

Material and Methods: All primary whole-body FDG-PET/CT examinations performed on the suspicion of HNC (n = 524 patients) between 1 January 2013 and 31 December 2016 at Umeå University Hospital in Sweden were retrospectively reviewed. After the exclusion of 189 examinations without evidence of primary HNC, 335 examinations were analyzed.

Results: Distant metastases were detected in 10 (3%) patients, all with advanced primary tumors corresponding to TNM stage 3–4, most frequently in salivary gland adenocarcinoma, where 50% of patients had distant spread. Four patients had metastases below the diaphragm, representing 20% of the salivary gland malignancies. In the remaining six patients, metastases were supraphrenic, of which all but one were identified by CT alone. Synchronous malignancies were discovered in 14 (4.2%) patients, of which five were below the diaphragm.

Conclusion: The overall frequency of distant spread and synchronous malignancy in primary HNC was generally low. However, the risk for distant metastases below the diaphragm was relatively higher in salivary gland adenocarcinoma, supporting whole-body FDG-PET/CT in the primary diagnostic work-up in these patients.

Keywords

Head and neck cancer, metastases, synchronous neoplasms, PET-CT, 18F-FDG

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Introduction

Head and neck cancer (HNC) is a collective term for tumors in the lips, oral cavity, throat, larynx, nose and sinuses, and salivary glands as well as lymph node metastases of the neck with unknown primary tumor. Within each anatomical group, there are subtypes of malignancies that differ in terms of growth, risk of proliferation, prognosis, and treatment (1).

In Scandinavian countries, HNC is a relatively rare form of cancer, whereas globally it is a very significant disease group. In the western world, HNC is the fifth to

sixth most common type of cancer, while in developing countries it is the second to third most common type of cancer reported (2–5). The majority, approximately

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60%, of all new cases of HNC are diagnosed with an advanced tumor disease, that is, stage 3 or 4 (1). As a rule, Swedish patients with suspected malignant tumors in the head and neck area undergo a radiological investigation as part of the primary diagnostic work-up. The methods are primarily computed tomography (CT), magnetic resonance imaging (MRI), fluorine-18-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT), or ultrasound (1).

The occurrence of distant metastases in patients with HNC is lower than in many other primary malignancies, in the range of 4%–25%, with the lungs, bones, and liver being the most frequent sites (6–12). Distant spread usually occurs late during the course of the disease, while synchronous malignancies may be present in any stage.

Distant metastases and synchronous malignancies at the time of diagnosis are serious findings that have a significant impact on treatment decisions for patients with HNC (11,13). Patients diagnosed with distant spread are often considered incurable and will usually undergo treatment with palliative intent (11).

FDG-PET/CT is one imaging method recommended in the investigation of suspected HNC, according to the Swedish national care program (1). It is well-known that FDG-PET/CT can increase the accuracy of the locoregional staging in HNC (14–17).

However, most prior studies on the value of FDG-PET/CT in screening for distant metastases and synchronous malignancies in HNC are based on Asian populations with a different disease pattern and prevalence compared to western populations and may not be directly transferable to western conditions (15). It is therefore important to assess the frequency of distant metastases and synchronous malignancies in a Scandinavian population in order to evaluate whether FDG-PET/CT is preferable for primary staging or if a CT, MRI, or FDG-PET/MR of the neck combined with a CT of the thorax might be sufficient as primary work-up in some patients with HNC.

Material and Methods

In this retrospective study, all patients with a clinical suspicion of a primary HNC who underwent a whole-body FDG-PET/CT at the Department of Radiology at Umeå University Hospital between January 2013 and December 2016 were included. During this period, the local clinical guidelines prescribed that all patients with a suspected HNC, except early-stage laryngeal cancer, should undergo whole-body FDG-PET/CT. Umeå University Hospital is the only PET center in the northern Swedish region, with a catchment area for a population of approximately 0.9 million inhabitants. Scanning was made on a General Electric

DISCOVERY 690 64-slice PET/CT scanner after 6 h of fasting. Imaging was done 1 h after intravenous administration of 4 MBq/kg of ¹⁸F-FDG. The PET acquisition was made separately for the head and neck region with high-resolution reconstruction (SHARP) in the head and neck area. A standard acquisition protocol and reconstruction was applied for the rest of the body. After PET sampling, a contrast-enhanced CT thorax and abdomen was performed. The neck was then scanned separately using a dedicated, contrast-enhanced neck CT protocol. Total scanning time was 45 min. The CT scans and corresponding PET data were fused for integrated interpretation. Follow-up FDG-PET/CT investigations were excluded. Patients with early-stage laryngeal cancer do not routinely undergo FDG-PET/CT and were thus not included in the study. Cases with malignancies other than primary HNC in the head and neck region—for example, lymphoma, thyroid or esophageal cancer, malignant melanoma of the skin, neck metastases from other types of malignancies and infectious, or other benign changes—were also excluded from the study.

The reports from the FDG-PET/CT investigations were collected from the digital radiology information system. Documentation from multidisciplinary conferences and journal entries on other patient-related information was collected from the digital hospital information system. Sex, age, TNM classification, histopathology, proliferation marker Ki-67, and synchronous malignancies were recorded as background data. Localization of the primary tumor, divided into eight different tumor sites according to the Union for International Cancer Control (UICC) (18), was recorded (i.e. nasal cavity and sinuses, nasopharynx, mouth and lips, oropharynx, hypopharynx, larynx, salivary glands, and unknown primary tumors). Most patients had undergone ultrasound-guided fine needle aspiration cytology (US-FNAC) of pathologically conspicuous lymph nodes in the neck. In addition, the expression of proliferation marker Ki-67 was classified in three levels: grade 1 (1%–30%); grade 2 (30%–50%); and grade 3 (>50%).

The final histopathological diagnosis of the HNC was noted for each case. The histopathological type of synchronous malignancies was also recorded.

The final TNM classification (18) used in this study was decided on in a multidisciplinary conference, weighing together all relevant information available.

Ethical approval

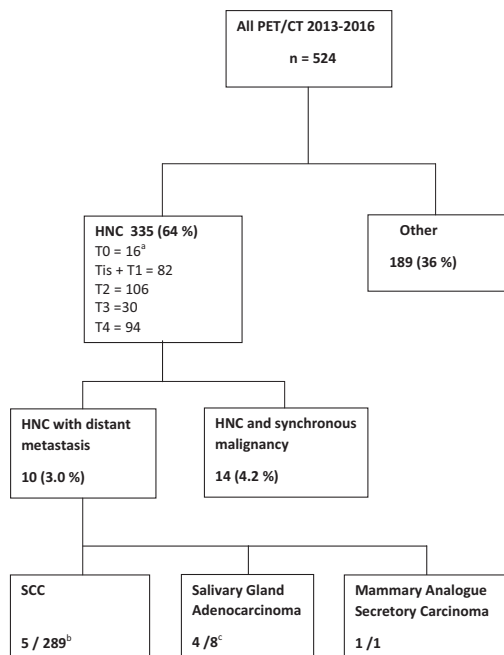
Approval from the Institutional Review Board was obtained from the regional ethics committee before the study. Since the study was retrospective, informed consent by patients was not required.

Results

A total of 524 FDG-PET/CT investigations were performed due to a clinical suspicion of primary HNC during January 2013 to December 2016. In 335 (64%) FDG-PET/CT examinations, a primary HNC was discovered in 226 (67.5%) men and 109 (32.5%) women with a mean age of 63 years (age range = 19–93 years) (Fig. 1, Table 1). The remaining 189 (36%) studies revealed either a type of malignancy other than primary HNC or benign changes and were hence excluded from further analysis (Fig. 1). One patient had a presumed primary HNC with lung metastases, but this patient died before the radiologic findings could be verified; hence this case was excluded from the study.

Primary HNC localization

The most common localization of HNC was in the oropharynx, found in 130/335 (38.8%) instances, and in the mouth and lips, found in 115 (34.3%) instances (Table 1). The most predominant histopathological type of HNC was squamous cell carcinoma (SCC), found in 289 (86.2%) patients, followed by adenocarcinoma in 11 (3.2%) cases (Table 1).



^aT0 = Carcinoma Unknown Primary, in seven patients T-stage was lacking in records.^b283 SCC and 6 basaloid SCC. ^c8 adenocarcinomas out of 20 salivary gland malignancies.

Fig. 1. Flow chart of study design. n, FDG-PET/CT investigations performed on the suspicion of HNC; HNC, head and neck cancer; SCC, squamous cell carcinoma. ^aT0, Carcinoma Unknown Primary. In seven patients T-stage was lacking in records. ^bA total of 283 SCC and six basaloid SCC. ^cEight adenocarcinomas out of 20 salivary gland malignancies.

Distant metastases

Distant metastases were found in 10 (3.0%) of the 335 FDG-PET/CT studies of patients with primary HNC (Fig. 1). In the 10 patients with distant spreading, a total of 21 distant metastases were found; the locations of these are shown in Table 3. Sixty-seven percent of the distant metastases were located in the thoracic region (Fig. 2). Four patients had distant metastases below the diaphragm; all these patients had a primary salivary gland cancer (Fig. 3).

Locoregional staging (TN category only, without regard to M) of the 10 HNCs with distant spread was stage 4A in five cases and stage 4B in three cases. In two cases, the definite TN classification was missing in the patient records (Table 2); however, retrospective review of the images revealed that these primary tumors were locally advanced stage 4.

Five of the 289 HNC patients with SCC had distant metastases. Three of these primary SCC were in the oropharynx, one was located in the hypopharynx and one in the larynx. The other five primary tumors with distant spreading were all major salivary gland carcinomas: four adenocarcinomas (of eight major salivary gland adenocarcinomas) and one was a mammary analogue secretory carcinoma (Table 2).

In all, there were a total of 20 primary salivary gland malignancies in our material (Tables 1 and 2).

The rate of proliferation marker Ki-67 in the 10 HNCs with distant metastases classified as grade 3 in five cases and grade 2 in three cases. In two cases, information on Ki-67 was missing (Table 2).

Synchronous malignancies

A synchronous tumor was discovered in 14 (4.2%) patients (Fig. 1). None of these exhibited distant spread of HNC. The distribution of synchronous malignancies is shown in Table 3. In all cases of HNC with a synchronous tumor, the primary HNC was SCC, most of them arising from the oral cavity. Eight of 14 synchronous malignancies were found in the neck or thorax. The most common form of synchronous malignancy was thyroid cancer, which occurred in four cases. One synchronous chronic lymphatic leukemia was diagnosed histopathologically and not radiologically. The other five synchronous malignancies were located below the diaphragm (Table 3).

Discussion

The presence of distant metastases in HNC is crucial for prognosis and treatment decisions, as well as the occurrence of synchronous malignancies, which also may affect treatment decisions. That is one reason why the use of whole-body FDG-PET/CT in primary

Table 1. Anatomical distribution and histologic type of head and neck cancers in 335 patients.

Diagnosis	Region								Total (n (%))
	Nasal cavity and sinuses	Nasopharynx	Lips and oral cavity	Oropharynx	Hypopharynx	Larynx	Salivary glands	CUP	
SCC	9	7	102	121	11	17		16	283 (84)
Adenocarcinoma	1		4				8		13 (4)
Verrucous cancer			7						7 (2)
Basaloid SCC				5	1				6 (2)
Adenocystic cancer				2			4		6 (2)
Sarcomas	1			1			2		4 (1)
Mucoepidermoid cancer							3		3 (1)
MASC							1		1 (<1)
Odontogenic carcinoma			1						1 (<1)
Lymphoepithelial cancer, EBV+		1							1 (<1)
Malignant myoepithelioma			1						1 (<1)
Undifferentiated malignant tumor	1						1		2 (<1)
Poorly differentiat- ed malignant tumor								2	2 (<1)
Small cell cancer					1				1 (<1)
Acinic cell cancer	1						1		2 (<1)
Myelosarcoma				1					1 (<1)
Sarcomatoid spin- dle cell carcinoma	1								1 (<1)
Total (n (%))	14 (4)	8 (2)	115 (34)	130 (39)	13 (4)	17 (5)	20 (6)	18 (5)	335

CUP, carcinoma unknown primary; EBV, Epstein-Barr virus; MASC, mammary analogue secretory carcinoma; SCC, squamous cell carcinoma.

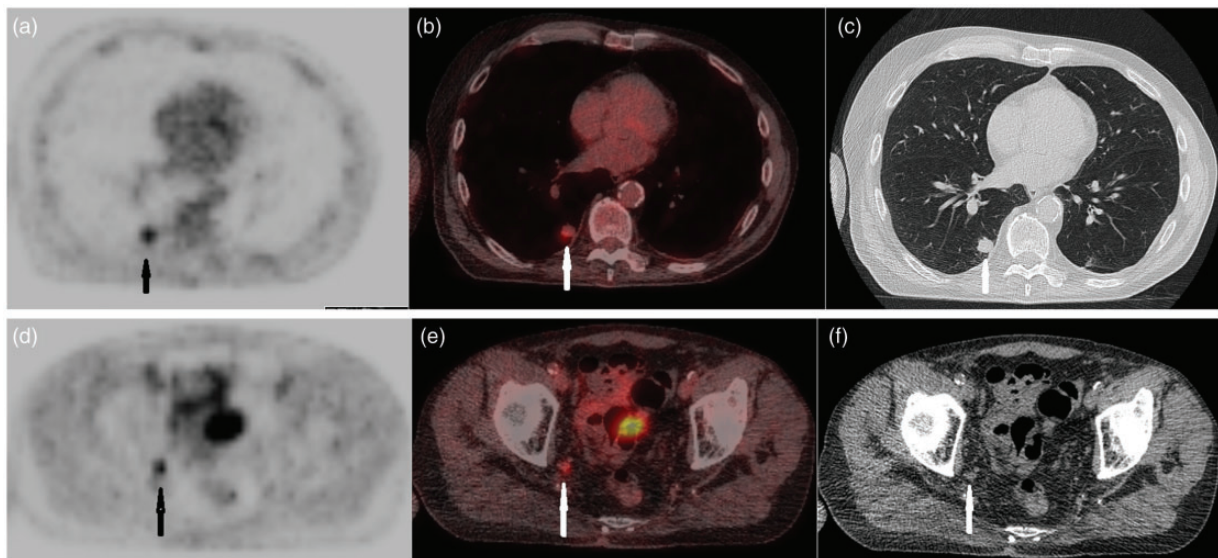


Fig. 2. Patient with oropharyngeal squamous cell carcinoma. (a, b) 18F-FDG-PET/CT demonstrates a subpleural metastasis in right lung (arrows), clearly depicted on CT of the thorax (c). (d–f) A lymph node in lesser pelvis with slightly elevated FDG uptake was considered an equivocal finding (arrows). The patient died in palliative care seven months later from progression of neck and lung manifestations before follow-up of this lymph node.

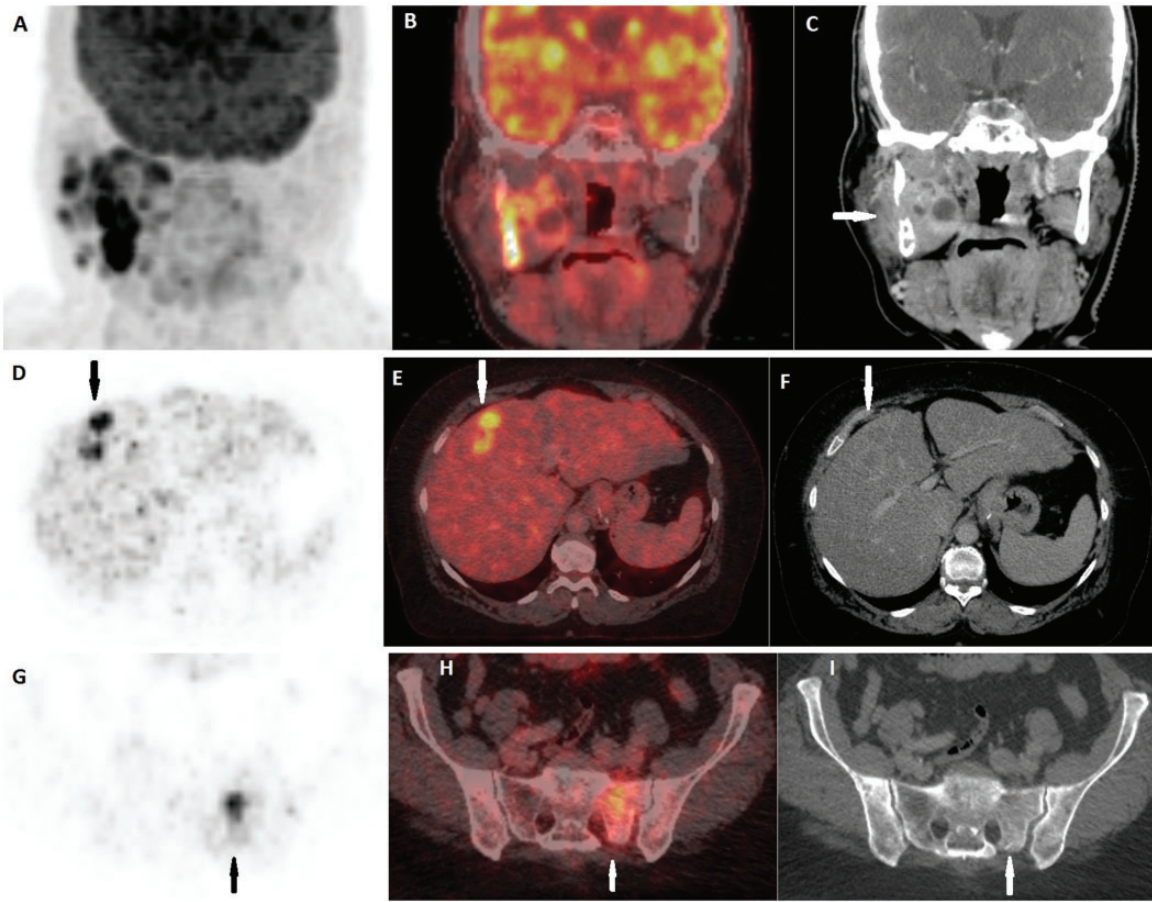


Fig. 3. Patient with a locally advanced salivary gland adenocarcinoma. (a–c) I8F-FDG-PET/CT demonstrates advanced primary tumor with mandibular invasion (white arrow). Body images reveal metastases in lower liver (d–f) and sacrum (g–i). These findings would probably be overlooked on a CT of the thorax.

Table 2. Localization and histopathology of primary tumor and distant metastases in 10 patients with primary HNC and distant metastasis; staging based on locoregional spread (TN) only.

Primary HNC location	Histopathology	TNM classification	Staging (locoregional)	PI6	Ki-67 (%)	Localization of distant metastases	Age (years)	Sex
Oropharynx	SCC	T1N3M1	IV-B	N/A	50	Lung	67	Male
Oropharynx	SCC	T4aN2cM1	IV-A	–	100	Mediastinal lymph nodes, hili, pleura, thoracic wall and breast.	89	Female
Oropharynx	Basaloid SCC	T2N2bM1	IV-A	+	High	Skeleton (acromion)	60	Male
Hypopharynx	SCC	T4bN2bM1	IV-B	–	100	Lung	77	Male
Larynx	SCC	T3N2bM1	IV-A	N/A	N/A	Lung	68	Male
Salivary gland	Adenocarcinoma	T4aN2bM1	IV-A		30	Liver and skeleton (sacrum and collum femoris)	68	Female
Salivary gland	Adenocarcinoma	TN N/A, M1	N/A		N/A	Lung and mediastinal lymph nodes, hilus	74	Female
Salivary gland	Adenocarcinoma	TN N/A, M1	N/A		70	Skeleton (L5) and lung	91	Female
Salivary gland	Adenocarcinoma	T4aN3M1	IV-B		>75	Liver, axillary lymph nodes and adrenal	63	Male
Salivary gland	MASC	T4aN1M1	IV-A		40	Liver	54	Male

HNC, head and neck cancer; MASC, mammary analogue secretory carcinoma; SCC, squamous cell carcinoma.

Table 3. Distribution of primary tumor and synchronous malignancies in 14 patients with HNC.

Localization of HNC	TNM classification	Histopathology of HNC	Synchronous malignancies	Age (years)	Sex
Sinus and nose	T1N0M0	SCC	Hodgkin's lymphoma	71	Male
Oral cavity	T2N0M0	SCC	Lung cancer (adenocarcinoma)	73	Female
Oral cavity	T1N0M0	SCC	Prostate cancer (high-grade PIN)	65	Male
Oral cavity	T4aN0M0	SCC	Thyroid cancer (follicular and papillary)	79	Male
Oral cavity	Missing	SCC	Esophagus adenocarcinoma	70	Male
Oral cavity	T2N0M0	SCC	Thyroid cancer (follicular) and carcinoid	70	Female
Oral cavity	T2N0M0	SCC	Bladder cancer	69	Male
Oral cavity	T1N0M0	SCC	Esophagus cancer (SCC)	64	Male
Oral cavity	T3N0M0	SCC	Thyroid cancer (papillary)	59	Male
Oral cavity	T2N0M0	Verrucous cancer	Uterine cancer (serous cancer)	86	Female
Oropharynx	T1N1M0	SCC	Chronic lymphatic leukemia	69	Male
Oropharynx	T1N2bM0	SCC	Thyroid cancer (follicular)	59	Male
CUP	T0N3M0	SCC	Bile duct cancer (adenocarcinoma)	63	Male
CUP	T0N2aM0	SCC	Rectal cancer (SCC)	80	Female

CUP, carcinoma unknown primary; HNC, head and neck cancer; SCC, squamous cell carcinoma.

diagnostic work-up of suspected HNC in recent years has increased worldwide (6,19) and also why it is one of the medical imaging methods recommended by the Swedish national healthcare program for HNC (1).

The rate of distant metastases in patients with SCC in the head and neck region is relatively small in comparison to other malignancies and is related to primary tumor localization and initial TN stage. Patients with advanced regional metastatic disease (N stage) have a higher frequency of distant metastases, especially in the presence of vascular ingrowth or extensive soft tissue disease (20). In our study, 10 (3.0%) of 335 patients with primary HNC exhibited distant spreading, which is lower than in previous studies reporting distant spreading in 6%–21% (11,21).

The low occurrence of distant metastases in our study compared with previously reported studies might be due to several different causes. Many of the previously published studies were conducted in Asian populations with a different disease panorama. For instance, endemic forms of nasopharyngeal cancer, i.e. lymphoepithelioma, are common in south-east Asia, with incidence rates up to 9.5 per 100,000, but rare in Scandinavia, with incidence rates <0.5 per 100,000 (4,5). The public healthcare organization may also play a role. The results in our study indicate that patients in northern Sweden generally seek medical care early in the course of disease compared with an international context, which may explain a lower tumor grade at diagnosis and hence less risk for tumor spreading. For example, the clinical course and prognosis of cancer of the salivary glands vary greatly, depending on histopathological subtype. The most important factors predicting survival outcomes are histological grade and clinical stage at presentation (13).

The majority of the distant metastases, 14 of 21 findings, were located in the thoracic region, which is slightly lower than reported in a recently published Danish study on oropharyngeal and laryngeal cancer, in which all patients with distant metastases (18/307) had thoracic involvement (7). In this study, all nine distant metastases from a head and neck SCC were situated above the diaphragm; all but one could be identified by CT of the thorax alone. The difference between the present study and the Danish study is attributed to the salivary gland malignancies included in our material, which were responsible for all sub-diaphragmal metastases.

A surprisingly high proportion of adenocarcinomas, 4 out of 11 cases, had distant spreading. These four adenocarcinomas were located in the major salivary glands and accounted for half of all salivary gland adenocarcinomas.

Twenty-five percent (5/20) of the primary salivary gland malignancies exhibited distant spreading. This is a higher proportion than previously reported by Park et al. (10), who reported distant spread in 6%, but more in line with a recent North American study, which showed that 20% of patients with cancer of the salivary glands had distant metastases, especially in the lungs (22). This could be predicted by several clinical and pathological factors, such as histologically high malignancy level, locally advanced tumor growth, perineural invasion, and N stage (22).

The proportion of patients with synchronous malignancies, 4.2% (14 of 335) in this study, falls within the range of previously published rates of 2.3%–12% (6,7,23–26).

One drawback with FDG-PET/CT is nodal staging in HNC, in which the method has a low specificity,

meaning that a considerable number of false-positive findings are detected (e.g. reactive lymph nodes); in this sense, it has a restricted positive predictive value (9,27). A general limitation of radiological methods available today is also a limited sensitivity for microtumors, posing a diagnostic restraint, especially in patients with limited disease and clinical N₀ head and neck cancers (28). Although the value of whole-body FDG-PET/CT for screening of distant spread has been proven in patients with increased risk factors (29–31), this is not necessarily transferable to patient groups with limited disease and no other evident risk factors for metastases. The diagnostic value of performing a FDG-PET/CT in addition to CT or MRI in patients with oropharyngeal SCC without clinically palpable cervical lymph nodes has been disputed in previous studies (32,33). In contrast, other studies show a high negative predictive value of FDG-PET/CT for cervical nodal staging in HNC patients (17). This is of value mainly in regimes with elective neck dissection. However, such regimes have been challenged even in advanced HNC by the results from a recent study by Mehanna et al. (34) where survival rates were similar among patients who underwent PET-CT guided surveillance and those who underwent planned neck dissection.

Since there were few patients with distant metastases and synchronous malignancies in this study, it could be debated whether it is optimal to perform whole-body FDG-PET/CT in all patients with clinical suspicion of HNC. In a recent Danish study by Krabbe et al., there was no difference in the rate of detection between a CT of the thorax and FDG-PET for the detection of intrathoracic distant metastases (30), which is in line with our findings concerning the distant metastases in the thorax, of which all but one of the metastases were detectable with only CT. In addition, the risk for distant spread is low in patients with SCC stage 1–2. In fact, all patients with distant spreading in our study had locoregionally advanced tumors corresponding to TN(M) stage 3–4. Therefore, it may be reasonable to use contrast-enhanced CT or MRI of the neck and CT of the thorax for initial staging in patients with limited disease, that is, clinical stage 1 or 2. In contrast, for patients with advanced locoregional tumor disease as well as in patients with adenocarcinomas, who according to our results seem to have a higher risk of distant spreading (e.g. skeletal metastases or metastases distal to the diaphragm), a whole-body FDG-PET/CT may add important diagnostic information in the initial pretherapeutic work-up. Based on our results, another potentially useful strategy in HNC patients with clinically limited disease could be the use of FDG-PET/MR for locoregional staging combined with a (preferably contrast-enhanced) CT of the thorax for the detection of distant spread. According to our own limited

experience, FDG-PET/MR occasionally offers superior visualization and delineation of the primary tumor compared to FDG-PET/CT, especially in the suprahyoid region. This is primarily due to the superior soft-tissue differentiation offered by MR. The superiority of FDG-PET/MR is also proposed in a comparative study on nasopharyngeal carcinomas, conducted with non-contrast-enhanced FDG-PET/CT versus contrast-enhanced FDG-PET/MR (12). The results from other studies comparing FDG-PET/MR to FDG-PET/CT in HNC patients, however, remain equivocal (35). The choice of hybrid modality for assessment of HNC M-stage remain a delicate balance between perspectives. As PET/MR is a slow modality it is not well-suited for whole-body imaging; another caveat is the limited availability and high cost of such equipment. A compromise to consider when choosing hybrid imaging modality for the detection of distant metastases in HNC may be the different performance of CT and MRI in specific morphological detection. Small lung metastases are better detected with CT (even without contrast enhancement), while MR is superior for the detection of small liver metastases. In both instances, the FDG uptake in such small lesions may be ambiguous due to respiration artefacts and limited spatial resolution.

The study group consisted of patients from northern Sweden only and there are no similar, comparable published data on the general population of Sweden, which limits the generalization of the results. However, there is no obvious reason to believe that the panorama of disease would be substantially different in other parts of the country; some of our results correlate well with previous studies in similar Scandinavian populations (31). Another limitation is that in this retrospective study, including only patients with FDG-PET/CT in the primary diagnostic work-up, it is possible that we missed patients with especially minor salivary gland malignancies. In addition, we excluded early-stage laryngeal cancer, which constitutes a non-negligible part of HNC, since these patients rarely undergo FDG-PET/CT in the pre-treatment work-up; this may affect comparison with other studies on HNC. A prospective study including FDG-PET/CT in laryngeal cancer might be valuable in assessing the diagnostic value of this entity. Although the study group consisted of a large number of patients from a vast catchment area, the subgroups remain small, making it difficult to draw conclusions based on specific histology or tumor location. As the spectrum of HNC includes a diverse range of tumors with different behaviors, this weakness is shared with most, if not all, previous studies on the subject. Still, since it is of interest to map the entire panorama of the different HNC subtypes in respect of the risk for distant spread and potential concurrent

synchronous malignancies, a larger cohort comprising data from several hospitals would be advocated for improved statistical foundation and representativeness.

In conclusion, the results confirms that the risk for distant spread or synchronous malignancies below the diaphragm is low in patients with HNC primary squamous cell carcinoma stages 1 and 2. In such patients without clinical evidence of nodal disease, the use of contrast-enhanced CT or MRI or FDG-PET/MR of the neck and CT of the thorax for initial staging may be a reasonable approach. However, in patients with advanced HNC, especially salivary gland adenocarcinoma, the risk of distant spreading is higher, thus motivating whole-body FDG-PET/CT in the primary diagnostic work-up.

Declaration of conflicting interests

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