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ORIGINAL ARTICLE

^{18}F-Fluoride PET/CT is highly effective for excluding bone metastases even in patients with equivocal bone scintigraphy

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Abstract
Purpose Bone scintigraphy (BS) has been used extensively for many years for the diagnosis of bone metastases despite its low specificity and significant rate of equivocal lesions. ^{18}F-Fluoride PET/CT has been proven to have a high sensitivity and specificity in the detection of malignant bone lesions, but its effectiveness in patients with inconclusive lesions on BS is not well documented. This study evaluated the ability of ^{18}F-fluoride PET/CT to exclude bone metastases in patients with various malignant primary tumours and non-specific findings on BS.
Methods We prospectively studied 42 patients (34–88 years of age, 26 women) with different types of tumour. All patients had BS performed for staging or restaging purposes but with inconclusive findings. All patients underwent ^{18}F-fluoride PET/CT. All abnormalities identified on BS images were visually compared with their appearance on the PET/CT images.
Results All the 96 inconclusive lesions found on BS images of the 42 patients were identified on PET/CT images. ^{18}F-Fluoride PET/CT correctly excluded bone metastases in 23 patients (68 lesions). Of 19 patients (28 lesions) classified by PET/CT as having metastases, 3 (5 lesions) were finally classified as free of bone metastases on follow-up. The sensitivity, specificity, and positive and negative predictive values of ^{18}F-fluoride PET/CT were, respectively, 100 %, 88 %, 84 % and 100 % for the identification of patients with metastases (patient analysis) and 100 %, 82 % and 100 % for the identification of metastatic lesions (lesion analysis).
Conclusion The factors that make BS inconclusive do not affect ^{18}F-fluoride PET/CT which shows a high sensitivity and negative predictive value for excluding bone metastases even in patients with inconclusive conventional BS.

Keywords PET/CT · ^{18}F-Fluoride · Nuclear medicine · Oncology · Bone scintigraphy

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Introduction

Bone scintigraphy (BS) with ^{99m}Tc-labelled radiopharmaceuticals, such as ^{99m}Tc-MDP has been used extensively for many years for the diagnosis of bone metastases. However, it has a relatively low specificity for detecting metastases with a significant rate of equivocal lesions since the skeleton can be affected by many different diseases [1]. Different procedures have been proposed for anatomical correlation and further evaluation of these equivocal lesions, such as bone radiography, CT, MRI and biopsy [1, 2]. These additional procedures can be time-consuming, specially in patients with multiple equivocal lesions, and anatomical correlation of the scintigraphic abnormalities is difficult in many patients. SPECT/CT is also an alternative [3] and can be complementary to BS, but it is also time-consuming, especially when multiple segments of the skeleton have to be examined.

^{18}F-Fluoride is a bone-seeking PET tracer that has been in use since the 1960s [4]. However, after the advent of ^{99m}Tc-labelled radiopharmaceuticals, its use declined [5, 6]. The use of FDG PET and, more recently, PET/CT, for tumour detection is rapidly growing. Because ^{18}F-fluoride is required for imaging with FDG, its increasing availability has led to the use of FDG in imaging again increasing [4, 7]. PET with ^{18}F-fluoride has many advantages over conventional BS. It provides images more rapidly (1 h or less after injection, and a short acquisition time) with greater sensitivity and specificity [4, 8–10]. Furthermore, precise anatomical location of lesions is possible due to CT correlation, which also increases the specificity of the study. This contrasts with the major limitation of BS, which is its non-negligible number of inconclusive results.

The use of PET/CT with ^{18}F-fluoride in patients with inconclusive lesions on BS is not well documented. Thus, the purpose of this study was to evaluate a specific subgroup of patients with several malignant primary tumours with inconclusive findings on BS, and to study the ability of PET/CT with ^{18}F-fluoride to exclude bone metastases in these patients. Furthermore, we were able to evaluate the specificity of ^{18}F-fluoride PET/CT in patients with inespecific findings on BS.

Material and methods

Patient selection

We prospectively studied 42 patients with cancer aged 34–88 years (mean age 60 years; 16 men, 26 women; Table 1). All patients had undergone BS with results considered to be inconclusive for bone metastases and were selected over a period of 10 months, depending on their agreement to participate in the study and on ^{18}F-fluoride availability (available once a week in our facilities at the time of the study). All BS images had been acquired for staging or restaging purposes.

Patients with the following primary malignancies were included: breast cancer (20 patients), prostate (9), lung (3) colon (1), oesophagus (1), rectum (2) ovary (1), liver (1), stomach (1), melanoma (1) and unknown primary (2). A total of 96 inconclusive lesions were identified in these patients on BS. All the patients underwent PET/CT using ^{18}F-fluoride with a mean interval of 16 days between examinations (ranging from 1 to 33 days). All abnormalities identified on BS were visually compared with their appearance on the PET/CT images. The study was approved by the local ethics committee and all patients provided written consent.

Bone scintigraphy

Whole-body BS was performed as part of the routine investigation of patients for staging or restaging. The images were obtained 3 h after intravenous injection of 740–930 MBq (20–25 mCi) of ^{99m}Tc-MDP in a dual head scintillation camera (Elscint HELIX; General Electric, Haifa, Israel) with a low-energy all-purpose collimator and a scanning speed of 10–12 cm/min. Additional static images (500–800 kcounts) of the equivocal areas were also obtained in most patients.

^{18}F-Fluoride PET/CT

^{18}F-Fluoride was obtained from the Nuclear and Energy Research Institute (IPEN, Sao Paulo, Brazil).

The ^{18}F-fluoride PET/CT images were obtained 1 h after intravenous injection of 370 MBq of ^{18}F-fluoride. The CT part of the PET/CT study was performed as a low-dose acquisition with 130 kV, 50–80 mA, 0.8 s per CT rotation, pitch 4–5 mm, field of view 500 mm and a scan speed of 24.6 mm/s.

The PET scan was performed immediately after the CT scan without changing the positioning of the patient, always in the craniocaudal direction from head to toes. Images were acquired in five to seven (head to thighs) and four or five (thighs to toes) bed positions with 2 min for each acquisition. The PET/CT images were acquired and processed using a Siemens Somatom Emotion Duo Biograph and interpreted using a Syngo VB10B WinNT 4.0 station, also from Siemens.

Analysis and interpretation of findings

Images were interpreted by visual analysis. The ^{99m}Tc-MDP BS and the ^{18}F-fluoride PET/CT scans were interpreted separately. BS and PET scans were interpreted in consensus by two nuclear medicine physicians and the CT scans were interpreted by an experienced radiologist.

BS reading BS was considered inconclusive when a patient had one or a few areas of uptake that could not be differentiated as a metastatic or benign lesion, such as joint damage, trauma or benign bone tumour.

^{18}F-Fluoride PET/CT reading All the inconclusive lesions found on BS images were correlated with their location on the PET/CT images. Lesions were classified as benign when degenerative changes (for example around joints or osteophytes) were detected on the CT images. The lesions were classified as malignant when the sites of increased ^{18}F-fluoride uptake were associated with characteristic morphological changes on the CT images, such as cortical

Table 1 Patient demographics, primary tumours, number of nonspecific lesions on BS, ^{18}F-fluoride PET/CT results, and findings on follow-up

Patient no.	Sex	Age (years)	Primary tumour	Nonspecific lesions on BS (*n*)	^{18}F-Fluoride PET/CT[a]		Follow-up[a]	
					Benign lesions (*n*)	Metastatic lesions (*n*)	Benign lesions (*n*)	Metastatic lesions (*n*)
1	F	55	Breast	1	1		1	
2	M	69	Prostate	2	2		2	
3	M	63	Prostate	3		3	3	
4	F	81	Breast	3	3		3	
5	F	76	Breast	3	3		3	
6	M	82	Prostate	4	4		4	
7	M	65	Lung	1		1		1
8	F	66	Colon	1		1		1
9	M	56	Prostate	2	1	1	1	1
10	F	58	Breast	2	1	1	1	1
11	M	68	Prostate	3	3		3	
12	F	80	Breast	2	2		2	
13	M	35	Unknown	1		1		1
14	M	59	Lung	8	7	1	7	1
15	F	51	Breast	3		3		3
16	F	60	Breast	1	1		1	
17	F	39	Breast	4		4		4
18	F	84	Breast	2	2		2	
19	M	78	Prostate	1	1		1	
20	M	51	Oesophagus	2	2		2	
21	F	41	Breast	1		1		1
22	F	67	Breast	3	1	2	1	2
23	M	50	Lung	2	1	1	1	1
24	M	69	Prostate	1	1		1	
25	F	35	Breast	1		1		1
26	F	64	Breast	1	1		1	
27	F	59	Breast	5	4	1	5	
28	F	82	Breast	2	1	1	1	1
29	F	47	Rectum	2	1	1	1	1
30	M	55	Stomach	2	2		2	
31	F	37	Breast	6	4	2	4	2
32	F	64	Breast	1	1		1	
33	F	47	Unknown	1	1		1	
34	M	34	Liver	1		1		1
35	F	63	Skin	2	2		2	
36	F	69	Rectum	3	3		3	
37	F	34	Ovary	1		1	1	
38	M	65	Prostate	1	1		1	
39	F	81	Breast	4	4		4	
40	M	58	Prostate	1	1		1	
41	F	88	Breast	4	4		4	
42	F	37	Breast	2	2		2	

[a] Additional lesions found on ^{18}F-fluoride PET/CT or during follow-up are not included in the table.

destruction, or location in the posterior aspect of a vertebral body or pedicle. Lesions positive on ^{18}F-fluoride PET images but negative on CT images were also considered as probably malignant.

Final diagnosis

The final diagnosis of bone metastasis was defined by follow-up studies (clinical and laboratory follow-up, BS, MRI and CT) and established at least 15 months after the ^{18}F-fluoride PET/CT study (ranging from 15 to 24 months). All lesions were defined as benign or malignant on follow-up, which was used as a standard for determining malignancy.

Statistical analysis

Based on the final diagnosis, sensitivity, specificity, and positive and negative predictive values were calculated.

Results

Analysis by patient

All the inconclusive lesions found on BS images of the 42 patients were identified on PET/CT images.

On ^{18}F-fluoride PET/CT 23 patients were classified as nonmetastatic and 19 patients as having metastatic bone disease (Table 2; Fig. 1).

PET/CT correctly excluded bone metastases in all the 23 patients classified as nonmetastatic, as demonstrated on follow-up.

Of the 19 patients classified by ^{18}F-fluoride PET/CT as having metastatic bone involvement, 3 were eventually classified as free of bone metastases on follow-up.

In the patient analysis, ^{18}F-fluoride PET/CT had a sensitivity of 100 %, a specificity of 88 % and an accuracy of 93 %. The negative and positive predictive values were 100 % and 84 %, respectively (Table 2).

Analysis by lesions identified on BS

During the analysis of the 96 inconclusive lesions found on BS in the 42 patients, ^{18}F-fluoride PET/CT identified 68 as benign lesions. All these lesions were confirmed as benign on follow-up. PET/CT images showed 28 lesions to be probably malignant, and 23 of these were confirmed as bone metastases in the final diagnosis (Table 3).

Table 2 ^{18}F-fluoride PET/CT findings and diagnosis on follow-up of lesions equivocal on whole-body BS: patient-based analysis

^{18}F-Fluoride PET/CT findings	Follow-up/final diagnosis (*n*)		
	Metastatic patients	Nonmetastatic patients	Total
Metastasis (*n*)	16	3	19
Nonmetastatic (*n*)	0	23	23
Total (*n*)	16	26	42

Five lesions classified as probably malignant on ^{18}F-fluoride PET/CT were considered benign on follow-up: three of them in one patient with prostate cancer (patient 3, Table 1), one in a patient with breast cancer (patient 27, Table 1) and one in a patient with ovarian cancer (patient 37, Table 1). Two of these five false-positive lesions had ^{18}F-fluoride uptake and no morphological changes on the CT images of PET/CT and could be related to trauma or enthesitis. Two other false-positive lesions on PET/CT corresponded to benign lesions associated with blastic components, possibly related to benign bone disease or fracture, and showed no changes on follow-up. The other false-positive PET/CT lesion corresponded to a lytic lesion in the parietal bone, considered benign on follow-up at 15 months (probably a bone cyst or fibrous dysplasia; Fig. 2).

The sensitivity, specificity, and positive and negative predictive values of ^{18}F-fluoride PET/CT in defining inconclusive bone lesions found on BS were 100 %, 93 %, 82 % and 100 %, respectively.

Additional lesions found on PET/CT images

In 11 patients, 24 additional bone metastases not detected on BS were also found, and confirmed as malignant on follow-up (Fig. 1).

Discussion

Skeletal scintigraphy with ^{99m}Tc-MDP is a sensitive whole-body method that is able to detect metastases several months before they become visible in conventional radiographs, but it has a low specificity which leads to a greater rate of inconclusive findings [1]. ^{18}F-Fluoride bone uptake is twice that of ^{99m}Tc-MDP, and it shows a faster blood clearance and a better target-to-background ratio [4, 9, 11, 12]. Different studies have demonstrated that ^{18}F-fluoride PET/CT has significantly better sensitivity and specificity than conventional BS in detecting metastatic bone lesions of different tumours [13–15]

In the present study we were able to evaluate the specificity of ^{18}F-fluoride PET/CT by studying only patients with inconclusive bone scans. We demonstrated that most of the factors that make BS inconclusive do not affect ^{18}F-fluoride PET/CT which has a high sensitivity and specificity for detecting bone metastases, even in this selected group of patients with equivocal BS findings. In a practical approach, we used fused PET/CT images to determine which of this selected group patients were free of bone metastases. We obtained a sensitivity and a negative predictive value for bone metastases of 100 % in both the patient and lesion analyses, with specificities of 88 % and 93 % in the patient and lesion analysis, respectively.

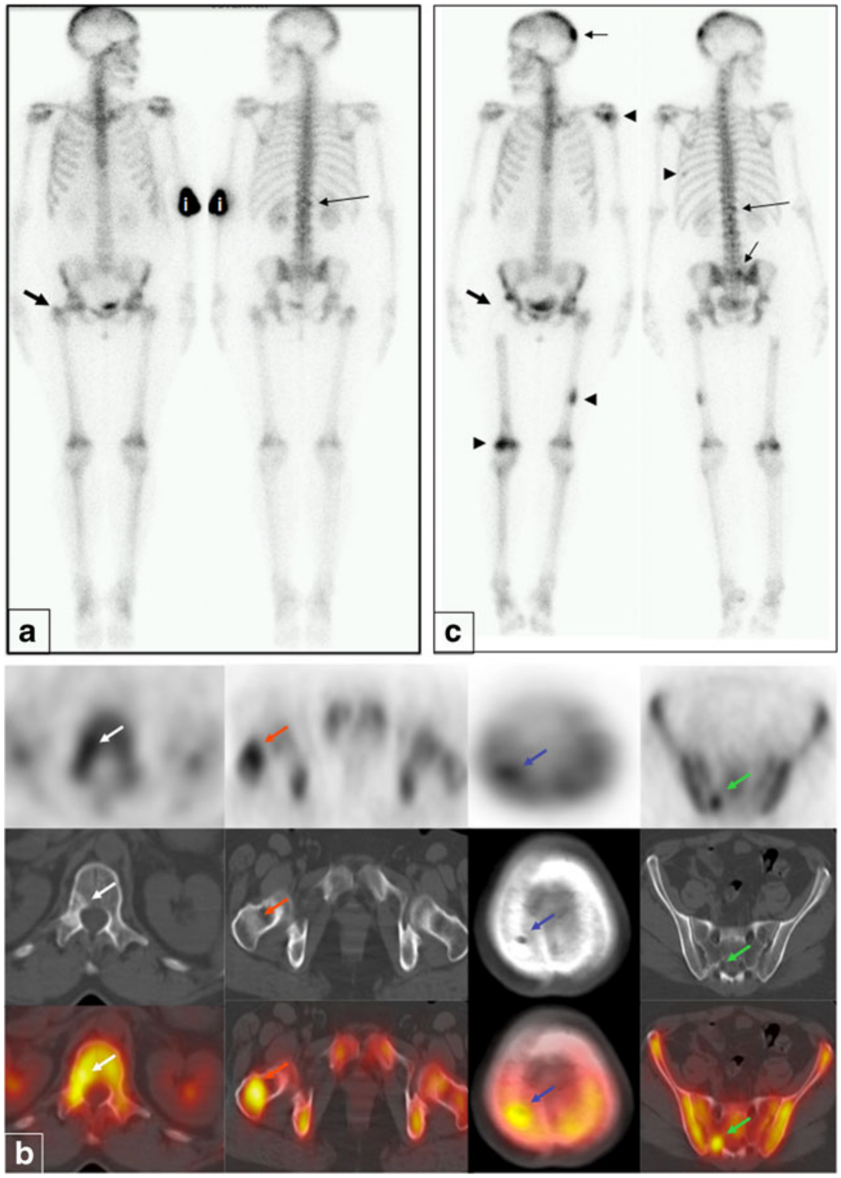

Fig. 1 Female patient with right breast cancer treated by right modified radical mastectomy and adjuvant chemotherapy (patient 21, Table 1). **a** ^{99m}Tc-MDP BS images show mild focal uptake in the right lateral edge of the L1 vertebra, which was considered an equivocal lesion (*long arrow*). Mild uptake in the right trochanter (*short arrow*) was initially considered degenerative disease (*i* injection site). **b** ^{18}F-Fluoride PET/CT images obtained 15 days later also show increased tracer uptake in L1 (*white arrows*) that corresponded to a predominantly lytic lesion in the right pedicle of L1, considered a metastatic lesion. Additional focal areas of increased ^{18}F-fluoride uptake are also clearly demonstrated in a blastic lesion in the right trochanter (*red arrows*), a lytic lesion in the right parietal region (*blue arrows*), and a blastic lesion in the sacrum on the right (*green arrows*). **c** Follow-up BS images obtained 22 months after ^{18}F-fluoride PET/CT show that the vertebral lesion has remained stable during treatment (*long arrow*), but an important progression of the right trochanteric lesion was eventually treated with surgical resection and metastatic disease was histologically confirmed (*thick short arrow*). Note also progression of the other lesions in the right parietal region and sacrum (*thin short arrows*). Advanced disease is again demonstrated with increase tracer uptake in new lesions in the left shoulder and both femurs (*arrowheads*)

Some of the false-positive lesions detected by ^{18}F-fluoride PET/CT could be attributed to the methodology used to read the scans, which favored the sensitivity of the procedure. Positive lesions on the ^{18}F-fluoride PET images and negative on CT images were considered as probably malignant since it was possible that they represented early osteoblastic changes in response to a metastatic deposit. In one patient, a lesion in the sacrum without any anatomical change was finally demonstrated to be benign, probably related to enthesitis (patient 27, Table 1). The lesions were also classified as malignant when the sites of increased ^{18}F-fluoride uptake were associated with morphological changes on the CT image, for example lytic

Table 3 ^{18}F-fluoride PET/CT findings and diagnosis on follow-up of lesions equivocal on whole-body BS: lesion-based analysis

^{18}F-Fluoride PET/CT findings	Follow-up/final diagnosis (*n*)		
	Malignant lesions	Benign lesions	Total
Malignant (*n*)	23	5	28
Benign (*n*)	0	68	68
Total (*n*)	23	73	96

lesions. One lytic lesion with ^{18}F-fluoride uptake was considered benign on follow-up (patient 37, Table 1; Fig. 2).

When comparing these two bone imaging procedures, dosimetry is also an important issue. Various studies have addressed the several factors that affect the radiation dose of ^{18}F-fluoride relative to that of ^{99m}Tc-MDP in bone scans [8, 16]. At the prescribed administered activities, the effective doses of ^{18}F-fluoride and ^{99m}Tc-MDP are similar in most patients (4.0 and 3.0 mSv, respectively, in a 70-kg patient) [8]. The main difference in dosimetry between the two procedures is related to the addition of the CT component of a PET/CT or SPECT/CT study. Regularly exposing all clinical patients to a high-resolution or a low-dose CT scan is a subject of debate even for FDG PET/CT [17, 18]. In our study, although using a low-dose CT sequence, the CT component of a ^{18}F-fluoride PET/CT study can provide differentiation between benign and malignant lesions in most patients, since the morphological aspects of the lesions can be observed.

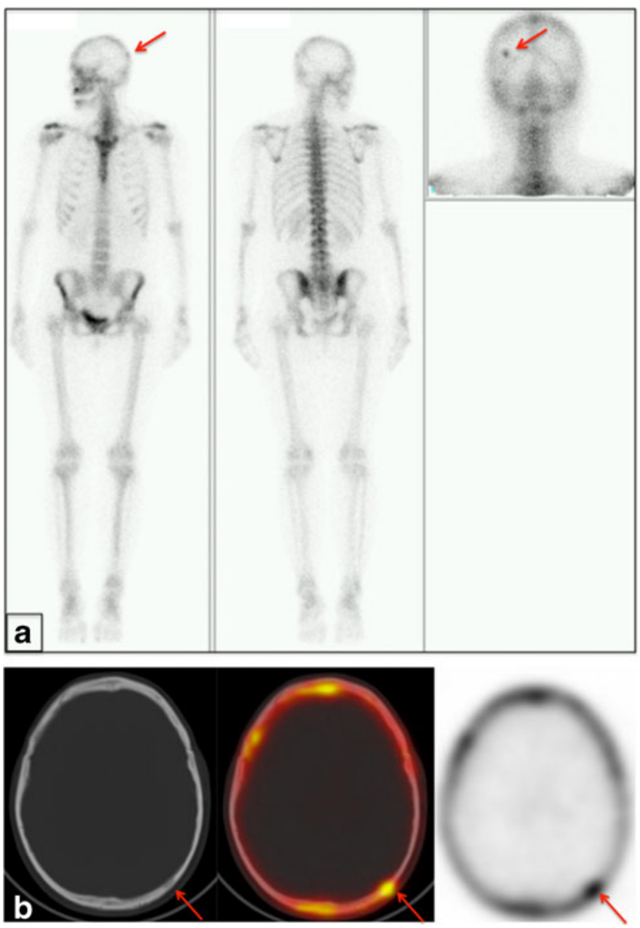

Fig. 2 Female patient aged 34 years with ovarian cancer. **a** ^{99m}Tc-MDP BS images show a single area of focal uptake in the left parietal region (*arrows*). **b** ^{18}F-Fluoride PET/CT images obtained 2 days later show increased tracer uptake in a lytic lesion in the left parietal bone, classified as probably malignant (*arrows*). During a follow-up of 15 months without any specific treatment, radiographs of the skull showed no change, no clinical evidence of disease progression was demonstrated, serum tumour markers remained stable and chest radiography was normal. The lesion was considered benign, probably a bone cyst or an atypical fibrous dysplasia

The main limitation of the study was that a hybrid imaging technique (PET/CT) using one tracer was compared with a functional imaging technique (BS) alone using another tracer. Since the CT components of PET/CT studies were available, we could have correlated the equivocal BS findings with the CT findings and compared them with the PET/CT findings. This would, of course, have increased the accuracy of the BS, but it would have been an "artificial" approach, and we aimed to compare the two procedures under "real" clinical practice conditions. A routine BS acquisition takes as long as 30 min including whole-body and static images and up to 45 min when a SPECT or SPECT/CT acquisition is included. Image acquisition is started 3 h after ^{99m}Tc-MDP injection. If a complementary radiological examination is also obtained, the patient has to spend as long as 4–5 h in the imaging department. On the other hand, for a ^{18}F-fluoride PET/CT study, the patient has to stay less than 1.5 h in the nuclear medicine department, with all possible CT correlations already performed, which is a clear advantage over SPECT/CT. New PET/CT equipment is even faster and, if the image acquisition is started 30–45 min after ^{18}F-fluoride injection, patients may spend less than 1 h in the imaging department.

Our results suggest that in difficult cases, such as in patients with high-risk cancer with bone pain and known osteoarticular comorbidities, in which the possibility of an inconclusive bone scan is greater, ^{18}F-PET/CT might be indicated as the first-line diagnostic imaging method for detection of bone metastases. In these sicker patients, the use of a quick and more effective staging method certainly provides more comfort to the patient, and a more rapid clinical decision, although the cost-effectiveness of ^{18}F-fluoride PET/CT in comparison to that of BS is still not determined.

Conclusion

^{18}F-Fluoride PET/CT has a high sensitivity and a high negative predictive value for excluding bone metastases even in patients with inconclusive conventional BS.

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Conflicts of interest None.

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