Clinical Use of Quantitative Computed Tomography and Peripheral Quantitative Computed Tomography in the Management of Osteoporosis in Adults: The 2007 ISCD Official Positions

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Abstract

The International Society for Clinical Densitometry (ISCD) has developed Official Positions for the clinical use of dual-energy X-ray absorptiometry (DXA) and non-DXA technologies. While only DXA can be used for diagnostic classification according to criteria established by the World Health Organization, DXA and some other technologies may predict fracture risk and be used to monitor skeletal changes over time. ISCD task forces reviewed the evidence for clinical applications of non-DXA techniques and presented reports with recommendations at the 2007 ISCD Position Development Conference. Here we present the ISCD Official Positions for quantitative computed tomography (QCT) and peripheral QCT (pQCT), with supporting medical evidence, rationale, controversy, and suggestions for further study. QCT is available for bone mineral density measurements at the spine, hip, forearm, and tibia. The ISCD Official Positions presented here focus on QCT of the spine and pQCT of the forearm. Measurements at the hip may have clinical relevance, as this is an important fracture site; however, due to limited medical evidence, definitive advice on its use in clinical practice cannot be provided until more data emerge.

Key Words: Bone mineral density; diagnosis; fracture assessment; guideline; monitoring; osteoporosis; position; pQCT; QCT; standards.

Introduction

Quantitative computed tomography (CT) is a three-dimensional non-projectional technique to quantify bone mineral density (BMD) in the spine, proximal femur, forearm, and tibia with a number of advantages to other densitometric techniques: cortical and trabecular bone can be separated,
trabecular volumes of interest (VOI) are largely independent of degenerative changes in the spine, and 3D geometric parameters can be determined. Bone mineral density (BMD), as measured by QCT, is a true density measured in g/cm\(^2\), in contrast to dual-energy X-ray absorptiometry (DXA), which determines an areal density (BMD\(_a\)) measured in g/cm\(^2\). Peripheral quantitative computed tomography (pQCT) at the forearm (1) was introduced shortly after computed tomography (CT) for medical imaging (2) and several years before the development of spinal QCT (3), as a volumetric extension to Cameron’s projection technique for bone mineral measurements (4). For a long period the technical implementations of QCT using clinical CT scanners and pQCT using smaller dedicated forearm scanners remained virtually unchanged. A number of single-slices, e.g., one slice for each lumbar vertebra L1-L4, were scanned. For each acquired slice a CT image was reconstructed in which dedicated regions of interest (ROI) for trabecular and cortical compartments are analyzed. BMD values are then derived, either from a calibration procedure using an in-scan calibration phantom measured below the patient, or from stored calibration values obtained before the patient scan. However, for reasons that included better precision, a smaller dose of ionizing radiation, greater availability, simpler scanner operation, and lower cost, DXA, rather than QCT, became the gold standard modality for measuring BMD in the 1990s. During the last two decades BMD\(_a\) of the spine and hip, as measured by DXA, was typically the second most important endpoint in almost all pharmaceutical studies investigating the efficacy of new drugs in reducing osteoporotic fractures. Consequently, there is a wealth of epidemiological data correlating fracture risk with BMD\(_a\) as measured by DXA. Hip and spine BMD\(_a\) T-scores derived from DXA, became the basis of the World Health Organization (WHO) densitometric criteria with which to classify a patient as being normal, osteopenic or osteoporotic.

Renewed interest in QCT/pQCT has been stimulated for a number of reasons. One is the rapid progress in computed tomography (CT) technology since the introduction of spiral CT (5), enabling the acquisition of volumetric scans of skeletal sites other than the spine, such as the femur. Another reason is the unique ability of CT to measure cortical and trabecular bone separately, and to provide information of bone geometry and trabecular structure, as discussed below. Also, the quantification of BMD with QCT is independent of bone size, which is not the case for DXA (6). This may explain why BMD\(_a\) as measured by DXA, is typically better correlated with body weight and height than is BMD, as measured by QCT (7), or a volumetric estimation of bone mineral density (BMD\(_m\)) from DXA measurements, for example, by dividing BMD\(_m\) by the square root of bone area (8,9). Finally, it has been reported in several pharmaceutical trials that increases in BMD, as measured by DXA, do not entirely explain the observed reduction in fracture risk (10,11), highlighting some challenges in monitoring treatment with DXA.

QCT and pQCT to date have rarely been integrated in large epidemiological studies with fracture endpoints. Thus, from the perspective of evidence-based medicine, QCT and pQCT are less well characterized than DXA. According to previous ISCD Official Positions, 2D slice-based QCT of the spine and pQCT of the forearm can be used for fracture prediction and for treatment- or age-related monitoring of BMD, but not for the diagnosis of osteoporosis.

Due to the renewed interest in QCT and the rapid expansion of the use of 3D QCT, it is the aim of the ISCD to review the evidence and update the ISCD Official Positions for the clinical use of QCT/pQCT.

**Overview of QCT Technology**

**Computed Tomography (CT)**

**CT Calibration**

Computed tomography is an X-ray based technique and as such gives an image of the total linear X-ray absorption coefficient \(\mu\). For clinical CT applications, the values of \(\mu\) are calibrated to the X-ray attenuation of water (\(w\)), resulting in a CT number measured in Hounsfield Units (HU):

\[
\text{CT number} = \frac{\mu - \mu_w}{\mu_w} \times 1000 \text{ [HU]}
\]

where \(\mu\) is the linear X-ray attenuation coefficient of the voxel under consideration and \(\mu_w\) the attenuation coefficient of distilled water at room temperature. In an appropriately calibrated scanner the CT number of water is 0. Thus, in contrast to DXA, all CT scanners are calibrated equivalently. Important terms and abbreviations used in CT are listed in the Appendix 1.

**CT Data Acquisition**

In CT, first a survey radiograph, often called a scout scan or topogram, is acquired in order to locate the scan range for the tomographic images. Historically, single-slices, e.g., one per lumbar vertebra, were acquired in step and scan mode (see Fig. 1), while the couch of the CT scanner was at rest. In step and scan mode, a larger volume could be assembled by acquiring contiguous single-slices, but scan times for such acquisition are long and patient movement is a limiting factor with image quality. Until the introduction of spiral technology in which the patient is continuously moved through the scanner gantry during the acquisition CT techniques remained restricted to single slices. Spiral CT acquisition protocols are used to scan larger volumes, e.g., encompassing one, or several, complete vertebrae.

Early spiral CT systems also assembled a stack of images by acquiring one slice at a time, but compared to the step and scan mode, the required time to scan a volume was reduced by more than an order of magnitude. Newer systems equipped with multiple rows of detectors that acquire up to 64 slices simultaneously are designated as multi-slice CT (MSCT) (12) Scan times for MSCT are typically below 10 s for the lumbar spine or the proximal femur. A further development in MSCT is the use of areal detectors, which acquire even larger volumes in one rotation,
so that in many applications a spiral motion of the X-ray tube relative to the body is no longer necessary. This true volumetric data acquisition is used in a new dedicated forearm scanner, but has not yet been introduced in whole body CT scanners.

CT Image Reconstruction

The image generation in CT is a two step process. The first step is the data acquisition addressed in the previous paragraph. The second step is the tomographic reconstruction, which describes the mathematical process of calculating the image from the acquired data. It is important to separate these two steps, as the operator can select a variety of parameters for both that influence image quality. Table 1 lists the acquisition and reconstruction parameters most relevant for QCT. While a detailed discussion of this topic is beyond the scope of this paper, the table indicates how a variation of these parameters impacts on image quality and radiation exposure. Typical values used in clinical QCT investigations are given in Table 2. In particular, for spiral acquisitions of the spine and the hip, there are no standard protocols and a systematic investigation of the influence of the different scan and acquisition parameters on analysis results has not yet been published.

Quantitative Computed Tomography

In general radiology, the term QCT describes the analysis of the CT images beyond a visual radiological evaluation. Typically, the analysis involves the use of dedicated software to extract quantitative parameters. As such, the term QCT is not restricted to bone densitometry, in which QCT describes a technique for measuring BMD in specific regions or volumes of interest in trabecular or cortical bone. The term peripheral QCT (pQCT) defines the application of QCT to appendicular skeleton sites, such as the arms or legs, thus QCT is more general than pQCT.

From the perspective of bone densitometry, differences in the acquisition scheme (step and scan vs spiral CT) are of lesser importance than the image analysis approach: the traditional 2D analysis of regions of interest (ROI) on one or multiple slices that can also be applied to data from spiral CT acquisitions, should be distinguished from the 3D analysis of volumes of interest (VOI) in a contiguous stack of
slices. Therefore, the term 3D QCT should be used to differentiate the analysis approach and not the acquisition technique. As an alternative to three dimensional (3D) QCT the term volumetric QCT (vQCT) may be used. Three-dimensional analysis algorithms for QCT have been developed following the introduction of spiral CT. It is important to understand that with QCT it is always a volume of bone that is analyzed. In the analysis of a 2D ROI on single CT slices the volume is the area of the ROI multiplied by the slice thickness.

QCT measurements of the spine and the hip are performed on clinical all-purpose, total body CT scanners equipped with special analysis software. In contrast, smaller scanners have been specifically developed for the quantitative determination of BMD in the forearm and the tibia (1). They are less expensive and more mobile than whole body clinical CT scanners. Similar to DXA, pQCT scanners are dedicated to bone densitometry; consequently, the operator has fewer choices for acquisition and reconstruction parameter settings than with whole body CT scanners. The term pQCT is sometimes used to designate such dedicated peripheral scanners. However, pQCT measurements can also be performed on clinical whole body CT scanners; therefore, the term pQCT covers all peripheral QCT measurements. Data acquisition and reconstruction on pQCT and whole body CT scanners is identical: after selection of the scan location on a survey radiograph, single or multiple CT slices are acquired. Acquisition and reconstruction parameters for pQCT scanners are summarized in Table 2.

### QCT of the Spine

QCT of the lumbar spine is one of the standard procedures in bone densitometry. Historically, a single 8 mm to 10 mm thick midvertebral slice was analyzed per vertebra (13–15). Typically, three to four vertebrae in the range T12 to L4 were used (Fig. 1). Since the introduction of spiral CT there is a trend to scan two complete vertebrae in the range T12 to L3. The reason for limiting scanning to two vertebrae is to minimize the radiation exposure (see section on radiation exposure below). Also, with spiral CT the slice thickness is greatly reduced from 8–10 mm to 1–3 mm, which improves spatial resolution in the tomographic images.

### Table 1

<table>
<thead>
<tr>
<th>Acquisition</th>
<th>Reconstruction</th>
<th>Main impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray tube voltage (kV)</td>
<td></td>
<td>BMD calibration/radiation exposure</td>
</tr>
<tr>
<td>Table height</td>
<td></td>
<td>BMD calibration</td>
</tr>
<tr>
<td>Product of acquisition time and X-ray tube current (mAs)</td>
<td></td>
<td>Image noise/radiation exposure</td>
</tr>
<tr>
<td>Detector Collimation (mm)</td>
<td></td>
<td>Spatial resolution/image noise</td>
</tr>
<tr>
<td>Pitch</td>
<td></td>
<td>Spatial resolution</td>
</tr>
<tr>
<td>Reconstructed field of view (FoV) (cm)</td>
<td></td>
<td>Spatial resolution/image noise</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td></td>
<td>Spatial resolution</td>
</tr>
<tr>
<td>Reconstruction kernel</td>
<td></td>
<td>Spatial resolution/image noise</td>
</tr>
</tbody>
</table>

On dedicated peripheral devices most if not all of these parameters are preset by the manufacturer.

### Table 2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Step and scan</th>
<th>Spiral</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray tube voltage (kV)</td>
<td>80–120</td>
<td>120</td>
</tr>
<tr>
<td>Spine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Forearm&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Spine&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Product of acquisition time and X-ray tube current (mAs)</td>
<td>100–150</td>
<td>100–200</td>
</tr>
<tr>
<td>Spine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hip&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Forearm&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Detector collimation (mm)</td>
<td>8–10</td>
<td>1–3</td>
</tr>
<tr>
<td>Spine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hip&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Forearm&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Pitch</td>
<td>n/a</td>
<td>1–3</td>
</tr>
<tr>
<td>Reconstructed field of view (FoV) (cm)</td>
<td>250–400</td>
<td>150–500</td>
</tr>
<tr>
<td>Spine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hip&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Forearm&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Slice thickness (mm)</td>
<td>8–10</td>
<td>150–500</td>
</tr>
<tr>
<td>Spine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Hip&lt;sup&gt;b&lt;/sup&gt;</td>
<td>FOREARM&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Reconstruction kernel</td>
<td>Standard/Bone</td>
<td>Standard/Bone</td>
</tr>
</tbody>
</table>

<sup>a</sup>Using clinical whole body CT scanners.

<sup>b</sup>Using dedicated pQCT scanners.

<sup>c</sup>Xtreme CT using volumetric data acquisition.
In single-slice QCT of the spine, the main output of all analysis programs is a midvertebral trabecular volume using either an elliptical- or a Pacman-shaped ROI in which BMD is determined (13-16). Unfortunately, standardization for different QCT scanner types, comparable to that applicable to DXA (17), has not been published, but a comparison of the University of California at San Francisco (UCSF) and the German QCT reference data, using the elliptical and the Pacman shaped ROI for analysis, shows good agreement (18). For single-slice spinal QCT, there are several commercial analysis packages that are either implemented on the CT scanner, or on workstations to which the acquired CT data are transferred.

Following the introduction of spiral CT technology, 3D QCT of the spine, based on acquisition of complete vertebrae, was developed. Currently, one commercial package (QCT Pro, Mindways Software, Inc., Austin, TX) and some advanced university-based research tools are available for 3D analysis. Apart from the midvertebral trabecular VOI that in size and location is similar to the volume analyzed in single-slice mode, various additional VOI can be measured by 3D QCT. However, to date there is no agreement on the locations, sizes, or shapes of VOIs. Additionally, the definition of these VOIs typically depends more on the bone segmentation process than does the midvertebral trabecular VOIs, so that the different segmentation approaches, ranging from simple global thresholding to more complicated adaptive approaches, will have a greater impact on differences between the analysis algorithms (19). A direct comparison between existing 3D segmentation approaches has not yet been published. Thus, at this point in time, results obtained with 3D QCT from different analysis programs should not be compared directly with the BMD of the midvertebral VOI.

QCT of the Proximal Femur

As with 3D QCT of the spine, 3D QCT of the hip is a new procedure and not yet clinically established. QCT of the proximal femur is carried out on clinical whole body CT scanners. Early approaches using single-slice QCT of the hip based on step and scan acquisition protocols failed due to the complex geometry of the femur and poor precision. For 3D QCT, the scan region typically starts 1-2 cm above the femoral head and extends a few centimeters below the lesser trochanter. To date, only one commercial and a few advanced university-based research tools are available for 3D analysis. The principal VOIs analyzed are the femoral neck, the trochanter, and the intertrochanteric region, but there are significant differences among analysis programs and standardization has not yet been implemented.

pQCT of the Forearm

Standard pQCT scanners work in step and scan mode. Some acquire single-slices, and others operate in multi-slice mode. Measurement locations are defined with respect to the length of the radius, measured from the radio-carpal joint surface to the olecranon. Typically, scan locations with single-slice CT scanners are distal sites (4% of radius length) containing mainly trabecular bone and a shaft location (15%-65% of radius length), consisting predominantly of cortical bone. Multi-slice scanners use a distal site between 4% and 10% of the length of the radius (see Fig. 2) and also a shaft location (20,21). Multiple slice techniques are advantageous with respect to measurement precision by evaluating a larger VOI (22) and for matching analysis volumes of interests between baseline and follow-up measurements (23). A decrease in slice thickness, e.g., from 2 mm to 1 mm, increases the geometrical resolution.

Currently, only a few types of pQCT scanners are in use. Most of the literature has been published for the XCT 2000 (Stratec Medizintechnik, Pforzheim, Germany) and its predecessors, the XCT 960 and the isotope based XCT 900. These are scan and step scanners (see Table 2 for characteristic parameters) that are predominantly used to determine BMD, BMC, cortical width and volume, or cross-sectional area of the radius (to derive biomechanical parameters such as stress strain index (SSI) and moment of inertia). The ISCD Official Positions listed below are valid for this class of scanners.

Radiation Exposure

Table 3 shows the radiation exposure associated with QCT. Values are expressed as effective dose equivalent (EDE) values. In modern spiral CT scanners, techniques are implemented to significantly reduce radiation exposure by optimally adapting the X-ray tube current to the individual subject being scanned (24). The level of dose reduction depends on
anatomical location. Compared to standard protocols, reductions in radiation dose are greatest in the shoulder, lung and pelvis, where the dose can be reduced by up to 50% (25-27).

QCT Parameters

The goal of densitometric techniques is the measurement of parameters to determine bone strength, to predict fractures, and to differentially assess effects of aging and treatment on these parameters. BMD is the most important single parameter acquired for this purpose. However, BMD does not fully explain bone strength. Fracture prediction can be improved by measuring additional parameters that, together with BMD, better account for bone strength. In contrast to DXA, QCT is well suited for this purpose, as it is a 3D technique from which the 3D geometry of bones can be measured in addition to density. The only constraint is the spatial resolution; thus, in vivo studies are limited principally by radiation exposure in humans. Current concepts and approaches to determine BMD, measure bone geometry and more advanced parameters using QCT will be summarized. Results of in vivo studies, their clinical impact, and the resulting clinical recommendation are provided in following sections.

Determination of BMD

In QCT, BMD is determined from the measured CT parameters. This step is based on a linear calibration of CT number to BMD using a phantom with bone equivalent calibration materials of density. QCT-derived BMD is typically reported in mg/cm


Projective modalities, such as DXA, evaluate a projected area of the investigated volume but not the volume itself. As a consequence, only a so-called ‘areal’ bone mineral density BMDa, typically measured in g/cm


Separation of Cortical and Trabecular Bone

In QCT, cortical and trabecular bone compartments can be assessed separately. This is advantageous, as the spine trabecular bone is about eight times more metabolically active than cortical BMD; thus, age- and treatment-related changes are greater than in integral (cortical + trabecular) BMDa as measured in DXA. Due to limited spatial resolution of CT, an accurate determination of the cortical VOI is not possible in the spine. Consequently, cortical QCT BMD analyzed by some applications always contains some subcortical bone (Fig. 1).

Another parameter of interest is cortical thickness. Most of the work to quantify this parameter has been performed with pQCT because in the spine the spatial resolution of the clinical CT scanners is inadequate to assess cortical thickness with accuracy (19). Also, a slice thickness of 8-10 mm selected for the central part of the vertebral body to reduce noise is not appropriate for cortical thickness measurements. Newer spiral protocols, in particular for scans of the hip, may be more successful for measuring cortical thickness because thinner slice thicknesses (1-3 mm) are used. Cortical thickness in the hip is greater than in the spine. Modern multi-slice spiral CT scanners offer isotropic spatial resolution down to

Table 3

<table>
<thead>
<tr>
<th>Technique</th>
<th>Time current Voltage (kV) product (mAs)</th>
<th>Approx. effective dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-slice QCT spine L1–L3 10 mm slice thickness</td>
<td>80 120</td>
<td>&lt;0.2\textsuperscript{a}</td>
</tr>
<tr>
<td></td>
<td>120 200</td>
<td>\textsim 1\textsuperscript{a}</td>
</tr>
<tr>
<td>3D QCT spine L1 and L2 (10 cm scan range)</td>
<td>120 100</td>
<td>\textsim 1.5\textsuperscript{a,b}</td>
</tr>
<tr>
<td>3D QCT proximal femur (15 cm scan length)</td>
<td>120 200</td>
<td>\textsim 2.5-3\textsuperscript{a,b,c}</td>
</tr>
<tr>
<td>pQCT forearm on clinical CT scanners 10 cm scan length</td>
<td>120 100</td>
<td>&lt;0.01\textsuperscript{a}</td>
</tr>
<tr>
<td>pQCT forearm or tibia on dedicated single-slice pQCT scanners</td>
<td>&lt;70 &lt;1</td>
<td>&lt;0.003 per slice\textsuperscript{d}</td>
</tr>
<tr>
<td>High resolution pQCT forearm (XtremeCT) scan length 15 cm</td>
<td>60 1</td>
<td>&lt;0.005\textsuperscript{d}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Monte Carlo calculations performed with Impact Dose (Vamp GmbH, Möhrendorf, Germany) based on Adam and Eva Phantoms (225).

\textsuperscript{b}Assuming the use of dose reduction algorithms implemented on newer spiral CT scanners, that reduce the effective dose in spine and hip by approximately 50% (24,25).

\textsuperscript{c}A third of these values is associated with gonadal dose alone.

\textsuperscript{d}Manufacturer specifications.

*The first part of this section has been adopted from the forthcoming ICRU report on bone densitometry that has in parts been published (75).
(0.5 mm$^3$) as compared with older equipment for which the resolution along the scanner axis was often limited to 2 mm.

**Advanced Parameters**

One strategy to identify additional parameters that would explain bone strength and improve fracture prediction is the use of in vitro studies to predict the mechanical competence (structural strength or failure load) of bones under given loading conditions. Regression analyses between osteodensitometric parameters (independent variables) and mechanical competence (dependent variable) allow for the evaluation of advantages and disadvantages of various methods and parameters. For the assessment of biomechanical properties the following testing methods are typically performed:

- For the shaft of the radius, 3-point bending
- For the vertebrae or for sections of the distal metaphysis, axial compression
- For the forearm, fall simulation on the outstretched hand, with a wide variety of fixation methods and load setups
- For the hip, single leg stance and fall simulations

Several studies have determined the association between whole bone strength, QCT-derived BMD, and bone geometry. In particular, QCT measures have been related to bone density measurements and geometric measurements. The relationship between mechanical competence might be similar for geometric and bone mass measurements.

**Optimized Locations of Scan and Analysis VOI**

In the forearm, the scan location with the strongest capability to predict mechanical competence has not yet been identified. Some studies found higher correlation coefficients for measurements at the shaft as compared to measurements at the distal end of the bone. Others, however, reported similar correlations for both sites (33,42). Compression tests of the ultra-distal region revealed the highest correlations between ultimate strength and BMC ($r = 0.83$–$0.87$). The loads to produce distal radius fractures by simulating a fall on to the outstretched hand (56,57) have been accurately predicted by density measurements and geometric measurements. The most accurate predictors of fracture strength were BMC at the ultra-distal site ($r = 0.94$) (54), area of cortical bone at the shaft site ($r = 0.84$–$0.89$) (54,57), and combinations of BMC with moments of inertia ($r = 0.93$) (40).

In the spine and the hip, there is less discussion of scan locations because a 3D acquisition can be performed. However, the optimum VOI to be analyzed has not been investigated systematically. One approach applied to the trabecular ROI of the spine, using single-slice non spiral CT (58–60), is the separation of a larger ROI/VOI into smaller sub ROI/VOI in order to detect relevant regional differences in BMD, or in response to treatment.

**Bone Structure**

Another avenue to derive relevant parameters for QCT scans is the assessment of trabecular structure in high resolution images of the forearm or the spine. Two different approaches have been reported in the literature. The first approach is the analysis of parameters determined in equivalence to classical histomorphometry, such as trabecular spacing or number of trabeculae. The second approach is the quantification of texture or similar parameters that depend less on the segmentation of individual trabeculae. It has been difficult to translate results obtained in in-vitro studies of cadavers and excised bones (53,61–67) or bone cubes (68,69) to the in vivo situation because spatial resolution and signal to noise characteristics are usually inferior in in vivo scans due to the limitations in radiation doses that are acceptable in humans.

For theoretical reasons, geometry-based parameters are expected to provide a more accurate prediction of structural strength because they consider the spatial distribution of bone material and the bone architecture, rather than bone mass alone. However, the distribution of available bone mass is thought to be subject to an optimization process that provides adequate mechanical strength, and is influenced by mechanical stimuli (55). Therefore, the strength of the relationships between mechanical competence might be similar for geometric and bone mass measurements.
For this scanner, the use of the T-score criterion of the WHO definition (78–80) for osteoporosis by the WHO definition (78–80) is a strong predictor of failure load than single parameters alone (48).

**Finite Element Analysis**

Finite element analysis (FEA) potentially integrates density and geometry and better accounts for regional variations than the separation of a bone into sub-volumes. Several in vitro studies have shown QCT-based FEA to be a strong predictor of whole bone strength, with some (34,46), though not all (35,44), studies reporting stronger correlations for FEA than for DXA or QCT-based measures. It has not yet been demonstrated that FEA provides additional advantages compared to a combination of densitometric and geometrical QCT parameters. For the hip, it has been shown that a combination of QCT-derived densitometric and geometric parameters is a better predictor of failure load than single parameters alone (48).

**General Remarks on Diagnosis, Fracture Prediction, and Monitoring**

In general, a diagnosis should primarily answer the question of whether a subject is healthy, diseased, or perhaps in an intermittent state. For this purpose, we need a definition of the disease. Then, diagnostic criteria must be specified for a given method, ideally assessing the severity of the disease by a quantitative scale. Ideally, treatment decisions based on this scale should be possible.

Conceptually, osteoporosis is defined as a disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk (76). Unfortunately, this definition does not provide explicit diagnostic criteria that allow one to decide whether an individual is osteoporotic or not. It only identifies low bone mass and micro-architectural deterioration as the two fundamental defining characteristics of osteoporosis. With clinical tools currently available, the micro-architectural status and bone fragility cannot be measured. Therefore, DXA-measured BMD has been selected as the key measure to define osteoporosis (77).

Diagnostic criteria based on BMD have been provided by the definition of osteoporosis developed by a working group of the WHO, based on the T-score concept. The WHO (77) definition classification uses ‘areal’ BMD at the spine, hip and forearm, as measured by DXA, to categorize a subject into one of four groups:

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMDa T-score Criteria</th>
</tr>
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<tbody>
<tr>
<td>Normal</td>
<td>BMDa T-score -1.0 or higher</td>
</tr>
<tr>
<td>Low bone mass or osteopenia</td>
<td>BMDa T-score between -1.0 and -2.5</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>BMDa T-score -2.5 or less</td>
</tr>
<tr>
<td>Established (severe) osteoporosis</td>
<td>BMDa T-score -2.5 or less and at least one fragility fracture</td>
</tr>
</tbody>
</table>

It is very important to understand that this operational definition of diagnostic classification is valid for DXA only. It does not apply to any other densitometric method, including QCT, because the standard deviation and the age-related decline in the normal population of all other techniques differ from that of DXA. As a consequence, the application of the “T-score -2.5 or less” criterion to spinal QCT, for example, would increase the number of subjects classified as osteoporotic by the WHO definition (78–80). The discordance of T-scores between QCT and DXA has been recorded in several studies (79,81–84), but there are only three publications, one for males (80) and two for females (78,85), which more extensively compared T-scores between DXA and spinal single-slice QCT. Despite the fact that the WHO criteria apply only to DXA, equivalent T-scores may be defined for QCT using the concept of comparable sensitivity and specificity. Details will be given in the section ‘Can QCT of the Spine be Used to Diagnose Osteoporosis?’ below.

The use of the WHO criteria for DXA alone has raised concern that other important predictors of fracture risk, such as the age of the patient, are not considered. Thus, for treatment decisions in the future, the diagnostic classification use of the BMDa T-score will be supplemented by absolute fracture risk (fracture probability) estimation (86–88). Details of this concept are still under discussion (89), but the patient’s age and a variety of other clinical risk factors (CRFs) for osteoporotic fractures (e.g., body mass index, previous low trauma fracture occurring after age 50 yrs, glucocorticoid use, rheumatoid arthritis, smoking, alcohol consumption, parental history of fracture), and low BMD will be included. The recently updated German osteoporosis guidelines (90), for example, use age, BMD, and prevalent vertebral fractures to estimate absolute fracture risk.

The absolute fracture risk for an individual patient can be calculated from the individual relative risks of the factors included in the model. If BMD is selected as a contributing factor, then from the measured BMD value of the patient, the fracture risk relative to a reference population (RR) of the same age as the patient must be calculated. RR is proportional to the standardized age-adjusted risk gradient of the method used to determine BMD (sRR) to the negative power of the Z-score of the measurement:

\[ \text{RR} \sim \text{sRR}^{-Z} \]

sRR is typically obtained by normalizing the unstandardized risk gradient with the standard deviation of the young-adult reference population. Thus, in order to use a QCT measurement for the calculation of a patient’s absolute fracture risk, reference data and the risk gradient for this particular measurement are required.

Reference data for a variety of populations have been published for single-slice QCT of the spine (Table 4). Trabecular BMD and, for some populations, cortical BMD has also been measured. For the hip, reference data exist for the Rochester...
Table 4  
Populations for Which Normative Data for QCT Have Been Published

<table>
<thead>
<tr>
<th>Population</th>
<th>Gender</th>
<th>Age range</th>
<th>Parameters</th>
<th>Scanner (voltage setting)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single-slice QCT of the spine and hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Male/female</td>
<td>20–80</td>
<td>Spine: trab BMD</td>
<td>GE 8800 (120 kV)</td>
<td>(226)</td>
</tr>
<tr>
<td>US</td>
<td>Female</td>
<td>20–80</td>
<td>Spine: trab BMD</td>
<td>GE 9800 (80/120 kV)</td>
<td>(227)</td>
</tr>
<tr>
<td>British</td>
<td>Male/female</td>
<td>18–75</td>
<td>Spine: trab BMD</td>
<td>Philips 350 (120 kV)</td>
<td>(228)</td>
</tr>
<tr>
<td>Swedish</td>
<td>Male/female</td>
<td>20–90</td>
<td>?</td>
<td>? (120 kV)</td>
<td>(229)</td>
</tr>
<tr>
<td>US</td>
<td>Female</td>
<td>20–80</td>
<td>Spine: trab BMD</td>
<td>GE CT/T (80 kV)</td>
<td>(112)</td>
</tr>
<tr>
<td>German</td>
<td>Male/female</td>
<td>20–80</td>
<td>Spine: trab and cort BMD</td>
<td>Siemens Somatom DR (80/120 kV)</td>
<td>(18)</td>
</tr>
<tr>
<td>Greek</td>
<td>Male/female</td>
<td>30–70</td>
<td>Spine: trab BMD</td>
<td>? (120 kV)</td>
<td>(231)</td>
</tr>
<tr>
<td>Irish</td>
<td>Male/female</td>
<td>?</td>
<td></td>
<td>? (120 kV)</td>
<td>(233)</td>
</tr>
<tr>
<td>Icelandic</td>
<td>Female</td>
<td>35–65</td>
<td>Spine: trab BMD</td>
<td>Toshiba 600 S (120 kV)</td>
<td>(234)</td>
</tr>
<tr>
<td>Italian</td>
<td>Male/female</td>
<td>30–80</td>
<td>Spine: trab BMD</td>
<td>Toshiba 600 S (120 kV)</td>
<td>(235)</td>
</tr>
<tr>
<td>Turkish</td>
<td>Male/female</td>
<td>10–70</td>
<td>Spine: trab and cort BMD</td>
<td>Siemens Somatom HiQ (85 kV)</td>
<td>(236)</td>
</tr>
<tr>
<td>Japanese</td>
<td>Female</td>
<td>20–85</td>
<td>Spine: trab BMD</td>
<td>Ge ProSeed EF (120 kV)</td>
<td>(237)</td>
</tr>
<tr>
<td>Chinese</td>
<td>Male/female</td>
<td>10–80</td>
<td>Spine: trab BMD</td>
<td>Siemens Somatom DR 3 (120 kV?)</td>
<td>(146)</td>
</tr>
<tr>
<td>Thai</td>
<td>Male/female</td>
<td>20–76</td>
<td>Spine: trab BMD</td>
<td>Siemens Somatom Plus (kV not provided)</td>
<td>(150)</td>
</tr>
<tr>
<td>Turkish</td>
<td>Female</td>
<td>20–80</td>
<td>Spine: trab BMD</td>
<td>GE 9800 Advantage (80 kV)</td>
<td>(238)</td>
</tr>
<tr>
<td>3D QCT of the spine and hip</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US (MrOS population)</td>
<td>Male</td>
<td>65–85</td>
<td>Neck: CSA total hip: int, trab, cort BMD and Vol L1 and L2: int, trab, cort BMD, compressive strength</td>
<td>Multiple scanners (80 kV)</td>
<td>(92)</td>
</tr>
<tr>
<td>Icelandic (subset of the AGES-REYKJAVIK study)</td>
<td>Male/female</td>
<td>67–93</td>
<td>Neck: int, trab, cort BMD, CSA, strength indices Trochanter: int, trab, cort BMD, strength indices</td>
<td>Siemens Volume Zoom (120 kV)</td>
<td>(93)</td>
</tr>
<tr>
<td>Single-slice pQCT of the forearm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swiss</td>
<td>Female</td>
<td>20–80</td>
<td>Radius: trab, BMD</td>
<td>Laboratory scanner</td>
<td>(239)</td>
</tr>
<tr>
<td>German</td>
<td>Male/female</td>
<td>20–80</td>
<td>Radius trab and int BMD</td>
<td>Stratec XCT900</td>
<td>(171)</td>
</tr>
</tbody>
</table>

(Continued)
population, together with some geometrical parameters. As with the spine, only a single slice through the neck has been analyzed \(^{(91)}\). Reference data for 3D QCT scans of the complete proximal femur have been published for the MrOS population \(^{(92)}\); however, they cannot be used to standardize a risk gradient as they do not contain data of younger (<65 yr) individuals. This is also true for the Icelandic 3D QCT reference data in the spine and the hip \(^{(93)}\). Table 4 also contains published reference data for pQCT of the forearm.

A performance measure of a densitometric technique for monitoring purposes is the monitoring time interval (MTI). It is calculated from the least significant change (LSC), which is defined as the change that can be measured with 95% confidence. Assuming Gaussian characteristics (two-tailed test) then for a two-point measurement:

\[
\text{LSC} = \frac{1}{1.96} \sqrt{2 \times CV^2 z^2} \]

where CV denotes the coefficient of variation of the technique. Tables 6 and 7 give in vivo precision values for QCT. LSC is given in percent. The MTI is defined as the time required between two measurements so that the change is equal to the LSC. It is calculated using the median longitudinal response rate of a cohort of subjects:

\[
\text{MTI} = \frac{\text{LSC}}{\text{median relative response rate}_{\text{long}}}
\]

To use a technique for monitoring purposes, its precision and the expected response rate of the measurement to the process to be monitored, e.g., a pharmaceutical intervention, must be known.

With respect to monitoring BMD with anti resorptive pharmaceutical treatment, DXA BMD changes often do not correlate closely with changes in fracture risk \(^{(10,11,95,96)}\). Thus, the value of monitoring BMD changes may be limited, irrespective of the technique used. However, this is not a topic of the current publication.

### Table 4 (continued)

<table>
<thead>
<tr>
<th>Population</th>
<th>Gender</th>
<th>Age range</th>
<th>Parameters</th>
<th>Scanner (voltage setting)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>Male/female</td>
<td>20–80</td>
<td>Radius: trab BMD</td>
<td>Stratec XCT960</td>
<td>(^{(157)})</td>
</tr>
<tr>
<td>German</td>
<td>Female</td>
<td>20–80</td>
<td>Radius: trab and int BMD</td>
<td>Stratec XCT960</td>
<td>(^{(159)})</td>
</tr>
<tr>
<td>Japanese</td>
<td>Female</td>
<td>20–80</td>
<td>Radius: trab and int BMD</td>
<td>Stratec XCT960</td>
<td>(^{(160)})</td>
</tr>
<tr>
<td>Japanese</td>
<td>Female</td>
<td>20–90</td>
<td>Radius: trab and tot BMD</td>
<td>Stratec XCT960</td>
<td>(^{(161)})</td>
</tr>
<tr>
<td>US (subset of Rochester Epidemiology Project)</td>
<td>Male/female</td>
<td>20–90</td>
<td>Radius: CSA, strength</td>
<td>Scanco Densican</td>
<td>(^{(198)})</td>
</tr>
</tbody>
</table>

### 3D pQCT of the forearm


### Single-slice pQCT of the tibia

| Italian (subset of the in CHIANTI study) | Male/female | 20–100 | Tibia: int, cort, trab BMD, int, cort area, max/min MoI, eccentricity index | XCT2000/Geanie Bonalyze software | \(^{(243)}\) |
Methodology


### Table 5

<table>
<thead>
<tr>
<th>Modality</th>
<th>Measurement location</th>
<th>Variable</th>
<th>Spinal fractures</th>
<th>Hip fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>DXA</td>
<td>Femur</td>
<td>BMD&lt;sub&gt;a&lt;/sub&gt;</td>
<td>1.9 (1.8–2.1) (244)&lt;sup&gt;*&lt;/sup&gt;</td>
<td>60 yr: 3.1 (2.4–3.9) (245)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>70 yr: 2.8 (2.4–3.2) (245)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80 yr: 2.3 (2.1–2.5) (245)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.4 (2.2–2.6) (244)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>PA BMD&lt;sub&gt;a&lt;/sub&gt; L1-L4</td>
<td>1.9 (1.8–2.0) (244)&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
<td>1.5 (1.3–1.7) (244)&lt;sup&gt;*&lt;/sup&gt;</td>
</tr>
<tr>
<td>Single-slice pQCT</td>
<td>Integral BMD</td>
<td>1.1&lt;sup&gt;**&lt;/sup&gt; (152)</td>
<td>2.6 (152)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trabecular BMD</td>
<td>1.2&lt;sup&gt;**&lt;/sup&gt; (152)</td>
<td>2.4 (152)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.3&lt;sup&gt;**&lt;/sup&gt; (84)</td>
<td>1.1&lt;sup&gt;**&lt;/sup&gt; (154)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cortical BMD</td>
<td>1.2&lt;sup&gt;**&lt;/sup&gt; (84)</td>
<td>1.6 (151)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cortical area</td>
<td>1.4 (151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radius diaphysis</td>
<td>1.5 (151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Radius metaphysis</td>
<td>2.0 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ultra-distal radius 4% site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-slice pQCT</td>
<td>Distal radius</td>
<td>1.5 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Trabecular BMD</td>
<td>1.6 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Relative cortical area</td>
<td>2.0 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Integral BMD</td>
<td>1.8 (21)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single-slice QCT</td>
<td>Spine</td>
<td>Trabecular BMD</td>
<td>2.3 (115)&lt;sup&gt;*&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6.9 (113)&lt;sup&gt;**&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.0 (21)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.2 (85)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.9 (246)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2.9 (84)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.4 (247)</td>
<td></td>
</tr>
<tr>
<td>3D QCT</td>
<td>Spine</td>
<td>Trabecular BMD</td>
<td>1.2 (117)</td>
<td></td>
</tr>
</tbody>
</table>

Relative risks or Odds ratios for QCT from the referenced publications have been standardized to DXA of the spine for vertebral and DXA of the femur for hip fractures according to the procedure described in section General Remarks on Diagnosis, Fracture Prediction, and Monitoring to using the risk gradients in the first two rows of this table (adapted from (94)).

<sup>*</sup>Prospective studies.
<sup>**</sup>Very high standardized Odds ratio for QCT (3.67) and very low for PA-DXA (1.54).

Most of the literature for QCT and pQCT covers the older, single-slice techniques for spine, forearm and tibia. However, it is likely that the newer volumetric techniques will soon replace the older techniques. Therefore, the approach taken in the evaluation of the pQCT/QCT technology is two-fold:

- To summarize the older techniques, which are important to the understanding of the potential of QCT (without a systematic and complete review of all available publications); and
- To systematically review the 3D QCT approaches.

In vitro studies, which provide insight into the relationship between BMD determined by QCT and bone strength, will also be summarized without a systematic review.

A systematic review was carried out for the following techniques:

- 3D QCT BMD measurements of the lumbar spine and the hip.
- The assessment of geometry and structure with QCT and pQCT.
- The use of finite element analysis in the spine, hip and forearm based on QCT data.
- pQCT BMD measurements of the forearm and the tibia.

We only evaluated studies in humans; animal studies were not included in the systematic review. Also, we did not include measurements in children, as this is the topic of another ISCD review and publication. Orthopedic applications, such as the quantification of BMD in the vicinity of prostheses, were also not considered. Furthermore, we only evaluated measurements at the skeletal locations in the list above, i.e., mandibular or alveolar measurements, or measurements in the calcaneus were not included. Papers in languages other than English were not included in the systematic review, but may be cited to support the evidence.

The methods used to develop and grade the ISCD Official Positions, are presented in the Executive Summary that follows.

---

**Table 6**
Short Term In Vivo Precision of Spinal Trabecular BMD as Measured by QCT

<table>
<thead>
<tr>
<th>Author</th>
<th>Technique</th>
<th>Cohort</th>
<th>Short-term precision CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genant (14)</td>
<td>Single-slice L1-L3?</td>
<td>n = ?, premenopausal females</td>
<td>1.6</td>
</tr>
<tr>
<td>Louis (104)</td>
<td>Single-slice L1-L3</td>
<td>n = 20</td>
<td>2.4</td>
</tr>
<tr>
<td>Steiger (16)</td>
<td>Single-slice T12-L3</td>
<td>n = 9, age = 21–73</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Single-slice L1 + L2</td>
<td></td>
<td>1.5</td>
</tr>
<tr>
<td>Gudmundsdottir  (234)</td>
<td>Single-slice T12-L3</td>
<td>n = 22, females</td>
<td>1.9</td>
</tr>
<tr>
<td>Lang (147)</td>
<td>3D QCT L1 + L2</td>
<td>n = 10, postmenopausal females</td>
<td>1.3–1.7</td>
</tr>
</tbody>
</table>

---

**Table 7**
In Vivo Precision of BMD Measurements of the Ultra-Distal Forearm and the Tibia by pQCT

<table>
<thead>
<tr>
<th>Author</th>
<th>Device</th>
<th>Cohort</th>
<th>Short-term precision CV (%)</th>
<th>Long-term precision CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Müller (249)</td>
<td>DensiScan 1000</td>
<td></td>
<td>−/−/0.3</td>
<td>1.7/0.9/0.8</td>
</tr>
<tr>
<td>Butz (171)</td>
<td>XCT900</td>
<td>n = 179, age = 20–79</td>
<td></td>
<td>1.6/0.9/0.8</td>
</tr>
<tr>
<td>Gumielmi (250)</td>
<td>XCT960</td>
<td>n = 386, age = 51</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grampp (84)</td>
<td>XCT960</td>
<td>n = 20, age = 31</td>
<td>0.9/1.5/1.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 20, age = 62</td>
<td>1.8/1.7/2.2</td>
<td></td>
</tr>
<tr>
<td>Hasegawa (193)</td>
<td>XCT960</td>
<td>n = 6, age =?</td>
<td>1.1/1.2/1.1</td>
<td></td>
</tr>
<tr>
<td>Tsurusaki (21)</td>
<td>DensiScan 1000</td>
<td>n = 5, age = 25</td>
<td>0.4/−/−/0.7</td>
<td></td>
</tr>
<tr>
<td>Ito (149)</td>
<td>DensiScan 1000</td>
<td>n = 22, age = 50</td>
<td>2.2/−/−/−</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>n = 27, age = 66</td>
<td>3.5/−/−/−</td>
<td></td>
</tr>
<tr>
<td>Rittweger (195)</td>
<td>XCT2000 radius</td>
<td>n = 26, age = 32</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>XCT2000 tibia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boutroy (72)</td>
<td>XtremeCT</td>
<td>n = 15, age = 21–47</td>
<td>0.9/1.7/1.0</td>
<td>3.0/3.2/2.8/1.2</td>
</tr>
</tbody>
</table>

---
accompanied this paper. In brief, all positions were rated by the Expert Panel on quality of evidence (Good; Fair; Poor: where Good is evidence that includes results from well-designed, well-conducted studies in representative populations; Fair is evidence sufficient to determine effects on outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; and Poor is evidence that is insufficient to assess the effects on outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or information), strength of the recommendation (A; B; C; where A is a strong recommendation supported by the evidence; B is a recommendation supported by the evidence; and C is a recommendation supported primarily by expert opinion) and applicability (worldwide = W or variable, according to local requirements = L). Necessity was also considered with a response of “necessary” indicating that the indication or procedure is “necessary” due to the health benefits outweighing the risk to such an extent that it must be offered to all patients and the magnitude of the expected benefit is not small.

In the following, we will present the ISCD Official Positions. We will first cover fracture prediction, treatment initialization, and monitoring separately for QCT of the spine and pQCT of the forearm. QCT of the proximal femur is a new and promising technique; however, due to the lack of reference data and insufficient evidence of fracture risk prediction, its use in clinical practice is premature. Also, the use of pQCT at the tibia cannot be recommended in clinical practice due to a lack of data.

In a third section, we present the ISCD Official Positions for quality control and reporting together for all skeletal sites. Table 8 gives a detailed overview of the published in vivo 3D QCT studies to determine BMD, BMC, and volume in the spine and the hip. Some studies also include geometrical and strength measurements. These will be discussed separately below. The table does not include predominantly technical studies describing the method (97–100), studies with reference data (92,93), studies in which patient groups with characteristics not primarily related to osteoporosis (101,102) were investigated, or studies in which only a single-slice was analyzed although a stack of images had been acquired with spiral QCT (91,103).

ISCD Official Positions: QCT of the Lumbar Spine

Technical Issues

ISCD Official Position

- With single-slice QCT, L1-L3 should be scanned; with 3D QCT L1-L2 should be scanned.
  Grade: Fair-B-W-Necessary

Rationale. Single-slice 8 mm–10 mm thick QCT and 3D QCT are equivalent techniques for assessing midvertebral trabecular BMD of the lumbar spine. In single-slice CT, the protocols most often used in newer studies include L1 to L3 (7,104–108) or L1 to L4 (84,85,109). Almost all reference data listed in Table 4 have been acquired for these three of four lumbar vertebrae. With single-slice QCT, T12 or L4 may be scanned as substitutes if one of the three vertebrae L1 to L3 is not assessable (16). For 3D QCT, the radiation exposure is higher than for single-slice QCT (see Table 3). As a consequence, in 3D QCT only two vertebrae (L1 and L2) are generally scanned. With 3D QCT, T12 or L3 may be scanned as substitutes if either L1 or L2 is not assessable.

Discussion. Single-slice 8 mm–10 mm thick QCT and 3D QCT are equivalent techniques for assessing midvertebral trabecular BMD of the lumbar spine; both techniques determine trabecular BMD in approximately the same volume, and the correlation between the two techniques is very high: Link et al. reported \( r^2 = 0.99 \) (110). Differences in precision are negligible (111). Thus, statements with regard to diagnosis, fracture prediction and monitoring apply similarly to both techniques. However, the techniques are not interchangeable as due to differences in the exact location and size of volume analyzed there is an absolute offset between the resulting trabecular BMD values (110,111).

In addition to the midvertebral trabecular VOL, 3D QCT allows for the analysis of several other VOIs, such as that of the total vertebral body, which is not comparable to the volume assessed in single-slice QCT. Further attention must be paid to the particular implementation of QCT protocols (e.g., by different manufacturers), minor differences exist among the single-slice QCT techniques: 8 mm or 10 mm slice thickness, 80 kV or 120 kV, differences in algorithms to determine trabecular BMD values. Consequently, precision of 3D QCT using two vertebrae in single-slice QCT) are accounted for by differences in the technique implemented. We therefore recommend the use of three vertebrae for single-slice QCT. For 3D QCT whole volumes are scanned instead of single-slices, so artifacts due to patient movement that may occur between the localizer and the tomogram in single-slice QCT are no longer relevant, and the analysis is not affected by such artifacts. Consequently, precision of 3D QCT using two vertebrae is comparable to precision of single-slice QCT using three or four vertebrae. The absolute trabecular BMD difference between the two techniques is also comparable to those of different implementations of single-slice QCT (see Table 7). In order to reduce the radiation exposure it is therefore advisable to scan two vertebrae only.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Study Duration (yr)</th>
<th>Population</th>
<th>Technique/Devices</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Black Path Study (125)</td>
<td>Postmenopausal osteoporotic females (with 93.3% other 6.7%)</td>
<td>1</td>
<td>A: PTH, age 69.4 ± 7.3, n=119</td>
<td>3D QCT: spine and hip GE 9800, analysis software UCSI, DXA: PA and L-spine, hip Hologic QDR 4500 or Delphi X-rays: lateral spine</td>
<td>RMD changes</td>
<td>A: PTH (1–84) 100μg daily sc. B: alendronate 10mg daily C: PTH (1–84) 100μg sc and alendronate 10mg daily All groups: 500 mg Calcium and 400 I.E. Vit. D daily</td>
<td>After year 1 3D QCT spine: Trab BMD: PTH = 25.5%, comb. +12.9%, alend +10.5%; increase sig higher in PTH than in comb and alend Int BMD: PTH = +6.5%, comb. +6.1%, alend. +4.6%; group diff** Cort BMD: PTH = +7.4% 3D QCT: Hip (similar results for total hip and neck) Trab BMD: PTH = +8.6%, smaller increases in comb and alend; group diff** Cort BMD: PTH = -1.7%, comb. 0.1%, alend +1.2% Cort Vol: PTH = +3.5%, comb. ns, alend ns; increase sig higher in PTH than in comb and alend DXA spine: Comparable to QCT int BMD results DXA hip: (comparable to neck): PTH 0.3%, comp 1.9%, alend 3%; no sign group diff</td>
<td>Publication does not contain cortical data for QCT</td>
</tr>
<tr>
<td>Baccarini Path Study (127)</td>
<td>First year as above second year: Group A (from year 1) split into groups A and B in year 2</td>
<td>2</td>
<td>A: alendronate, age 68.7 ± 7.4, n=59</td>
<td>3D QCT: spine GE 9800, analysis software UCSI, DXA: PA and L-spine, Hologic QDR 4500 or Delphi</td>
<td>A: PTH (1–84) 100μg daily sc. B: alendronate 10mg daily C: PTH (1–84) 100μg sc and alendronate 10mg daily All groups: 500 mg Calcium and 400 I.E. Vit. D daily</td>
<td>Groups A, B, C: alendronate 10 mg/daily All groups: 500 mg Calcium and 400 I.E. Vit. D daily</td>
<td>After year 2 3D QCT spine: Trab BMD: PTH/alen = +31%, comb/alen +11%, alend/alen +6% (p = 0.06), PTH/ placebo = +14% (that is decrease in year 2), PTH/alen increase sig higher than in other 3 groups 3D QCT hip (similar results for total hip and neck) Trab BMD: PTH/alen +13%, comb/alen +11%, alend/alen +4% (ns), PTH/placebo +4% (ns) (that is decrease in year 2) Cort BMD: PTH/alen = -3%, comb/alen +1% (ns), alend/alen -2%, PTH/placebo +3%, between group diff** Cort Vol: PTH/alen +6%, comb/alen +7%, alend/alen +6%, PTH/placebo +1% DXA spine: PTH/alen = -12%, comb/alen +8%, alend/alen +8%, PTH/placebo +4% (that is decrease in year 2), PTH/alen increase sig higher than in other 3 groups DXA hip: PTH/alen = +4%, comb/alen +3%, alend/alen +3%, PTH/placebo +6%, PTH/alen increase sig higher than in other 3 groups</td>
<td>For QCT publication only contains trabecular BMD data</td>
</tr>
<tr>
<td>Black Path Study (124)</td>
<td>Postmenopausal osteoporotic females</td>
<td>1</td>
<td>A: alendronate, age 70.0 ± 4.9, n=21</td>
<td>3D QCT: spine GE 9800, 80kV, 140mA, 1mm slice thickness, analysis software UCSI, DXA: PA and L-spine, Hologic QDR 4500</td>
<td>RMD changes of the spine 1D QCT: spine and comb BMD L1 + L2 (mg/cm²) QCT 10 mm midvertebral slice: trab and int BMD L1 + L2 (mg/cm²)</td>
<td>A:Raloxifene (RLX) 60 mg/day or 120 mg/day (data pooled from two treatment groups) B: Placebo All groups: 500 mg Calcium and 400-600 I.E. Vit. D daily</td>
<td>3D QCT spine: trab BMD: RLX +0.5%, placebo -2.4%, sig between group diff cort BMD: RLX +0.1%, placebo -0.8%, no sig between group diff QCT 10 mm midvertebral slice: trab BMD: RLX +0.1%, placebo -0.3%, no sig between group diff int BMD: RLX +1.0%, placebo -2.0%, sig between group diff DXA spine: RLX +1.5%, placebo +3.5%, no sig between group diff</td>
<td>3D QCT for measuring effects in small groups</td>
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<tr>
<td>Giannotto subset of MOPSI Study (126)</td>
<td>Postmenopausal females (no fsc: T-score hip, or spine, or neck &lt;−3 fsc: T-score &lt;−2.5)</td>
<td>1</td>
<td>A: PTH, age 66.4 ± 7.4, n=37</td>
<td>3D QCT: spine and hip Analysis software UCSI, DXA: PA and L-spine, hip Hologic QDR 4500</td>
<td>RMD changes 3D QCT: spine: Trab BMD L1 (mg/cm²), Hip: trab BMD: neck, trochanter; Total hip: comb and int BMD and int BMC: Total hip DXA: L-spine and hip (mg/cm²)</td>
<td>A: daily injections of 100 mg PTH (1–84) B: placebo</td>
<td>3D QCT PTH vs placebo: Spine: trab BMD: +36.7%, sig between group diff Hip trab BMD: neck +4.5%, trosh +4.3%, total hip +4.7% Total hip: cort VOY: BMD +4.7%, BMC +4.8%, Vol +0.0 DXA No separate results given for QCT subgroup</td>
<td>3D QCT was done at one site in a subset of 120 study patients Scanner type and model not provided Although vertebral fx were primary endpoints, RR for densitometric measurements not contained in manuscript</td>
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<tr>
<td>Greenspan (128)</td>
<td>1.5</td>
<td>2</td>
<td>A: Placebo age 64.5 ± 7.9 B: Placebo age 64.5 ± 7.9</td>
<td>3D QCT spine, hip Eclatcare PS 1440, 130 kV, 200 mAs, 3 mm slice thickness Custom analysis software</td>
<td>RMD changes of the spine 3D QCT: spine: Trab BMD L1 (mg/cm²), Hip: trab BMD: neck, trochanter; Total hip: comb and int BMD and int BMC: Total hip DXA: L-spine and hip (mg/cm²)</td>
<td>A: daily injections of 100 μg PTH (1–84) B: placebo</td>
<td>3D QCT PTH vs placebo: spine: trab BMD: neck +37.6%, sig between group diff Hip trab BMD: neck +4.5%, trosh +4.3%, total hip +4.7% Total hip: cort VOY: BMD +4.7%, BMC +4.8%, Vol +0.0 DXA No separate results given for QCT subgroup</td>
<td>3D QCT was done at one site in a subset of 120 study patients Scanner type and model not provided Although vertebral fx were primary endpoints, RR for densitometric measurements not contained in manuscript</td>
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<tr>
<td>Cindy (231)</td>
<td>n.a.</td>
<td>5</td>
<td>White females A: low trauma fresh neck fracture, age 70.1 ± 4.2, n=30 B: control group (age, height, weight-matched) no fracture, age 69.6 ± 3.9, n=18</td>
<td>3D QCT hip Healthcare PS 1440, 130 kV, 200 mAs, 3 mm slice thickness Custom analysis software</td>
<td>RMD discrimination using BMD differences 3D QCT: neck, trochanter: trab, comb, int BMD (mg/cm²), Vol (cm³)</td>
<td>Group diff (p-values): trab BMD neck 0.05, trab BMD trochanter 0.77, int BMD neck 0.07 head width 0.001, NAL 0.35, neck width 0.023</td>
<td>Low trauma defined as fracture resulting from fall from standing height or lower</td>
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<tr>
<td>Study</td>
<td>Participants</td>
<td>Methods</td>
<td>Findings</td>
<td>Notes</td>
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<td>Lang (2007)</td>
<td>Osteoporotic weight females: A: vertebral fracture, age 71.6 ± 4.1, n = 20; B: control group (age, height, weight-matched) no fracture, age 69.4 ± 5.1, n = 42;</td>
<td>DQCT: spine GE 9000, 80 kV, 140 mA, 3 mm slice thickness analysis software UCSF; DXA: PA and lat L-spine, hip Holologic QDR 4500</td>
<td>Discrimination using BMD differences: 3D QCT: trab and cort BMD L1 + L2 (mg/cm²) QCT 10 mm midvertebral slice: trab and int BMD L1 + L2 DXA: hip (g/cm²)</td>
<td>N/A</td>
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<td>Lang (2017)</td>
<td>White females: A: cervical hip fracture, age 74.3 ± 7.3, n = 34; B: trochanteric hip fracture, age 76.8 ± 7.0, n = 20; C: control group (age, height, weight-matched) no fracture, age 72.5 ± 7.0, n = 59;</td>
<td>DQCT: spine GE 9000, 80 kV, 140 mA, 3 mm slice thickness analysis software UCSF; DXA: hip Holologic QDR 4500</td>
<td>Discrimination in terms of RR: 3D QCT: trab and cort BMD L1 + L2 (mg/cm²) QCT 10 mm midvertebral slice: trab and int BMD L1 + L2 DXA: hip (g/cm²)</td>
<td>N/A</td>
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<td>Cheng (2022)</td>
<td>Chinese females &gt; age 65: A: atrumatic fresh hip fracture, age 74.7 ± 5.9, n = 45; B: controls, age 70.7 ± 4.7, n = 66;</td>
<td>DQCT hip GE CT Pro HU, 120 kV, 200 mAs, 3 mm slice thickness analysis software UCSF</td>
<td>Discrimination using BMD differences: 3D QCT: neck, trochanter, total hip: trab, cort, int BMD (mg/cm²), Vol (cm³)</td>
<td>N/A</td>
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<td>Lang (2023)</td>
<td>Italian females: A: vertebral fracture, age 76.1 ± 6.5, n = 26; B: Control group, age 71.5 ± 4.4, n = 45;</td>
<td>DQCT: spine GE 9000, 80 kV, 180 mA, 3 mm slice thickness Analysis software UCSF; DQCT: hip GE 9000, 120 kV, 150 mAs, 3 mm slice thickness Analysis software UCSF</td>
<td>Discrimination using BMD differences: 3D QCT: Spine: Trab and cort BMD L1 + L2 (mg/cm²) Hip: Trab cort int BMD total fem (mg/cm²) QCT 10 mm midvertebral slice: Trab and int BMD L1 + L2 DXA: PA-L-spine, hip (g/cm²)</td>
<td>N/A</td>
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<tr>
<td>Guglielmi (2014)</td>
<td>Control group from above was split into: A: subjects with degenerative changes 1.1.4 grade 0, n = 29; B: subjects with degenerative changes 1.1.4 grade 1, n = 22;</td>
<td>DXA: PA-L-spine, hip Norland XR-26</td>
<td>Group differences (degenerative changes) based on BMD: 3D QCT: spine: trab and cort BMD L1 + L2 (mg/cm²) Hip: trab cort int BMD total fem (mg/cm²) QCT 10 mm midvertebral slice: trab and int BMD L1 + L2 DXA: PA-L-spine, hip (g/cm²)</td>
<td>N/A</td>
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<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Study Duration (yr)</th>
<th>Population</th>
<th>Technique/Devices</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td>Hamton (255)</td>
<td>6</td>
<td>n.a.</td>
<td>Caucasian females with Turner Syndrome A: sub receiving Estrone replacement &gt; 75% of time since diagnosis, age 41 ± 1.4, n=54 B: sub receiving Estrone replacement &lt; 75% age 41 ± 2.0, n=16, female</td>
<td>3D QCT: spine GE Highspeed Advantage analysis software QCPro DXA: PA L-spine, hip Hologic QDR-4500A</td>
<td>Group differences (Estrone vs. age) based on BMD 3D QCT: trab BM1 L1 = L2 (mg/cm²) DXA: PA L-spine L2-4 (g/cm²)</td>
<td>n.a.</td>
<td>Sig group diff (p-values) for: 3D QCT spine: trab BMD 0.005 DXA: PA L-spine 0.0001</td>
<td>Retrospective combined analysis of cases and controls, which were recruited for different studies. Study population partly overlapped with study population from Rehm in Cases and controls were sig different in age and ysm.</td>
</tr>
<tr>
<td>Lian (256)</td>
<td>6</td>
<td>n.a.</td>
<td>Postmenopausal Caucasian females with low BMD, (DXA T-score &lt; −2) A: glucocorticoid treatment for 13.4 ± 12.0 years, mean dose 8.02 ± 4.8 mg, age 62.8 ± 10.3, n=63 B: controls no treatment, age 74.6 ± 4.13, n=120</td>
<td>1D QCT: hip GE 9800, 120kV, 280 mAs, 3mm slice thickness, controls: GE 9800, 80kV, 280 mAs, 3mm slice thickness analysis software UCSF DXA: hip Hologic QDR 4500</td>
<td>Group differences based on BMD 1D QCT: hip: trab, cort, int BMD (mg/cm²); cort Vol (cm³) group differences based on geometry 1D QCT: CSA neck, FAC DXA: hip (g/cm²)</td>
<td>n.a.</td>
<td>Group diff (p-values): 1D QCT: total hip: int BMD 0.0001, trab BMD 0.006, Cort BMD 0.001 neck: int BMD 0.0001, trab BMD 0.028, Cort BMD 0.001 trochanter: int BMD 0.0001, trab BMD 0.002, Cort BMD 0.001 total hip, neck, trochanter: cort vol 0.001, trab vol ns CSA and FAC ns DXA: total hip, neck and trochanter all 0.001</td>
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<td>Rehmann (257)</td>
<td>6</td>
<td>n.a.</td>
<td>Postmenopausal women with low BMD, (DXA T-score &lt; −2) and inflammatory disease A: vertebral fracture, age 72 ± 11, n=30 B: control group, age 62 ± 9.8, n=84</td>
<td>1D QCT: spine and hip GE 9800, 80kV, 3 mm slice thickness analysis software UCSF DXA: PA L-spine, hip Hologic QDR 1000 (n=51) and QDR 4500 (n=63) lateral spine X-rays, prevalent vertebral fracture defined as 20% or 4 mm height decrease</td>
<td>R discrimination using of BMD differences 1D QCT: spine: trab BM1 L1 = L2 (mg/cm²) hip: trab BMD total hip; int BMD total neck, neck; cort Vol (cm³) DXA: PA L-spine, hip (g/cm²)</td>
<td>n.a.</td>
<td>Group diff (p-values): 1D QCT: Trab BM1: spine 0.0003, total hip 0.01 Int BMD: total hip 0.007, neck 0.02, trochanter 0.007 Femoral neck BMD 0.02 DXA: spine 0.34, total hip 0.03, neck 0.14, trochanter 0.32</td>
<td>3D QCT hip performed in subgroup of 17 Fractured and 42 control subjects CART analysis: vertebral fracture threshold value of 65 mg/cm² for 3D QCT trab spine</td>
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<tr>
<td>Lang (258)</td>
<td>8</td>
<td>4-6 mo</td>
<td>Astronauts on ISS male (n=13), female (n=1), age 44.6 ± 4</td>
<td>3D QCT: spine and hip GE Highspeed Advantage, 80kV, 280 mAs, 3 mm slice thickness analysis software UCSF DXA: PA L-spine and hip Hologic QDR-4500</td>
<td>BMD-BMC changes during space flight 1D QCT spine L1+L2: trab BMD, int BMD 1D QCT hip: total hip, neck, trochanter, int, trab, cort BMD, BMC and Vol DXA: PA L-Spine L1+L1.4, 1.4 hip geometry changes during space flight 1D QCT spine: CSA strength parameter changes during space flight 1D QCT neck: CSA, bending (BIS) and compressive (CSI) strength indices</td>
<td>Space Flight</td>
<td>Sig % change/month 1D QCT spine: trab BMD -0.67, Int BMD -0.03 1D QCT total hip: trab BMD / BMC -0.001 to −1.9 to −2.4 cort BMD / BMC / Vol: −0.3 to −0.45 to −1.6 to −1.7 to −1.2 to −1.3 int BMD / BMC: −1.2 to −1.5 to −1.5 to −1 1D QCT Neck: BSI −2.6, CSI −2.3 DXA L-spine = 0.81 ns changes for: int Vol hip, CSA mid vertebral slice, CSA neck and trochanter</td>
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</table>

**Abbr:** cort, cortical; CSA, cross sectional area; diff, difference; fx, fracture; int, integral—trabecular and cortical; L-spine, lumbar spine L1-L4; ns, not significant; sig, significant; trab, trabecular; ysm, years since menopause.

*a*Study type: 1: Randomized controlled trial; 2: Non-randomized trial with contemporaneous controls; 3: Non-randomized trial with historic controls; 4: Cohort study; 5: Case-Control Study; 6: Cross-sectional study; 7: Surveillance (e.g., using databases or registries); 8: Series of consecutive cases.

*A, B, C… denote different study groups.*
Can QCT of the Spine be Used for Fracture Risk Assessment?

ISCD Official Position

- Spinal trabecular BMD, as measured by QCT, has at least the same ability to predict vertebral fractures as AP spinal BMD measured by central DXA in postmenopausal women. There is lack of sufficient evidence to support this position for men.

Grade: Fair-B-W-Necessary

Rationale. Age-adjusted standardized risk gradients can be calculated from a variety of cross-sectional studies in which PA-DXA and QCT of the spine have been determined in the same populations (Table 5). In all studies, QCT could predict spinal fractures as well as, or better than PA-DXA. In those studies that compared spinal fracture discrimination between total BMD as measured by posterior/anterior (PA)-DXA to trabecular BMD, as measured by QCT (7,84,113,114), the discriminatory capability of QCT was comparable to, or better than, that of DXA.

Discussion. In Table 5 there is good evidence that trabecular BMD as determined by QCT can be used to predict spinal fractures, although the evidence is not as strong as for DXA because, with only one exception (115), prospective studies have not been published for QCT. Two studies have examined other fractures in addition to vertebral fractures (85,116) but only the one from Bergot et al. reported odds ratios. In this publication standardized odds ratios for peripheral fractures (Colles’, clavicle, humerus, and metatarsals) were not significantly different for QCT and DXA. In the future, prospective fracture studies should include QCT so that the level of evidence can be improved.

ISCD Official Position

- There is lack of sufficient evidence to recommend spine QCT for hip fracture prediction in either women or men.

Grade: Good-A-W-Necessary

Rationale. There is only one cross-sectional study investigating the discrimination of hip fractures with spinal QCT compared to DXA of the hip (117). In this study, the performance of trabecular BMD as measured by spinal QCT was poorer than that of DXA of the hip. In another study, the relation between spinal QCT and hip fractures was investigated but relative risks or odds ratios were not given (118).

Discussion. In the study by Lang et al. (117), 3D QCT of the spine was performed. In addition to the elliptical VOI on which the statement is based, several other VOIs were measured. Using BMD of the total vertebral body increased the age-adjusted relative risk for hip fracture from 1.4 to 1.46. However, this VOI may not be comparable to the volume measured in single-slice QCT (see section on QCT technology). Also, the trochanteric and cervical fractures were assessed separately in the study. While BMD of the elliptical VOI measured in QCT was a better predictor of trochanteric vs all hip fractures (RR: 4.2 vs 1.7), this was also true for total femur BMD as measured by DXA (RR: 7.0 vs 3.9), so that the ratio of the logarithms of the two techniques differed by less than 10%. This statement also holds for trochanteric fractures.

Using the formulae explained in the Introduction on diagnosis, fracture risk and monitoring, the RR of 1.4 given by Lang et al. translates into an age-adjusted standardized risk gradient of 1.2, listed in Table 5. DXA of the hip is a much stronger predictor of hip fractures than DXA of the spine. Consequently, it would be of interest to compare the predictive value for hip fractures of DXA and QCT of the spine, but no published data are yet available to do this.

Can QCT of the Spine be Used to Diagnose Osteoporosis?

ISCD Official Position

- The WHO diagnostic classification cannot be applied to T-scores from measurements other than DXA at the femur neck, total femur, lumbar spine, or one-third distal (33%) radius because those T-scores are not equivalent to T-scores derived by DXA.

Grade: Good-A-W-Necessary

Rationale. The exclusive applicability of the WHO diagnostic classification to DXA is inherent in the definition. Thus, the absence of an equivalent classification for techniques other than DXA does not indicate problems of these techniques but a deficiency of the WHO classification. This limitation is historically understandable, since at the time of the formation of the WHO classification appropriate epidemiological data were only available for DXA. At the spine, T-scores measured with QCT are lower than those measured with DXA.

Discussion. T-scores define an age-independent threshold that depends on the mean BMD and standard deviation of the young normals of the DXA reference population. It is an intrinsic deficiency of the WHO definition that it cannot be adapted to other densitometric techniques, as standard deviation and age-related decline are different from that of DXA. Nevertheless, some studies comparing fracture discrimination between DXA and spinal QCT may be used to estimate a diagnostic threshold for spinal QCT comparable to a DXA T-score of −2.5.

Equivalent 75% sensitivity for spinal QCT and PA-DXA to discriminate vertebral fractures was shown to be 72 mg/cm³ (single-slice QCT of the spine) vs 855 mg/cm³ (PA-DXA L1-L4) (116). For these BMD values specificity for QCT was 48% vs 45% for DXA. A DXA T-score of −2.5 (equivalent to 795.6 mg/cm³) would correspond to an equivalent QCT T-score of −3.4 using reference data published for the scanner manufacturer (Siemens) and analysis mode (18) used in this study.
In a second publication (13), 78% sensitivity for spinal QCT to discriminate vertebral fractures was shown to be a trabecular BMD of 90 mg/cm\(^2\) (single-slice QCT of the spine). Using the reference data included in that paper a T-score of \(-3.1\) would result for QCT.

In a third publication (119), a 75% sensitivity for spinal QCT to discriminate vertebral fractures resulted in an equivalent T-score of \(-3.4\). The average of these three published QCT T-scores results in T-score of \(-3.3\) for spinal QCT.

The publication of Lafferty (116) is the only one directly comparing sensitivity and specificity of DXA and QCT for spinal fracture discrimination in the same population. The scaling factor of 0.93 = 795.6/855 that was used to normalize the DXA results to a T-score of \(-2.5\) was applied to the QCT BMD values and reported for the 75% sensitivity criterion of all three studies. This assumes that the relation between QCT and DXA of the spine is the same for all three populations. All three study groups were females with the exception of Lafferty’s, which also included 9% males.

Correlations (r-values) of trabecular BMD of the spine, as measured by QCT with spinal PA-DXA, are between 0.6 and 0.7 (84,85,107,113,116,120) in healthy females and between 0.5 and 0.6 in subjects with vertebral fractures. Correlations improve if, instead of the trabecular BMD, the integral vertebral BMD is used for QCT (84). This effect had also been observed in earlier studies using DPA instead of DXA (121).

In studies including DXA at other skeletal sites, correlations between QCT and PA-DXA were comparable (84,116) or slightly lower (113) to correlations between lateral and PA-DXA and to correlations between DXA of the spine and the femoral neck (84), although the standard error of the estimate of the correlation between QCT and DXA was higher than that of the correlations among DXA measurements (84).

In clinical practice with single-slice QCT of the spine trabecular BMD, thresholds of 120 mg/cm\(^2\) for osteopenia (equivalent to a DXA T-score of \(-1.0\)) and 80 mg/cm\(^2\) for osteoporosis (equivalent to a DXA T-score of \(-2.5\)) corresponding to equivalent T-scores of \(-1.5\) and \(-2.9\) have been suggested (122). Others indicated equivalent QCT T-scores of \(-3.8\) (123). The average of this expert advice results in a T-score of \(-3.4\).

Lafferty reported very similar specificities for DXA and QCT at 75% sensitivity. Most other authors who published ROC curves for the discrimination of spinal fractures reported larger area under the curve values for QCT compared to DXA (7,84,113,114). For 75% sensitivity in a UCSF study, specificities of 70% for QCT and 45% for PA-DXA were found (7,113). In the already cited study of Cann, which did not include DXA scans, for 78% specificity for QCT and 65% for PA-DXA were found (13). Thus, at a QCT T-score of \(-3.3\), which is sensitivity equivalent to a PA-DXA T-score of \(-2.5\), the QCT measurement should result in at least equivalent, but probably better specificity, for vertebral fracture than PA-DXA.

In the future, the WHO absolute fracture risk algorithm will supplement the diagnostic T-score criteria by utilizing age-dependent thresholds. In combination with additional clinical risk factors, this will enable clinicians to more accurately define diagnostic equivalence among densitometric techniques, for example by using age-dependent Z-scores or T-scores. Detailed population- and potentially region-specific algorithms still have to be developed (89), because the fracture incidence rates differ among populations. As described above, for densitometric techniques, the age-adjusted standardized risk gradients must be known, and these depend on reference data and therefore are population-dependent. Currently, exact values for the age dependent Z-scores to be used for diagnosis cannot be given. For example, for females Table 9 shows age dependent Z-scores for QCT derived from the recently published German guidelines (94). The values are calculated for a 20% 10-yr absolute fracture risk based on BMD and age for spine and hip fractures. The age-adjusted standardized risk gradients are taken from Table 5 and are averages for spine and hip fractures, i.e. for a measurement of trabecular BMD of the spine by QCT a risk gradient of (2.3 + 1.2)/2 = 1.75 was used. The resulting Z-scores are almost equivalent to those for AP-spine DXA but different from those for DXA of the hip, as the mean age-adjusted standardized risk gradient for spine and hip fractures is 2.15.

The use of absolute fracture risk will also improve comparability of methods. For example, the diagnostic threshold of a T-score of \(-3.3\) for spinal QCT is based on equivalent sensitivity between spinal DXA and QCT for prevalent vertebral fractures. However, due to a higher age-adjusted risk gradient for spinal QCT, the population identified with QCT using this T-score is at higher future fracture risk compared to the population identified by a T-score of \(-2.5\) with spinal DXA. This discrepancy will be largely reduced by the use of absolute fracture risk.

**Can QCT of the Spine be Used to Initiate Treatment?**

**ISCD Official Position**

- Central DXA measurements at the spine and femur are the preferred method for making therapeutic decisions and should be used if possible. However, if central DXA cannot be done, pharmacologic treatment can be initiated if the fracture probability, as assessed by QCT of the spine using device specific thresholds and in conjunction with clinical risk factors, is sufficiently high.

  Grade: Fair-B-W-Necessary

**Rationale.** As stated in section II, QCT of the spine can be used for prediction of spinal fractures. Thus, if spinal BMD as measured by QCT is sufficiently low, and additional risk factors are present, initialization of treatment is justified. However, at present this advice can only be based on expert opinion since currently there is insufficient scientific evidence to provide specific thresholds for QCT.

**Discussion.** The definition of a threshold to initiate treatment requires prospective studies, which for QCT are not yet available. According to expert opinion from Japan, the US, the United Kingdom, and Germany for Siemens QCT scanners,
a threshold for spinal trabecular BMD is 80 mg/cm³ without additional risk factors. This translates into a T-score of −2.9 using the German reference population (18). A T-score of −3.3 discussed in the section on diagnosis with QCT would result in an absolute BMD value of 70 mg/cm³ on Siemens scanners. Thus, to generalize this expert opinion to other CT manufacturers would result in a T-score threshold of around T = −3.0.

**Can QCT of the Spine be Used to Monitor Treatment?**

**ISCD Official Position**

- Trabecular BMD of the lumbar spine measured by QCT can be used to monitor age-, disease- and treatment-related BMD changes.
  Grade: Fair-B-W-Necessary

**Rationale.** An inspection of the reference data listed in Table 4 shows that between the ages of 25 and 75 yrs trabecular QCT BMD of the lumbar spine decreases between 1% to 1.2% (mean: 1.18%) annually, relative to the BMD value at the age of 25. During the menopause, the QCT BMD decrease is accelerated to about 1.8% to 2.2% relative to age 50. In postmenopausal women, the BMD decrease is reduced to 1.5% to 1.8% (mean: 1.67%). According to published data listed in Table 6, the precision of spinal trabecular BMD as measured by QCT, is between 1.3% and 2.4%, resulting in LSC between 3.3% and 6.6%. Consequently, with a 2% change, the MTI would be between 1.7 and 3.3 yr; for a 1% change the MTI would be twice as long.

As evident from Table 4, most publications on reference data also contain data for males. Age-related changes are smaller for males (mean: 0.91%) and there is no period of accelerated bone loss. Compared to age 25 yr, the reported annual BMD loss in males varies between 0.85% and 1.05%, resulting in an MTI of 5 to 6 yrs under the assumption of a 2% precision.

With respect to treatment, 3D QCT of the spine in women has been used successfully to monitor trabecular BMD in prospective studies of alendronate (124,125), raloxifene (126) and PTH (124,125,127,128) (see details in Table 8). Prospective studies using the older single-slice QCT approach have been reported for alendronate (129), calcitonin (130,131), calcium (132,133), estrogen (132,134–138), exercise (48), prednisone (139), PTH (138,140) and tibolone (141). In most of the studies, postmenopausal women were evaluated, although, premenopausal or early postmenopausal women have also been investigated (130,132,136,137,141,142). DXA of the spine (129,130,138,142) and of the hip (130,137,138,140,142) were also used in several of these studies. In men, prospective studies using the older single-slice QCT approach have been reported for alendronate/PTH (143), testosterone (144) and calcium (145).

**Discussion.** With a 2% precision and a 2% annual loss during menopause the MTI would be around 3 yrs. For fast losers, assuming a 4% annual BMD loss, the MTI would be halved (1.5 yrs). In postmenopausal women of older age with 1% annual BMD loss the MTI would be around 5 to 6 yrs, and for subjects loosing bone more quickly, e.g., at a rate of 2% per year, the MTI would be 3 yrs. These numbers are comparable with those suggested for DXA (146), for which precision errors are smaller by a factor of about two, but so are age-related DXA BMDa changes. Thus, spinal QCT is well suited for monitoring age-related bone loss. Three-dimensional QCT will probably have an advantage as precision is better than that for single-slice QCT (147).

The MTI should be calculated using long term precision errors, which are typically higher than short-term precision errors. Unfortunately, long-term precision errors have not yet been published for spinal QCT. In vivo precision is also affected by the age of the individuals who are scanned. For instance, Table 7 shows that for pQCT, significantly different precision errors were found for cohorts of healthy premenopausal, healthy postmenopausal, and osteoporotic women (148,149). In these two studies, the same effect was found for DXA and QUS and therefore it is likely that the effect will be the same in spinal QCT. Thus, compared to the MTI periods calculated above, in clinical practice in postmenopausal women periods may be longer by a factor of 1.5 to 2.

Reference data have been published for a variety of populations (Table 4). While there were significant differences in absolute BMD values, differences in age-related changes were small, and depended more on the regression models fitted to the data than on population differences (18,112,146,150).

In males, age-related bone loss is about 20% less than in females (146). As a result, the MTI for males is longer than for females. For elderly men, differences in decreases in BMD in the populations investigated in the studies listed in Table 4 are rather small, although absolute BMD differences exist, thus percent changes vary. No data have been published for males on the age dependency of the precision errors, but it is conceivable that in elderly men precision errors may also be higher than in younger men, thus extending the MTI by a factor of 1.5 to 2 in this older age group.

The long list of prospective treatment studies cited above demonstrates that QCT can be used for monitoring changes in spinal trabecular BMD with a variety of osteoporosis therapies, both anti resorptive bone protective, and bone enhancing, pharmaceutical compounds. There are fewer prospective treatment studies in men than in women and, as a consequence, the evidence that spinal QCT assessing midvertebral trabecular BMD can be used for treatment monitoring is weaker in men than in women.

**ISCD Official Positions: pQCT of the Radius**

**Can pQCT of the Radius be Used for Fracture Risk Assessment?**

**ISCD Official Position**

- pQCT of the forearm at the ultra-distal radius predicts hip, but not spine, fragility fractures in postmenopausal women.
There is lack of sufficient evidence to support this position for men.
Grade: Fair-B-W-Necessary

Rationale. Age-adjusted standardized risk gradients can be derived from four cross-sectional studies (151–154) in which DXA of the hip was also determined in the same populations (Table 5). In the studies, ultra-distal pQCT could predict hip fractures with an average age-adjusted standardized risk gradient of 1.85 for trabecular BMD and 1.75 for total BMD.

In Caucasian postmenopausal females (Table 5), two studies found that single-slice pQCT could not be used to predict vertebral fractures (84,152), whereas a third study found that pQCT could predict vertebral fractures (151). In Japanese postmenopausal females, one study using multi-slice pQCT found that vertebral fractures could be predicted from total and trabecular BMD of the distal radius (21).

Discussion. There is evidence that trabecular and total BMD of the ultra-distal radius as determined by single-slice QCT can be used to predict hip fractures (Table 5). The risk gradients are higher than those for spinal QCT and PA-spine DXA, but it remains to be shown whether this difference is significant. Single-slice pQCT can predict hip fractures as least as well as DXA of the spine, and better than QCT of the spine. Trabecular BMD may be the superior parameter to use as in one study the use of total BMD gave non significant results, although on average the fracture risk gradient for total BMD was still 1.75.

Corresponding data for multi-slice pQCT scanners have not yet been published; however, it is likely that BMD measured at the distal site using multi-slice scanners can also predict hip fractures because the ultra-distal slice measured in single-slice scanners is included in the distal site of multi-slice scanners.

Given the limited number of studies and their individual limitations, (e.g., different populations and different types of scanners (single vs multi-slice)), it is difficult to interpret the results for ultra-distal radial BMD for the purpose of predicting vertebral fractures. Additionally, the two studies that showed non significant results in Caucasian females were carried out in the United States, whereas the other study, which showed a significant discriminatory capability for vertebral fractures, was done in the United Kingdom, also perhaps indicating population differences.

Age-adjusted standardized risk gradients (Table 5) for ultra-distal BMD, as determined by multi-slice scanners for predicting vertebral fractures in the Japanese females, were significant but relatively low. In summary, in clinical practice the use of ultra-distal or distal pQCT is not advisable for the prediction of vertebral fractures. Further studies should explore whether the disparate results are due to different scanning techniques (single- vs multi-slice), differences in scan locations (ultra-distal vs distal), or differences between the populations studied.

Can pQCT of the Radius be Used to Diagnose Osteoporosis?

ISCD Official Position

- The WHO diagnostic classification cannot be applied to T-scores from measurements other than DXA at the femur neck, total femur, lumbar spine or one-third (33%) radius because those T-scores are not equivalent to T-scores derived by DXA.

Grade: Good-A-W-Necessary

Rationale. See Rationale on QCT above.

Discussion

In principle, BMD as measured by pQCT at the ultra-distal forearm, can be used to identify patients at very high and low risk of fracture. However, the pQCT T-score thresholds that stratify these groups strongly depend on the reference population selected. Specific absolute BMD threshold values are not available. Data on equivalent sensitivities for prevalent fracture discrimination have not been published for pQCT, although in principle, data should be available from studies comparing fracture discrimination among techniques (21,148,151,152). More importantly, due to the smaller age-related changes of pQCT compared to DXA (see Fig. 3), a sensitivity equivalent fracture prevalence threshold would result in a pQCT T-score considerably higher than −2.5. Simultaneously, the age-adjusted standardized risk gradient for pQCT is smaller than for DXA (see Table 5), so that the population identified using a hypothetical pQCT equivalent T-score would have a much lower future fracture risk compared to that identified with DXA.

Because of this dilemma, Clowes et al. (155) introduced the concept of a dual threshold. At the lower pQCT threshold, there is 95% certainty that a subject has osteoporosis below that threshold; at the upper threshold there is 95% certainty that a subject does not have osteoporosis above that threshold. In contrast to Lafferty et al. (116), who based their analysis on discrimination of prevalent fractures, Clowes et al. based their analysis on discrimination of a DXA hip T-score of −2.5, so that the lower threshold defines a WHO specificity equivalent relative risk threshold for pQCT. This approach reliably identifies subjects only at very high or at very low risk of fracture.

For radial BMD measured by pQCT at the 4% site (Stratec XCT 2000), a low threshold of T = −2.84 and a high threshold of T = −1.35 was calculated, based on a young normal reference population of 100 premenopausal women (age 20–40) also recruited in the study (155). In contrast, using the NHANES III reference data for hip DXA and manufacturer-specific reference population data for pQCT, resulted in thresholds of T = −4.5 and T = −2.7, respectively. This imposes severe limitations for pQCT application to clinical diagnosis of osteoporosis as it remains unclear which thresholds should be used. The young-normal BMDa hip T-score from the NHANES study is equivalent to a BMD of...
0.642 g/cm², whereas Clowes et al. reported the −2.5 T-score of their reference population to be equal to 0.694 g/cm², which is an 8% difference, whereas the pQCT thresholds differed by about 35%. The threshold dependence on the selected reference data set was also observed for the other peripheral techniques included in the study, but for most other techniques the dependence was less than for pQCT.

When compared to DXA of the hip, using the two threshold approach, pQCT correctly (with 95% confidence) identified 60% of subjects being above or below the DXA T-score = −2.5 threshold, thus a measurement of pQCT would suffice to identify individuals at very high or low future fracture risk. For the remaining 40% of subjects with T-scores between the two thresholds, pQCT would not be a suitable method to use for diagnosis. Using lower confidence levels increased the percentage of subjects (82% at 80% confidence) that could be identified by pQCT.

In clinical practice, the approach suggested by Clowes et al. is limited by the choice of the young-normal reference population, which may result in larger differences for the two T-score thresholds to be defined. Without definitive threshold values being specified the concept can not be applied in clinical practice.

As discussed earlier, the problem with diagnostic equivalence for peripheral bone densitometry techniques will be greatly reduced with the introduction of the fracture risk concept. Table 9 also includes Z-scores for 20% 10-yr absolute fracture risk that is based on the mean age-adjusted risk standardized gradients derived from the values in Table 5. Otherwise, the same comments as made in the corresponding statement for QCT, where the use of Z-scores for spinal QCT was discussed, apply to pQCT.

### Table 9

<table>
<thead>
<tr>
<th>Age</th>
<th>DXA spine</th>
<th>DXA hip</th>
<th>QCT spine trab BMD</th>
<th>Single-slice pQCT ultra-distal forearm tot BMD</th>
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<td>50</td>
<td>−3.3</td>
<td>−2.5</td>
<td>−3.6</td>
<td>−4.1</td>
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<td>−2.5</td>
<td>−1.9</td>
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<td>−1.3</td>
<td>−1.8</td>
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<td>−0.8</td>
<td>−0.9</td>
<td>−0.9</td>
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<td>70</td>
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<tr>
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<td>0.4</td>
<td>0.8</td>
<td>1.0</td>
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<td>80</td>
<td>1.6</td>
<td>0.9</td>
<td>1.4</td>
<td>1.5</td>
</tr>
</tbody>
</table>

The model included age and BMD (see text).

### Can pQCT of the Radius be Used to Initiate Treatment?

**ISCD Official Position**

- Central DXA measurements at the spine and femur are the preferred method for making therapeutic decisions and should be used if possible. However, if central DXA cannot be done, pharmacologic treatment can be initiated if the fracture probability, as assessed by pQCT of the radius using device specific thresholds and in conjunction with clinical risk factors, is sufficiently high.
  
  Grade: Fair-B-W-Necessary

**Rationale.** As stated in Methodology, pQCT of the ultra-distal radius can be used for the prediction of hip fractures. Thus, if BMD as measured by pQCT, is sufficiently low and additional risk factors are present, initialization of treatment is justified. However, at present this advice can only be based on expert opinion since currently there is insufficient scientific evidence to provide specific thresholds.

**Discussion**

For adults, there is even less evidence for using pQCT than QCT for the specification of treatment initialization thresholds. This is to be expected as pQCT is less widely and frequently used than central QCT. Larger numbers of pQCT scanners are only in use in Japan and Germany thus, overall expert opinion is sparse. Even among the authors of this article, agreement on a BMD treatment initialization threshold was not achieved.

### Can pQCT of the Radius be Used to Monitor Treatment?

**ISCD Official Position**

- Trabecular and total BMD of the ultra-distal radius measured by pQCT can be used to monitor age-related BMD changes.
  
  Grade: Fair-B-W-Necessary
Rationale. Female reference data for the full age range have been published in six studies (Table 4). These data indicate that in adult Caucasian and Asian women there is no, or little, change in trabecular and total BMD until the age of 40 yrs or, depending on the particular model used to fit the data, even until the onset of the menopause at around 50 yrs. In addition to the studies listed in Table 4, age-related BMD changes in the forearm have been investigated in detail in several other studies in which the analysis has often been carried out separately for pre-, peri- and postmenopausal periods (see Table 10).

In elderly postmenopausal women, ultra-distal trabecular BMD decreases by about 1% to 1.5% annually relative to the BMD at age 50; total BMD decreases by about half the value. As shown in Table 7, published precision values of pQCT for determining BMD are between 1% and 2%, resulting in an LSC between 2.8% and 5.5%. Accordingly, for a 1.5% change the MTI would be between 1.9 and 3.7 yrs, for a 1.0% change the MTI would be between 2.8 and 5.5 yrs. During the menopause, the data shown in Table 10 indicate a more rapid bone loss.

Male reference data for the full age range have been published in three studies (Table 4), but the European study (157) does not contain data on total BMD. After the age of 50, the annual decline of trabecular BMD of the ultra-distal cortex in the three studies varies from 0.5% to 0.6%, relative to the BMD at age 50.

Although prospective studies of pQCT for monitoring treatment in women at the ultra-distal radius have been reported for alendronate (159), calcium (160–162), estrogen (163), estrogen/calcium (164), fluorides (165,166), parathyroid hormone (PTH) (166), vitamin D (167) and vibration training (168) (see Table 11) in general, monitoring at the spine or hip is superior to monitoring with pQCT at the forearm. Cross-sectional studies investigating treatment have also been reported for teriparatide (169).

Discussion

For monitoring age-related changes of trabecular bone during the early menopause a MTI of about 1.5 yrs can be achieved if a precision of 1% can be obtained, but the MTI

### Table 10

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study type</th>
<th>Study duration (yr)</th>
<th>Ethnicity</th>
<th>Sample size</th>
<th>Mean cohort age</th>
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<th>Cortical BMD</th>
<th>Total BMD</th>
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<td></td>
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<td>Change/yr</td>
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<td>39</td>
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<td>—</td>
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<td>Japanese</td>
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<td>56</td>
<td>— -3.53</td>
<td>—</td>
<td>—</td>
<td>-2.63</td>
<td>DensiScan 1000</td>
</tr>
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<tr>
<td></td>
<td>2</td>
<td>Japanese</td>
<td>38</td>
<td>62</td>
<td>— -2.45</td>
<td>—</td>
<td>—</td>
<td>-1.58</td>
<td>DensiScan 1000</td>
</tr>
<tr>
<td>Ito (170)</td>
<td>2</td>
<td>Japanese</td>
<td>38</td>
<td>62</td>
<td>— -2.45</td>
<td>—</td>
<td>—</td>
<td>-1.58</td>
<td>DensiScan 1000</td>
</tr>
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<td>1</td>
<td>Cauc.</td>
<td>126</td>
<td>187 -0.46</td>
<td>—</td>
<td>—</td>
<td>356 -0.44</td>
<td>XCT960</td>
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<tr>
<td>Guglielmi (241)</td>
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<td></td>
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<tr>
<td>Qin (259)</td>
<td>2</td>
<td>Chinese</td>
<td>179</td>
<td>54</td>
<td>214 -2.21</td>
<td>1358 -0.85</td>
<td>548 1.77</td>
<td>XCT960</td>
<td></td>
</tr>
</tbody>
</table>

For better comparison, values were recalculated from the cited references and refer to age 30 for premenopausal and age 50 for peri- and postmenopausal women.

*Study type: 1: cross sectional; 2: longitudinal; *ns (adapted from [156]).
increases significantly at older ages. The goal of high precision favors multi-slice scanners for monitoring (22).

For elderly postmenopausal women, the data in Table 10 indicate either a higher bone loss in Asian than in Caucasian women, or a difference due to scanner type. In a large European study (157), there were no differences in absolute BMD values between the Densiscan (Scanco Medical, Zürich, Switzerland) and the Stratec XCT900 scanners after a standardized calibration. Thus there should be no differences between the two types of scanners when assessing age-related changes.

For a 1.5% precision and a 1% annual change, a MTI of approximately 4 yrs is required; for a 2% annual change, a MTI of approximately 2 yrs will result. However, as already discussed for spinal QCT, the precision error increases with advancing age. In clinical practice this effect increases the MTI by a factor of 1.5 to 2 in elderly people compared to the numbers calculated in younger populations.

Several studies in females have compared age-related changes of BMD of the ultra-distal forearm site by pQCT with that of DXA (84,149,170). Two studies found higher age-related changes in the total ultra-distal BMD<sub>a</sub> as measured by DXA or single-energy photon absorptiometry (SPA), than for trabecular BMD as measured by pQCT (84,157), whereas Ito et al. found comparable, or in perimenopausal women even slightly higher, loss rates for pQCT (149,170).

To date, reference data for men have only been published for European populations. Total BMD data were included in the two studies investigating the German population (158,171). In these two studies decline of total BMD was comparable to the decline of trabecular BMD. As the age-related change declines after age 50 from the two German studies are very similar to the European study, it is conceivable that the values for total BMD can be generalized and should be applicable to Caucasian men. For a 1.5% precision and a 0.5% annual change a MTI of approximately 8 yrs is required, for a 1% annual change, the MTI will be approximately 5.5 yrs.

The assessment of the use of pQCT for monitoring intervention related BMD changes is difficult for a number of reasons. In general, the use of the forearm to monitor interventions is still controversial (172,173). For example, in a sub-study of the large multi-center alendronate intervention trial, forearm DXA was not effective in monitoring therapy (174). The Fracture Intervention Trial (FIT) showed a 50% wrist fracture reduction in the alendronate treatment group accompanied by a 1.5% increase in distal forearm BMD<sub>a</sub> vs controls as measured by DXA. However, in the same trial, the 50% hip fracture reduction was accompanied by a 4.7% increase in total femur BMD<sub>a</sub> also determined by DXA (175). Using forearm DXA incremental treatment effects were reported withibandronate (176), tibolone (177), calcitomin (178), and teriparatide (169).

Some prospective pQCT studies exist which demonstrate that in women BMD change after intervention can be monitored (Table 11). However, the design of the studies was quite diverse and several parameters, such as trabecular, cortical or total BMD, and in some also BMC, were measured. Uncertainty about the comparability and consistency of anatomical locations (ultra-distal vs distal) remains when pooling the studies in Table 11. Currently, there is only one prospective study of pQCT in men, which investigated trabecular BMD changes of the radius with and without testosterone treatment in hypogonadal men (179).

Only some of the studies listed in Table 11 also included DXA measurements of the spine or the hip but not of the forearm (159,161—163,166,168). The study of Schneider et al. (159) confirmed that for alendronate, pQCT was less suitable for monitoring BMD changes when compared to central DXA techniques. The other studies showed some disparity between DXA and pQCT results, but the duration of most studies listed in Table 11 was rather short and the number of subjects relatively small and, therefore, the studies lack power. As a consequence, direct comparison between DXA and pQCT for monitoring purposes cannot be made based on the data currently available.

Most of the studies listed in Table 11 reported trabecular and cortical BMD, and some also total BMD. Whether total or trabecular BMD at the ultra-distal site is more appropriate for monitoring cannot be deduced from these data. Therefore, the parameter (trabecular, cortical, or total BMD) that is predicted to be most responsive to a particular treatment should be used. The use of cortical BMD at the ultra-distal site is problematic due to partial volume artifacts as discussed below.

ISCD Official Positions: What are the Quality Assurance and Quality Control (QA/QC) Criteria for QCT and pQCT?

**ISCD Official Positions**

- For QCT and pQCT bone density measurements from different devices cannot be directly compared.
  
  Grade: Good-A-W-Necessary

- For QCT and pQCT, different devices should be independently validated for fracture risk prediction by prospective trials or by demonstration of equivalence to a clinically validated device.
  
  Grade: Good-B-W-Necessary

- For QCT and pQCT device-specific education and training should be given to the operators and interpreters prior to clinical use.
  
  Grade: Good-A-W-Necessary

- Quality control procedures should be performed regularly.
  
  Grade: Good-A-W-Necessary

**Discussion**

For QCT of spine and hip the following steps are strongly recommended to ensure the quality of the CT acquisition and analysis:

- In vivo precision of new QCT techniques must be established. However, due to radiation considerations it is not recommended to reconfirm in vivo precision for each
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Study Duration (y)</th>
<th>Population</th>
<th>Technique/Devices</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>pQCT radius</td>
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<tr>
<td>Sawka (163)</td>
<td>1 1</td>
<td>Postmenopausal Japanese females</td>
<td>A: HRT, age 53.4 ± 9.7, n=10 B: control, age 54.7 ± 3.2, n=10</td>
<td>DXA: lumbar</td>
<td>BMD changes of the spine and the forearm</td>
<td>A: conjugated estrogen 0.625 mg + 600 mg Ca daily; B: 600 mg Ca daily</td>
<td>% BMD changes from baseline: A: pQCT: trab BMD = 0.7% (ns), cort BMD = 1.8% (ns)\nDXA: trab BMD = 1.88%, cort BMD = 0.7% (ns)\nDXA: trab BMD = 1.88%, cort BMD = 0.7% (ns)</td>
<td>A third group consisted of subjects that were given Ca and/or estrogen in addition to DMPA due to ethical reasons, c.g., if large BMD decrease was observed during the study</td>
</tr>
<tr>
<td>Merki-Feld (184)</td>
<td>1 2</td>
<td>Healthy Caucasian premenopausal females</td>
<td>A: age 40.4 ± 2.2, n=16 B: control, age 37.4 ± 5.5, n=10</td>
<td>DXA: lumbar</td>
<td>BMD changes</td>
<td>A: Depot medroxyprogesterone acetate (DMPA) 150mg every 12 weeks</td>
<td>% BMD changes from baseline: A: pQCT: trab BMD = 0.6% (ns), cort BMD = -0.1% (ns)\nB: pQCT: trab and cort BMD = ns.</td>
<td></td>
</tr>
<tr>
<td>Fujita (181)</td>
<td>1 0.3</td>
<td>Pre- and postmenopausal Japanese females</td>
<td>A-C: different types of Ca\nA: age 60 ± 4, n=10\nB: age 55 ± 2, n=11\nC: age 53 ± 2, n=11 B: control, age 50 ± 5, n=6</td>
<td>DXA: lumbar</td>
<td>BMD changes of the spine and the forearm</td>
<td>A: AAA Ca: Oyster shell heated under reduced pressure with alginate gradient\nB: AAA Ca: same as A but no alginate\nC: CaCO3\nD: Placebo A-C: 900 mg daily</td>
<td>% BMD changes from baseline: A: pQCT: trab BMD = 0.6% (ns) Cort BMD as DXA: L-spine n.s\nB-C: no significant changes for any parameter</td>
<td>Baseline age and BMD values were different among groups</td>
</tr>
<tr>
<td>Schneider subset of the FOST study (139)</td>
<td>1 12</td>
<td>Postmenopausal white females</td>
<td>A: Adenotome age 61.8, n=51 B: control, age 60.8, n=52</td>
<td>DXA: lumbar</td>
<td>BMD changes of the spine and the forearm</td>
<td>A: adrenotome 10mg + 500 mg Ca daily; B: placebo 500 mg Ca daily</td>
<td>% BMD changes from baseline: A: pQCT: trab BMD = 5.5% (ns), tot BMD 6.5%, BSID = 10.9% (ns), BSID prox -2.4% (ns)\nDXA: L-spine = 5.5%, neck =13.4%\nB: pQCT: trab BMD = -2.7% (ns), tot BMD 0.6% (ns), BSID = -4.0% (ns), BSID prox =-3.2% (ns)\nDXA: trab BMD = 8.2%, neck 9.2% (ns)\nsig. group differences at 12 month for pQCT tor BMD, BSID n.s (p = 0.01) and DXA spine and hip</td>
<td></td>
</tr>
<tr>
<td>Reeve (166)</td>
<td>2 2</td>
<td>White females with 2 l vert fr</td>
<td>A: PTH - hreton, age not provided, n=12 B: NAF, age not provided, n=12</td>
<td>DXA: lumbar</td>
<td>BMD changes of the spine and the forearm</td>
<td>A: Parathyroid peptide (PTH) 1-34 sc daily (in first study year) + estrogen or randomised decanoate (after month 4 till end of study)\nB: NAF = calcium (for complete two year period</td>
<td>% BMD changes from baseline: A: pQCT: trab BMD = -15.5% (ns)\nQCT = 3.5%\nB: pQCT: trab BMD = +3.5% (ns)\nQCT = -5.5%</td>
<td>Groups were not matched, no comparison was performed</td>
</tr>
<tr>
<td>Dambacher (165)</td>
<td>2 3</td>
<td>Postmenopausal Caucasian females with 1 vert fr</td>
<td>A: NAF, age 65.0 ± 2.1, n=15 B: control, age 68.2 ± 1.7, n=14</td>
<td>DXA: lumbar</td>
<td>BMD changes of the spine and the forearm</td>
<td>A: NAF 80mg daily B: untreated</td>
<td>% BMD changes from baseline: A: radii trab BMD = 4% trab: BMD no change B: radii trab BMD = -3% trab: BMD = 18% trab of the tibia but not for total BMD of the radius</td>
<td>Trabecular BMD of the radius was also measured and decreased in both groups but significance and group comparison not provided</td>
</tr>
<tr>
<td>Prince (162)</td>
<td>6 n.a.</td>
<td>Australian females age 75 years at the end of a five year study</td>
<td>A: Calcium, age 80.3 ± 2.7, n=730 B: placebo, age 80.1 ± 2.7, n=730</td>
<td>DXA: lumbar</td>
<td>Group differences</td>
<td>A: 600 mg Ca twice daily, placebo</td>
<td>Group diff (p-values): pQCT: sign differences: cort area = (0.001), SI = (0.01)\nDXA: sign differences: neck BMD = (0.001), neck area (0.05)</td>
<td>The study is a 5 year randomised placebo controlled study but pQCT results were only reported from the end of the study and so here DXA results are also given for the last measurement, only</td>
</tr>
<tr>
<td>Zucchetti subset of the fracture prevention trial (169)</td>
<td>6 n.a.</td>
<td>Postmenopausal females with 21 moderate or mild vert fracture</td>
<td>A: PTH, age 57.5 ± 5.6, n=28 B: PTH, age 97.5 ± 5.8, n=28 C: control, age 68.3 ± 7.3, n=35</td>
<td>DXA: lumbar</td>
<td>Group differences</td>
<td>A: teriparatide 20ug daily sc\nB: teriparatide 40ug daily sc\nC: placebo\nAll groups: 400 mg Calcium and 400 IE Vit D daily</td>
<td>Group diff (p-values): pQCT: trab BMD and cort area: sig. increases of A and B vs C\nCort and cort BMD: sig. diff of A and 3 vs C\nCSMI; sig. increase of A and B vs C\nPercent circ: sig. increase of A and B vs C</td>
<td>pQCT measurements were performed at 18 mo time point</td>
</tr>
<tr>
<td>Study Authors</td>
<td>Category</td>
<td>Group 1</td>
<td>Group 2</td>
<td>Description</td>
<td>BMD Changes Before and After Treatment</td>
<td>Before Treatment</td>
<td>Notes</td>
<td></td>
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</tr>
<tr>
<td>Dambacher</td>
<td>1: Randomized controlled trial</td>
<td>55 males with primary (p) and secondary (s) hypogonadism</td>
<td>4 treatment groups</td>
<td>A: age 34.5 ± 3.9; n=4, p=9</td>
<td>Decrease trab and cort BMD</td>
<td>trab BMD declined by 6.6% annually; cort BMD by 1.7%</td>
<td>trab BMD was stable; cort BMD declined by 0.24% annually</td>
<td></td>
</tr>
<tr>
<td>Schubert</td>
<td>2: Non-randomized trial with contemporaneous controls</td>
<td>15 females with radial trabecular and cortical</td>
<td>BMD changes before and after treatment</td>
<td>trab BMD declined by 6.6% annually; cort BMD by 1.7%</td>
<td>trab BMD was stable; cort BMD declined by 0.24% annually</td>
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<tr>
<td>Rüegger</td>
<td>3: Non-randomized trial with historic controls</td>
<td>1.6 Postmenopausal females</td>
<td>BMD changes before and after treatment</td>
<td>trab BMD declined by 6.6% annually; cort BMD by 1.7%</td>
<td>trab BMD was stable; cort BMD declined by 0.24% annually</td>
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</tr>
<tr>
<td>Ritmeyer</td>
<td>4: Cohort study</td>
<td>36 young healthy males with bedrest</td>
<td>Laboratory multi-slice pQCT: distal radius</td>
<td>trab BMD declined by 6.6% annually; cort BMD by 1.7%</td>
<td>trab BMD was stable; cort BMD declined by 0.24% annually</td>
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</table>

**Abbr:** cort, cortical; CSA, cross sectional area; diff, difference; fx, fracture; int, integral—trabecular and cortical; L-spine, lumbar spine L1-L4; ns, not significant; sig, significant; trab, trabecular; ysm, years since menopause.

*a*Study Type: 1: Randomized controlled trial; 2: Non-randomized trial with contemporaneous controls; 3: Non-randomized trial with historic controls; 4: Cohort study; 5: Case-Control Study; 6: Cross-sectional study; 7: Surveillance (e.g., using databases or registries); 8: Series of consecutive cases.

*A, B, C...* denote different study groups.
clinical facility. Instead, precision of acquisition should be established with phantom data; analysis precision should be established by re-analysis of patient data.

- The scanner stability should be controlled longitudinally by scanning a quality assurance (QA) phantom at least once a week whenever patients are to be scanned.
- The scan protocol must be kept constant for all visits of an individual patient.

**How Should QCT and pQCT be Interpreted and Reported?**

**ISCD Official Position**

- For QCT and pQCT the report should combine the following standard elements:
  - Date of test
  - Demographics (name, date of birth or age, sex)
  - Requesting provider
  - Names of those receiving copy of report
  - Indications for test
  - Manufacturer and model of instrument and software version
  - Measurement value(s)
  - Reference database
  - Skeletal site/region of interest
  - Technical quality of test
  - Limitations of the test including a statement that the WHO diagnostic classification cannot be applied to T-scores obtained from QCT, pQCT, QUS, and pDXA (other than one-third (33%) radius) measurements
  - Clinical risk factors
  - Fracture risk estimation
  - A general statement that a medical evaluation for secondary causes of low BMD may be appropriate
  - Recommendations for follow up imaging

For QCT the report should include the following technical elements:

- Tomographic acquisition and reconstruction parameters
  - kV
  - mAs
  - collimation during acquisition
  - table increment per rotation
  - table height
  - reconstructed slice thickness
  - reconstruction increment
  - reconstruction kernel

- Analysis parameters
  - Name of analysis program
  - Version of analysis program
  - Analysis Date

For pQCT the report should include the following technical elements:

- Tomographic acquisition and reconstruction parameters
  - reconstructed slice thickness

- single/multi-slice acquisition mode
- length of scan range in multi-slice acquisition mode

- Analysis parameters
  - Name of analysis program
  - Version of analysis program
  - Analysis date

  Grade: Fair-C-W-Necessary

**Rationale and Discussion**

The report should contain two sections: the first should list the important clinical information, and the second the technical information that includes the tomographic acquisition and reconstruction parameters. These parameters should be kept constant from visit to visit: thus it is essential to list them on the report so that potential deviations can be easily detected.

**ISCD Official Position**

- For QCT and pQCT, the report may include the following optional item:
  - Recommendations for pharmacological and non-pharmacological interventions.

  Grade: Fair-C-W

**Rationale and Discussion**

According to the ISCD Official Positions listed above, in principle treatment initialization with QCT at the spine and pQCT at the forearm is possible. Recommendations for treatment should be an optional item in the report as is the case for central DXA.

**Additional Questions for Future Research**

**The Need of Prospective Studies**

For central QCT of the spine, and to a lesser extent for pQCT of the radius, prospective studies are required to determine the capability of trabecular BMD to predict fracture risk with a higher level of evidence. The following questions should be addressed:

- What is the relative risk for vertebral fractures for a decrease of trabecular BMD measured at the spine, hip, or forearm?
- What is the relative hip fracture risk for a decrease of trabecular BMD measured at the spine, hip, or forearm?
- Are there subvolumes of interest, e.g., the neck or the trochanter for which the relative risk per standard decrease in trabecular BMD is higher than for other subvolumes?

**The Need for Treatment Thresholds**

As shown above, evidence for treatment thresholds for QCT is low and for pQCT does not exist. Thus the following questions should be investigated:

- What are treatment initialization thresholds for spinal QCT?
- What are treatment initialization thresholds for qQCT of the ultradistal and proximal radius?
- Can treatment initialization thresholds be defined for hip QCT?
### Table 12

In vivo Single-Slice QCT Studies Reporting Geometrical Parameters

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population</th>
<th>Technique/Devices</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Link (260)</td>
<td>Peri- and postmenopausal women, age 51.7 ± 5.2, n=195</td>
<td>Philips Tomoscan LX 120 kV, 200 mAs, 10 mm slice thickness</td>
<td>Spinal fx discrimination</td>
<td>L2-L4: CSA, trab and cort BMD,</td>
<td>n.a.</td>
<td>ROC analysis: AUROC: BMD 0.86, CSA 0.69</td>
</tr>
<tr>
<td></td>
<td>A: vert fx, n=36</td>
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<td></td>
<td></td>
<td></td>
<td>no information whether cortical or trabecular BMD was reported, no information whether age, height, weight etc of fx group matched non fx group</td>
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<tr>
<td></td>
<td>B: no fx, n=129</td>
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<td></td>
<td>CSA, geometry in spine and hip</td>
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<tr>
<td>Bouxsein (261)</td>
<td>Two groups of healthy females</td>
<td>QCT radius 128 kV, 100mA, 3mm slice thickness</td>
<td>Group comparison subperiosteal (TA), medullary (MA), cortical area (CA), min/max area Mol, polar Mol</td>
<td>n.a.</td>
<td>Sig differences (p-values) CA &lt; 0.005, MA &lt; 0.005, all other after normalizing for bone length: TA &lt; 0.005, MA &lt; 0.001, CA min Mol m, max Mol &lt; 0.001, polar Mol &lt; 0.01</td>
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<td>A: age 24.0 ± 2.7, n=21</td>
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<td>B: age 69.7 ± 5.4, n=22</td>
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<td></td>
<td>CSA, geometry in radius and tibia</td>
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<tr>
<td>Hasegawa (183)</td>
<td>Japanese females</td>
<td>QCT radius, Statec XCT960</td>
<td>fx discrimination trab, cort, int BMD, cort area, cort thickness area Mol, polar Mol</td>
<td>n.a.</td>
<td>ROC analysis: AU did not differ sig for the endpoint variables</td>
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<tr>
<td></td>
<td>A: premenopausal, age 34.9 ± 2.6, n=115</td>
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<td></td>
<td>B: postmenopausal osteoporotic vert fx, age 72.2 ± 5.1, n=48</td>
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<td></td>
<td>C: age-matched postmenopausal no fx, age 71.3 ± 3.9, n=78</td>
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</tr>
<tr>
<td>Schneider (262)</td>
<td>Caucasian females, age 45 ± 8</td>
<td>QCT radius, Statec XCT960</td>
<td>fx discrimination trab, cort, int BMD and BMC, cort area, CSMI</td>
<td>n.a.</td>
<td>Sig group differences (p-values) &lt; 0.001; trab BMC, trab BMC, tot BMC cort area, &lt; 0.005 cort BMC, &lt; 0.05 CSMI, &lt; 0.05 tot BMC, ns Cort BMC</td>
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<tr>
<td></td>
<td>A: with Coffee+fx, n=107</td>
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<td></td>
<td></td>
<td>ROC analysis: AU: trab BMC 79.2, trab BMC 759, cort area 74.6, tot BMC 72.6, CSMI 67.5, tot BMC 58.3</td>
</tr>
<tr>
<td></td>
<td>B: retrospectively matched controls n=107</td>
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<tr>
<td>Zanchetta (169)</td>
<td>Postmenopausal women</td>
<td>QCT radius, Statec XCT960</td>
<td>Group comparison int and cort BMC, BMC, area, cort thickness, periosteal circ (PC), endosteal circ (EC) axial and polar Mol</td>
<td>66 triradiate (TPTD) 1 day (38 TPTD20, 28 TPTD40) and 35 plus-obs</td>
<td>Sig group diff (p-values) vs group A B: polar Mol &lt; 0.001, PC &lt; 0.005, EC &lt; 0.005, int BMC &lt; 0.05, CSA &lt; 0.01, cort area &lt; 0.01 C: polar and axial Mol &lt; 0.001, PC &lt; 0.001, EC &lt; 0.001, int BMC &lt; 0.05, CSA &lt; 0.01, cort area &lt; 0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>A: Placebo, age 68.3 ± 7.3, n=35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Analysis of 18-mo data</td>
</tr>
<tr>
<td></td>
<td>B: TPTD20, age 67.5 ± 5.6, n=38</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>C: TPTD40, age 67.8 ± 5.8, n=28</td>
<td></td>
<td></td>
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</tbody>
</table>

All listed studies are cross sectional studies.

**Abbr:** AUROC, area under the ROC curve; CSA, cross sectional area; CSMI, cross sectional moment of inertia; cort, cortical; fx, fracture; int, integral—trabecular and cortical; Mol, moment of inertia; ns, not significant; sig, significant; trab, trabecular.

“A, B, C…. denote different study groups.
Table 13
In vivo QCT studies to determine structure and texture in the spine

<table>
<thead>
<tr>
<th>Reference</th>
<th>Population*</th>
<th>Technique/Devices</th>
<th>Endpoint</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andersen (263)</td>
<td>Men, mean age 52, n=5 females, mean age 62, n=35 subgroups</td>
<td>A1: 1 fs, n=4 B1: &gt; 1 fs, n=7</td>
<td>QCT: L1 – L3 Somatom DR-H, 85 kV, 440 mAs, 8 mm slice thickness</td>
<td>Group differences trab and cort BMD trab and cort texture</td>
<td>Sig group differences for: trab BMD, cort BMD, trabtexture Questionable analysis, number of cases in subgroup is small, no analysis of fs vs non fs, males and females pooled</td>
</tr>
<tr>
<td>Andersen (264)</td>
<td>Subjects mean age 57, n=246 with back pain A: no fs, age7, n=7 B: 1 fs, age7, n=7 C: &gt; 1 fs, age7, n=7</td>
<td>QCT: L1 – L3 trab and cort BMD trab BMD distribution Somatom DR-H, 85 kV, 440 mAs, 8 mm slice thickness</td>
<td>fx discrimination spine trab BMD L1.1 + L2 (mg/cm^2) Visual grading of spongiosa structure</td>
<td>Sig group differences for: group B vs C: spongiosa structure Significance levels for BMD results not given</td>
<td></td>
</tr>
<tr>
<td>Chervat (265)</td>
<td>A: females, age 55.5 ± 2.7, n=71 A1: BMD Z-score &lt; -1, n=28 A2: BMD Z-score &lt; 0, n=23 A3: vert fs, n=20 B: females, age 64.0 ± 3.0, n=94 B1: BMD Z-score &gt; -1, n=44 B2: BMD Z-score &gt; 0, n=42 B3: vert fs, n=47</td>
<td>QCT: L3 GE CGER CE 10000, 130 kV, 1.5 mm slice thickness</td>
<td>Spinal fx discrimination trab BMD trab fracture index (TFI)</td>
<td>Sig group differences for TFI: A1 vs A3, A2 vs A3, B1 vs B2 and B3, B2 vs B3 Z-score differences between groups were higher for trab BMD than for TFI ROC analysis: AUC TFI &lt; AUC trab</td>
<td></td>
</tr>
<tr>
<td>Engelke (266)</td>
<td>Females A: healthy premenopausal, age 41 ± 2, n=52 B: healthy early postmenopausal, 53 ± 4 years, n=119 C: mild (&lt;25%) spinal deformities age 65 ± 5, n=119 D: osteoporosis (deformities &gt;25%), age 67 ± 5, n=26</td>
<td>QCT: T12 – L3 trab BMD and its standard deviation (SD) GE 9800, 120 kV 10 mm slices</td>
<td>Group differences trab BMD SD of trab BMD</td>
<td>Sig group differences for SD: group A vs C and D, group B vs C and D SD did not independently contribute to group separation in addition to BMD</td>
<td></td>
</tr>
<tr>
<td>Gordon (267)</td>
<td>Females, DXA T-score spine or hip -2.5 &lt; T ≤ -2.5, n=61 A: vert fs, age 71.6 ± 4.1, n=20 A: no vert fs, age 69.4 ± 5.1, n=41</td>
<td>3D QCT: L1 – L2 contiguous slices BMD: 80 kV, 140 mAs, 3 mm slice thickness, 2D: single-slice L1 and L2 trab structure: 120 kV, 340 mAs, 1.5 mm slice thickness GM: 9800 Q</td>
<td>Spinal fx discrimination trab BMD histomorphometric equivalent parameters, marrow connectivity (averag (HA) and max HLM hole size)</td>
<td>ROC analysis: AUC: HA 0.76, BMD 0.75, L1Th 0.71, L1Sp 0.68 sig 0.002, HA 1.94, BMD 2.33, L1Th 1.63, L1Sp 1.91, BTV 2.21</td>
<td></td>
</tr>
<tr>
<td>Ito (268)</td>
<td>Japanese females, age 18 – 86, n=209 subgroups: A: vert fs, A1: age 64.9 ± 2.4, n=25; A2: age 72.8 ± 2.4, n=42 B: no fs, B1: age 63.4 ± 2.9, n=24; B2: age 71.4 ± 2.6, n=7</td>
<td>QCT: L1 – L3 trab BMD: 8 mm slice thickness trab BMD: 125, 83 kV</td>
<td>Spinal fx discrimination trab BMD trab fracture (run-length analysis)</td>
<td>Sig group differences (p-values) for: A1 vs B1: trab BMD &lt; 0.001, texture &lt; 0.05 A2 vs B2: trab BMD &lt; 0.05, texture &lt; 0.01 Fisher Exact Test: Sensitivity (Sen) and Specificity (Spe): age 60 – 69: Sen: trab BMD 81, texture 34, BMD and texture 73, Spe: trab BMD 60, texture 72, BMD and texture 72 age 70 – 79: Sen: trab BMD 79, texture 66, BMD and texture 86, Spe: trab BMD 71, texture 86, BMD and texture 86 Overlapping populations</td>
<td></td>
</tr>
<tr>
<td>Ito (268)</td>
<td>Japanese females, age 55 – 79, n=122 subgroups: A: vert fs, A1: age 57.2 ± 1.6, n=18; A2: age 64.5 ± 2.7, n=26; A3: age 72.8 ± 2.0, n=14 B: no fs, B1: age 56.7 ± 1.2, n=28; B2: age 63.2 ± 2.6, n=25; B3: age 72.4 ± 2.8, n=12</td>
<td>QCT: L3 trab texture: 2 mm slice thickness trab BMD: 125, 83 kV</td>
<td>Spinal fx discrimination trab BMD trab fracture (run-length analysis)</td>
<td>Sign Odds Ratio: age 50–59: trab BMD 7.14 texture 2.8 age 60–69: trab BMD 2.64 age 70–79: cort BMD 1.61 texture 3.42</td>
<td></td>
</tr>
<tr>
<td>Beatrroy (172)</td>
<td>Females A: premenopausal, age: 34 ± 7, n=108 B: postmenopausal osteoporotic (DXA T-score), age 69 ± 7, n=106 C: postmenopausal osteoporotic (DXA T-score), age 69 ± 5, n=33 C1: group C with history of fs, age 68 ± 7, n=78 C2: group C without fs, age 70 ± 5, n=35</td>
<td>3D pQCT: radius, tibia XrateCT DXA: L-spine, hip Hologic QDR 4500</td>
<td>Group comparison 3D pQCT radius and tibia: int, cort, trab BMD, microstructure (BVT, TV, Th, Tb, Tb.Sp, Tb.Sp SD), cortical thickness, CSA DXA BMD, and T score: L1-L4, neck</td>
<td>Sig differences (p-values) A vs B: all pQCT variables except from CSA of radius and tibia &lt; 0.001 A vs C: all pQCT variables apart from CSA of radius and tibia &lt; 0.001 No DXA values reported for group A</td>
<td></td>
</tr>
</tbody>
</table>

Studies investigating structure or texture in the spine

Studies investigating structure or texture in the forearm
QCT of the Hip

QCT of the hip should be considered for clinical use. However, this would require development of optimized acquisition protocols with lower radiation doses in order to increase the clinical acceptability of the method. In addition, protocols developed for this purpose would have to address the following questions:

- Can the combination of BMD in optimized volumes of interest, potentially in combination with geometrical information, significantly improve hip fracture prediction compared to DXA?
- Should QCT of the hip specifically be used to identify subjects with high fracture risk?
- Can QCT of the femur become a preferred tool to differentiate effects of different anti-osteoporotic pharmaceutical interventions?

pQCT of the Radius

Further research is required to determine the application of pQCT for monitoring purposes. The following questions should be addressed:

- Are potential limitations in applying pQCT for monitoring interventions related to the biological response of the forearm per se, or to technical limitations of pQCT, when compared to other densitometric techniques applied to the forearm?
- Which parameters of BMD (trabecular, cortical, total) should be measured with pQCT and for which intervention?
- Since trabecular and cortical structures and densities change rapidly from the ultra-distal to the distal location, which is the optimum anatomical site to scan?

The Use of Cortical BMD

The differentiation of cortical and trabecular bone is one of the unique advantages of QCT compared to DXA. However, the determinations of cortical VOI, and thus the measurement of cortical BMD, BMC and thickness heavily depend on the type of CT scanner and the analysis software utilized. The spatial resolution of the CT images is often less than, or equivalent to the cortical thickness, causing accuracy errors because inevitably the cortical parameters, such as density and thickness are strongly influenced by segmentation. As a consequence, the cortical VOI may include subcortical bone adjacent to the endosteal surface or soft tissue adjacent to the periosteal surface; cortical thickness may therefore be under- or over-estimated and BMD may be underestimated.

The spatial resolution of a CT scanner not only depends on its specific hardware, such as detector pixel size, but also on the location of the object in the scan field of view and on various scan and reconstruction parameters (see Table 2); cortical measurements will be affected by all these factors.

In pQCT devices, often a global threshold is used, based on the fact that cortical BMD is between 1000 and 1200 mg/cm³. However, this approach is only valid if the...
### Table 14

In vivo 3D QCT Studies Including Finite Element Analysis (FEM)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Study Duration (y)</th>
<th>Population</th>
<th>Technique/Devices</th>
<th>Endpoint</th>
<th>Intervention</th>
<th>Results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keaveny (271)</td>
<td>QCT subset of FACL study</td>
<td>1</td>
<td>1.5</td>
<td>Osteoporotic postmenopausal females (DXA T-score range -2.5 to -4.0 at lumbar spine or hip)</td>
<td>3D QCT spine: L1 = L3, 120 kV, 3 mm slice thickness</td>
<td>3D QCT: trab BMD FEM strength parameters</td>
<td>TPTD: 20 microgram/day, ALN: 10 mg/day</td>
<td>6 month results (% changes) TPTD: QCT trab BMD +10.9%, DXA spine +3.4%, compress strength +13.0% Allen: QCT trab BMD +2.8%, DXA spine +2.0%, compress strength +4.9% sig between gr diff: QCT trab BMD, compress strength +18 mo results (% charge) TPTD: QCT trab BMD +15.9%, DXA spine +10.0%, DXA hip +4.2%, compress strength +21.2% Allen: QCT trab BMD +6.6% (ns), DXA spine +4.9%, DXA hip +1.5%, compress strength +3.7% sig between gr diff: QCT trab BMD, DXA spine, compress strength</td>
</tr>
<tr>
<td>Cody (251)</td>
<td>5</td>
<td>n.a.</td>
<td>White females</td>
<td>3D QCT hip: Technicare PS 1440, 130 kV, 400 mA, 3 mm slice thickness custom analysis software</td>
<td>IT discrimination using FEA stiffness in fall and stance config</td>
<td>n.a.</td>
<td>Group diff ns for FEA predicted stiffness in both loading conditions</td>
<td>Low trauma defined as fracture resulting from fall from standing height or lower</td>
</tr>
<tr>
<td>Faulkner (272)</td>
<td>6</td>
<td>n.a.</td>
<td>Females, age 20 – 62</td>
<td>3D QCT: GE 9800, 80 kV, 80 mA, 16–18 contiguous 5 mm slices custom analysis software</td>
<td>IT discrimination using FEA Yield stress at 2% plastic deformation of L1 and L2</td>
<td>n.a.</td>
<td>Group diff p-values</td>
<td>Cortical contribution to Yield stress: A 56.2%, B 12.4%</td>
</tr>
<tr>
<td>Lian (256)</td>
<td>6</td>
<td>n.a.</td>
<td>Postmenopausal Caucasion females with low BMD, (DXA T-score &lt;-2)</td>
<td>3D QCT: hip: GE 9800, 120kV, 280 mA, 3 mm slice thickness, controls: GE 9800, 80kV, 280 mA, 3mm slice thickness BMD analysis software UCSF FEM custom analysis software</td>
<td>Group differences based on BMD 3D QCT: Hip trab, cort, int BMD mg/cm²) cort Vol (cm³) group difference based on geometry 3D QCT: CSA neck, FA LDXA: hip (g/cm²) Group differences based on FEM failure loads in stance and fall</td>
<td>n.a.</td>
<td>Group diff p-values</td>
<td>3D QCT: total hip: int BMD 0.001, trab BMD 0.006, Cort BMD 0.001 neck: int BMD 0.001, trab BMD 0.028, Cort BMD 0.001 trochanter: int BMD 0.001, trab BMD 0.002, Cort BMD 0.001 total hip, neck, trochanter: cort vol 0.001, trab vol 0.01 CSA and FAL ns FEM: failure load stance 0.01, failure load fall 0.07 DXA: total hip, neck and trochanter all 0.001</td>
</tr>
</tbody>
</table>

**Abbr:** cort, cortical; CSA, cross sectional area; diff, difference; fx, fracture; int, integral— trabecular and cortical; L-spine, lumbar spine L1-L4; ns, not significant; sig, significant; trab, trabecular.

*aStudy Type: 1: Randomized controlled trial; 2: Non-randomized trial with contemporaneous controls; 3: Non-randomized trial with historic controls; 4: Cohort study; 5: Case-Control Study; 6: Cross-sectional study; 7: Surveillance (e.g., using databases or registries); 8: Series of consecutive cases.*

*bA, B, C.... denote different study groups.*
cortical thickness is about three times as large as the spatial resolution of the scanner (19). Once this condition is violated, cortical density (180,181) and cortical thickness can no longer be accurately determined. Several approaches have been suggested to adapt thresholds (182,183), by using cortical BMC or maximum cortical BMD values (184), or the product of BMC and cortical thickness (185). However, all of these fail if neither cortical BMD nor cortical thickness can be determined accurately due to partial volume artifacts. For any particular scan it is not possible to know if there is a problem with partial volume effect, and so the feasibility of correcting values is limited. Different scanners also have different spatial resolutions complicating the comparison of cortical parameters, particularly at the ultra-distal site (186).

Limited cortical reference data exist for the spine and the forearm, but none are yet available for the hip, and standardized age-adjusted risk gradients have not been published. Nevertheless, in the PaTH study significant treatment effects on cortical BMD of the femoral neck (124,125) have been shown. Reference values for the cortical ROI of the spine have been published for several populations (Table 4) for single-slice QCT using the Osteo program optionally implemented on Siemens scanners (Siemens, Erlangen, Germany). Changes in vertebral cortical bone were observed with glucocorticoid therapy (187). The role of cortical bone in the hip has been addressed in in-vitro studies investigating bone strength (48). Although accuracy of cortical measurements is impaired due to partial volume artifacts, longitudinal changes may still be detectable (19).

In the forearm, partial volume artifacts and segmentation techniques may explain why several studies were more successful using cortical parameters at the ultra-distal site than total or trabecular BMD, for example for fracture prediction (84), age-related bone loss (188), or monitoring treatment (160,162). Partial volume artifacts probably also explain some of the controversial findings on differential age-related bone loss in cortical and trabecular bone. In cross sectional studies of healthy women some authors reported higher trabecular than cortical losses (189–191), while others showed comparable losses (148,192,193).

If cortical parameters are to be measured at the forearm, they should be measured at the 1/3 or mid site, but not at the ultra-distal or distal sites. The 1/3 site where the cortex is thicker has been used in several studies (21,151,159,161,166,190,194–197). Unfortunately, in these studies there is a large diversity of scan locations and extracted parameters, and therefore, while a proximal location for pQCT measurements is currently interesting from the perspective of clinical trials and research studies, it cannot be recommended for routine clinical use.

In summary, there is evidence that under standardized conditions changes in cortical parameters may be detectable and thus it is highly recommended to include the measurement of cortical parameters in research studies and clinical trials. However, it is too early to recommend these measurements for routine clinical practice. Thus the following questions should be specifically addressed for cortical bone:

- At what skeletal locations can cortical BMD and thickness be measured accurately and precisely?
- How can acquisition and analysis protocols and segmentation algorithms specifically be optimized for the assessment of cortical bone?
- Is cortical BMC a better variable than cortical BMD to address fracture risk and treatment monitoring?

**Macro and Micro-Structure and FEM**

A systematic overview of single-slice QCT in vivo studies reporting geometrical parameters is given in Table 12: the studies using 3D QCT have already been included in Table 8. The tables do not include predominantly technical studies describing the method, studies with reference data (91,108,198,199), gender differences (196,200), or studies in patient groups with disorders not primarily related to osteoporosis (201–213).

Table 13 gives a systematic overview of published in vivo studies employing structural and textural parameters. The Table does not include predominantly technical studies describing the method (23,70,214–220), studies with reference data, or studies in subject groups with disorders not primarily related to osteoporosis (221–224). Table 14 gives a systematic overview of published in vivo studies employing finite element analysis.

All the parameters mentioned above are still in the early phase of being evaluated. Reference data and standardized age-adjusted risk gradients have not yet been published. QCT structural or textural parameters for the characterization of bone structure and QCT based finite element analysis are potentially promising techniques to improve the assessment of bone strength; however, they should not be used in clinical practice at this time.

Research is encouraged to further evaluate the potential of macro-structural parameters describing geometry, as several in vitro studies in which QCT parameters were correlated with failure loads have indicated their value as independent predictors of bone strength. The potential and limitations of FEM should be further investigated and prospective randomized studies are encouraged. Thus the following questions should be addressed:

- Does a more comprehensive assessment of bone strength, for example by integrating bone density and bone geometry using finite element method (FEM), result in an improvement of fracture risk prediction or treatment monitoring?
- Is FEM superior to a combined QCT measurement of BMD in optimized regional VOI and simple macroscopic parameters such as moments of inertia that also relate to bone strength?
- How can acquisition and analysis protocols and segmentation algorithms specifically be optimized for the assessment of structural parameters?
- Is it useful to measure structural parameters in the radius for treatment monitoring?
Summary

The ISCD Official Positions provided here address the application of QCT for fracture risk assessment, diagnosis, treatment initiation, and monitoring BMD for the clinical assessment of osteoporosis. Based on an extensive review of QCT technology and applications for bone densitometry, evidence supporting the ISCD Official Positions is presented. Since QCT is in a phase of rapid development, it is recommended that this technology be reviewed again at future ISCD Position Development Conferences as new information becomes available.

Appendix. General Terminology and Abbreviations Used in CT

**3D QCT:** differentiates the image analysis approach. In single-slice QCT a 2D region of interest is determined. The analyzed volume is then calculated as area of the ROI multiplied by slice thickness. In contrast in 3D QCT a 3D volume of interest is determined during the analysis of a stack of slices.

**Convolution kernel:** In connection with image reconstruction for CT, a special function that can be varied within a certain range in order to tune the pixel noise and the geometrical resolution.

**CT number:** The final result of the CT measurement; the CT number is calculated from the linear attenuation coefficient $\mu$. Synonymous with CT value.

**CT value:** Synonymous with CT number.

**BMD:** bone mineral density in g/cm$^3$. This is a volumetric variable that can be measured by QCT but not by DXA. Synonymous with areal bone mineral density.

**BMD$_a$:** areal bone mineral density in g/cm$^2$. This is an areal density, that can be measured by projectional techniques such as DXA.

**DXA:** Dual-energy X-ray absorptiometry (manufacturer specific acronyms: DER, DEPR, QDR, DPX). Two different energy spectra are used.

**Field of measurement (FOM):** Machine-characteristic region or volume for which complete data sets can be acquired; the size depends on the scanner geometry and the fan angle; the object to be scanned has to be within the FOM to avoid artifacts due to truncation effects.

**Field of view (FOV):** Region or volume reconstructed from the acquired data. The FOV can be equal to or smaller than the FOM.

**Gantry:** The mechanical CT assembly, including the detector and the X-ray source, as the main part of the entire measurement system.

**Gantry tilt:** Tilt of the CT gantry with respect to the patient’s longitudinal axis by typically up to 30°; the scan plane is rotated around the x-axis such that the axis of rotation and the direction of table feed are not the same.

**Helical CT:** Synonymous with spiral CT.

**Hounsfield Unit (HU):** Unit of the CT number scale

**Image matrix:** In CT, the 2-dimensional arrangement of reconstructed values of the attenuation coefficient at discrete positions; the single elements are called pixels.

**Image noise:** Noise contributions to the final image.

**Image reconstruction:** Calculation of the CT image from the projection.

**LSC:** least significant change; the change between two measurements that can be measured with 95% confidence.

**Matrix:** 2D arrangement of numbers; in the context of CT, used synonymously with the image matrix.

**Multi-row detector:** Detector array with at least two, but typically between 4 and 64, independent detector rows; see multi-slice CT system.

**Multi-slice CT system:** CT scanner capable of measuring more than one slice simultaneously, based on multi-row detectors or 2D detector arrays.

**Multi-slice spiral CT (MSCT):** Spiral CT scanning technique with the simultaneous acquisition of more than one independent slice; performed on multi-slice CT systems.

**MTI:** monitoring time interval; time required between two measurements so that the change in $q$ is equal to the LSC. It is calculated using the median longitudinal response rate of a cohort of subjects.

**Partial volume artifact:** Artifact caused by severe inhomogeneities of the materials within the beam on the corresponding attenuation measurement (e.g., bone and air). The averaging of the incident intensity within the detector element is not equivalent to an averaging of the attenuation coefficient itself; this is a source of nonlinear errors and thereby inconsistencies for attenuation measurements along different directions.

**pQCT:** Peripheral quantitative computed tomography.

**QCT:** Quantitative computed tomography.

**ROI:** Region of interest; subset of pixels which lie within an arbitrary (circular, rectangular etc.) geometrical shape at a freely selectable position within a 2D image.

**ScoutView:** See survey radiograph.

**Sequential CT:** Conventional CT scanning technique in which each requested slice is measured at a fixed z-position followed by an appropriate transport of the object in the z-direction; for most applications today, the sequential CT technique has been replaced by spiral CT.

**Slice thickness:** Often used synonymously with slice width; thickness of the reconstructed CT image.

**Spiral CT:** Method of CT scanning with continuous gantry rotation and simultaneous continuous object translation in z-direction; by contrast with the sequential scan technique, with spiral CT the volume to be examined is sampled continuously along the z-axis; during data acquisition the focus of the X-ray tube follows a spiral trajectory relative to the object; the z-interpolation is introduced as an additional step during data preprocessing and allows a retrospective and arbitrary selection of the positions at which images are reconstructed.

**Survey radiograph:** A projection image similar to a conventional radiograph measured with the CT scanner by moving the patient through the gantry without gantry rotation; the survey radiograph is generated by displaying the projections measured from a fixed X-ray tube position for numerous table positions; by contrast with a conventional
radiograph, the digital survey radiograph in CT has a cylindrical projection geometry; the various manufacturers denote this imaging modality e.g., as Topogram, Scout View, or Scanogram.

**Tomogram:** Two-dimensional image representing a slice or section through a three-dimensional object

**Topogram:** See survey radiograph.

**VOI:** Volume of interest; subset of voxels which lie within an arbitrary (cubical, spherical etc.) geometrical shape at a freely selectable position within a 3D image cube.

**vQCT:** see 3D QCT

**Zoom factor:** Ratio of the diameter of the field of measurement and the diameter of the volume shown in the image; together with the image center the zoom factor determines which region of the object is reconstructed.

**References**

34. Crawford RP, Rosenberg WS, Keaveny TM. 2003 Quantitative computed tomography-based finite element models of the human lumbar vertebral body: effect of element size on stiffness,


55. Huiskes R. 2000 If bone is the answer, then what is the question? J Anat 197(Pt 2):145–156.


151. Clowes JA, Eastell R, Peel NF. 2005 The discriminative ability


Engelke et al. Osteoporos Int 2(3):153


