ORIGINAL ARTICLE

PROSPECTIVE STUDY OF 18FDG-PET IN THE DETECTION AND MANAGEMENT OF PATIENTS WITH LYMPH NODE METASTASES TO THE NECK FROM AN UNKNOWN PRIMARY TUMOR. RESULTS FROM THE DAHANCA-13 STUDY

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Abstract: *Background.* The benefit of a complementary fluorodeoxyglucose-positron emission tomography (FDG-PET) scan to standard workup for carcinoma of unknown primary (CUP) and metastatic neck lesions was prospectively studied.

Methods. Sixty-seven patients underwent standardized diagnostic workup according to national guidelines including panendoscopies, multiple mucosal biopsies, and diagnostic CT/MRI scans. Median follow-up was 40 months (range, 2–65 months).

Results. In 60 eligible patients, FDG-PET indicated a primary tumor or metastatic disease in 30 patients (50%). Additional investigations confirmed a primary tumor in 18 patients: hypopharynx in 5, oropharynx in 5, nasopharynx in 2, lung in 1, axilla in 1, bone in 1, rectum in 1, as well as multiple metastatic lesions from CUP in 2 patients. In retrospect, MRI was able to detect 1 of the PET-detected primaries, leading to an overall detection rate of PET of 29% in CUP. A therapeutic change of treatment was made in 25% as a consequence of FDG-PET. PET before panendoscopy demonstrated fewer false-positive pathological foci.

Conclusion. FDG-PET is a valuable tool in addition to conventional extensive workup in CUP and neck metastases. Consequently, FDG-PET is now recommended as an early diagnostic modality in the workup of these patients.   © 2007 Wiley Periodicals, Inc. *Head Neck* **30:** 471–478, 2008

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Several retrospective studies have indicated that [18F]fluorodeoxyglucose-positron emission tomography (18F-FDG PET) is a valuable diagnostic tool

in the detection of a carcinoma of unknown primary (CUP) in patients with a metastatic neck lesion. Detection rates of a primary tumor by FDG-PET in addition to standard clinical workup have been reported from 20% to 35% in studies including more than 20 patients.[1–8] However, due to the retrospective nature of most of these studies as well as the heterogeneity in terms of workup and patient selection, there are still questions to be answered regarding the added value of FDG-PET in CUP. We therefore conducted a prospective study to evaluate the additional benefit of FDG-PET, as well as its timing in relation to the clinical examinations.

The study was established as a diagnostic amendment to the treatment protocols of the Danish Head and Neck Cancer Study Group (DAHANCA-13). The hypothesis was that FDG-PET as a supplement to standard imaging techniques would have significant consequences on individual treatment decisions of patients with CUP. Detection of a primary tumor would allow individual modifications of treatment decisions such as radiation volumes and fractionation schemes, compared to the wide-field radiotherapy that predominantly has been used in CUP in Denmark.[9] The study also allowed us to describe survival rates in a prospective cohort of CUP patients.

PATIENTS AND METHODS

Patients with neck node metastases from a suspected CUP were prospectively recruited to the study from February 2000 to January 2003. The study had a prospective observational design without randomization. There were no strict inclusion criteria regarding histology. However, only CUP patients with a potential primary arising from the head and neck region were enrolled.

The diagnostic procedures consisted of an 18F-FDG PET scan in addition to a comprehensive diagnostic workup program according to national guidelines of the Danish Society of Head and Neck Oncology, http://www.dshho.suite.dk/UPREF2003_ 25juni.pdf (in Danish). The guidelines recommended panendoscopies of the pharynx, larynx, bronchi, and esophagus, and random mucosal biopsies from sites of predilection of a primary tumor. This included a rachlatio, ipsilateral tonsillectomy, and a base of tongue biopsy. Diagnostic imaging included a chest X-ray or a CT scan, ultrasonography of the neck, and CT or MRI of the head and neck.

Patients were recruited from 2 university oncology centers with in-hospital PET facilities. Here, the patients underwent a thorough examination under anaesthesia (EUA) and diagnostic imaging if necessary to comply with the protocol directions as outlined earlier. Patients were either diagnosed at the oncology centers or had been referred with CUP from 10 different ear, nose, and throat (ENT) community departments. A retrospective review assured that all patients in the present analysis had undergone office pharyngolaryngo endoscopies or panendoscopies under anesthesia by ENT specialists before referral to the university hospitals. For logistic reasons, the CUP patients were allowed to have a PET scan either before or after panendoscopy at the oncology centers. This divided the patients into 2 groups, namely a pre-endoscopy PET group ($n = 19$) and a post-endoscopy PET group ($n = 41$).

Patients who were diagnosed with a primary tumor from a random routine biopsy, including a tonsillectomy, before referral to the oncology center, were excluded. The study was done according to the Helsinki Declaration II and approved by the local ethics committees. Accordingly, informed and written consent was obtained from all the patients. Diabetes, pregnancy, lactation, and severe claustrophobia were exclusion criteria.

FDG-PET scans were performed on 3 different systems over the study period: a GE Advance PET scanner ($n = 27$) or a GE Discovery LS PET/CT scanner (GE Medical Systems, Milwaukee, WI) ($n = 11$), and a Siemens ECAT EXACT HR-47 camera ($n = 26$) (CTI, Knoxville, TN/Siemens Medical Systems, Hoffman Estates, IL).

We used intravenous (IV) 18F-FDG in the range of 281 to 534 MBq (median 400 MBq). Patients fasted for a minimum of 6 hours prior to injection and were advised to drink abundant tap water. The scans were performed approximately 60 minutes after injection. Emission scans were 5 minutes per field-of-view. PET images were reconstructed with iterative reconstruction using ordered set expectation maximization (OSEM). Images were corrected for photon attenuation using a 68Ge rod source transmission scan (GE Advance, Siemens Ecat Exact) or by means of the CT scan (GE Discovery). The image resolution was 6.7 mm full width at half maximum (FWHM) (Siemens ECAT EXACT), 6.0 mm (GE Discovery), and 6.0 mm GE Advance.

Of 64 patients undergoing PET, the scans were done as either a whole-body scan ($n = 43$) or a half-body scan, ie, head to umbilicus ($n = 21$). Twenty-two scans were performed as nonenhanced low-dose PET-CT scans with 140 kV and 80 mA.[10]

Standardized uptake values were not calculated. The scans were interpreted visually. Pathological foci (volumes with high focal FDG uptake compared to background activity) as reported by the nuclear physician were further investigated as decided by a weekly joint head and neck clinic to confirm a potential primary tumor or metastatic disease. This was done by additional diagnostic imaging of PET-positive sites in the chest or abdomen or by EUA with appropriate biopsies of PET-positive sites in the head and neck region. MR images and CT scans were reviewed in the pre-endoscopy group in case of a true-positive PET finding to see if the tumor was present on standard imaging techniques.

Sixty-seven patients entered the study, 48 men and 19 women with a median age of 56.5 years (range, 32–78 years). Three patients did not have a PET scan: 2 patients abstained, and 1 patient's scan was cancelled due to obesity. Another 4 patients were ineligible for the data analysis: 1 with lymphoma, 1 with adenocarcinoma, and 2 patients with benign branchiogenic cysts. This left 60 patients for the data analysis.

As described, all pre-endoscopy PET patients had been examined by a qualified ENT specialist before referral to the oncology center. PET-guided mucosal biopsies were done at a median of 8 days after PET (range, 1–26 days). Thus, PET results were available for the ENT surgeon at EUA in some cases. The post-endoscopy PET group had a PET scan a median of 34 days (range, 5–118 days) after the initial EUA.

Patients were followed at 3-month intervals at the oncology center. This consisted of a clinical examination including a rhino-laryngo fiberendoscopy. Additional image investigations and EUAs were conducted on patient-specific indications. Clinical data were recorded according to DAHANCA forms.

Response data were analyzed after a median follow-up of 22 months (range, 2–47 months). Additional data on vital status was obtained from the Danish Ministry of Interior Affairs and Health's Central Office of Civil Registration and survival data were analyzed after a median of 40 months (range, 2–65 months).

Treatment. The general treatment strategy regarding CUP was adopted from national guidelines of the Danish Society of Head and Neck Oncology. A modified radical neck dissection was recommended as primary treatment in patients with N1 disease and in selected patients with N2a disease.

Primary radiation treatment was given if a primary head and neck cancer was detected in the pharynx or larynx, in patients with clinical N2 and N3 disease, or as postoperative radiotherapy in case of extracapsular nodal extension.

CUP patients were irradiated to the entire mucosa of oropharynx, hypopharynx, and larynx to at least 62 Gy, with inclusion of the nasopharynx being optional. In case of any macroscopic disease, 66 to 68 Gy in 33 to 34 fractions was recommended. Primary radiotherapy also included elective treatment to 46 to 50 Gy to both sides of the neck including the supraclavicular regions, all given in 2-Gy fractions, 5 fractions per week.

Patients with a detected primary head and neck cancer received a slightly accelerated schedule of 6 fractions per week to a total dose of 66 to 68 Gy in 33 to 34 fractions over 5½ weeks with the hypoxic radiosensitizer nimorazole according to DAHANCA guidelines.[11]

Statistics. Actuarial estimates of survival were calculated by the Kaplan–Meier method. Comparison between groups was made by the Mann–Whitney rank-sum test. Chi-square and Fisher's exact test were used, when appropriate, to describe differences between group frequencies. All p values describe the 2-tailed probabilities of the observations.

RESULTS

Forty-four of the patients (73%) had metastatic neck disease from a squamous cell carcinoma, 12 from an undifferentiated carcinoma (20%), while 2 patients had adenosquamous carcinoma, and 2 patients had unspecified histology. Nine patients had N1 disease, 34 had N2 disease, and 17 had N3 disease. That is, 49 (82%) of 60 patients had stage IV disease according to the Union Internationale Contre le Cancer (IUCC) 1997 classification system.

FDG-PET demonstrated pathological uptake in all residual metastatic neck lesions. Pathological foci indicative of a primary tumor was found in 30 patients who were seen with 33 pathological sites altogether. This was in 22 sites above the clavicles and in 11 sites below. Further investigations confirmed a primary carcinoma or distant metastatic disease in 18 patients, namely, in 12 of the 22 sites above the clavicles and in 6 of the 11 sites below the clavicles with the following locations: hypopharynx in 5, oropharynx in 5, naso-

Table 1. Numbers and sites of pathologic focal FDG-PET uptake as well as location of primary tumors in 60 patients with CUP.

| | No. of patients | | | |
	PET pos. sites	True pos. PET (primary tumor)	False pos. PET sites	False neg. PET sites
Nasopharynx	3	2	1	1
Oropharynx	12	5	7	2
Hypopharynx	6	5	1	
Maxillary sinus	1	0*	1	
Lung/mediastinum	3	1	2	
Axilla	1	1		
Bone	1	1		
Rectum	2	1	1†	
Abdomen/multiple	4‡	2‡		
Total numbers	33	18	13	3

Abbreviations: FDG-PET, fluorodeoxyglucose–positron emission tomography; CUP, carcinoma of unknown primary.
*Upper gingival carcinoma 2 years later.
†Primary in the tonsil but benign rectal uptake.
‡Including 2 patients with a detected primary of the hypopharynx and base of tongue and distant metastases.

pharynx in 2, lung in 1, axilla in 1, bone in 1, rectum in 1 (primary adenocarcinoma), and multiple metastatic lesions from CUP in 2 patients (Table 1).

Multiple PET-positive sites occurred in 2 patients who had distant metastases from a primary in the hypopharynx and the base of tongue, respectively, and in 1 patient who had a primary carcinoma in the tonsil and a benign rectal lesion. Thus, FDG-PET was able to detect a primary tumor or previously unknown distant metastatic disease in 18 of 60 patients corresponding to a detection rate of 30%.

The PET detection rate of a primary tumor was 7 (37%) of 19 in the pre-endoscopy PET patients and 11 (27%) of 41 in the post-endoscopy PET group ($p = .43$). In the retrospective review of the MR images and CT scans in the pre-endoscopy group, MRI was able to identify a primary tumor independently of PET in 2 cases in the base of tongue. In 1 of these cases, PET also found distant metastatic disease in the lung and the liver. In 2 other cases, PET alone detected skeleton metastases and a rectal cancer, respectively, while in another 3 cases, positive PET scans led to repeated EUAs, which later confirmed a primary tumor from subsequent biopsies in the base of tongue, hypopharynx, and nasopharynx, respectively. Thus, in the pre-endoscopy group, PET was confirmatory in 2 patients of whom 1 had distant metastatic disease on PET. The true value of PET could be adjusted accordingly in the pre-endos-

copy group to 6 (33%) of 18 patients with an overall detection rate of the whole study group of 17 (29%) of 59 patients.

Three primary cancers went undetected by FDG-PET (false-negative PET). In 2 patients who had a negative PET scan (SIEMENS ECAT-EXACT 47 PET) before panendoscopy, a primary carcinoma was detected in the nasopharynx and in the tonsil at EUA. In a third patient, a base of tongue cancer (PET/CT negative) appeared subsequent to primary surgery.

One PET scan was positive but the primary tumor was not found initially. This occurred in a patient with evident focal uptake in the maxillary sinus. The following biopsy did not show any signs of malignancy. However, 2 years later the patient was referred with a gingival carcinoma inside the area of the previous focal PET activity. To be consistent with our clinical approach, this PET scan was however considered false-positive PET for the present analysis.

From these observations, the sensitivity, specificity, and positive predictive value of FDG-PET in individual patients were found to be 86%, 69%, and 60%, respectively. If the same calculations were done with the FDG-uptake observations from all the pathological foci, the sensitivity, specificity, and positive predictive value changed very little, namely, 87%, 68%, and 61%, respectively. The negative predictive value was high, namely, 90%.

Adherence to the national workup guidelines for CUP is shown in Table 2 in relation to the timing of PET. In the pre-endoscopy group, a false-positive result was found in 1 of 8 patients compared to 11 of 22 patients in the post-endoscopy group ($p = .10$). This corresponds to 20% for the whole study group and was ascribed to post-bioptic inflammatory reactions.

The false-positive findings could have been attributed to the larger proportion of post-endoscopy PET patients having a whole-body PET scan compared with the pre-endoscopy group, namely, 83% versus 37% ($p = .03$). However, the number of positive PET findings below the umbilicus was low, 1 rectal cancer and 1 benign rectal lesion, indicating that whole-body versus half-body PET only exerted a minor influence on the overall results.

We investigated whether PET up-front, as opposed to PET after panendoscopy, would shorten the time delay from diagnosis to treatment. To this end, we calculated the time from the day when the patient was diagnosed with a metastatic

Table 2. Diagnostic workup in 60 patients with neck node metastases from a carcinoma of unknown primary.

Investigations	No. of patients (%)	No. of patients (%)	
		Pre-endoscopy PET	Post-endoscopy PET
Biopsy	60 (100)	19	41
Open biopsy	56 (93)	18	38
Fine needle aspiration	51 (85)	15	36
CT/MRI/ultra sound of the neck	58 (97)	19	39
Chest X-ray	60 (100)	19	41
Chest CT scan	25 (42)	8	17
Examination under anaesthesia			
Pharyngolaryngoscopy	59 (98)	18	41
Bronchoscopy	42 (70)	16	26
Esophagoscopy	44 (73)	16	28
Random mucosal biopsies	58 (97)	19	39
Tonsillectomy	52 (87)	18	34
Base of tongue	27 (45)	11	16
Nasopharynx	46 (77)	17	29
PET scan	60 (100)	19	41
Half-body PET		10	7*
Whole-body PET		9	34*
False-positive PET	12 (20)	1	11

Abbreviation: PET, positron emission tomography.
Notes: See text for explanation.
$*p = .03$.

neck disease until the start of treatment, whether it was surgery or radiotherapy. The cases that did not have any treatment were scored by the time between the cancer diagnosis and the day of the final diagnostic procedure from which the clinical decision of no treatment was taken. The pre-endoscopy PET group had a median delay of 71 days (range, 0–126 days) compared to median 70 days (range, 0–167 days) in the post-endoscopy PET group ($p = .78$).

As a consequence of the true-positive PET findings in 18 patients, a therapeutic change of treatment was possible in 15 patients (25%) in accordance with the details described in the Patients and Methods section. This change included a reduction of radiation treatment volumes covering the primary site in contrast to wide-field irradiation of CUP including a change to accelerated radiotherapy with concomitant hypoxic sensitizer ($n = 10$). No treatment or palliative treatment was offered to 4 patients due to the discovery of extensive metastatic disease, and 1 patient had surgery for rectal cancer.

Radical treatment was offered to 48 patients. Thirty-seven patients received primary radiation treatment, whereas 11 patients had a neck dissection, 6 with postoperative radiotherapy. Two patients were offered palliative radiotherapy and 2 patients received palliative chemotherapy. In 8 cases, no treatment was given other than the diagnostic procedure such as a lymph node biopsy, either because the patients abstained from further treatment or were considered to be in a poor general condition to be offered any curative treatment.

After a median follow-up time of 40 months, the median survival was 45 months. The 3-year survival rate was 55% (42% to 68%, 95% confidence interval [CI]) (Figure 1A). The corresponding 3-year survival for the 48 patients who received treatment with a curative intent was 65% (95% CI, 51% to 78%) (Figure 1B).

DISCUSSION

In this prospective study, FDG-PET was able to detect 12 primary head and neck cancers as well as 6 other primary carcinomas or extensive metastatic disease in 60 patients, resulting in a detection rate of of 30%. Thus, FDG-PET is a valuable tool in addition to the conventional extensive workup program in CUP and neck metastases.

Further, PET resulted in a therapeutic change in 25% of the patients because of the detection of a primary tumor or widespread disease. In 10 patients, individual changes of radiation treatment volumes as well as an accelerated radiotherapy schedule was prescribed to cover only primary tumor sites in contrast to the standard extensive mucosal irradiation of CUP. In 4 patients in whom
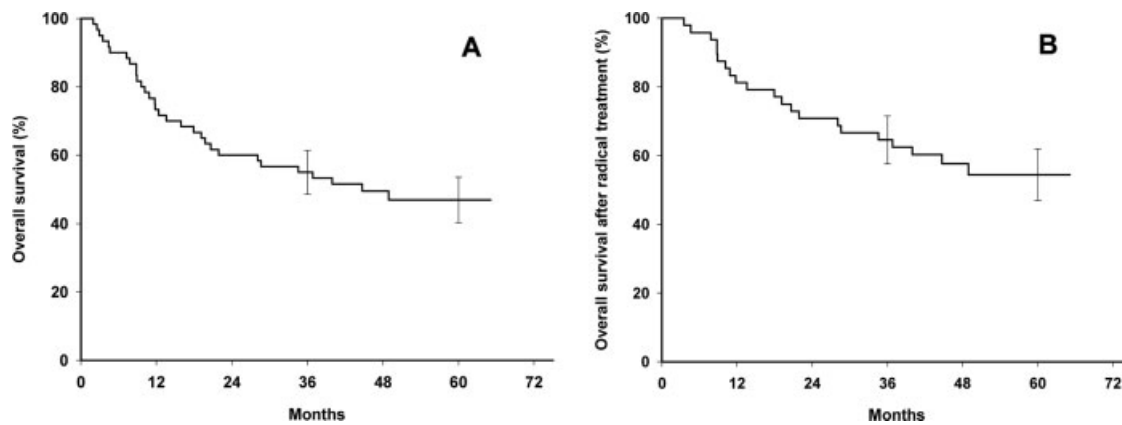
FIGURE 1. (**A**) Overall survival of 60 patients with carcinoma of unknown primary and PET including 12 patients who had no treatment or palliative treatment. (**B**) Survival rates in 48 patients treated with curative intent. Error bars are 95% confidence intervals.

PET detected distant metastatic disease, a palliative strategy could be implemented, and in 1 patient, surgery was offered for a coincidental rectal cancer.

In a recent review of FDG-PET and CUP comprising 302 patients in 16 studies, Rusthoven et al[8] described a detection rate of a primary lesion of 24.5% in patients with neck node metastases. A therapeutic benefit attributed to FDG-PET was observed in 25%. These findings are very much in line with the present prospective study. This is remarkable in light of the retrospective nature of the reviewed studies as well as their heterogeneity regarding patient selection, histology, and the variation of clinical and radiological diagnostic procedures.

For logistic reasons, patients in the present study were allowed to have a PET scan either before or after the panendoscopy. The timing of PET did not seem to have a significant effect on the detection rates of a primary tumor, 37% versus 27% for the pre-endoscopy and post-endoscopy PET, respectively. It could be argued that the higher detection rate in the pre-endoscopy group was due to PET-positive occurrences in patients who were not adequately investigated for CUP before PET. However, all the patients had been diagnosed with CUP by an ENT specialist before enrolling in the study.

A review was done regarding the pre-endoscopy PET group to evaluate the relative contribution of PET in relation to the standard workup program, ie, whether a primary tumor was detected by PET independently of other diagnostic modalities or whether PET was just confirmatory. Nineteen patients had a PET scan before endoscopy. In the review, MRI and EUA together were able to identify a primary tumor in just 2 of 7 PET-positive cases; in 1 of these, the patient also had distant metastatic disease detected by PET. The review therefore supports the use of early PET—also in light of the low number of false-positive PET scans—provided that patients with malignant neck lesions are seen by a qualified ENT specialist beforehand for a likely CUP diagnosis prior to PET.

Our findings in the pre-endoscopy group is compatible with previous publications, which have demonstrated a detection rate of 28% to 30.8% in patients with CUP who had PET followed by panendoscopy.[12,13]

PET showed a high sensitivity (86%) but a low specificity (69%) for the detection of a primary tumor in our study. This reflects 1 of the disadvantages of FDG-PET in CUP, namely, a high rate of false-positive results. In the present study, the false-positive detection rate was 20%, which was slightly higher than in the review by Rusthoven et al,[8] who found a false-positive PET rate of 16%.

It must be realized, though, that the true rate of false-negative PET examinations in CUP is unknown since occult malignant lesions may be eradicated from extensive radiation to potential primary mucosal sites in the head and neck. Therefore, false-negative PET scans may not be recognized. If clinicians tend to reduce treatment volumes in light of negative PET scans, this in turn may give rise to a number of previous undiagnosed primaries whereby the sensitivity, the specificity, and the negative predictive value of FDG-PET will decrease even further. If the negative predictive value of PET in CUP is truly around

90%, as in our study, however, it seems to be safe to take action on a negative PET and prescribe surgery or local radiotherapy in contrast to wide-field irradiation. Previous retrospective studies with a smaller number of patients have shown a negative predictive value of 62% to 76%,[12–14] while a large review comprising 122 patients found a negative predictive value of 86%,[15] which is close to our findings.

Rusthoven et al[8] found that the base of tongue was the most common site of a false-negative PET, whereas the tonsils were the most common site of false-positive FDG uptake. The latter is thought to be associated with muscle twitches or saliva or focal activity in the sites of the previous random mucosal biopsies. We observed a false-positive FDG uptake in only 1 of the pre-endoscopy PET group (nasopharynx) compared to 8 false-positive pharyngeal sites in the post-endoscopy PET group. These were predominantly located in the ipsilateral tonsillar region; however, in 3 cases, false-positive uptake was also observed in the contralateral tonsil, hypopharynx, and soft palate.

The biopsies from 8 patients with false-positive pharyngeal sites were obtained 5, 10, 24, 30, 35, 37, 44, and 52 days before PET. For comparison, the corresponding figures of 19 PET-negative patients of the post-endoscopy PET group showed an equivalent biopsy rate, with biopsies taken at a median of 29 days before PET (range, 8–118 days), which was not different from the false-positive group ($p = .77$). This indicates that the occurrence of a false-positive FDG uptake on PET is not necessarily associated with the time from the random biopsies to PET and there does not seem to be a "safe" period to avoid false-positive findings.

The relatively high rate of false-positive PET scans in the pharynx may also be ascribed to the learning curve in this head and neck trial. An insufficient description of the patient story to the nuclear physician might increase the rate of false-positive results, especially concerning posttonsillectomy PET-scan interpretations.

It has been shown that FDG uptake levels in benign lesions of the head and neck region overlap with the range of uptake values in malignancies,[16] which may explain why some PET findings were regarded as positive for a likely primary tumor. There were no indications of an institutional association with the false-positive investigations of the oropharynx.

Eleven of the patients were scanned in the GE Discovery LS PET/CT scanner. The initial routine was to perform CT scans as low-dose PET/CT[10] without the use of any contrast media. The CT component of these PET/CT scans are therefore not to be compared with diagnostic quality CT scans using IV contrast media and higher CT radiation doses.

It must be anticipated that the introduction of PET-CT as a routine, especially with the CT scan performed as a diagnostic CT with the use of IV contrast media, most likely will reduce the number of misinterpretations and further increase the sensitivity and specificity of PET in CUP.[17]

The median time delay from the cancer diagnosis to the first day of treatment for CUP patients was 71 and 70 days in the pre-endoscopy and post-endoscopy PET group, respectively. Primdahl et al[18] found that the time spent in health care for a "standard" head and neck cancer patient was 64 days in 2002 in Denmark. This included an 18-day period for diagnostics and almost 7 weeks for treatment preparation which was primarily due to a delay for 3-dimensional conformal radiotherapy.

The first interpretation of our time delay observation is that up-front PET was not able to accelerate the time from the diagnosis until treatment. The second interpretation is that despite the extensive workup program in CUP patients and the limited availability of PET facilities, these patients seem to have a time delay that does not seriously exceed the time of other head and neck patients.

The optimal timing of PET in relation to panendoscopy in CUP is debatable. PET-guided panendoscopy and directed mucosal biopsies have demonstrated a high detection rate of a primary tumor,[12,13] and confirmed in this study. However, using this procedure, a fraction of patients will unnecessarily have to undergo PET since extensive clinical and radiological investigation would have detected most of the primary tumors,[13] or excluded branchiogenic cysts as in the present study. On the other hand, PET investigations after panendoscopy carries a high risk for a false-positive result that eventually will take the patient through another EUA to verify a potential true malignant lesion.

The survival rates of the present study are satisfactory compared with data from the pre-PET era which reported a 5-year overall survival rate of 36% in 277 patients with CUP treated with curative intent.[9] The present 5-year survival rate was 55% (95% CI, 40% to 70%).

We have previously demonstrated in a large cohort of patients with CUP and neck node metas-

tases that radiation treatment to both sides of the neck plus extensive elective irradiation of the mucosal sites the pharynx and larynx produced superior locoregional tumor control and 5-year survival rates as opposed to treatment to the affected side only. Although such extensive treatment also reduces the 5-year risk more than 3-fold of experiencing a primary tumor, it also increases the risk of acute and late morbidity markedly.[9] In the present study, the PET results allowed individualized head and neck treatment planning to be done due to the detection of 10 primaries in the oropharynx and hypopharynx. Hereby, treatment volumes could safely be reduced from the standard wide-field technique involving the nasopharynx, thereby decreasing toxicity. Moreover, 4 patients could be offered appropriate palliative treatment and were spared the morbidity of aggressive radical treatment when PET detected metastatic disease.

In conclusion, FDG-PET is a valuable diagnostic tool in the armamentarium of investigational procedures in CUP with metastatic neck lesions. The detection rate of a primary tumor was high both above and below the clavicles (30%). A high proportion of false-positive FDG uptake (20%) was observed, especially after random biopsies. Despite uncertainties of true-negative PET scans, this study demonstrated a high negative predictive value of FDG-PET, which may allow individualized treatment alterations to be achieved in head and neck cancer patients even after a negative PET scan. The optimal timing of FDG-PET in relation to panendoscopy is unclarified, however, from the present results, and taking into account the advantages and disadvantages described above, FDG-PET is now used in Denmark as an early diagnostic modality in the workup of patients with CUP—preferentially before panendoscopy at the oncology center.

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