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**Vertebral Fracture Assessment: a simple and valid tool to detect
vertebral fracture in the osteoporosis assessment of patients treated
with aromatase inhibitors for breast cancer**

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ABBREVIATIONS

AI: Aromatase inhibitors

BMD: Bone mineral density

BMI: Body Mass Index

DXA: Dual energy X-ray absorptiometry

ER: Estrogen receptor

μSv : Micro Sieverts

VFA: Vertebral fracture assessment

WHO: The World Health Organization

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Vertebral Fracture Assessment: a simple and valid tool to detect vertebral fracture in the osteoporosis assessment of patients treated with aromatase inhibitors for breast cancer

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INTRODUCTION

Histopathologic studies have shown that about 80% of breast cancers express the estrogen receptor (ER+). In postmenopausal women, the estrogenic stimulation of breast cancer can be suppressed either by targeting the ER directly using selective ER modulators such as tamoxifen, or indirectly by blocking the aromatization of androgens and their conversion to estrogens in peripheral tissues using aromatase inhibitors (AIs). The current AIs third generation, letrozole, anastrozole and exemestane has become the standard of care for the adjuvant endocrine treatment of ER+ breast cancer, either as initial therapy or as sequenced treatment after 2-3 years of tamoxifen. The substantial reduction in estrogen concentrations induced by AIs is associated with increased bone turnover and leads to a decreased bone mineral density (BMD) [1] and an increased risk of fracture [2]. Thus, it is now largely recommended that all women starting AIs therapy should be carefully assessed for their baseline risk of osteoporotic fractures including a full evaluation of all clinical risk factors and a dual energy X-ray absorptiometry (DXA) examination [3]. In a context of osteoporosis, introduction of anti-resorptive treatment depends on BMD, clinical risk factors and depends also on osteoporotic fracture history and particularly vertebral fracture history. Vertebral fracture is the most common osteoporotic fracture, being present in 15 to 20% of women aged 50-59 years and in 50% of women aged more than 85 years [4]. Nearly 50% of vertebral fractures are asymptomatic and occur in women with an intermediate BMD (T-score > -2.5) [5]. The presence, the severity and the number of osteoporotic vertebral fractures are important predictors of further vertebral and non-vertebral fracture risk. Subjects with a prevalent vertebral fracture have a fivefold increased risk of further vertebral fracture and a threefold risk of hip fracture than those without an incident vertebral fracture [6-7-8]. Therefore, osteoporotic fracture is associated with reduced quality of life [9] and increased mortality [10]. Spinal radiography remains the gold standard to detect vertebral fractures, however this procedure delivers a significant irradiation and is sometimes difficult to interpret because of geometric distortion. Vertebral morphology can be directly assessed during the BMD measurement by a new device called vertebral fracture assessment (VFA). VFA realizes an image of the T4 to L4 vertebrae in 15 seconds with the fan-beam of the dual-energy X-ray absorptiometry scan. A lateral and antero posterior scan can be done without moving the patient from the supine position thanks to a rotating C-arm. VFA has been already tested in

the last five years, mostly in postmenopausal patients, showing good results for detecting vertebral fractures.

The aim of our study was to investigate the effectiveness of VFA in a population of postmenopausal women treated with AI for breast cancer, according to three criteria: legibility of the spine, detection of vertebral fracture and reproducibility of the technique.

PATIENTS AND METHODS

PATIENTS

Both the department of medical oncology and the department of rheumatology of the University Hospital of Angers conducted this retrospective study. Population of this study has already been described [11]. Briefly, 497 women with ER+ breast cancer had an osteoporosis assessment within the first three months of AIs therapy, 362 of them had a second evaluation three years later including VFA. After exclusion of patients with bone metastasis, we conserved 61 patients with at least one vertebral osteoporotic fracture on spinal radiography reported by the referent physician of the cohort at the second evaluation (EL). Sixty other women of the cohort without vertebral fracture were randomly chosen.

METHODS

CLINICAL PARAMETERS

An extensive medical history and a physical examination were obtained for each subject included age, age at onset of menopause, family history of osteoporosis, personal history of fracture, medications, treatment of cancer (radiotherapy, chemotherapy, tamoxifen), alcohol and tobacco use, physical activity and food intake.

BONE MINERAL DENSITOMETRY

BMD was measured at lumbar spine, total hip and femoral neck using dual energy X-ray absorptiometry operating in fan beam mode (Hologic® QDR 4500A densitometer, Hologic Inc. Waltham, MA, USA). All the measures were performed by the same technician using the same DXA. As usually, the results were expressed in absolute values (g/cm^2) and using the T-score (standard deviation). The T-scores were calculated using manufacturer references and expressed the difference between the subject value and mean value of healthy young women. The World Health Organization has defined normal BMD as a T-score >-1 in

one of the three-measured site, low bone density as a T-score between -1 and -2.5, osteoporosis as a T-score < -2.5.

IDENTIFICATION OF VERTEBRAL FRACTURE

Two investigators (TB, BB), who were unaware of the patient fracture status and BMD, analyzed spinal radiographs and VFA independently. The 2 investigators were trained in spinal radiography analysis but they had no experience in VFA analysis.

Vertebral fractures were described according to the Genant classification [12]. This classification is a semi quantitative analysis used to describe vertebral fracture grade on spinal radiography and on VFA; vertebral fractures are classified as:

- normal if there is no reduction in any height,
- mild or grade 1 for a reduction of 20-25% of anterior, middle, and/or posterior height,
- moderate or grade 2 for a reduction of 26-40% in any height,
- severe or grade 3 for a reduction > 40% in any height.

A vertebral fracture in VFA and spinal radiography was defined if both readers independently found the same fracture at the same level. A normal vertebra was considered as normal if both readers independently found the same vertebra as normal. When the readers disagreed for vertebral fracture in VFA or in radiography, the images were reviewed in conference by both investigators. The same procedure was done for evaluated the legibility of the spine of VFA and spinal radiography.

VERTEBRAL FRACTURE ASSESSMENT

VFA was acquired on the same time as BMD. The VFA scan was performed from T4 to L5 in anteroposterior and lateral view without moving the patient, by the same technician. Interpretation was done on digital scan. Investigators should specify the legibility of each vertebra in lateral and anteroposterior view and detect vertebral fractures by providing their grade.

RADIOGRAPHIC ASSESSMENT

Anteroposterior and lateral lumbar and thoracic spinal radiographs were taken the same day as DXA. Interpretation was done on digital radiography. Investigators should

specify the legibility of each vertebra in lateral and anteroposterior view and detect vertebral fractures by providing their grade.

DATA ANALYSIS

Data analysis was carried out using the Statistical Package for Social Sciences (SPSS release 15.0; SPSS Inc., Chicago, IL). Population characteristics were expressed as the mean $\pm$ 1 SD. The nominal significance level was set at 0.05. At the vertebral level, vertebra legibility was defined on VFA and on spinal radiographs. A vertebra was considered as readable if one or both of the anteroposterior and lateral views allowed to accurately describe the vertebrae. Subjects were divided in 2 subgroups to analyze factors influencing VFA legibility, one group with subjects with a least two unreadable vertebrae and a second one with the other patients. The agreement between readers was calculated with the Kappa Cohen score using data of the two readers before consensus. Effectiveness of VFA in fracture assessment was calculated after consensus using specificity, sensibility, positive and negative predictive values at both patient level and vertebral level. At the patient level, patients were considered as fractured if at least one fracture was detected and patients were considered as non-fractured if no fracture was detected. A conservative approach was preferred, considering the unreadable vertebrae as none fractured. If a fracture was detected in one of the technique at the patient level but non-visualized in the other technique the analysis was not done.

RESULTS

POPULATION CHARACTERISTICS

One hundred and nineteen patients were included in the study. Two patients were excluded because of a lack of data. The mean age was 65.8 ± 9.2 years and mean BMI was 27.1 ± 5.1 kg/m². Twenty-eight percent of patients were obese (BMI > 30 kg/m²), 32% were overweight (>25 - ≤ 30 kg/m²) and 40 % had a normal weight. The mean height was 157.8 ± 6.2 cm. The mean BMD was 0.686 ± 0.101 g/cm² at femoral neck, 0.824 ± 0.119 at total hip, and 0.861 ± 0.369 g/cm² at lumbar spine. The mean T-score was -1.394 ± 0.851 at femoral neck, -0.911 ± 0.906 at total hip, and -1.239 ± 1.432 at lumbar spine. According to the WHO definition based on BMD, 20% of the patients had an osteoporosis (T-score < -2.5 at one of the three measured site).

LEGIBILITY OF THE SPINE (FIGURE 1)

There were a total of 1666 evaluable vertebrae. On spinal radiographs, 1652 vertebrae (99.1 %) were readable and 12 unreadable vertebrae out of 14 (86 %) were upper T6 level. On VFA, 1488 vertebrae (87 %) were readable. One hundred and thirty-four unreadable vertebrae out of 178 (75 %) were also upper T6 level, 56% of all T4 vertebrae and 47 % of all T5 vertebrae were unreadable.

All vertebrae from T4 to L5 were readable in 112 patients on spinal radiographs and in 56 patients with VFA.

Two subgroups were done to analyze factors influencing VFA legibility by comparing baseline characteristics of the patients with a least two unreadable vertebrae and the other patients. A low BMD at the femoral neck and lumbar spine was significantly associated with a lack of legibility of vertebral fractures on VFA (BMD at lumbar spine $0.598 \pm 0.864 \text{ g/cm}^2$ in patients with at least 2 unreadable vertebrae vs $0.907 \pm 0.145 \text{ g/cm}^2$ in the other patients); ($p = 0.001$). There was no significant impact of age ($p = 0.061$), BMI ($p = 0.88$) or weight ($p = 0.8$).

IDENTIFICATION OF VERTEBRAL FRACTURES

Forty-six patients (39%) had at least one vertebral fracture on spinal radiographs, 42 patients (36%) had at least one vertebral fracture on VFA.

Seventy-six fractures were detected on spinal radiographs: 45 grade 1 (59%), 27 grade 2 (36%) and 4 grade 3 (5%). Sixty-two fractures were detected on VFA: 46 grade 1 (74%), 14 grade 2 (23%), and 2 grade 3 (3%). Ninety-five percents of vertebral fractures not detected in VFA were grade 1 on spinal radiographs. Repartition of vertebral fractures was represented in figure 2. According to Genant classification, VFA and spinal radiographs were concordant for 1440 vertebrae: 1405 normal vertebrae, 23 grade 1, 10 grade 2 and 2 grade 3 (Table 2).

PERFORMANCE OF VFA ANALYSIS

Inter-observer agreement was good at the vertebral level with a Kappa score of 0.782 +/- 0.036 for spinal radiographs and 0.634 +/- 0.051 for VFA. At the patient level, Kappa

score was also good with a score of 0.880 +/- 0.044 for spinal radiographs and 0.579 +/- 0.078 for VFA.

At the vertebral level, as shown in table 3, performance of VFA was good at the vertebral level with a specificity of 99.2 % and a sensibility of 72.9 %. Negative predictive value was 98.7% and positive predictive value was 80.9 %. Positive likelihood ratio was 86 and negative likelihood ratio was 0.274. After exclusion of grade 1 vertebral fractures, specificity for grade 2 and 3 was 100 % and sensibility 96.3%.

At the patient level, specificity was 94.12 % and sensibility was 80.43 %, positive predictive value was 90.24 %, and negative predictive value was 87.7 %. Positive likelihood ratio was 13.6 and negative likelihood ratio was 0.208.

DISCUSSION

This aim of this study was to evaluate the effectiveness of VFA compared to spinal radiography in the osteoporosis assessment of patients treated by AIs for breast cancer. We voluntarily choose a group with a high number of fractures to increase the interest of the statistical interpretation. Spinal radiograph and VFA analysis was performed by two readers to increase accuracy of the diagnosis of vertebral fracture and to analyze and compare the reproducibility of the technics. We have confirmed in this study that VFA is a suitable means to detect vertebral fractures and shown for the first time its relevance in the fracture risk assessment in patients with breast cancer treated by AIs. The main limit of VFA is the legibility of upper thoracic vertebrae as related in other studies [13-14-15]. This limit, which might be resolved with new generations of DXA, has a low clinical impact because of the low incidence of osteoporotic fracture upper T6; indeed vertebral fracture prevalence is predominant at the mid-lower thoracic spine and at lumbar spine [16]. In our study, only one vertebral fracture upper T6 was observed. Forty seven percents of our patients were completely explored from T4 to L5 which is comparable to others studies [13-17]. To increase vertebral legibility, analysis could be only done from T6 to L4 as in the study of Vokes et al. in which 85 % of patients were completely analyzed [18]. As previously described [13], we showed that low BMD is associated with a lack of legibility in VFA; this is a true limitation of the VFA because of the higher risk of fractures in patients with low BMD. As other authors

[14], we showed that most of the non-individualized vertebral fractures by VFA were mild (grade I) (95%). Mild vertebral fractures are also often non-individualized on radiographs, as shown by the IMPACT study [19] in which 34 % of vertebral fractures were false negative and the majority of grade 1 (56 %). In our study, VFA Kappa score is good and close to other studies [13, 20] and shows that the reproducibility of VFA is good despite a lack of experience of the readers. Kappa score for spinal radiographs was excellent, better than VFA, and as good as other studies [13-14-21]. The weaker concordance of VFA compared to radiographs could probably be improved by training and by the use of new generations of DXA. As other studies, specificity per vertebra and patient was excellent, upper than 90% [13-14-15-20]. The good negative predictive value at the patient and vertebral level shows that VFA is a good test to exclude vertebral fractures. The weaker sensibility of VFA is in link with the difficulty to analyze mild vertebral fractures, which is also a limit with radiographs. Sensibility of VFA is better for grade 2 and 3 vertebral fractures. It is now largely recommended that all women starting AIs therapy should be carefully assessed for their baseline risk of osteoporotic fractures including a DXA examination. Spinal radiographs are not systematically realized in the assessment of osteoporosis. However, a large percentage of asymptomatic vertebral fractures remains unknown and impact the osteoporosis treatment decision. Detection of asymptomatic vertebral fracture is important because of the risk of recurrence; the incidence of new vertebral fracture is 19 % at one year after a first vertebral fracture [22]. There is also an increased risk of hip fracture (RR = 2.5) with severe consequences [6] [23]. Mortality risk increases to 32 % in post-menopausal women with one or more incidence vertebral fractures in an 8-year follow-up [8]. Patients can also develop spine deformation as kyphosis and chronic low back pain. Considering the results of our study, in link with other studies, we can consider that VFA realized during DXA scan could improve the diagnosis of vertebral fracture without side effects. VFA is quickly performed in a simultaneous evaluation with BMD. VFA delivers a lower irradiation than spinal radiographs: 3 - 8 micro Sieverts (μSv) versus 600 μSv for spinal radiographs from thoracic to lumbar spine [24]. The X-rays source in VFA is in theory always orthogonal to the vertebral bodies avoiding geometric distortion, which is a limit of radiography legibility. Furthermore, VFA has a lower cost than radiographs, estimated in US at \$40 versus \$80 [25]. Thus, VFA by DXA has clear benefits compared with spinal radiography and could be a simple and valid tool to detect vertebral fracture. However, spinal radiography remains the gold standard to analyze osteoporotic vertebral fracture and it is necessary to confirm each

vertebral fracture detected on VFA by spinal radiographs, particularly in a context of breast cancer.

In conclusion, VFA is a suitable means to detect osteoporotic vertebral fracture. The legibility is good except upper T6, the specificity is excellent and the reproducibility between readers is quite good. Considering its easy feasibility during DXA and its low irradiation, VFA should be proposed in the osteoporotic risk assessment in the context of AI therapy.

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FIGURES

Figure 1: Repartition of vertebrae legibility on VFA and spinal radiographs.

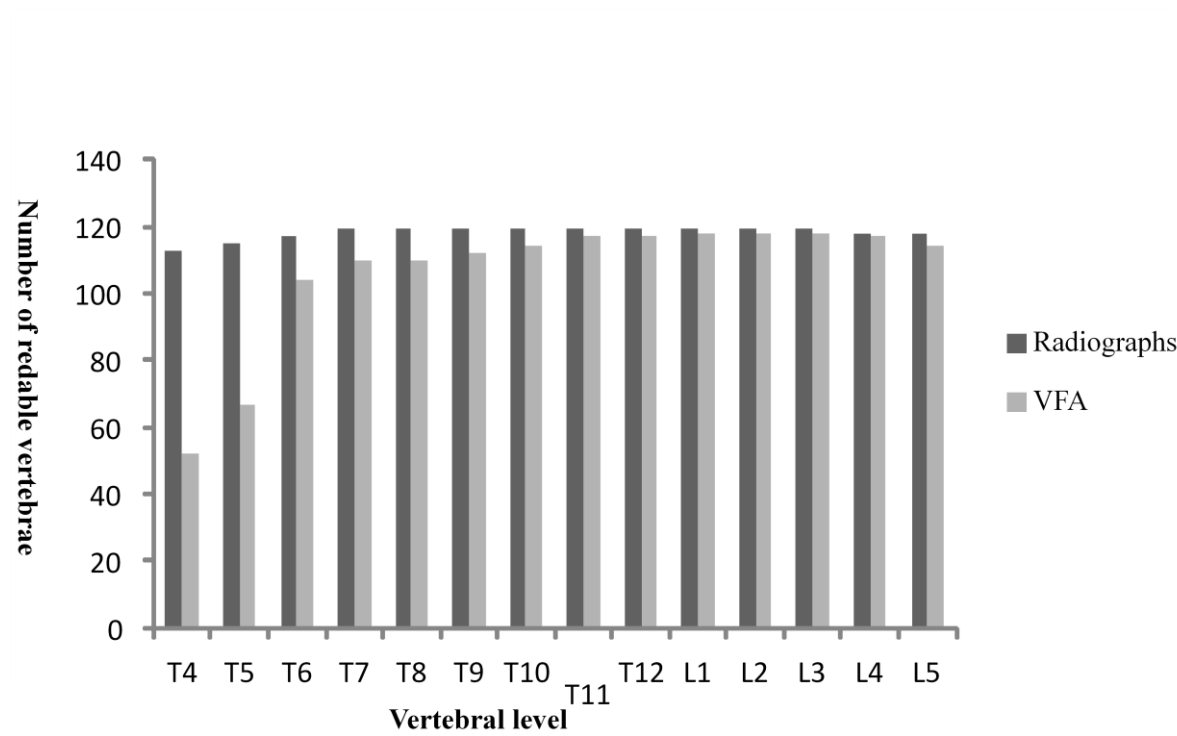
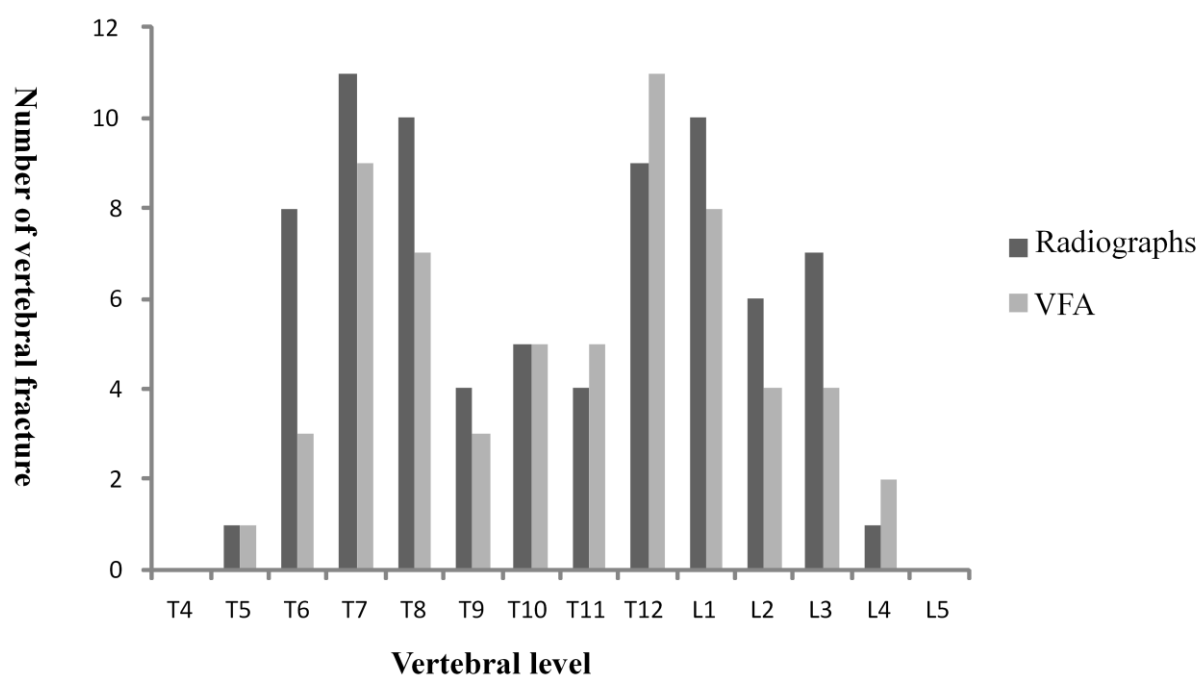


Figure 2: Repartition of vertebral fractures on VFA and spinal radiographs



TABLEAUX

Table I: Concordance between VFA and spinal radiographs according to the Genant classification

VFA	Spinal radiographs				
	Normal	Genant 1	Genant 2	Genant 3	Total
Normal	1405	18	1	0	1424
Genant 1	12	23	13	1	49
Genant 2	0	1	10	1	12
Genant 3	0	0	0	2	2
Total	1417	42	24	4	1487

Table II: Performance of VFA to detect vertebral fracture (per vertebra) and to detect fractured patient (per patient) compared with spinal radiographs.

Sensibility		Specificity		Positive predictive value		Negative predictive value	
Per Vertebra	Per patient	Per Vertebra	Per patient	Per Vertebra	Per Patient	Per Vertebra	Per Patient
72.9 %	80.43%	99.20%	94.1%	80.95%	90.24%	98.67 %	87.67 %

ANNEXES

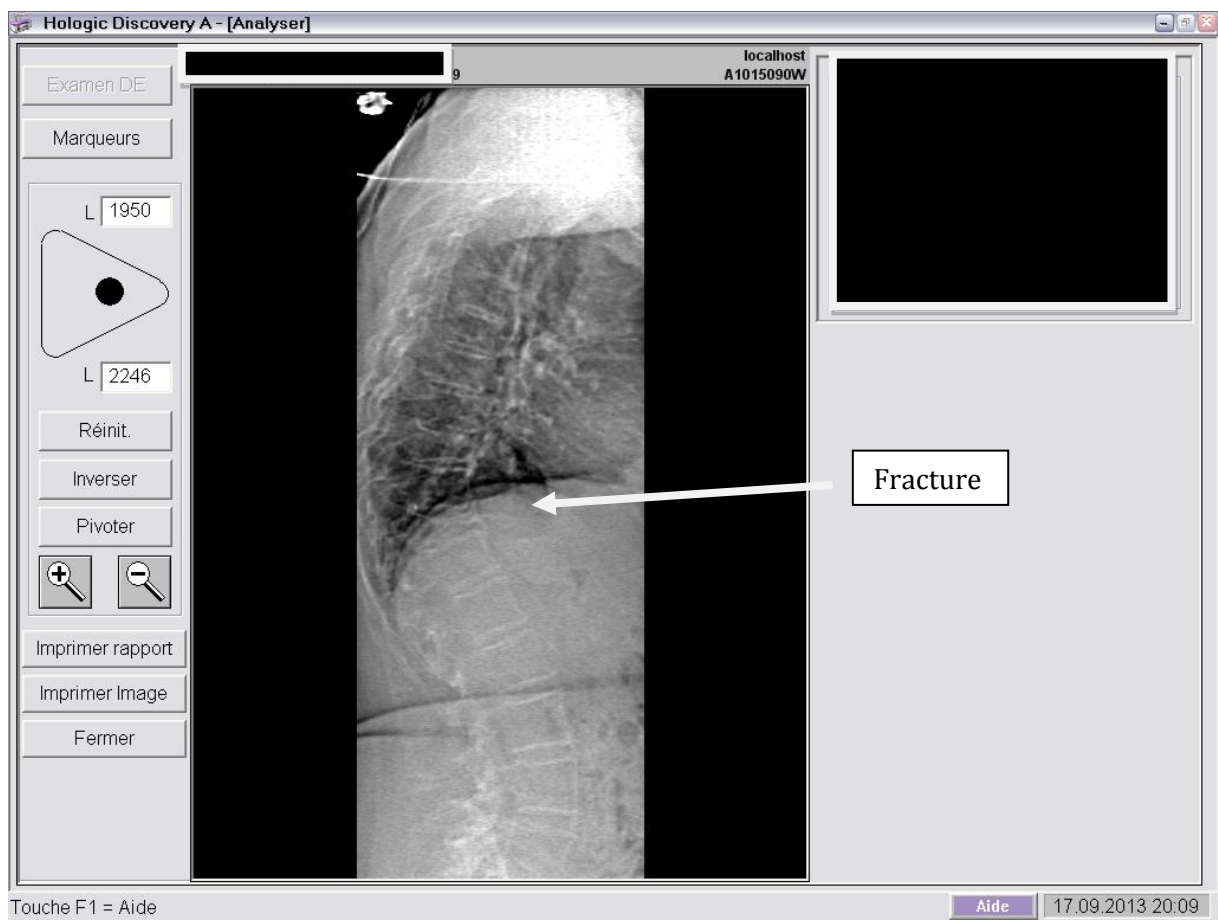
VFA 1



VFA 2



VFA 3



GENANT CLASSIFICATION

Mild deformity
(Grade 1)



Moderate deformity
(Grade 2)



Severe deformity
(Grade 3)



Indications for VFA [26], the 2005 ISCD Official Positions

Consider VFA when the results may influence clinical management.

Postmenopausal women with low bone mass (osteopenia) by BMD criteria, PLUS any one of the following:

- Age greater than or equal to 70 years
- Historical height loss greater than 4cm (1.6 in.)
- Prospective height loss greater than 2 cm (0.8 in.)
- Self-reported vertebral fracture (not previously documented)
- Two or more of the following;
 - o Age 60 to 69 years
 - o Self-reported prior non-vertebral fracture
 - o Historical height loss of 2 to 4 cm
 - o Chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease)

Men with low bone mass (osteopenia) by BMD criteria, PLUS any one of the following:

- Age 80 years or older
- Historical height loss greater than 6cm (2.4 in)
- Prospective height loss greater than 3cm (1.2 in)
- Self-reported vertebral fracture (not previously documented)
- Two or more of the following
 - Age 70 to 79 years
 - Self-reported prior non-vertebral fracture
 - Historical height loss of 3 to 6 cm
 - On pharmacologic androgen deprivation therapy or following orchidectomy
 - Chronic systemic diseases associated with increased risk of vertebral fractures (for example, moderate to severe COPD or COAD, seropositive rheumatoid arthritis, Crohn's disease)

Women or men on chronic glucocorticoid therapy (equivalent to 5 mg or more of prednisone daily for three (3) months or longer).

Postmenopausal women or men with osteoporosis by BMD criteria, if documentation of one or more vertebral fractures will alter clinical management

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