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ORIGINAL ARTICLE

Defining risk groups of patients with cancer of unknown primary site and cervical nodal metastases by F-18 fluorodeoxyglucose positron emission tomography and computed tomography imaging

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Abstract We sought to investigate the clinical utility of F-18 fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) in Taiwanese patients with cancer of unknown primary site (CUP) and cervical nodal metastases. We also aimed to study the impact of F-18 FDG PET/CT on clinical treatment priority in this patient group. Between September 2006 and May 2014, patients with CUP and cervical nodal metastases who underwent F-18 FDG PET/CT imaging study were retrospectively identified. The clinicopathological risk factors and PET parameters were analyzed in relation to 2-year overall survival (OS) rates using univariate and multivariate analyses. Two-year OS curves were plotted with the Kaplan

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—Meier method. Of the eligible patients ($n = 54$), 12 (22.2%) had distant metastases (DM) at presentation. A total of 13 (24.1%) and 15 (27.8%) primary tumors were identified by FDG PET/CT imaging and an additional triple biopsy, respectively. The results of multivariate analysis identified smoking [$p = 0.033$, 95% confidence interval (CI) = 1.197—40.342], a maximum standardized uptake value (SUV_{max}) of cervical nodes $\geq$ 14.2 ($p = 0.035$, 95% CI = 1.134—28.029), and DM at presentation ($p = 0.031$, 95% CI = 1.257—114.854) as independent predictors of 2-year OS. Specifically, patients who carried $\geq$ 2 risk factors showed poorer outcomes (70.3% vs. 11.8%, $p < 0.001$). Fifteen study patients (27.8%) had their treatment modified by FDG PET/CT findings. We conclude that FDG PET/CT is clinically useful in CUP patients not only for tumor staging, but also for modifying treatment regimens.

Introduction

Patients with cancer of unknown primary site (CUP) continue to pose significant clinical challenges both in Asian and Western countries [1,2] mainly because of their heterogeneous clinical presentations which can lead to diagnostic dilemmas and lack of implementation of appropriate therapeutic regimens [3]. The management of patients who present with cervical lymphadenopathy and are eventually diagnosed with CUP and cervical nodal metastases is especially problematic for head and neck oncologists in Taiwan [4,5]. Several CUP patients also present with distant metastases (DM) at the time of diagnosis, making the components of diagnostic evaluation unclear in the absence of a primary mass [2,3]. Clinically, these patients generally undergo a thorough diagnostic work-up [i.e., physical examination, fiberscope, computed tomography (CT) or magnetic resonance imaging (MRI), and triple biopsy] aimed at identifying the primary tumor site and guiding the treatment approach. When the primary tumor continues to remain unidentified, F-18 fluorodeoxyglucose (FDG) positron emission tomography and computed tomography (PET/CT) should be added to the diagnostic armamentarium [6].

Previous studies have suggested the value of FDG PET/CT not only for identifying the primary tumor site missed by conventional diagnostic work-up, but also in the detection of DM [7—10], which may potentially alter the therapeutic management [6,9,11—15]. Furthermore, the early detection of an occult primary tumor may also prolong the median survive time [16].

Although the use of FDG PET/CT in CUP patients with cervical nodal metastases is increasing because of the above-mentioned reasons, no previous studies in the field have been conducted in the Taiwanese population. This lack of knowledge is surprising owing to the endemic use of betel quid chewing in Taiwan, which is in turn related to the recently observed increasing incidence rates of head and neck cancer [15]. The diagnostic accuracy of FDG PET/CT imaging in this patient group is influenced by a number of factors, including the tumor biological behavior, size, and anatomical location [11,17]. In addition, detailed information on tumor biology and disease status is frequently lacking in these patients, ultimately making the formulation of an accurate treatment plan difficult. All of these factors may explain the generally poor outcomes in CUP patients with cervical nodal metastases. Clarifying the priority of definitive treatment in CUP patients with cervical nodal metastases is clinically relevant in order to select the most cost-effective approach and improve outcomes. In this scenario, we designed the current retrospective study with two main goals: (1) we sought to investigate the clinical utility of FDG PET/CT in Taiwanese patients with CUP and cervical nodal metastases; and (2) we aimed to study the impact of F-18 FDG PET/CT on the treatment priority in this patient group.

Methods

Patient population

Between September 2006 and May 2014, we identified patients who presented with cervical lymphadenopathy pathologically diagnosed as being metastatic lymph nodes (either by fine needle aspiration or core needle biopsy) and undetermined primary tumor site despite a conventional diagnostic work-up (i.e., physical examination, fiberscope, CT or MRI, triple biopsy). All participants were enrolled in the Chung Gung Memorial Hospital, Taoyuan, Taiwan. Potential candidates were required to have both FDG PET/CT imaging aimed at identifying the primary tumor site and/or DM) [6] and additional triple biopsy (regardless of the presence of any suspicious lesion on FDG PET/CT). Patients with a previous history of malignancy ($n = 4$), incomplete clinical data ($n = 17$), or neck metastases from papillary thyroid cancer ($n = 3$) were excluded. The final study cohort for this retrospective study consisted of 54 patients. The general characteristics of the study participants (i.e., sex, age, smoking, duration of lymphadenopathy, lower neck involvement) and FDG PET/CT imaging parameters (i.e., SUV_{max} of the cervical nodes) were retrospectively collected from medical records. The sites of triple biopsy were selected either according to the surgeon's clinical judgment or based on clinical or imaging suspicion (e.g., suspected lesions identified on FDG PET/CT imaging). Current smoking was defined as current use of cigarettes and/or other tobacco products. Lower neck involvement was considered to be present when metastatic lymph nodes

were identified in neck levels 4/5 or in the supraclavicular fossa. Distant metastases were diagnosed in presence of lesions involving distant lymph nodes, visceral organs, or bones on FDG PET/CT images (with lesions showing a score of $\geq$ 3). The Institutional Review Board of Chung Gung Memorial Hospital approved the study.

PET/CT imaging acquisition and interpretation

All of the FDG PET/CT scans were acquired using a Discovery ST 16 PET/CT scanner (GE Healthcare, Milwaukee, WI, USA). The procedures used for image acquisition and reconstruction have been previously described in detail [17]. Patients fasted 4–6 hours before examination to obtain a plasma glucose level $<$ 200 mg/dL. Imaging acquisition started 60 minutes after the intravenous injection of 370–555 MBq (10–15 mCi) of F-18 FDG. Regions of interest were drawn all over the suspicious lesions identified on FDG PET scans or—in the event of such lesions being absent—using the corresponding CT images. After measuring the highest activity within each region of interest, the standardized uptake value (SUV) was calculated as the highest activity concentration per injected dose (per body weight in kg) after correction for the radioactive decay. Abnormal foci of increased FDG uptake were scored on a 5-point scale as previously described [18]. In general, visual scores of 3–4 were considered as positive, a score of 2 indicated equivocal results, whereas scores of 0–1 were regarded as negative. All of the FDG PET/CT images were interpreted in consensus by two experienced nuclear medicine physicians and one radiologist.

Treatment approach

The treatment approach was based on the results of FDG PET/CT imaging and additional triple biopsy. Patients who had their primary tumor identified by FDG PET/CT underwent staging of the primary malignancy and were treated according to established guidelines. Palliative treatment was given to patients with DM. Definitive concurrent chemoradiotherapy (CCRT) was started within 1 month of diagnosis in all patients in whom both FDG PET/CT and the additional biopsy did not identify the primary tumor and DM. Radiotherapy (RT) was administered using 6-MV photon beams at 2 Gray (Gy) per fraction, five fractions per week. The initial large-field prophylactic RT dose was 46–50 Gy. A sequential cone-down boost technique was used to escalate the dose to the gross tumor and the involved node areas to 72–76 Gy. The gross target volume (GTV) was defined as all of the known areas of gross regional nodal disease based on the staging work-up. The initial clinical target volume (CTV) for prophylaxis included all of the pharynx and neck but spared the laryngeal box below the level of the hyoid bone. The margins between CTV and GTV were at least 1 cm for the initial large-field and 0.5 cm for the boost field, respectively. All of the patients received RT with a sequential boost technique. A 3-mm three-dimensional margin was applied to CTV to create a planning target volume. The minimum doses delivered to the GTV, CTV, and planning target volume were 100%, 95%, and 90%, respectively. During the RT course, concurrent chemotherapy was administered biweekly. The CCRT regimens were based on intravenous cisplatin (30–40 mg/m^2 weekly or 100 mg/m^2 every 3 weeks) [19].

Data analysis

Continuous variables are expressed as mean $\pm$ standard deviation (SD), whereas categorical data are given as counts and percentages. All clinicopathological factors and PET parameters were analyzed in relation to 2-year OS using univariate and multivariate analyses which was performed by logistic regression. The Youden's index was utilized as the criterion for selecting the optimum cut-off point for the maximum SUV (SUV_{max}) of cervical nodes [20]. All statistical analyses were performed using the IBM SPSS statistical package (version 21; IBM Corp., Somers, NY, USA). A p value $<$ 0.05 (2-tailed) was considered statistically significant.

Results

Patients

The general characteristics of the 54 study patients are summarized in Table 1. DM was identified by FDG PET/CT imaging (i.e., lesions with a score of $\geq$ 3 [17]) in 12 (22.2%) patients. The distribution of DM was as follows: distant lymph nodes (n = 2), bone (n = 4), visceral organs (n = 2), and multiple sites (n = 4). The follow-up was continued until November 2015. All of the participants were followed for at least 24 months after primary surgery or censored at the date of the previous follow-up. The entire study cohort was followed for a median of 24.4 months (mean, 30.9 months; range, 3.0–108.8 months). The median follow-up time of the surviving patients was 44.5 months (mean, 52.4 months; range, 28.1–108.8 months). At the end of the study, 22 patients (40.7%) were alive and 32 patients (59.3%) were dead.

Table 1 Patient characteristics.

Variables	Patients
Age (y)	55.6 $\pm$ 10.3
Male sex	50 (92.6)
Smoking	35 (64.8)
Average duration of LAP symptom (mo)	6.0 $\pm$ 16.8
Initial neck lymph node pathology	
Metastatic SCC	42 (77.8)
Metastatic undifferentiated carcinoma	8 (14.8)
Positive for malignancy	2 (3.7)
Metastatic adenocarcinoma	2 (3.7)
Lower neck involvement	30 (55.6)
Mean SUV_{max} of cervical nodes on PET	10.92 $\pm$ 5.22

Data are presented as n (%) or mean $\pm$ standard deviation.
LAP = lymphadenopathy, PET = positron emission tomography; SCC = squamous cell carcinoma; SUV_{max} = maximum standardized uptake value.

Identification of primary tumor sites

Of the 12 patients diagnosed with DM at presentation, eight also had their occult primary tumor identified (i.e., lesions with a score of ≥ 3 [17]). Specifically, six were diagnosed with FDG PET/CT and subsequently confirmed by addition triple biopsy, whereas two were identified with additional triple biopsy only. In patients without DM ($n = 42$), seven and 13 primary tumors were successfully diagnosed by FDG PET/CT and additional triple biopsy, respectively. In total, FDG PET/CT and additional triple biopsy were able to identify 13 (24.1%) and 15 (27.8%) primary tumors, respectively. A representative case is illustrated in Figure 1.

Among the eight primary tumors identified in patients with DM, the six diagnosed by FDG PET/CT imaging had the following distribution: oropharyngeal cancer ($n = 1$), esophageal cancer ($n = 3$), lung cancer ($n = 1$), and gastric cancer ($n = 1$). The remaining two malignancies identified with repeated triple biopsy only were oropharyngeal neoplasms (Table 2).

In patients without DM ($n = 42$), the seven tumors diagnosed by FDG PET/CT imaging had the following distribution: nasopharyngeal cancer ($n = 3$), oropharyngeal

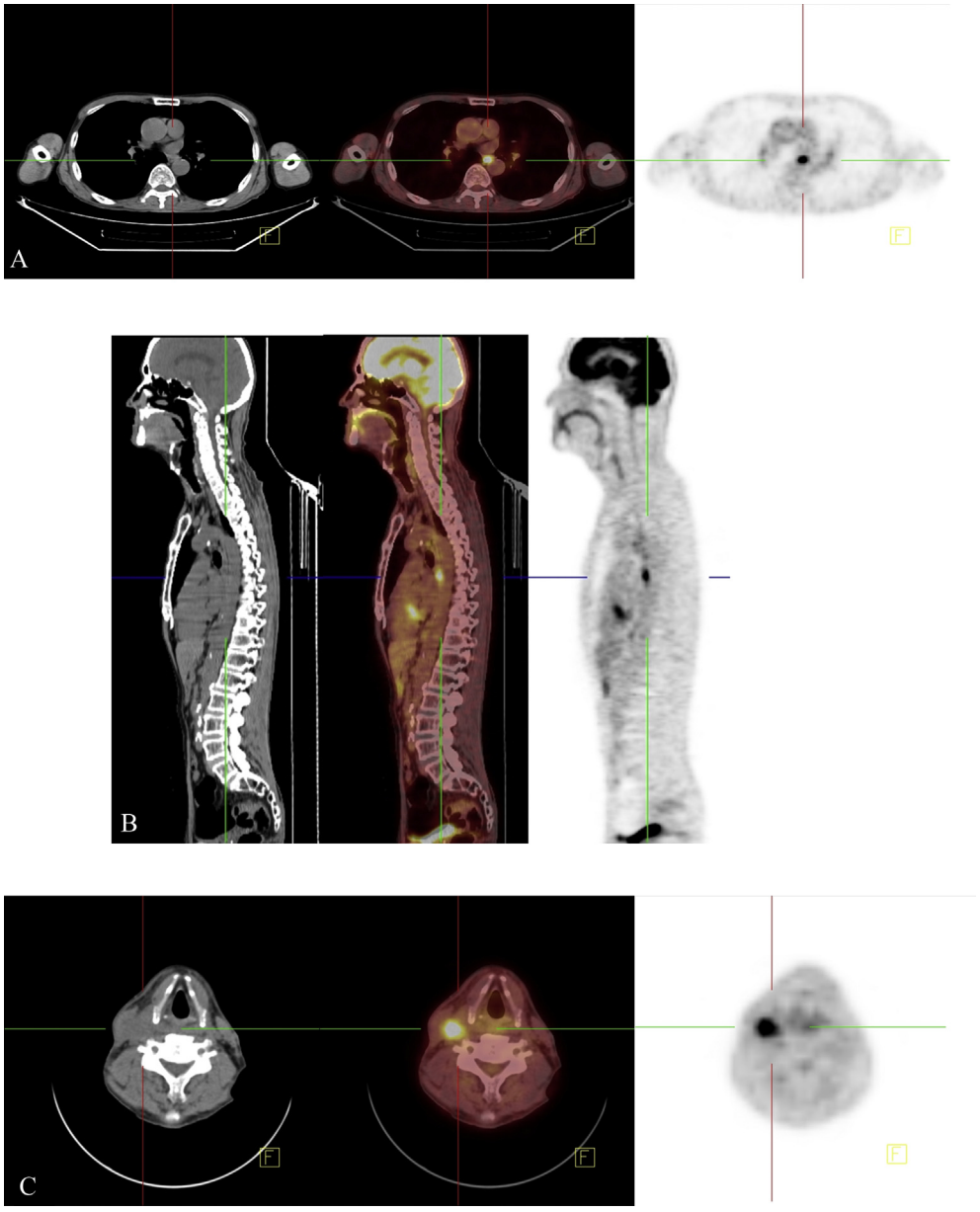

Figure 1. Representative images of a 57-year-old male patient diagnosed with esophageal cancer. FDG PET/CT imaging revealed a strong uptake ($SUV_{max} = 9.6$) in the middle third esophagus; this lesion was assigned a score of 4 (Panels A and B). By contrast, CT only revealed the presence of a necrotic lymph node in the level IV area of the neck (which showed a SUV_{max} of 4.7 on the corresponding FDG PET/CT image; Panel C). CT = computed tomography; FDG = F-18 fluorodeoxyglucose; PET = positron emission tomography.

Table 2 Distribution of primary tumor sites identified in the current study.

Primary tumor sites	PET findings			
	M0 (n)		M1 (n)	
	TP	FN	TP	FN
Head & neck				
Nasopharynx	3	1		
Oral cavity		2		
Oropharynx	3	7	1	2
Hypopharynx		3		
Esophagus	1		3	
Lung			1	
Gastric			1	
Overall	7	13	6	2

FN = false negative, FP = false positive, TP = true positive.

cancer ($n = 3$), and esophageal cancer ($n = 1$). Thirteen additional malignancies were identified with repeated triple biopsy, as follows: nasopharyngeal cancer ($n = 1$), oral cavity cancer ($n = 2$), oropharyngeal cancer ($n = 7$), and hypopharyngeal cancer ($n = 3$). Occult primary tumors located in the oral cavity, oropharynx, or hypopharynx had poor detection rates on FDG PET/CT (Table 2).

Risk stratification

Table 3 depicts the results of univariate and multivariate analyses in the 54 patients with CUP and cervical nodal metastases. Univariate analysis identified smoking, lower neck lymph nodes (level 4, 5, or supraclavicular fossa) involvement on FDG PET/CT imaging, SUV_{max} of cervical nodes ≥ 14.2, and DM as significantly associated with the 2-year cumulative OS. Other risk factors—including duration of lymphadenopathy < 5 months, bilateral cervical lymph nodes involvement on PET/CT imaging, and no identification of the occult primary tumor—were not significantly associated with 2-year OS on univariate analysis. After allowance for potential confounders in multivariate analysis, smoking, SUV_{max} of the cervical nodes, and DM were identified as significant independent predictors of 2-year OS rates. Patients were then divided into different risk groups based on a score obtained by assigning one point for each independent risk factor. There were 37 patients with a score of 0–1, whereas 17 patients had a score of 2–3. The 2-year OS rates in the two groups were 70.3% and 11.8%, respectively ($p < 0.001$; Figure 2).

Discussion

Head and neck cancer continues to pose a significant health burden to Asian countries, and cervical nodal metastases are common in this clinical entity. Notably, mounting evidence indicates that FDG PET/CT may be clinically useful for detecting occult primary neoplasms and/or DM, ultimately influencing the clinical management of this patient group [9,10,16,21–23]. Current curative-intent treatment plans for patients with malignancies are largely dependent on disease status and the nature of the primary tumor. Unfortunately, tailored treatment plans for patient with CUP remain difficult to develop. Starting from these premises, this study was specifically designed to investigate the potential utility of FDG PET/CT in CUP patients presenting with cervical nodal metastases.

The mean detection rate of occult neoplasms and/or DM in our study was 24.1%, a finding in line with the previous literature (showing a mean detection rate of ~25%) [11]. As expected, 78.6% (22/28) of the primary tumors identified in our CUP patients were head and neck malignancies. However, only seven of these 22 neoplasms (31.8%) were diagnosed with FDG PET/CT. This phenomenon may be explained by the known limitations of FDG PET/CT imaging including the small size of the primary tumor (lesions < 7 mm in their short axis are frequently undetectable) and/or the presence of a high FDG background activity in the tumor area (due to physiological uptake in the salivary glands, inflammatory reactions, and/or the presence of lymphoid tissue). The latter issue can ultimately degrade the quality of PET scans by reducing the lesion-to-background ratio [15,16]. In this scenario, further studies are necessary to identify the optimal cut-off points for PET-derived parameters in the identification of occult primary tumors. In our study, we found that FDG PET/CT imaging was more sensitive in the detection of: (1) nasopharyngeal cancer; and (2) malignancies located outside of the head and neck area (a finding in line with previous observations [22]). By contrast, 68.2% (15/22) of all head and neck tumors were identified by additional triple biopsy. The sites of additional triple biopsy were selected according to the results of FDG PET/CT, clinical suspicion, and/or based on the surgeon's judgment. The high clinical

Table 3 Univariate and multivariate analyses of risk factors associated with 2-year overall survival.

Parameter (*n*)	Univariate analyses			Multivariate analyses		
	95% CI	HR	*p*	95% CI	HR	*p*
Smoking	1.234–14.294	4.200	0.022	1.197–40.342	6.948	0.031
Lower neck nodes involvement on PET	1.815–19.837	6.000	0.003	0.561–11.277	2.516	0.228
Bilateral neck nodes involvement on PET	1.001–14.050	3.750	0.050	—	—	—
SUV_{max} of cervical lymph nodes ≥ 14.2	1.120–12.001	5.143	0.032	1.134–28.029	5.638	0.035
Initial distant metastases	1.575–41.926	8.125	0.012	1.257–114.854	12.017	0.031
Unidentified occult primary tumor sites	0.531–4.566	0.643	0.420	—	—	—

CI = confidence interval; HR = hazard ratio; PET = positron emission tomography; SUV_{max}, maximum standardized uptake value.

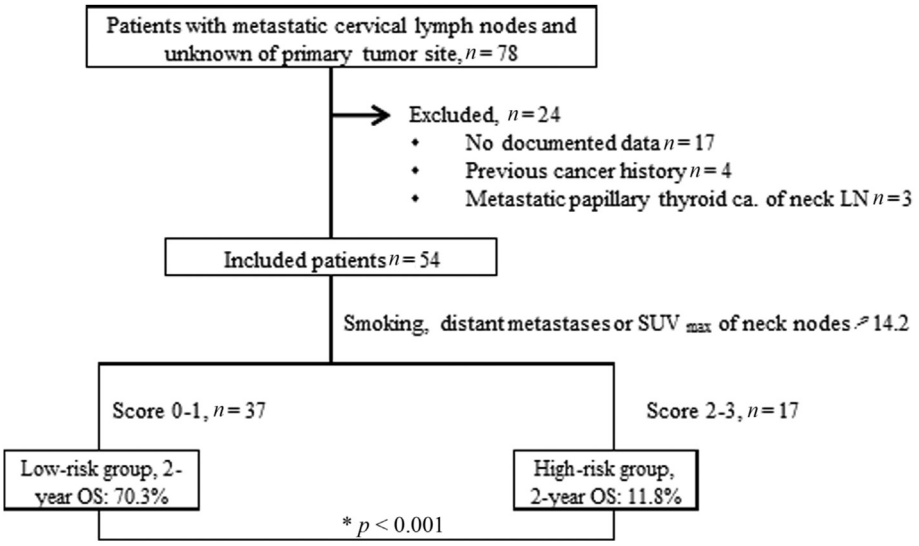

Figure 2. Flowchart of risk stratification for the study participants. ca = carcinoma; LN = lymph nodes; OS = overall survival; SUV_{max}: maximum standardized uptake value.

experience of the surgeons involved in the study may explain the higher positive rates associated with the use of additional triple biopsy. Based on these findings, we believe that repeated triple biopsy should be recommended to all patients with CUP and negative FDG PET/CT findings.

In addition to disease staging, FDG PET/CT can be clinically useful for risk stratification of this patient group [24,25]. Our results are in line with those of a previous report showing that smoking, high SUV values of the cervical nodes, and DM predict poor outcomes [1,26—28]. However, it should be noted that an unidentified occult primary tumor and bilateral cervical nodal metastases were not independently associated with 2-year OS in our report, a finding at variance with the published literature [29,30].

Smoking is a well-known risk factor for a number of different malignancies, including CUP [25]. We also demonstrated that it can serve as an independent predictor of OS in CUP patients. Unfortunately, we did not specifically investigate the amount of smoking (a variable that could have had an impact on our findings). The adverse prognostic significance of cervical SUV_{max} and DM at presentation could reflect a high biological tumor aggressiveness in patients with CUP and cervical nodal metastases, ultimately serving as an unfavorable prognostic biomarker.

Curative-intent treatment for patients with CUP who present with cervical lymph nodes metastases consists of neck node dissection, postoperative radiotherapy, and/or CCRT [11,17]. Several different chemotherapy and RT regimens have been investigated so far, generally resulting in acceptable outcomes (despite some expected complications) [28,29]. In the absence of DM, it is our policy to treat all patients with CUP and cervical lymph nodes metastases with curative-intent CCRT. In this scenario, an improved prognostic stratification is paramount to avoid overly aggressive or futile treatments. We therefore believe that our current prognostic scoring system may be useful in this setting.

Although the generalizability of our findings may be limited by the small sample size and the retrospective single-center nature of our research, all of the study participants were followed by an expert multidisciplinary head and neck care team. Altogether, our data may represent a valuable addition to the literature on the potential clinical utility of FDG PET/CT imaging in Asian patients with CUP presenting with cervical node metastases.

In conclusion, our results indicate that approximately one-third of patients with CUP and cervical node metastases had their treatment modified by FDG PET/CT findings (through the identification of the occult primary tumor and/or DM). The priority of definitive treatment for patients with CUP and cervical node metastases can be stratified according to FDG PET/CT results.

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