FDG PET/CT and Conventional Imaging Methods in Cancer of Unknown Primary: an Approach to Overscanning

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Abstract

Purpose To compare the performance of fluorine-18 fluorodeoxyglucose positron emission tomography and computed tomography (FDG PET/CT) with conventional imaging methods (CIM), including computed tomography (CT), magnetic resonance imaging (MRI), and mammography (MMG) in cancer of unknown primary (CUP).

Methods A total of 36 patients with CUP, who referred to our clinic for a FDG PET/CT scan, were enrolled in this study. Thirty of the patients were also examined through either diagnostic CT/MRI and/or MMG. The diagnostic performance of both methods for the primary cancer location was analyzed. The results of FDG PET/CT and CIM were compared based on the standard reference of the histopathology and/or clinical and laboratory follow-up.

Results The primary cancer locations were detected in 24 patients (66.6%, 24/36) by FDG PET/CT, whereas CIM identified the locations in 16 patients (53.3%, 16/30). Sensitivity, specificity, PPV, NPV, and accuracy rates of the detection of the primary tumor localizations were as follows: 83, 70, 89, 58, and 79% for FDG PET/CT; 70, 62, 84, 42, and 68% for CIM, respectively. There was no statistical significance between modalities regarding any of the categories in 30 patients.

Conclusion FDG PET/CT detected the primary tumors of the patients with CUP more than CIM did. However, the difference between them was not found to be statistically significant. It may be considered that FDG PET/CT scan can be performed as a first-line tool in the initial diagnosis of the patients with CUP and to add radiodiagnostic imaging in selective cases. We conclude that if the first-line examination of a CUP patient has been already performed by a CIM and the result was negative or inconclusive, FDG PET/CT can be considered to avoid unnecessary imaging procedures.

Keywords FDG PET/CT · Oncology · Cancer of unknown primary origin · CT · MRI

Introduction

With the development of personalized therapy for malignancies, it has become essential to determine the origin of the primary tumor in order to provide optimized care for cancer

of unknown primary (CUP)-diagnosed patients. There is a great challenge in this regard, related to the CUP, which is a disease of biopsy-proven metastatic tumors whose origin cannot be determined despite extensive research [1]. Among the imaging methods, diagnostic computed tomography (CT) and

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magnetic resonance imaging (MRI) are widely performed in the diagnostic work-up of CUP. Given to their lack of ability to identify the metabolic processes, they may be insufficient to detect the primary cancer locations, as well as the metastatic spread, in some cases. FDG PET/CT provides a superior diagnostic accuracy than the conventional methods through its detection capability of the lesion's metabolic status at a molecular level in various malignancies [2–4]. In addition, defining whole body status of patients with CUP by FDG PET/CT to detect the primary focus allows to reveal the amenable biopsy sites, adequate surgical excision, radiation therapy delineation, and tumor-targeted therapy [5]. However, neither routine usage information for CUP nor definite recommendations for when to perform FDG PET/CT scan is clear according to the latest guidelines [6]. This leads to variable approaches to CUP with unnecessary additional procedures and radiation exposure to the patient, undesired time and money consume as well. Even if the anatomical details given by CIM and unique metabolic information provided by FDG PET/CT are complementary to each other, one of these modalities may just be enough to answer the clinician's question in some cases.

In the current study, we aimed to investigate the roles of FDG PET/CT and conventional imaging methods (CIM) including CT/MRI/MMG and compare the results of these methods in the initial diagnostic pathway of CUP.

Materials and Methods

Patients

A total of 100 patients who were referred for a FDG PET/CT scan between October 2014 and March 2016 due to metastases of unknown primary tumor were retrospectively reviewed. Patients who had a metastatic tumor confirmed by the biopsy or lesions with the high suspicion of metastases detected by the imaging methods were included in the study. Patients whose follow-up or clinical data were not accessible, who ended up with no malignancy or who had received chemotherapy before imaging methods, were excluded. According to these criteria, 36 patients (13 female and 23 male, the median age of 62 in a range of 25 to 92) with a mean follow-up of 8 months (1–16 months) formed the study population.

Thirty patients had at least one of the radiological imaging modalities on the basis of suspected primary malignancy localization. Among them, one patient had cervical CT or MRI, 3 patients had thoracic CT, 5 patients had abdominopelvic CT, 5 patients had cervical CT and/or MRI with thoracic CT, 12 patients had thoracic CT with abdominopelvic CT and/or MRI, 3 patients had cervical, thoracic, and abdominopelvic CT. Most of the CT and MR scans were performed with

intravenous contrast material. Besides, all four female patients with breast carcinoma and a female patient whose malignancy origin remained undetected had MMG. Additionally, brain CT or MRI was performed in two patients. Some of the patients had ultrasound imaging as well (cervical: 9, breast: 4, abdominal: 4, testicular: 1).

All imaging, biochemistry, histopathology, and other clinical records were collected. Demographic characteristics of the study group are denoted in Table 1. This retrospective study was approved by the Ethics Committee on Clinical Research of our hospital. All patients gave written informed consents for FDG PET/CT.

Imaging and Data Assessment

FDG PET/CT images were acquired after the patients had fasted for at least 4 h. Blood glucose levels were less than 200 mg/dl. Image acquisition occurred 1 h after injection of 0.1 mCi/kg (185–370 MBq) of FDG using a General Electric Discovery 710 PET/CT scanner (GE Medical Systems, Waukesha, WI, USA). The low-dose CT image acquisition was performed without injection of iodinated contrast material, followed by PET image acquisition using 3 min per bed position, extending from the skull vertex to the proximal thighs.

CT scans were acquired using the settings of 120 kV voltage and 120 mA tube current, 0.5 s/rotation, section thickness of 3.3 mm for the whole body, and 1.25 mm for the additional lung scan. PET imaging was performed using a matrix of 512×512 after CT scanning. Following processing of PET data with iterative reconstruction methods, PET, CT, and fused PET/CT images were available for review in axial, coronal, and sagittal planes.

At least two nuclear medicine physicians evaluated the FDG PET/CT data of patients in consensus. Both visual and semi-quantitative interpretation methods were used. For visual assessment, with or without corresponding anatomical changes, foci which have more intense FDG uptake than background activity and unlikely to be a benign pathological or physiological uptake suggestive of primary malignancy and/or metastases were determined. Additionally, for these foci, region of interest was drawn around the most intense FDG uptake and maximum standard uptake value (SUV_{max} corrected for body weight) was calculated as semi-quantitative method. SUV_{max} values were used to support visual interpretation results. It had no role to discriminate primary or metastatic tumor in this study. All available endoscopy/biopsy reports, reports of CIM (in 30 patients) such as thorax-abdominal CT, MRI and MMG for women were obtained and suggested that primary malignancy site metastases were noted as well.

When suggested primary site by FDG PET/CT and/or CIM was confirmed histopathologically or accepted by multidisciplinary clinical approach (with a clinical oncologist, a radiologist, nuclear medicine physicians) and follow-up, the scan

Table 1 All data about patient characteristics, results of the imaging methods and final diagnosis

Case no	Age/ gender	Metastasis localisation	Pathology/ histopathology	Primary by PET/CT	EP	Additional metastasis	Primary by CIM	EP	Additional metastasis	Superiority of PET/CT over CIM	Final Diagnosis
1	55/m	Cervical LN	Carcinoma	–	FN	–	–	FN	LN	–	thyroid
2	62/f	Cervical LN	SCC	–	FN	LN	Tonsil	TP	LN	–	tonsil
3	80/m	Cervical LN	Carcinoma	Tonsil	TP	–	Tonsil	TP	–	–	tonsil
4	57/m	Cervical LN	Undiff. ca	NF	TP	LN	NF	TP	LN	–	NF
5	66/f	Cervical LN	Epithelial tm	–	TN	LN	–	TN	LN	–	–
6	78/m	Cervical LN	Epithelial tm	–	TN	LN, bone	–	TN	LN, bone	–	–
7	72/m	Cervical LN	Epithelial tm	Lung	TP	Cerebrum, LN	Lung	TP	LN	–	lung
8	66/m	Cervical LN	SCC	Tonsil	TP	LN	Tonsil	TP	LN	–	tonsil
9	44/m	Cervical LN	Epithelial tm	NF	TP	LN, lung, liver, bone	NF	TP	LN, lung, liver	bone	NF
10	67/m	Suprac. LN	Epithelial tm	Lung	TP	LN	–	FN	LN	–	lung
11	92/m	Axillary LN	Small cell ca	Lung	TP	LN, bone	NA	NA	NA	NA	lung
12	59/m	Axillary LN	Adenoca	–	TN	LN	–	TN	LN	–	–
13	68/f	Axillary LN	Epithelial tm	Breast	TP	LN	Breast	TP	LN	–	breast
14	63/f	Axillary LN	Epithelial tm	–	FN	LN	–	FN	LN	–	breast
15	72/m	Md. LN	Epithelial tm	Lung, testicular	TP-FP	Lung, liver, bone, LN	Lung	TP	Lung, LN	Liver, bone	lung
16	25/m	Abd. LN	Sarcoma	Muscle	TP	Lung, LN	Muscle	TP	Lung, LN	–	muscle
17	79/f	Inguinal LN	Epithelial tm	R. breast	TP-TN	LN	L. breast	FP-FN	LN	–	R. breast
18	57/m	Bone	Adenoca	Lung	TP	Bone	Lung	TP	Bone	–	lung
19	69/m	Bone	NA	Lung	TP	Liver, bone, adrenal (R, L), LN	Lung	TP	Liver, bone, adrenal (L), LN	Adrenal (R)	lung
20	69/f	Bone	NA	–	FN	Bone	Breast	TP	Bone, LN	–	breast
21	60/m	Bone	NA	Breast, intestine	TP-FP	Adrenal, bone	NA	NA	NA	NA	breast
22	57/m	Bone	NA	Prostate	TP	Liver, bone, LN	NA	NA	NA	NA	prostate
23	64/m	Bone	NA	Prostate	TP	Bone, LN	–	FN	LN	–	prostate
24	73/m	Bone	Carcinoma	–	FN	Liver, bone	Liver	TP	Bone	–	liver
25	58/f	Liver	Adenoca	Colon	TP	Lung, LN	Colon	TP	Lung, LN	–	colon
26	70/f	Liver	NA	Stomach	TP	Bone, LN, peritoneum	NA	NA	NA	NA	stomach
27	83/f	Liver	NA	Rectum	TP	Lung, LN	Rectum	TP	Lung, LN	–	rectum
28	46/m	Peritoneum	SRCC	–	TN	–	–	TN	–	–	–
29	62/f	Peritoneum	Adenoca	Genital	TP	LN	–	FN	–	LN	genital
30	46/f	Abd. ascites	Adenoca	Genital	TP	Liver, LN, peritoneum	NA	NA	NA	NA	genital
31	67/m	Abd. ascites	Adenoca	–	TN	Peritoneum	Stomach	FP	Peritoneum	–	–
32	48/f	Psoas abscess	Epithelial tm	Genital	TP	Bone, adrenal, LN, peritoneum	–	FN	LN, peritoneum, adrenal	bone	genital
33	38/m	Appendix	Adenoca	Colon	FP	Peritoneum	Colon	FP	Peritoneum	–	–
34	80/f	Pl. ascites	Adenoca	–	TN	Peritoneum	–	TN	Peritoneum	–	–
35	61/m	cerebrum	NA	Lung	TP	Adrenal, bone, LN	lung	TP	Adrenal, bone, LN	–	lung
36	69/m	cerebrum	NA	Lung	TP	Lung, liver, bone, adrenal	NA	NA	NA	NA	lung

CIM conventional imaging modalities, EP end point, LN lymph node, Md mediastinum, Abd abdominal, SCC squamous cell ca, Undiff undifferentiated, SRCC signet-ring cell carcinoma, Supr supraclavicular, NF nasopharynx, Abd abdominal, Pl pleural, R right, L left, TP true positive, TN true negative, FN false negative, NA not available

was accepted as true positive, otherwise as false positive. If FDG PET/CT and/or CIM could not reveal any primary and so were the other diagnostic imaging and/or procedures in the initial thorough evaluation and during follow-up period, scans were considered as true negative. Furthermore, a negative FDG PET/CT and/or CIM were considered as false negative when the primary tumor was revealed by biopsy or clinical decision/follow-up. When there is more than one suggested primary origin, all of the results were used statistically.

Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy were calculated for FDG PET/CT in 36 patients and for CIM in 30 patients using MedCalc for Windows, version 18.0 (MedCalc Software, Ostend, Belgium). Chi-square test was used to identify the correlation between two modalities in 30 patients with both FDG PET/CT and CIM data in terms of sensitivity, specificity, PPV, NPV, and accuracy. *p* values of less than 0.05 were regarded as statistically significant.

Results

The study population included 17 patients with lymph node metastases (cervical *n* = 10; axillary *n* = 4; and *n* = 1 for each mediastinum, abdominal, and inguinal sites) and 19 patients with extranodal metastases (bone *n* = 8; liver *n* = 3; cerebellum *n* = 2; malignant pleural effusion *n* = 1; malignant ascites *n* = 2; appendix *n* = 1; peritoneum *n* = 1; psoas abscess *n* = 1). With the help of cytology/histopathology and/or formal clinical follow-up, final primary sites of cancer were determined as follows: lung (*n* = 9), breast (*n* = 5), tonsil (*n* = 3), nasopharynx (*n* = 2), thyroid (*n* = 1), internal genital (*n* = 3), prostate (*n* = 2), stomach (*n* = 1), colon (*n* = 1), rectum (*n* = 1), and muscle (*n* = 1).

Primary malignancy was accurately detected in 24 subjects (66.6%, 24/36) by FDG PET/CT with three false positives and five false negatives. False-positive results were as follows: A 72-year-old male patient with hypermetabolic foci in both lung and testicles suggesting lung or testicular cancer was diagnosed with lung cancer and testicular granulomatous infection confirmed by biopsy (case no: 15). Secondly, a 60-year-old male patient with multiple bone metastases observed on MRI had breast and ileum mass with pathological FDG uptake that one of the sites was possible primary origin. As the probability of breast carcinoma in a male patient was thought to be low, biopsy of the bowel mass was performed. The result was compatible with primary breast malignancy metastases (case no: 21). Moreover, the last false-positive case was a 38-year-old male who had adenocarcinoma metastases detected with an appendectomy. He had pathological findings suggesting rectosigmoid colon malignancy detected in both FDG PET/CT and diagnostic CT. However, colonoscopy and

biopsy results were negative for the colon malignancy in this patient (case no: 33). As a false-negative result, in a 73-year-old male patient with bone metastases, multiple hypermetabolic hypodense lesions in liver were interpreted as the metastases. Contrast-enhanced CT revealed hepatocellular carcinoma as the primary origin (case: 24). Thyroid, tonsil, and breasts (*n* = 2) were other primary origins in the patients with false-negative FDG PET/CT results. There was no pathological FDG uptake in the primary tumors of these patients.

On the other hand, among 30 patients whose radiological imaging data were available, the accurate detection of primary tumor locations was achieved by CIM with 3 false-positive and 7 false-negative suggestions in 16 patients (53.3%, 16/30). False-positive results were as follows: in a 79-year-old female patient with BIRADS4 (Breast Imaging Reporting and Data System) lesion in left breast detected by MMG, the diagnosis after biopsy was consistent with fibroadenoma (false positive). Primary lesion was found to be in the right breast, while it had not been detected by MMG (false negative) (case no: 17). In another case with malignant abdominal ascites, abdominal CT defined gastric wall thickening likely to be malignant; however, endoscopy of the stomach was negative for any malignancy (case no: 31). The last false-positive result was the case described above (case no: 33). As a false-negative result: in a 67-year-old male patient with tuberculosis history, the primary malignant lung tumor was interpreted as a tuberculosis scar tissue by the thorax CT (case no: 10). False-negative primary origins were thyroid, lung, breasts (*n* = 2), prostate, and internal genital organs (*n* = 2) detected by CIM.

In seven patients with false-negative CIM results, FDG PET/CT correctly revealed primary tumors in five patients (lung, breast, prostate, and genitals (*n* = 2) were the primaries) (Fig. 1). On the other hand, the primary locations were detected by CIM in 3 of the 4 cases with false-negative FDG PET/CT scan (tonsil, liver, and breast were the primaries). Detailed findings are given in Table 1.

FDG PET/CT exhibited additional metastases in 33 (27/36) patients, in which 5 of them could not be detected by CIM (5/30). However, FDG PET/CT failed to identify the metastatic axillary lymph node revealed by MMG in a patient with breast carcinoma (case: 20). Besides, FDG PET/CT depicted mildly hypermetabolic reactive cervical lymph nodes which were suggested as metastases correctly by CIM in a patient with thyroid carcinoma and confirmed pathologically later (case: 1).

Sensitivity, specificity, PPV, NPV, accuracy for localization of the primary site were as follows, respectively: 83, 70, 89, 58, and 79% for FDG PET/CT in 36 patients; 78, 78, 90, 58, and 78% for FDG PET/CT in 30 patients who had both FDG PET/CT and CIM; 70, 62, 84, 42, and 68% for CIM in 30 patients (Table 2).

Fig. 1 Contrast-enhanced CT **a** enlarged uterus and uterine myoma (arrow) are seen and there is no sign of malignancy. FDG PET/CT; PET (**b**) and CT (**c**) component, fusion (**d**) images: pathological FDG uptake is seen in the endometrial cavity which was confirmed by

pathology as the primary tumor (star). There are also focal hypermetabolic areas corresponding to metastasis of surrounding peritoneum (arrows) (patient no: 29)

Discussion

In the last two decades, along with the increase in the use of FDG PET/CT, this technique has been included in the guidelines for many malignancies [7]. However, FDG PET/CT is not widely applied in cancer of unknown primary. While radiodiagnostic imaging modalities, such as CT and MRI, are requisite in the diagnostic course, FDG PET/CT is still not recommended in the initial diagnosis

regarding the latest guidelines, except in some special situations [6]. Nevertheless, it is not uncommon to perform FDG PET/CT scan in the early course of the diagnostic evaluation among different centers. It is still debatable whether and when to perform FDG PET/CT in CUP patients.

In a meta-analysis about FDG PET/CT utility in unknown primary tumors, the detection rate of the primary origin was found to be ranged from 22 to 73% with an overall rate of 37%

Table 2 Comparison of FDG PET/CT and CIM results in the detection of the primary tumor locations

	PET/CT (<i>n</i> = 30)	CIM (<i>n</i> = 30)	<i>p</i> value of comparison
True positive	18	16	
True negative	7	5	
False positive	2	3	
False negative	5	7	
Sensitivity	78(56.30–92.54;95%CI)	70(47.08–86.79;95%CI)	0.4836
Specificity	78(39.99–97.19;95%CI)	62(24.49–91.48;95%CI)	0.1799
PPV	90(72.23–96.89;95%CI)	84(67.69–93.14;95%CI)	0.4932
NPV	58(37.43–76.62;95%CI)	42(23.96–61.82;95%CI)	0.2191
Accuracy	78(60.03–90.72;95%CI)	68(48.63–83.32;95%CI)	0.3870

with pooled sensitivity and specificity, both of them were 84% [8]. The heterogeneity among the studies mostly arises from differences in the methodology. Recent studies which consisted of patients with negative radiodiagnostic scans demonstrated lower rates (22.2 to 42.5%) of primary tumor detection [9–11].

Enrolling the patients with negative CIM into the studies represents the correct CUP definition and results in lower detection rates of the original malignant sites, as expected. Regarding CIM-negative patients in our study, FDG PET/CT revealed the primary sites in four cases (36.3%; 4/11), consistently with prior literature. Clearly, the definition of the diagnostic work-up before FDG PET/CT is required to be standardized by the guidelines to avoid variable approaches in both clinical practices and literature.

The utility of the FDG PET/CT detecting unexpected metastases in CUP is well-known, as well [12, 13]. In our study, FDG PET/CT depicted additional metastases by which CT or MRI failed to detect in six patients. Thereafter, the patient management was altered in three of these six patients (with either additional radiotherapy or change in chemotherapy regimen). Conversely, extra metastatic sites were also detected by CIM in two patients, which lead to change in patient management, as well. However, FDG PET/CT could not identify those lesions correctly. The diagnosis in these two cases was the thyroid and breast carcinoma, areas where FDG PET/CT had poorer diagnostic performance than other malignancies [7].

As many studies demonstrate, FDG PET/CT is an efficient technique to identify the occult primary in CUP [14, 15]. However, the first and perhaps the main question we need to ask at this point is whether there was a role for FDG PET/CT in the initial diagnostic pathway of CUP. The second one is: are we overscanning CUP patients when we use both radiologic imaging modalities and FDG PET/CT? Although the contribution of FDG PET/CT to CUP in a diagnostic sense has been shown by many researchers, there is not enough data on clinical benefit comparing radiodiagnostic methods. Moreover, the results are controversial in this aspect. Regelink et al. compared FDG PET with CT and/or MRI and panendoscopy findings and revealed the superiority of PET detecting the primary and distant metastatic sites with sensitivity and specificity of 100 and 94% for PET and 92 and 76% for the conventional diagnostic modalities, respectively [16]. Supporting these results, in the prospective study by Lee et al., FDG PET/CT detected 22 of 32 (69%) primary sites, while 11 of 27 (41%) tumors were identified by CT and/or MRI in the patients who had cervical metastases with unknown primary [17]. The diagnostic accuracy of FDG PET/CT (77%) was also significantly higher than that of CT (42%) or CT/MRI (48%), as well as the sensitivity. On the other hand, according to the results of the prospective study conducted by Moller et al.,

there were no statistically significant differences between FDG PET/CT and CT findings, regarding neither sensitivity and specificity nor accuracy in the CUP patients with extra-cervical metastases [18]. In our study group of 36 patients, the primary malignancy was correctly detected in 24 (66.6%, 24/36) patients by FDG PET/CT and in 16 patients by CIM (53.3%, 16/30). Even if FDG PET/CT has detected more primaries than CIM correctly, the results of the diagnostic accuracies were not statistically significant (Table 2).

In a considerable number of patients, one of the diagnostic imaging modalities (CIM or FDG PET/CT) was unnecessarily performed in our study group. A true primary focus was already suggested by conventional imaging methods before performing FDG PET/CT. This seems to happen remarkably often in other clinics as well, considering the studies in retrospective nature that compare the role of FDG PET/CT with radiodiagnostic methods in CUP. Unfortunately, this issue yields to the unnecessary radiation exposure and time/money waste. However, CIM is essential by virtue of providing the detailed anatomic information. Specifically, CIM is superior to FDG PET/CT in the imaging of pharyngeal tonsils, breasts, and liver tissues as we observed in our study, as well [19–21].

On the other hand, FDG PET/CT remains to be a valuable tool with its power in molecular level, scanning the whole body within a short period of time and with lower radiation exposure. More studies concerning late clinical course and survey could enlighten the feasibility of FDG PET/CT in initial diagnosis and may define a selected patient group to replace CIM.

One of our study limitations is retrospective design, which might have caused the selection bias. Secondly, the study group was small and heterogeneous to analyze deeper. Thirdly, follow-up period was limited. Even though short follow-up period seems to overestimate true negativity, negative imaging tests (both anatomic and metabolic) spare the patients who has inconclusive diagnostic investigation from unnecessary invasive procedures since there is a low detection rate of the primary site in this group [11]. Furthermore, during the follow-up, the primary tumor may be enlarged and begin to be visualized causing false-negative results in the initial imaging. Another limitation of the current study was the absence of the histopathological information of several subjects. However, it may not be applicable to perform—especially in bone and cerebellum—biopsies in all cases in clinical practice.

Conclusion

In patients with metastatic disease of unknown primary, FDG PET/CT can be a reliable method to detect the primary site and

unexpected metastases. Its role in this spectrum begins when the rest of the diagnostic methods are inconclusive. Using FDG PET/CT as a first-line tool in initial diagnosis and adding radiodiagnostic imaging in selective cases can be considered since CIM is not superior over FDG PET/CT. Consequently, large prospective studies with survey analysis are in need to conclude a definite decision.

Compliance with Ethical Standards

Conflict of Interest Neslihan Cetin Avcı, Filiz Hatipoğlu, Ahmet Alacacıoğlu, Emine Ebru Bayar, and Gonca Gul Bural declare that they have no conflict of interest or no fundings received.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

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