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ORIGINAL ARTICLE

Assessment of successful incorporation of cages after cervical or lumbar intercorporeal fusion with [(18)F]fluoride positron-emission tomography/computed tomography

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Abstract The purpose of this study is to assess the successful incorporation of cages in patients after cervical or lumbar intercorporeal fusion with positron-emission tomography/computed tomography (PET/CT). Twenty patients (14 female and 6 male; mean age 58 years, age range 38–73 years) with 30 cervical ($n = 13$) or lumbar ($n = 17$) intercorporeal fusions were prospectively enrolled in this study. Time interval between last intercorporeal intervention and PET/CT ranged from 2 to 116 months (mean 63; median 77 months). IRB approval was obtained for all patients, and written informed consent was obtained from all patients. About 30 min prior to PET/CT scanning, 97–217 MBq (mean 161 MBq) 18F-fluoride were administered intravenously. Patients were imaged in supine position on a combined PET/CT system (Discovery RX/STE, 16/64 slice CT, GE Healthcare). 3D-PET emission data were acquired for 1.5 and 2 min/bed position, respectively, and reconstructed by a fully 3D iterative algorithm (VUE Point HD) using low-dose CT data for attenuation correction. A dedicated diagnostic thin-slice CT was optionally acquired covering the fused region. Areas of increased 18F-fluoride uptake around cages were determined by one double-board certified radiologist/

nuclear physician and one board certified radiologist in consensus. In 12/20 (60%) patients, increased 18F-fluoride uptake around cages was observed. Of the 30 intercorporeal fusions, 15 (50%) showed increased 18F-fluoride uptake. Median time between intervention and PET/CT examination in cages with increased uptake was 37 months (2–116 months), median time between intervention and PET/CT examination in those cages without increased uptake was 91 months (19–112 months), p (Wilcoxon) = 0.01 (one-sided). 14/29 (48%) cages with a time interval > 1 year between intervention and PET/CT scan showed an increased uptake. In conclusion, PET/CT frequently shows increased 18F-fluoride uptake in cervical and lumbar cages older than 1 year (up to almost 8 years in cervical cages and 10 years in lumbar cages) possibly indicating unsuccessful fusion due to increased stress/microinstability.

Keywords 18F-fluoride PET/CT · Cage · 18F-fluoride uptake · Spine surgery · Intercorporeal fusion · Stress/microinstability · Cervical spine · Lumbar spine

Introduction

Cervical and lumbar intercorporeal fusions are performed to treat symptomatic segmental degeneration or instability in the cervical and lumbar spine [1–4]. A large number of studies assessing outcome in patients after spine surgery clinically, to a lesser extent by (combined) morphological and functional imaging techniques, e.g. bone SPECT and [(18)F]fluoride positron-emission tomography/computed tomography (PET/CT), have been performed since the late 1980s. Special interest is put on patients who lack osseous fusion after surgery including intercorporeal fusions [4–11].

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^{18}F -labeled NaF was already used for bone scintigraphy by Blau et al. in the early 1960s. Aftermath due to technical and availability reasons, $^{99\text{m}}\text{Tc}$ -labeled bone seeking agents like $^{99\text{m}}\text{Tc}$ -methylene diphosphonate (MDP) were preferred for bone scanning. In the early 1990s, ^{18}F -fluoride was readopted for PET scanning [12].

^{18}F -fluoride is a tracer depicting blood flow and osteoblastic activity. After i.v. administration, ^{18}F -fluoride diffuses from the bone capillaries into the bone extracellular fluid (ECF). Its plasma clearance is more rapid and its single-passage extraction efficiency is higher compared to $^{99\text{m}}\text{Tc}$ -MDP due to its smaller molecular weight and its negligible protein binding. From the bone ECF, ^{18}F -fluoride is taken up to form the mineral fluorapatite at the surface of bone crystals especially at sites of bone remodeling with high turnover. Its bone uptake is approximately twofold greater than that of the conventional tracer $^{99\text{m}}\text{Tc}$ -MDP and its blood to bone clearance reaches almost 100%, with the fast blood clearance resulting in a better target-to-background ratio. As a further advantage, ^{18}F -fluoride allows imaging shortly (in our protocol about 30 min) after i.v. administration in contrast to $^{99\text{m}}\text{Tc}$ -MDP [13, 14]. The current work presents a prospective study analyzing ^{18}F -fluoride uptake around cages in patients after cervical and/or posterior lumbar intercorporeal fusion. It is hypothesized that increased stress/microinstability and thus missing or incomplete osseous intercorporeal fusion shows concomitant increased ^{18}F -fluoride uptake. It was investigated

how long after last intercorporeal intervention increased uptake can be observed.

Patients and methods

Patient selection

20 patients (14 female and 6 male; mean age 58 years, age range 38–73 years) with 30 intercorporeal cervical (13/30) or lumbar (17/30) fusions were prospectively enrolled in this study between March 2008 and March 2009 (Table 1). We received approval from our Institutional Review Board (IRB) as well as written informed consent of each patient. Time interval between last intercorporeal intervention and PET/CT examination ranged from 2 to 116 months (mean 63 months; median 77 months). Patients had chronic back pain, the vast majority of the lower/lumbar spine. No clinical suspicion of infection was given. Only titan containing cages with autologous bone grafts had been implanted (Table 2).

Radiochemistry

^{18}F -fluoride was produced by proton irradiation of ^{18}O -enriched water (RWE Nukem) in a cyclotron (PETtrace 200, GE Medical systems). After an irradiation for other ^{18}F tracers, the cyclotron target was rinsed with water for injection to recover the remaining ^{18}F -fluoride. The

Table 1 20 patients with cervical and/or lumbar intercorporeal fusions

Patient no.	Gender	Age	MBq	Time of surgeries	No. of in-house-surgeries
1	f	64	145	2000–2007	6
2	m	67	215	2004–2007	7
3	m	70	180	2004–2005	2
4	f	65	175	2007–2008	2
5	f	55	97	1999–2005	3
6	m	62	184	1999–2007	5
7	f	70	155	2002–2008	8
8	m	52	217	2001–2006	5
9	f	63	175	2002–2004	6
10	f	38	136	2006–2007	3
11	f	60	214	2001	1
12	m	48	158	1999–2002	2
13	f	62	125	2007	1
14	f	73	156	2000–2005	3
15	f	48	124	2000–2005	2
16	f	39	116	1998–2003	4
17	f	47	153	2001–2007	4
18	f	54	129	1999–2001	2
19	f	59	172	1998–2004	7
20	m	56	194	2004–2008	3

Gender (*f* female, *m* male), Age (in years), Activity administered (in MBq), time and number of in-house-surgeries

Table 2 18F-fluoride uptake around cages in 20 patients with 30 cervical and/or lumbar intercorporeal fusions

Patient no.	Segment cervical spine	Segment lumbar spine	Time in months between last intercorporeal intervention and PET/CT	Increased uptake, yes (1)/no (0)	Material ^a
1	C4/5, 5/6, 6/7	–	92 (3×)	0, 0, 1	ID HWS Cage, Titanium (3×)
2	–	L5/S1 (left)	17	1	Telamon Titanium
3	C5/6, 6/7	–	30 (2×)	1, 1	ID HWS Cage, Titanium (2×)
4	–	L4/5	13	1	Telamon Titanium
5	–	L4/5, L5/S1	102 (L4/5), 35 (L5/S1)	0, 0	ProSpace Titanium, Telamon Titanium
6	–	L4/5	107	0	ProSpace Titanium
7	C5/6	L2/3, L4/5	37 (C5/6), 2 (L2/3), 69 (L4/5)	1, 1, 0	ID HWS Cage, Titanium, KZC, Titanium ^b , ProSpace Titanium
8	C3/4, C4/5	L5/S1	79 (C3–5), 80 (L5/S1)	1, 1, 0	ID HWS Cage, Titanium (2×), ProSpace Titanium
9	–	L4/5	47	1	Telamon Titanium
10	–	L5/S1	27	1	Telamon Titanium
11	C5/6	–	90	0	ID HWS Cage, Titanium
12	–	L5/S1	112	0	Diapason Titanium
13	–	L4/5	19	0	Telamon Titanium
14	–	L4/5	100	0	ProSpace Titanium
15	C5/6, C6/7	–	34 (2×)	0, 0	ID HWS Cage, Titanium (2×)
16	–	L5/S1	116	1	Harms Titanium
17	–	L5/S1	74	1	ProSpace Titanium
18	C5/6	–	84	1	ID HWS Cage, Titanium
19	C5/6	L3/4	91 (C5/6), 106 (L3/4)	0, 0	ID HWS Cage, Titanium, ProSpace Titanium
20	–	L5/S1	14	1	ProSpace Titanium

ID Implant design

^a Material named includes registered trademarks ®

^b KZC Karl Zweifel Cage

recovered amount was sufficient for up to eight patients. The 18F-fluoride in the target flush water was then purified and formulated in 0.9% sodium chloride for injection by an automated synthesis unit (FASTlab, GE Medical systems). The quality control for the sodium 18F-fluoride injection solution was according to the European Pharmacopoeia. The radiochemical and radionuclide purity was >98.5 and >99.9%, respectively.

Fluoride PET/CT scanning

We used a combined PET/CT system (Discovery RX or Discovery STE, GE Healthcare, Milwaukee, WI). This device integrates a PET scanner with a multi-slice helical CT (16 or 64 slices) and permits the acquisition of coregistered CT and PET images in the same session. Scanning started approximately 30–45 min after the i.v. injection of a dose of 97–217 MBq, mean 161 MBq of 18F-fluoride. Patients were examined in supine position. Immediately following the low-dose CT acquisition (FOV 50 cm, 80 mA, 120 kV, slice thickness 3.75 mm, 0.5 s rotation

time, standard reconstruction type), 3D-PET emission data were acquired for 1.5 and 2 min/bed position, respectively. The CT data were used for attenuation correction and images were reconstructed using a fully 3D iterative algorithm (VUE Point HD).

Additionally, a dedicated thin-slice CT (0.625 mm), FOV 50 cm, 0.5 s rotation time, smartmA (maximum 440 and 700 mA), 120 kV, was acquired optionally covering the fused region (standard and bone reconstruction type).

Diagnostic thin-slice CTs were available of cervical cages in 3/8 patients and of lumbar cages in all 15 patients. The acquired images were postprocessed with a dedicated software (Volume Viewer PET/CT, AW 4.4 workstation, GE Healthcare) providing multiplanar reformatted images of PET alone, CT alone and fused PET/CT with linked cursors.

PET/CT evaluation

PET/CT images were analyzed in consensus by a double-board certified radiologist and nuclear physician with special

training in musculoskeletal radiology and 5 years experience in PET/CT reading and one board certified radiologist with 1 year experience in PET/CT reading. The readers were blinded regarding the results of any previous imaging. Attenuation-corrected PET images as well as fused PET/CT images were used for analysis, using the CT for anatomical correlation. Increased ^{18}F -fluoride uptake around cages higher than normal appearing bone was interpreted as pathologic regardless of pathological changes on CT.

Statistical evaluation

Evaluation was done using nonparametric procedures in SAS 9.2. For comparisons between groups, Wilcoxon two-sample tests were applied using normal approximation to Z . Values for one-sided tests are displayed considering the alternative hypothesis of shorter time distance between intervention and PET/CT scan in patients with increased ^{18}F -fluoride uptake around cages.

Results

PET/CT findings

In 12/20 (60%) patients, increased ^{18}F -fluoride uptake around intercorporeal fusion material was found. 15/30 (50%) cages showed increased fluoride uptake. Median

time between intervention and PET/CT in cages with increased uptake was 37 months (2–116 months, $N = 15$, interquartile range = 62), median time between intervention and PET/CT in those cages without increased uptake was 91 months (19–112 months, $N = 15$, interquartile range = 67), p (Wilcoxon) = 0.01 (one-sided) (Table 2).

Analyzing cervical and lumbar intercorporeal fusions separately, there were 7/13 (54%) cervical cages showing increased uptake and 8/17 (47%) lumbar cages with increased uptake. Median time between intervention and PET/CT in cervical cages with increased uptake was 79 months (30–92 months, $N = 7$, interquartile range = 54), median time between intervention and PET/CT in cervical cages without increased uptake was 90.5 months (34–92 months, $N = 6$, interquartile range = 58), p (Wilcoxon) = 0.14 (one-sided). Median time between intervention and PET/CT in lumbar cages with increased uptake was 22 months (2–116 months, $N = 8$, interquartile range = 47), median time between intervention and PET/CT in lumbar cages without increased uptake was 100 months (19–112 months, $N = 9$, interquartile range = 37), p (Wilcoxon) = 0.02 (one-sided).

Regarding cervical intercorporeal fusions, there were four patients with more than one intervertebral fusions, three with two adjacent segments either both with or without increased uptake. One patient had received three adjacent intercorporeal fusions of which only the lowest showed increased uptake (Figs. 1, 2, 3).

Fig. 1 64-year-old female patient 92 months postoperatively with the lowest of three cervical cages (C4/5, C5/6, C6/7) showing increased fluoride uptake (patient no. 1). Sagittal low-dose CT, fused PET/CT, PET

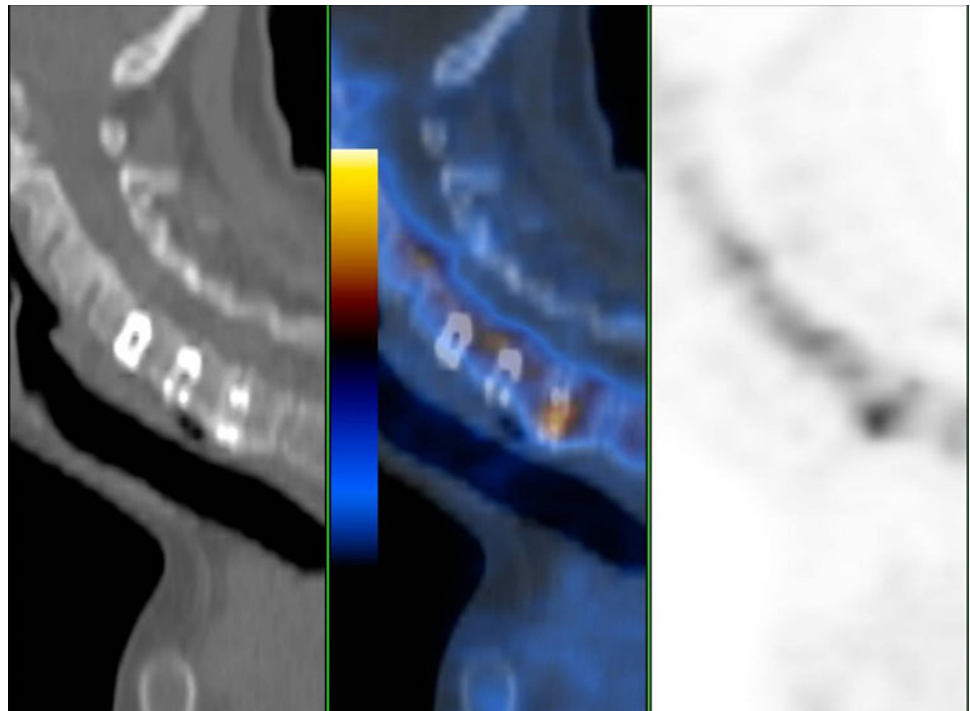


Fig. 2 52-year-old male patient 79 months postoperatively with both cervical cages (C3/4, C4/5) showing increased uptake (patient no. 8). Sagittal low-dose CT, fused PET/CT, PET

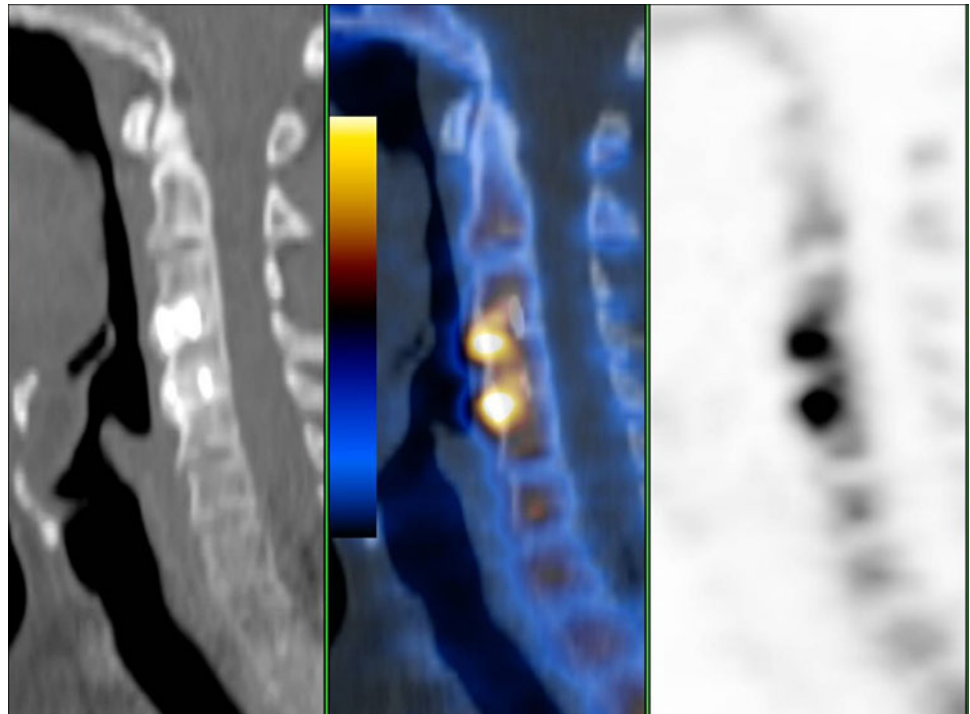
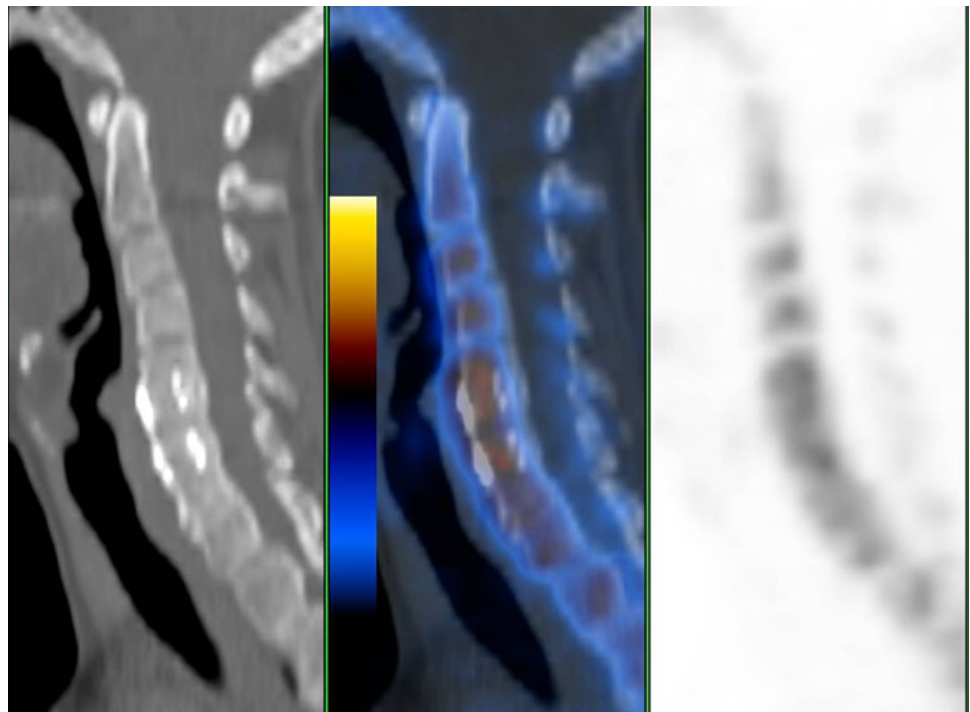


Fig. 3 48-year-old female patient 34 months postoperatively with no increased uptake around cervical cages (C5/6, C6/7) (patient no. 15). Sagittal low-dose CT, fused PET/CT, PET



Regarding lumbar intercorporeal fusions, there were two patients with two intercorporeal fusions showing either both no increased uptake or one an increased uptake (Figs. 4, 5). Three patients had received both cervical and lumbar intercorporeal fusions only one of them showing no increased uptake in both regions (Fig. 6).

Discussion

This study shows that even in those cervical and lumbar cages with a time interval of more than 1 year between surgery and fluoride PET/CT, increased ^{18}F -fluoride uptake can be observed. The longest time interval in

Fig. 4 55-year-old female patient 102 and 35 months postoperatively with no increased uptake around both lumbar/lumbosacral cages (L4/5, L5/S1) (patient no. 5). Sagittal low-dose CT, fused PET/CT, PET

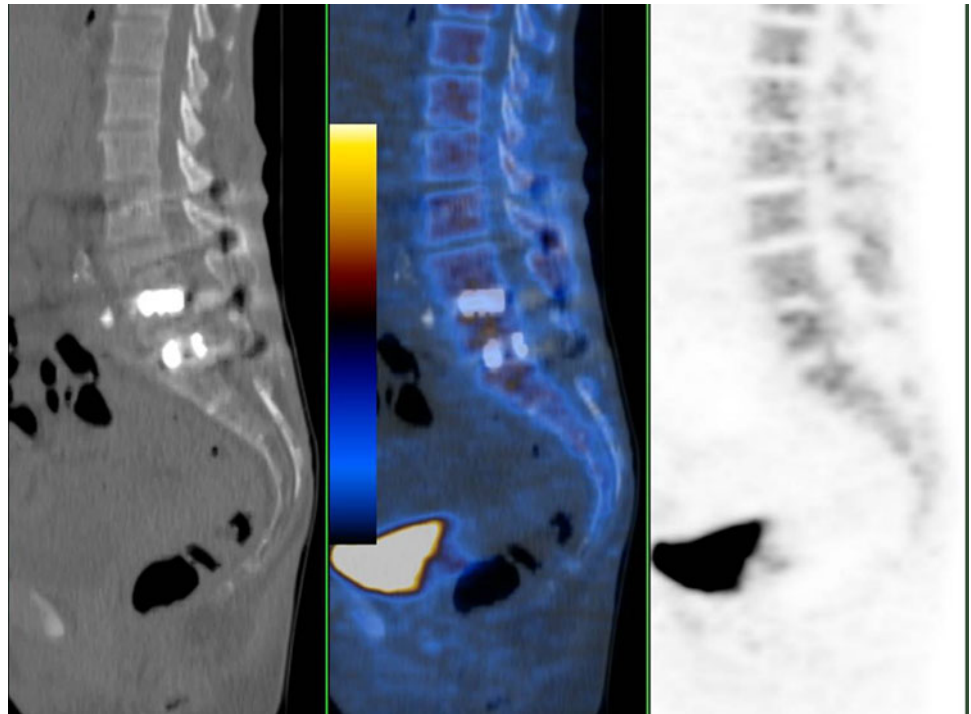
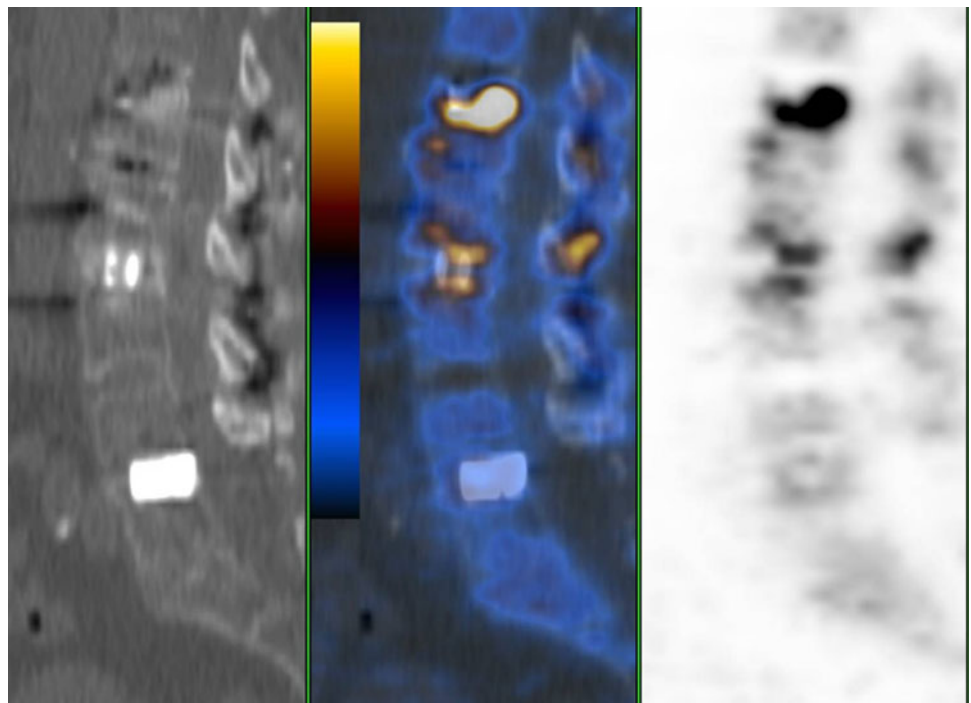


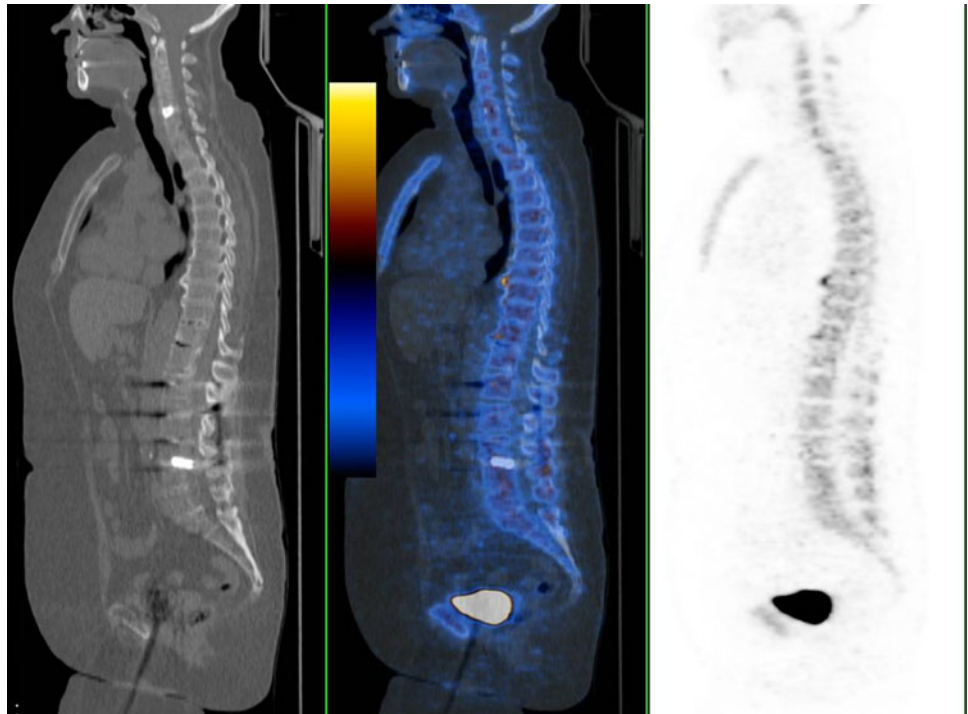
Fig. 5 70-year-old female patient 2 and 69 months postoperatively with increased uptake around one lumbar cage (L2/3) and no increased uptake around the other lumbar cage (L4/5) (patient no. 7). Sagittal low-dose CT, fused PET/CT, PET. Note additional increased uptake in fractured end-plate L1



lumbar cages with increased uptake was 116 months (almost 10 years) and in cervical cages 92 months (almost 8 years), though there was a significant difference in median time between PET/CT and last intercorporeal intervention between the group of cages with and without increased uptake ($p = 0.01$). If one takes the group of cervical and lumbar cages separately, only the group of

lumbar cages shows a significant difference in median time between PET/CT and last intercorporeal intervention ($p = 0.14$ in cervical cages, $p = 0.02$ in lumbar cages). Median time between PET/CT and last intercorporeal intervention in cages with increased uptake is 37 months in all cages, 79 months in cervical and 22 months in lumbar cages. In contrast, median time between PET/CT and last

Fig. 6 59-year-old female patient 91 and 106 months postoperatively with no increased uptake either around her cervical (C5/6) or lumbar cage (L3/4) (patient no 19). Sagittal low-dose CT, fused PET/CT, PET



intercorporeal intervention in cages without increased uptake is 91 months in all cages, 90.5 months in all cervical and 100 months in all lumbar cages. This is a small study group and it needs to be verified whether incorporation of cervical cages indeed takes longer than in lumbar cages. These results show that even many years after cage implantation, there can be increased fluoride uptake which is likely an expression of increased stress, overcharge and microinstability even in morphologically unsuspecting segments. It is also possible that cages show increased uptake after having formerly been metabolically silent due to secondary loosening. This information is only obtained by the functional PET part. Until now, most studies focus on morphological imaging techniques to evaluate the healing process of intercorporeal fusions. Obviously, there seems to be no uniform radiological criteria for assessing intercorporeal fusion by plain radiographs or CT [10, 15–18]. ^{18}F -fluoride PET/(CT) on the contrary has mostly been used in the assessment of malignant bone abnormalities [19–23]. However, promising results are also found in benign bone disorders, e.g. in the spine [11]. Considering our study results, ^{18}F -fluoride PET/CT might potentially play an increasing role in the evaluation of the postoperative spine, supporting and complementing diagnostic criteria to assess intercorporeal fusion after surgery. The supplement of PET to CT information in this study seems to help either to support diagnosis of non-fusion or to confirm the diagnosis of complete fusion. As ^{18}F -fluoride is taken up to form the mineral fluorapatite at the surface of bone crystals especially at sites of bone remodeling with

high turnover [14], segments with increased uptake around cages compared to adjacent bony structures might be considered as non-fused and those with the same uptake as fused in a metabolic sense. Hence, ^{18}F -fluoride PET/CT possibly has an impact on therapeutic decisions. By avoiding unnecessary surgery, costs would decrease [24].

Although we did not correlate increased uptake with pain in the present study, it is possible that fluoride PET/CT can provide additional functional information to explain persistent pain in patients after intercorporeal fusion surgery. In this study group, no difference was made concerning different cage types or graft material, due to the limited number and as only titanium containing cages and autologous grafts were used for fusion. A next step would be to compare fusion rates in different cage types and grafts (autologous, allogenic, bone graft substitutes) [25–30].

This study has several limitations. The study group is limited. No correlation with surgical re-exploration was done. Patients had mostly more than one spinal surgery (Table 1). Therefore, a bias concerning study population cannot be excluded. Also, only attenuation-corrected images were evaluated. Nevertheless, it was possible to differentiate cages with and without surrounding uptake in one patient (Figs. 1, 5).

Additional non-attenuation-corrected images might help diagnosing cases with rather faint surrounding uptake. Furthermore, it would be of interest to differentiate fusion rates in cages with and without additional (multisegmental) anterior or posterior fusion.

The effective dose equivalent for ^{18}F -fluoride is 0.023 mSv/MBq, which corresponds to a maximum effective dose equivalent of about 5 mSv in this study [31]. With this protocol, the radiation burden of a fluoride PET/CT is slightly superior to conventional SPECT/CT [12]. An administered activity of 100–200 MBq (corresponding to an effective dose equivalent of about 2.3–4.6 mSv) is quite adequate to provide diagnostic images. Another advantage is the short uptake time of ^{18}F -fluoride allowing imaging quickly after administration [13]. One clear limitation is the limited availability of ^{18}F -fluoride and number of PET/CT systems as well as the higher incremental costs of ^{18}F -fluoride PET compared to planar and SPECT bone scintigraphy (BS). Nevertheless, ^{18}F -fluoride PET/(CT) is an imaging modality which outperforms SPECT BS at least regarding spatial resolution and generates increasing interest with the worldwide shortage of molybdenum supply [12, 14, 32, 33].

Conclusion

Even around cages with a long time interval between surgery and fluoride PET/CT imaging (close to 8 years in cervical cages and 10 years in lumbar cages), increased uptake could be observed possibly indicating increased stress/microinstability and thus missing/incomplete osseous fusion.

This study was approved by the Institutional Review Board (IRB) and Swissmedic was duly notified. Amendments to the protocol for this study, suppressing bone scans and extending the number of subjects were also approved by the IRB; however, it was omitted to notify Swissmedic about these amendments.

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Conflict of interest None of the authors has any potential conflict of interest.

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