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Original research article

Carcinoma of unknown primary in the head and neck: The evaluation of the effectiveness of ^{18}F-FDG-PET/CT, own experience

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ABSTRACT

Aim: The aim of the present study was to estimate the clinical effectiveness of ^{18}F-FDG-PET/CT in the detection of the primary tumor in patients with histologically proven squamous cell carcinoma cervical lymph nodes metastasis from an unknown primary.
Background: ^{18}F-fluorodeoxyglucose positron emission tomography combined with CT (^{18}F-FDG-PET/CT) is believed to be very helpful in localization of primary tumor in CUP Syndrome patients.
Material and method: 41 patients referred to Poznan Medical University Department of Head and Neck Surgery from January 2010 to December 2013 with CUP Syndrome were included in the study. All patients presented fine-needle biopsy proven squamous cell carcinoma metastasis of the upper-, or mid neck lymph nodes. The final results were obtained from the histopathologic reports of tissue samples from anatomical regions suspected for primary tumor, additional imaging exams as well as clinical follow-up data.
Results: The ^{18}F-FDG-PET/CT successfully detected primary tumor in 7 out of 41 patients (17%). In two more cases the primary tumor was indicated in the lung. 24 of 41 patients (58.5%) analyzed in our study remained without evidence of a primary tumor. In 4 cases (9.75%) we did not reveal any pathology within the localizations indicated by PET/CT on panendoscopy. In 4 cases we obtained histological confirmation of neoplasm on panendoscopy despite the negative results of PET/CT examinations.
Conclusion: We may suppose a relatively high usefulness of ^{18}F-FDG-PET/CT in the diagnosis process of CUP Syndrome patients. High NPV may indicate patients with no symptoms of primary tumor, which allows to avoid extensive resection or extra imaging.

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1. Background

The diagnostic work-up of cervical lymph nodes metastasis from an unknown primary tumor (CUP Syndrome) includes physical examination with rigid or flexible endoscopy of upper aerodigestive tract, CT and/or MRI of the head and neck, additional imagings of chest and abdomen, fine-needle biopsy of the enlarged lymph nodes as well as panendoscopy with blind and directed tissue biopsies. Unfortunately, even such an extensive diagnostic process does not guarantee success – primary tumor detection. In consequence, detection rate of the primary tumor in patients with CUP Syndrome is less than 53.4%.[9]

In general, the prognosis for patients with CUP Syndrome is unfavorable. Their average survival is estimated for only a few months.[1] However, patients with lymph nodes metastasis, especially in the upper- or mid-jugular region are an exception. In 85% of these cases the primary tumor is localized in the head and neck region.[2] In consequence, the usual treatment of CUP Syndrome patients with highly suspected but not localized primary tumor in the head and neck includes neck dissection, bilateral tonsillectomy followed by adjuvant radiotherapy of all areas of the head and neck with high possibility of primary neoplasm.

It is obvious that correct primary tumor localization may carry through better locoregional treatment options for these patients and improve survival by reduction of side effects.

It is evaluated that conventional imaging modalities, like MRI or CT, detect approximately 10–35% of primary neoplasms in CUP Syndrome patients.[1] According to several studies, ^{18}F-fluorodeoxyglucose positron emission tomography combined with CT (^{18}F-FDG-PET/CT) is very helpful in localization of primary tumor. Its detection rate of the primary in patients with tumor metastasis in the head and neck, as well as in other body regions range between 24% and 53%.[3]

2. Aim

The aim of the present study was to estimate the clinical effectiveness of whole-body ^{18}F-FDG-PET/CT in the detection of the primary tumor in patients with histologically proven squamous cell carcinoma cervical lymph nodes metastasis from an unknown primary.

3. Materials and methods

This retrospective investigation included 41 patients referred to Poznan Medical University Department of Head and Neck Surgery from January 2010 to December 2013 with CUP Syndrome. All patients presented fine-needle biopsy proven squamous cell carcinoma cervical metastasis of the upper-, or mid neck (regions I–III and V according to Medina[4]) (Table 1). Patients with metastasis in the neck nodes in region IV were also involved in our analysis whereas the frequent primary tumor outside the head and neck area.

In the first step of the diagnosis process each patient underwent a thorough clinical examination with an indirect mirror and rigid or flexible endoscopy of the upper aerodigestive tract, neck ultrasound examination, X-ray of the thorax as well as contrast-enhanced CT of the head and neck region. Only patients with undetected pathological finding potentially related to cervical lymph node enlargement were further investigated. After receiving all the exam results and excluding distant metastasis in the thorax by imaging techniques, patients were qualified for (modified) radical neck dissection accompanied by panendoscopy consisting of bilateral tonsillectomy (if it had not been previously performed) and blind tissue specimens taken from macroscopically suspicious areas of mucosa of pharynx (naso-, oro-, hypopharynx), larynx and esophagus. If there was still no evidence of primary tumor, PET/CT examination was considered.

Table 1 – Cervical lymph nodes classification and probable primary tumor.[4]

Localization of lymph node metastasis	Probable primary tumor localization
Submental nodes	Anterior floor of mouth, lips
Submandibular nodes	Cheek, palate, tongue
Jugulodigastric nodes	Oropharynx, hypopharynx, nasopharynx, larynx, oral cavity
Upper jugular nodes	Hypopharynx, larynx, thyroid gland
Upper posterior cervical nodes	Nasopharynx
Mid jugular nodes	Thyroid gland, cervical esophagus
Lower jugular nodes	Thyroid gland, cervial esophagus
Supraclavicular nodes	Thyroid gland, lungs, gastrointestinal tract, urogenital tract, mammary gland
Posterior cervical triangle nodes	Nasopharynx

41 consecutive patients (8 women, 33 men; aged 37–75 years; mean age 60.75) underwent PET/CT examination (scanner Philips Gemini TF) using ^{18}F-FDG tracer in the amount of 9.3 mCi (SD 1.87 mCi) according to patient's body weight. PET/CT was recommended at least 6 weeks after surgical procedure and before adjuvant radiotherapy. Conditions for the implementation of the exam were normoglycemic after fasting for at least 6 h (70–130 mg/dl) and adequate rest. Each patient was obliged to drink at least 1 L of water. PET was performed 1 h after intravenous injection of FDG from head to proximal thigh. Attenuation-corrected and uncorrected slice images and maximum intensity projections were assessed and documented. Subsequently, contrast-enhanced CT of the whole body was acquired for anatomical accuracy and attenuation correction.

Each PET/CT examination was evaluated by one specialist in nuclear medicine. Lesions with increased tracer uptake were anatomically identified and their FDG uptake was quantified. Finally, each PET/CT exam was characterized as positive or negative for primary tumor. Furthermore, SUV max in every region of increased metabolic activity was measured and compared to the corresponding region on the contralateral side. In case of no visible primary tumor, SUV was measured in the tonsillar area and base of tongue as these are the areas where the tumor is most possible.

Table 2 – TNM classification of patients included in the study; feature T estimated according to PET/CT and histology results.

T/N feature	N1	N2a	N2b	N2c	N3	Total
Tx	1	6	11	4	6	28
T1	0	2	5	1	3	11
T2	0	0	0	0	2	2
Total	1	8	16	5	11	41

If possible, all the suspicious in PET/CT lesions were histologically assessed (fine-needle aspiration, core needle biopsy or open surgical biopsy). PET/CT scans were evaluated as true positive, if the histology revealed carcinoma in the suspected region. PET/CT exams with no dubious regions were characterized as true negative, provided that panendoscopy under general anesthesia as well as additional imagings did not reveal the primary tumor. PET/CT exams were false positive if the histological assessment or additional imagings did not confirm neoplastic infiltration in the suspected area. In case of primary tumor detection during panendoscopy while negative result of PET/CT, the exam was assessed as false negative.

The sensitivity, specificity, accuracy, positive and negative predictive value of PET/CT for the diagnosis of primary tumor in patients with CUP Syndrome were calculated. Finally, patients were staged using the 2010 American Joint Committee on Cancer (AJCC) staging system (Table 2).

4. Results

24 of 41 patients (58.5%) analyzed in our study remained without evidence of a primary tumor. All PET/CT examinations performed in this study subgroup did not reveal any suspicious area likely to be a primary neoplasm. As all the patients had already undergone neck dissection, PET/CTs showed mainly postoperative inflammatory uptake within the neck. However, in 7 cases the study indicated cervical lymph nodes with increased tracer uptake, as suspected of metastasis. Fine-needle biopsy performed under USG guidance confirmed squamous cell carcinoma metastasis in 3 patients (according to TNM classification: N1 in 1 case and N2a in 2 others), whereas in the remaining 4 the results were negative. The patients with confirmed cervical lymph nodes metastasis were qualified for neck reoperation. Of the 24 patients without occult primary tumor, so far 15 have been followed for at least 42 months. In 2 of these patients, follow-up examinations indicated primary oropharyngeal carcinoma. Our diagnostic tools have not as yet revealed distant metastasis in the above patients.

11 possible primary tumors were indicated in the head and neck region by PET/CT. 7 of these were confirmed on histopathological examination as shown in Table 3. In 3 of the 7 aforementioned cases, the tumor was also seen on panendoscopy (hypopharynx, base of tongue and tonsil). In further 3 localizations (2 tonsils and 1 nasopharynx), the tumors were suspected only on PET/CT exam, while physical examination did not reveal any worrying symptoms. 1 neoplasm (base of tongue) was submucosal.

We assessed above characterized PET/CT scans as true positive.

In 4 cases (9.75%) (1 nasopharynx, 2 tonsils, 1 vallecula) we did not reveal any pathology within the localizations indicated by PET/CT on panendoscopy. Furthermore, blind tissue biopsies did not confirm neoplasm. Additional imaging studies recommended during the follow-up (CT or MRI of the head, neck and thorax, US of the neck and abdomen) did not show any pathology suspected for primary tumor.

These PET/CT exams were characterized as false positive.

In 2 patients PET/CT examination indicated a solitary tumor within the lungs. These pathologies were also found on chest CT. The histopathology confirmation of neoplasm was achieved during mediastinoscopy in 1 case.

These PET/CTs were also estimated as true positive on the basis of additional exams results.

In 4 cases we obtained histological confirmation of neoplasm on panendoscopy despite negative results of PET/CT examinations (3 tonsils and 1 nasopharynx). These tumors did

Table 3 – Possible primary tumors indicated by PET/CT examinations.

No.	Primary tumor according to PET/CT	Additional exams results	PET/CT assessment
1	Hypopharynx	Histology confirmation	True positive
2	Tonsils	Histology confirmation	True positive
3	Tonsils	Histology confirmation	True positive
4	Tonsils	Histology confirmation	True positive
5	Tonsils	No histology confirmation	False positive
6	Tonsils	No histology confirmation	False positive
7	Nasopharynx	Histology confirmation	True positive
8	Nasopharynx	No histology confirmation	False positive
9	Base of tongue	Histology confirmation	True positive
10	Base of tongue	Histology confirmation	True positive
11	Lung	Histology confirmation, CT confirmation	True positive
12	Lung	CT confirmation	True positive
13	Vallecula	No histology confirmation	False positive

not exceed 15 mm in the greatest dimension. In consequence, we assessed these PET/CT scans as false negative.

Finally, PET/CT exam detection rate for primary tumor in the head and neck region was 17.07% (7/41). For the rest of the body it was estimated at 4.87% (2/41). That gives 21.95% (9/41) detection rate overall.

Summarizing, basing on presented results we assessed sensitivity of PET/CT examination at 69.2%, specificity of 85.7% and accuracy of 80.4%. The positive predictive value was 69.2%, the negative predictive value 85.7%.

We compared the SUVmax as well as the asymmetry of the ^{18}F-FDG tracer uptake in the group of 13 patients with diagnosed primary tumors and in 28 patients without it. As might be expected, these parameters were higher in the first group of patients but no definitive cutoff was estimated between the two groups.

5. Discussion

According to Kwee et al., who presented in their paper from 2009[5] a very precise definition of CUP Syndrome, CUP were the patients with histologically confirmed lymph node metastatic cancer and no evidence of primary tumor in physical examination, full blood count, basic biochemistry battery, urinalysis, stool occult blood testing, immunohistochemistry with specific markers as well as conventional imaging technology.

Cervical CUP Syndrome cases constitute between 3% and 11% of newly diagnosed head and neck cancers.[6,7] Pathologically isolated nodal metastases can be divided into squamous cell cancers, adenocarcinomas and undifferentiated tumors.[8] Squamous cell cancer metastases, which are the subject of the present analysis, of the upper and middle cervical lymph nodes primarily originate from the region of head and neck. In the case of lower neck lymph nodes metastases, we can expect primary tumor below the clavicles rather than in the head and neck.[4]

Usually, the diagnostic process of CUP Syndrome patients include exact physical examination extended by a rigid or flexible endoscopy of upper aerodigestive truct, CT and/or MRI of the head and neck, fine-needle biopsy of the enlarged lymph nodes as well as panendoscopy with blind and directed tissue biopsies. In case of adenocarcinoma or undifferentiated cancers metastasis, additional imaging of chest and abdomen is performed. Unfortunately, detection rate of primary tumor in CUP Syndrome cases is estimated at less than 53.4%[9] even despite such an extensive work-up as presented above.

The treatment of patients with cervical lymph nodes metastases from unknown primary tumor, when the primary neoplasm cannot be localized, usually involves neck dissection and tonsillectomy as well as adjuvant radiotherapy of all areas of the neck that may conceal the primary tumor.[9] Consequently, as can be expected, the identification of primary neoplasm will result in targeted treatment that may reduce the side effects of radiotherapy by limiting the field of irradiation and will increase the patient's chances of survival.[6] Furthermore, the detection of distant metastases or second malignancy would change the treatment.

There is a growing world literature that provides more and more evidence of the effectiveness of ^{18}F-fluorodeoxyglucose positron emission tomography combined with CT (^{18}F-FDG-PET/CT) in detecting the primary tumors in patients with CUP Syndrome. In consequence, the German Consensus Conference characterized the whole body FDG-PET as the one with scientifically proved benefit and established clinical use in CUP cases.[10] Of course, PET combined with CT has a clearly higher detection rate of primary neoplasm in comparison with PET alone as a result of simultaneous acquisition of accurately aligned whole body anatomical and functional images.[11]

Positron emission tomography in comparison with conventional work-up has a higher sensitivity and accuracy; for example Roh et al. demonstrated higher sensitivity of FDG-PET/CT than CT alone ($p = 0.016$).[12] Analyzing world literature from the last 20 years, we may report PET/CT detection rate of the primary of between 8% and 74%. Gutziet et al. reached the identification rate of primary cancer of 33% for 45 patients[13]; Nanni et al. estimated the detection rate of unknown primary tumor at the level of 57% basing on a group of 21 patients.[14] Overall, the PET/CT's average detection rate of primary neoplasm has been found to be approximately 32%.[7] Our study result of 22% of identification rate in a group of 41 patients is in the aforementioned range. Additionally, PET/CT revealed primary neoplasm below the clavicles in 2 cases. In both situations the tumor was located in the lung. We assessed these scans as true positive basing on the results of additional imaging studies and histopathology result in one patient.

The ^{18}F-fluorodeoxyglucose is not an optimal tracer for every anatomical region. For instance, the uptake in gastrointestinal tract, urinary tract, brain or even in some localizations of the head and neck, especially with concomitant inflammatory process, may conceal or even simulate the neoplasm, which produces false negative or false positive results.[15] Our analyzes showed 4 false positive PET/CT scans, that indicated the potential primary tumor in the nasopharynx, tonsils and vallecula, thus confirming the difficulties in differentiating the malignant and benign or even inflammatory process in the head and neck region by PET and, which is an obvious weakness resulting in low specificity of PET. Nowadays, another radiopharmaceuticals are evaluated for tumor staging, not only in the head and neck region. An example of this is ^{18}F-FLT (^{18}F-fluorothymidine). Vojtisek et al. confirmed great potential of ^{18}F-FLT PET/CT in the precise HNSCC staging in their research from 2015, which may potentially improve primary tumor recognition in the future. This, undoubtedly, requires further research.[16]

FDG-PET/CT scan did not indicate the primary tumor in 4 cases that were identified on panendoscopy afterwards. This relates to small tumors size (not more than 15 mm) that is on the borderline of PET scan resolution. Moreover, well-differentiated squamous cell carcinoma is characterized by a lower FDG uptake that may be wrongly interpreted as negative.[17]

Accuracy, sensitivity and specificity in this research were 80.4%, 69.2% and 85.7%, respectively. Our results were much lower than those obtained by Wang et al.[18] (the accuracy, sensitivity and specificity of FDG PET/CT scan were 93.7%, 95.7% and 91.7%, respectively) but similar to the results of Seve et al. study[19] (80.5%, 91.9% and 81.9%, respectively). Furthermore, comparatively high value of PET/CT specificity (85.7%) as well as NPV (85.7%) may allow identification of

the patients without occult primary tumor and therefore avoid further imaging or extra extensive resection. Relatively lower sensitivity from our research when compared with other studies is the result of many false negative scans in relation to relatively low true positive results when taking into account the number of patients analyzed. As mentioned previously, this results particularly from a small dimension of the primary tumor, tumor grading resulting in low FDG uptake in the case of low-grade epithelial neoplasms and, finally, a physiologically higher tracer uptake in some areas of the head and neck which may obscure the primary.

In this study, 31.7% (13/41) of patients received specific treatment due to the identification of the primary sites. In 5 cases (2 with lung cancer and 3 with confirmed cervical lymph nodes metastases) PET/CT results contributed to the change in the treatment plan.

6. Conclusions

In conclusion, we may confirm a high effectiveness of ^{18}F-FDG-PET/CT in the diagnosis process of CUP Syndrome patients with specificity showing a trend to significance. However, we must emphasize that accurate clinical examination, diagnostic imaging, like ultrasound scan, CT, MRI and panendoscopy with bilateral tonsillectomy or blind tissue biopsies especially from the nasopharynx and base of the tongue also play an important role in diagnostic work-up of cervical CUP Syndrome patients.

Conflict of interest

None declared.

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REFERENCES

1. Chorost MI, Lee MC, Yeoh CB, Molina M, Ghosh BC. Unknown primary. *J Surg Oncol* 2004;**87**(15 September (4)):191–203.
2. Nieder C, Gregoire V, Ang KK. Cervical lymph node metastases from occult squamous cell carcinoma: cut down a tree to get an apple? *Int J Radiat Oncol Biol Phys* 2001;**50**(1 July (3)):727–33.
3. Delgado-Bolton RC, Fernández-Pérez C, González-Maté A, Carreras JL. Meta-analysis of the performance of ^{18}F-FDG PET in primary tumor detection in unknown primary tumors. *J Nucl Med* 2003;**44**(August (8)):1301–14.
4. Medina JE. A rational classification of neck dissections. *Otolaryngol Head Neck Surg* 1989;**100**(March (3)): 169–76.
5. Kwee TC, Kwee RM. Combined FDG-PET/CT for the detection of unknown primary tumors: systematic review and meta-analysis. *Eur Radiol* 2009;**19**(March (3)): 731–44.
6. Miller FR, Karnad AB, Eng T, Hussey DH, Stan McGuff H, Otto RA. Management of the unknown primary carcinoma: long-term follow-up on a negative PET scan and negative panendoscopy. *Head Neck* 2008;**30**(January (1)):28–34.
7. Johansen J, Buus S, Loft A, et al. Prospective study of ^{18}FDG-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. *Head Neck* 2008;**30**(April (4)):471–8.
8. Regelink G, Brouwer J, de Bree R, et al. Detection of unknown primary tumours and distant metastases in patients with cervical metastases: value of FDG-PET versus conventional modalities. *Eur J Nucl Med Mol Imaging* 2002;**29**(August (8)):1024–30.
9. Cianchetti M, Mancuso AA, Amdur RJ, et al. Diagnostic evaluation of squamous cell carcinoma metastatic to cervical lymph nodes from an unknown head and neck primary site. *Laryngoscope* 2009;**119**(December (12)):2348–54.
10. Reske SN, Kotzerke J. FDG-PET for clinical use. Results of the 3rd German Interdisciplinary Consensus Conference, Onko-PET III, 21 July and 19 September 2000. *Eur J Nucl Med* 2001;**28**(November (11)):1707–23.
11. Waltonen JD, Ozer E, Hall NC, Schuller DE, Agrawal A. Metastatic carcinoma of the neck of unknown primary origin: evolution and efficacy of the modern workup. *Arch Otolaryngol Head Neck Surg* 2009;**135**(October (10)):1024–9.
12. Roh JL, Kim JS, Lee JH, et al. Utility of combined (18)F-fluorodeoxyglucose-positron emission tomography and computed tomography in patients with cervical metastases from unknown primary tumors. *Oral Oncol* 2009;**45**(March (3)):218–24.
13. Gutzeit A, Antoch G, Kühl H, et al. Unknown primary tumors: detection with dual-modality PET/CT – initial experience. *Radiology* 2005;**234**(January (1)):227–34.
14. Nanni C, Rubello D, Castellucci P, et al. Role of ^{18}F-FDG PET–CT imaging for the detection of an unknown primary tumour: preliminary results in 21 patients. *Eur J Nucl Med Mol Imaging* 2005;**32**(May (5)):589–92.
15. Stokkel MP, Bongers V, Hordijk GJ, van Rijk PP. FDG positron emission tomography in head and neck cancer: pitfall or pathology? *Clin Nucl Med* 1999;**24**(December (12)):950–4.
16. Vojtíšek R, Ferda J, Fínek J. Effectiveness of PET/CT with (18)F-fluorothymidine in the staging of patients with squamous cell head and neck carcinomas before radiotherapy. *Rep Pract Oncol Radiother* 2015;**20**(May–June (3)):210–6.
17. Kole AC, Nieweg OE, Pruim J, et al. Detection of unknown occult primary tumors using positron emission tomography. *Cancer* 1998;**82**(15 March (6)):1160–6.
18. Wang G, Wu Y, Zhang W, Li J, Wu P, Xie C. Clinical value of whole-body F-18 fluorodeoxyglucose positron emission tomography/computed tomography in patients with carcinoma of unknown primary. *J Med Imaging Radiat Oncol* 2013;**57**(February (1)):65–71.
19. Sève P, Billotey C, Broussolle C, Dumontet C, Mackey JR. The role of 2-deoxy-2-[F-18]fluoro-D-glucose positron emission tomography in disseminated carcinoma of unknown primary site. *Cancer* 2007;**109**(15 January (2)):292–9.