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Whole-Body Low-Dose Computed Tomography (WBLDCT) in Assessment of Patients with Multiple Myeloma – Pilot Study and Standard Imaging Protocol Suggestion

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

Background: For decades, the main imaging tool in multiple myeloma (MM) patients was plain radiography. However, computed tomography (CT) has been included in the updated criteria of MM. The main disadvantage of CT is a considerably high radiation dose. Therefore, low-dose CT protocols could be a solution. The aim of the study was to (1) preliminarily analyse the usefulness of Whole-Body Low-Dose CT (WBLDCT) in the evaluation of patients with MM and (2) to make adjustments in the standard CT imaging protocol.

Material/Methods: In 41 patients with MM, WBLDCT was performed. The following parameters were used: detector configuration – 80×0.5 mm, scanning range in a single spiral acquisition from the skull to the proximal femoral bones, tube voltage – 120 kVp, current tube time product – 86 mAs, slice thickness 1 mm. Two sets of axial images were reconstructed for bone and soft tissue assessment, respectively. Secondary coronal and sagittal reconstructions were generated. Typical MM features were analysed and qualitatively compared with radiography results.

Results: A potentially increased sensitivity of CT, as compared to radiography, in detecting lytic foci obscured by other structures or with a small degree of destruction was seen. A potentially increased specificity of CT was found in detecting cases of small foci suspicious of lytic lesions on skull radiographs, seen as arachnoid granulations fovea in CT. The following radiation parameters were recorded: max. CTDIvol – 7.4 mGy and DLP – 660–810 mGy×cm. WBLDCT was much shorter and more convenient to patients.

Conclusions: WBLDCT may become a valuable part of the assessment of MM features at a much lower radiation dose compared to standard CT protocols. It has a potential ability to increase diagnostic accuracy compared to radiography.

MeSH Keywords: Multiple Myeloma • Radiation Dosage • Tomography, Spiral Computed • Whole Body Imaging

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Background

Multiple myeloma (MM) or plasma cell myeloma (PCM) is a cytogenetically heterogeneous proliferative disorder of clonal plasma cells. It manifests itself with typical clinical features abbreviated as CRAB: hypercalcaemia, renal failure, anaemia, and bone lytic lesions.

MM is almost always preceded by an asymptomatic premalignant stage, termed monoclonal gammopathy of undetermined significance (MGUS) [1]. MGUS is found in about 3–4% of people older than 50 years [2,3]. The risk of progression of MGUS to MM is 0.5–1% per year, and it depends on many factors such as the concentration and type of monoclonal protein, serum free light chain ratio, bone marrow plasmacytosis, proportion of phenotypically clonal plasma cells and presence of immunoparesis [4].

Table 1. Revised International Myeloma Working Group diagnostic criteria for multiple myeloma and smouldering multiple myeloma.

Definition of multiple myeloma
Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:
- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min** or serum creatinine >177 μmol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT***
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved: uninvolved serum free light chain ratio# ≥100
    - >1 focal lesions on MRI studies##

Definition of smouldering multiple myeloma
Both criteria must be met:
- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT – ^{18}F-fluorodeoxyglucose PET with CT. * Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. ** Measured or estimated by validated equations. *** If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. # These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ## Each focal lesion must be 5 mm or more in size.

Smouldering multiple myeloma is an intermediate clinical stage between MGUS and MM, with a much higher risk of progression to malignant disease (about 10% per year) [5].

In MGUS as well as in smouldering multiple myeloma, CRAB features are absent.

Solitary plasmacytoma is a biopsy-proven solitary bone or soft tissue lesion with evidence of clonal plasma cells but normal bone marrow with no evidence of clonal plasma cells and no CRAB features; however, the risk of progression to MM is about 10% within 3 years [6].

For decades, the main imaging tool in MM patients was plain radiography covering typical locations of focal lesions, including the skull, spine, pelvis, ribs, humeral and femoral bones – sometimes called the "whole body X-ray survey" (WBXR). The technique is still commonly used; however, it has many limitations [7]. Some areas are not well visualized, sensitivity is limited (10–20% of lesions/abnormalities are missed), specificity is reduced (similar finding are seen in benign causes of osteopenia, e.g., steroids/postmenopausal), assessment is observer-dependent and time tolerance for a standard survey is not ideal.

After becoming popular, computed tomography (CT) and magnetic resonance imaging (MRI) also started to be used in MM patients.

CT [7] may detect small osteolytic lesions, is faster than a standard radiographic survey, provides 3D reconstructions, shows associated soft tissue disease, has greater sensitivity and specificity in comparison to standard radiography, allows estimation of fracture risk and is excellent for radiotherapy planning and for surgical intervention.

MRI [7] is also more sensitive than standard radiography, ensures excellent imaging of axial skeleton, discriminates myeloma from normal marrow, provides excellent diagnostic discrimination for spinal cord/nerve compression and soft tissue disease, can detect avascular necrosis of the femoral head, can detect amyloid/light chain deposits in the heart and other sites, can be used to assess disease status in MGUS, smouldering myeloma and solitary plasmacytoma, and can be used to monitor response to treatment.

Because of that, the results of CT and MR have been included in the updated International Myeloma Working Group (IMWG) criteria for the diagnosis of MM [1] – Table 1.

The main disadvantage of CT, compared to X-ray, is a much higher radiation dose delivered to patients. One solution may be to use dedicated low-dose CT protocols.

Several studies concerning such low-dose CT protocols for MM patients have been published, but so far no common standard has been accepted [8–16].

The aim of the study was to (1) preliminarily analyse the usefulness of WBLDCT in the evaluation of patients with MM and (2) to make adjustments in the standard CT imaging protocol.

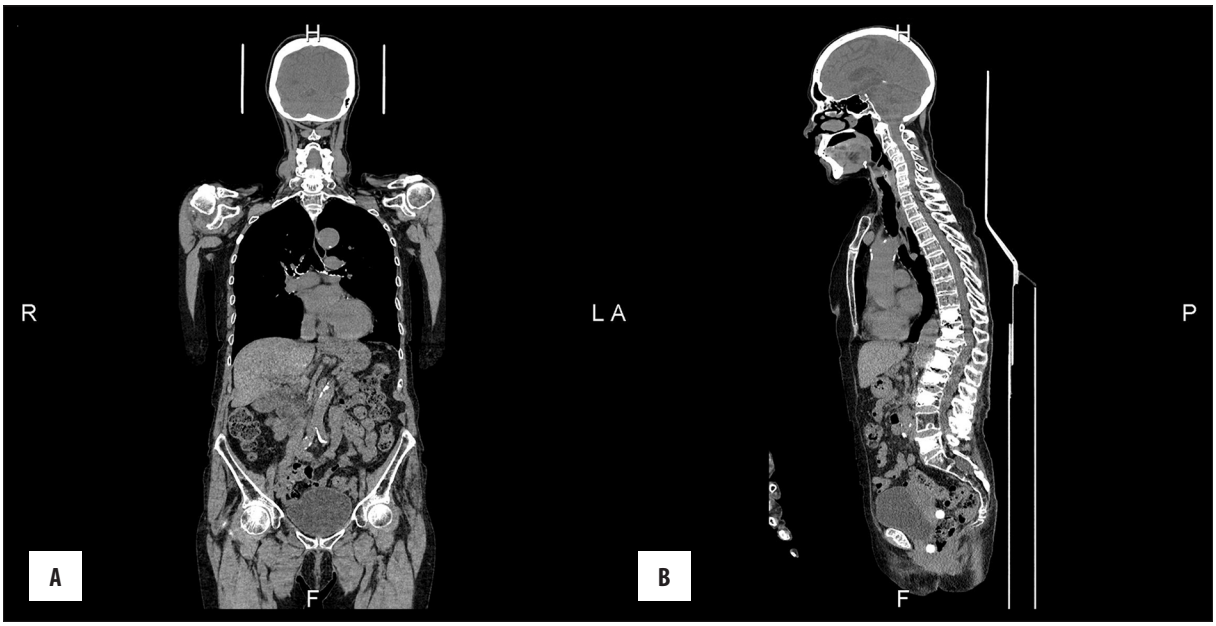

Figure 1. (**A**) Coronal and (**B**) sagittal reconstructions from WBLDCT.

Table 2. Suggested parameters of WBLDCT in MM patients.

• No i.v. contrast media
• Single spiral acquisition covering skull, neck, chest, abdomen and pelvis, proximal parts of humeral and femoral bones
• Field of view (FOV) initially set as 400 mm and adjusted to individual patients
• Tube voltage 120 kVp
• Pitch – the closest to 1 value from available settings
• Current tube time product 70–90 mAs
• Slice thickness 1 mm, slice increment 0.8 mm
• Two sets of axial images reconstructed from raw data: for bone assessment using sharp kernel and "bone" window, for soft tissue assessment using soft kernel and "soft tissue" window
• Secondary coronal and sagittal reconstructions using slice thickness 1mm and slice increment 1 mm

Material and Methods

In 41 patients (25 females, 16 males, aged 32–81 years, mean age of 61 years) with multiple myeloma diagnosed according to the current criteria of the International Myeloma Working Group, WBLDCT was performed, using an 80-row, 160-slice Toshiba Aquilion PRIME scanner.

No i.v. contrast media were used.

The scanning range in a single spiral acquisition covered the skull, neck, chest, abdomen and pelvis, encompassing proximal parts of the humeral and femoral bones. Field of view (FOV) was initially set at 400mm and was adjusted to individual patients during examination planning. Tube voltage was set at 120kVp. Pitch was chosen to be 0.813 (the closest 1.0 value from the available settings).

For the above pitch value and tube rotation time of 0.5s, tube current was set at 140 mA, resulting in current-tube time product of 86mAs. Detector configuration was set at 80× 0.5 mm.

Slice thickness was set at 1mm and slice increment at 0.8mm. Slice increment smaller than thickness was used to avoid step artefacts on secondary coronal/sagittal reconstructions, and because it provided much faster primary raw reconstructions compared to the increment value that was equal to slice thickness.

Two sets of axial images were reconstructed from the raw data obtained during scanning: for bone assessment using sharp (FC35) kernel, window width 2700 HU, window level 350 HU; and for soft tissue assessment using soft (FC08) kernel, window width 400 HU, window level 40 HU. From every set of axial images, secondary coronal and sagittal reconstructions were generated using slice thickness of 1mm and slice increment of 1mm (Figure 1).

The WBLDCT protocol parameters are summarized in Table 2.

All the images obtained were transferred to AGFA IMPACS hospital Picture Archiving and Communication System (PACS) and finally assessed on radiological workstations.

Typical features of MM were analysed on CT images and qualitatively compared with the available radiographic findings in order to define the most important potential ways of increasing accuracy. Qualitative rather than

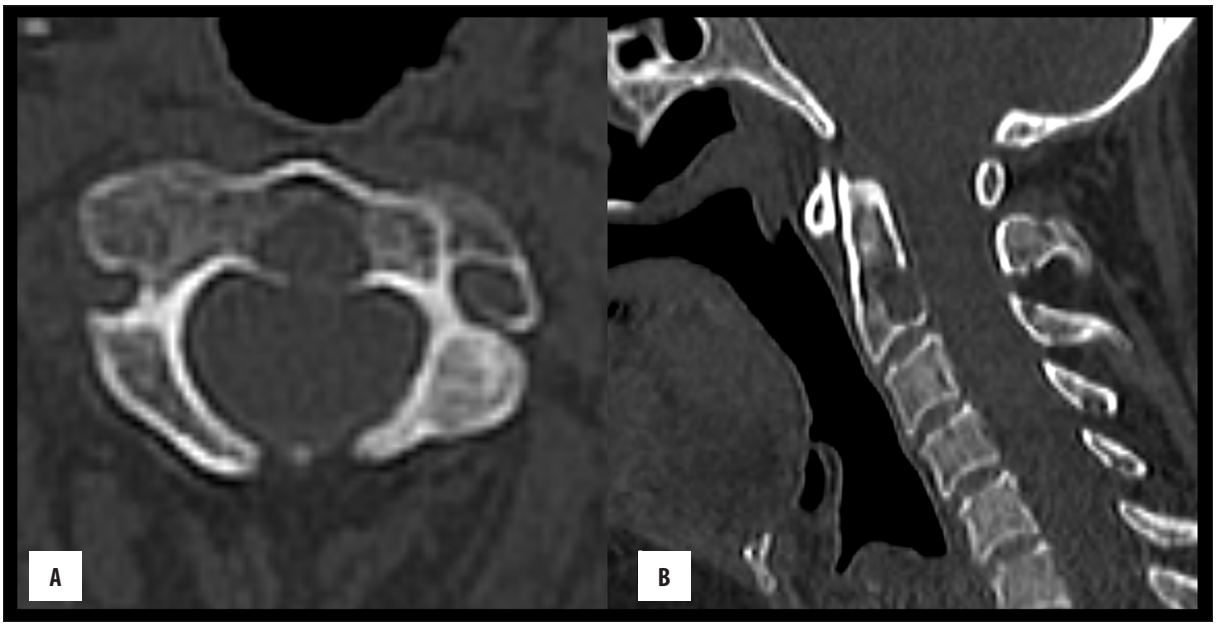

Figure 2. (**A**) Axial image and (**B**) sagittal reconstruction, lytic focus in dens of the axis.

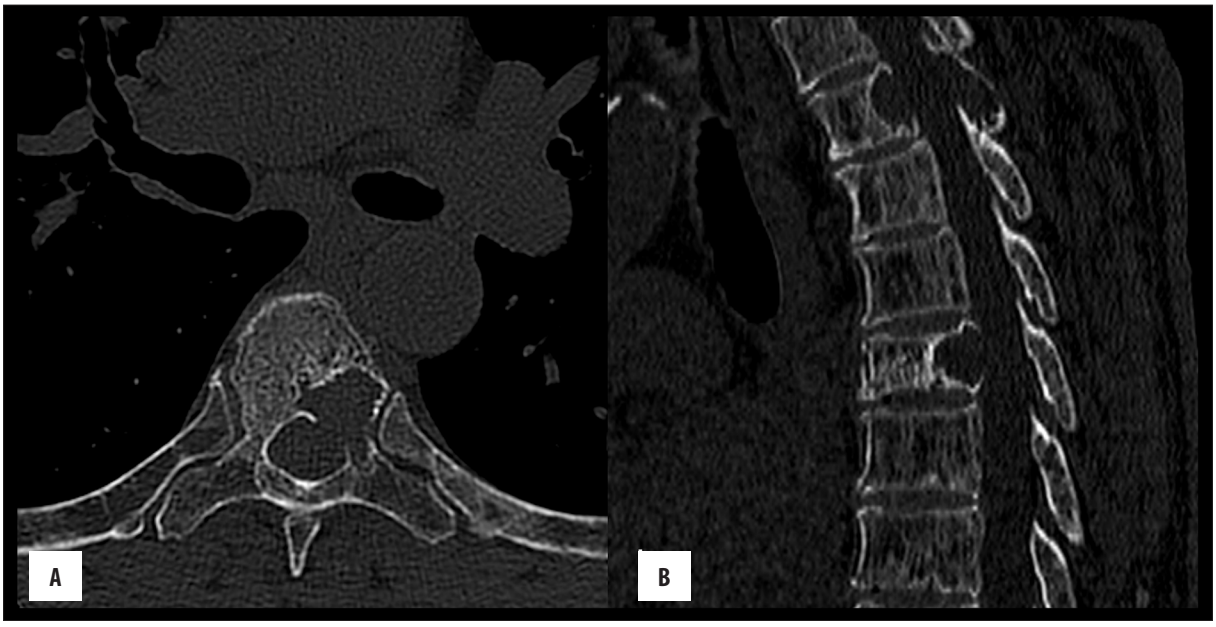

Figure 3. (**A**) Axial image and (**B**) sagittal reconstruction, lytic foci with sclerotic rim in the thoracic spine.

quantitative analysis was necessary because of a limited number of the available radiographic examinations performed within 1 month of the respective CT examinations.

The radiation parameters, i.e. max. CTDIvol (CT dose index) and DLP (Dose-Length Product) for the WBLDCT protocol, as defined above, were read from the examination summary reports generated by the CT scanner for each case.

Results

Typical features of MM in bone structures were very well visible on CT images: lytic foci (Figure 2), sometimes with sclerotic rim (Figure 3) or with cortical destruction, large regions of destruction (Figure 4) or osteopenia (Figure 5).

Extraosseous infiltrations (Figure 6) were also well visible in most cases with the use of soft tissue kernel/window images. WBLDCT was also a good tool for treatment response assessment in terms of extraosseous infiltrations.

The most important potential way of increasing the sensitivity of CT, relative to radiography, was its ability to detect lytic foci that were obscured by other structures on radiographs (Figure 7) or to detect lytic foci with a small degree of bone destruction.

It was particularly important for the sternum and shoulders that are in general difficult to assess with the use of radiography.

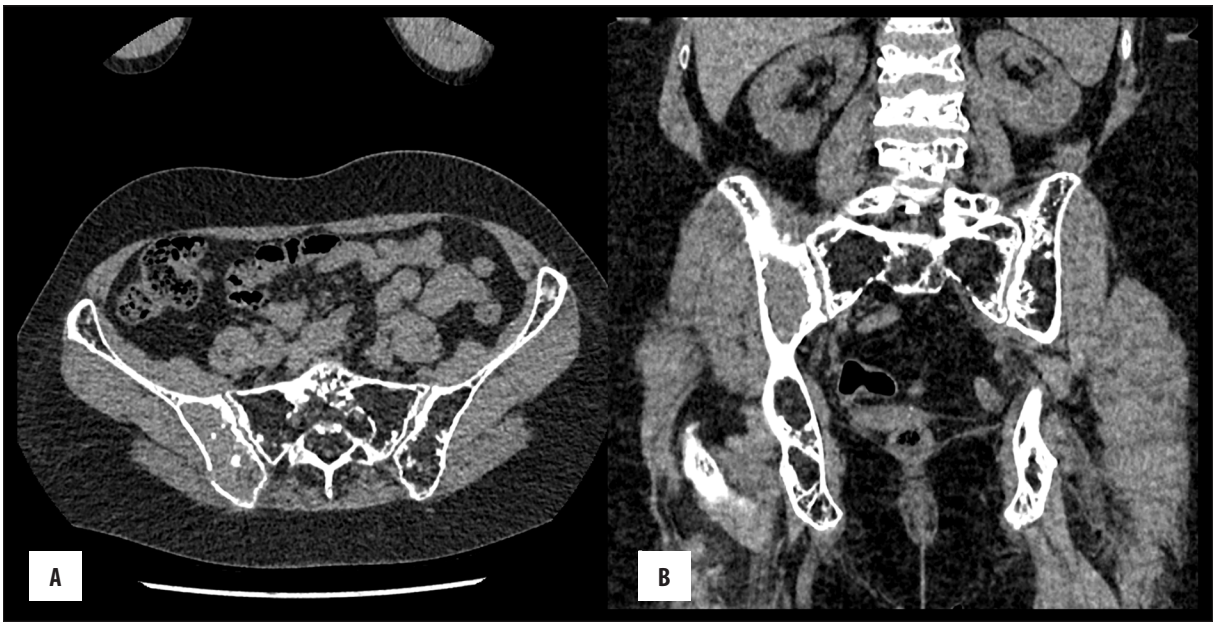

Figure 4. (**A**) Axial image and (**B**) coronal reconstruction, large region of destruction in the right iliac bone.

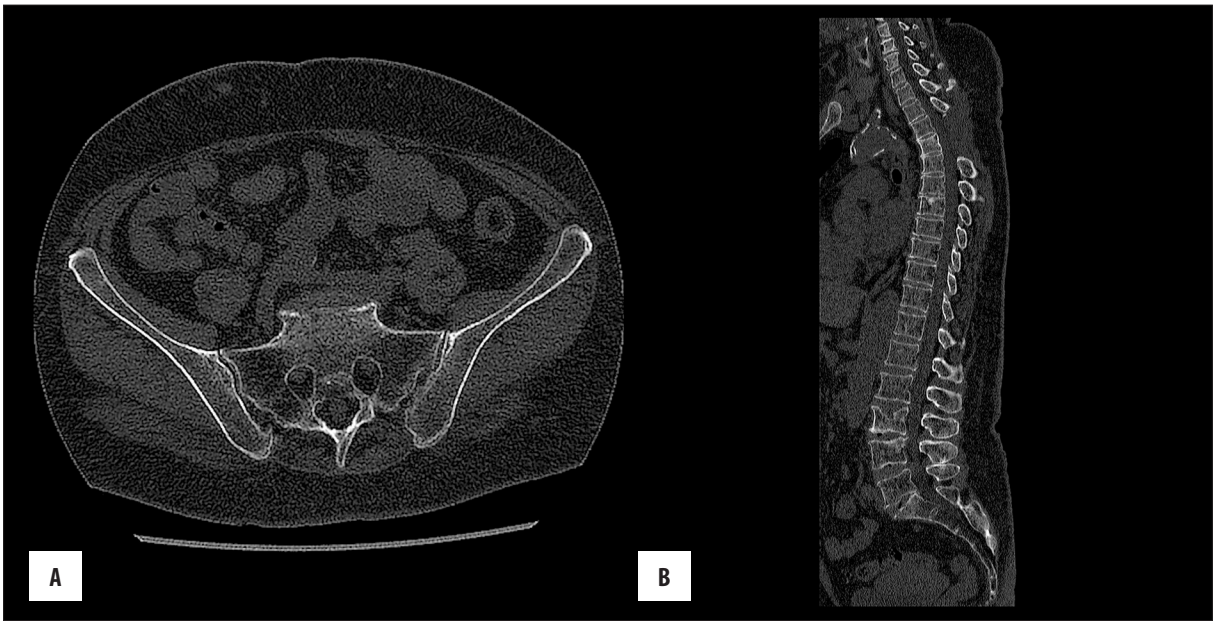

Figure 5. (**A**) Axial image and (**B**) sagittal reconstruction, osteopenia.

The potential way of increasing the specificity of CT, as compared to radiography, was found in cases of small foci suspected to be lytic lesions on skull radiographs that on CT turned out to be arachnoid granulations fovea (Figure 8).

WBLDCT, using 2D reconstructions, could well present vertebral fractures and assess secondary spinal stenosis, which could be very useful for planning surgery, radiotherapy or vertebroplasty.

It also allowed for a fracture risk assessment, especially in cases where almost an entire bone cross-section was replaced by neoplastic infiltration - for example in dens of the axis or femoral neck.

WBLDCT could also present spinal canal and intervertebral foramina infiltration but of course not as precisely as MR.

Importantly, WBLDCT could be performed in patients with metallic implants.

In one case of a suspected solitary bone plasmacytoma, new foci in other locations were detected in WBLDCT, confirming MM (Figure 9).

Radiation parameters obtained for the above-defined values were: max. CTDIvol (CT dose index) – 7.4 mGy, DLP (Dose Length Product), depending on patient's size, – 660–810 mGy×cm.

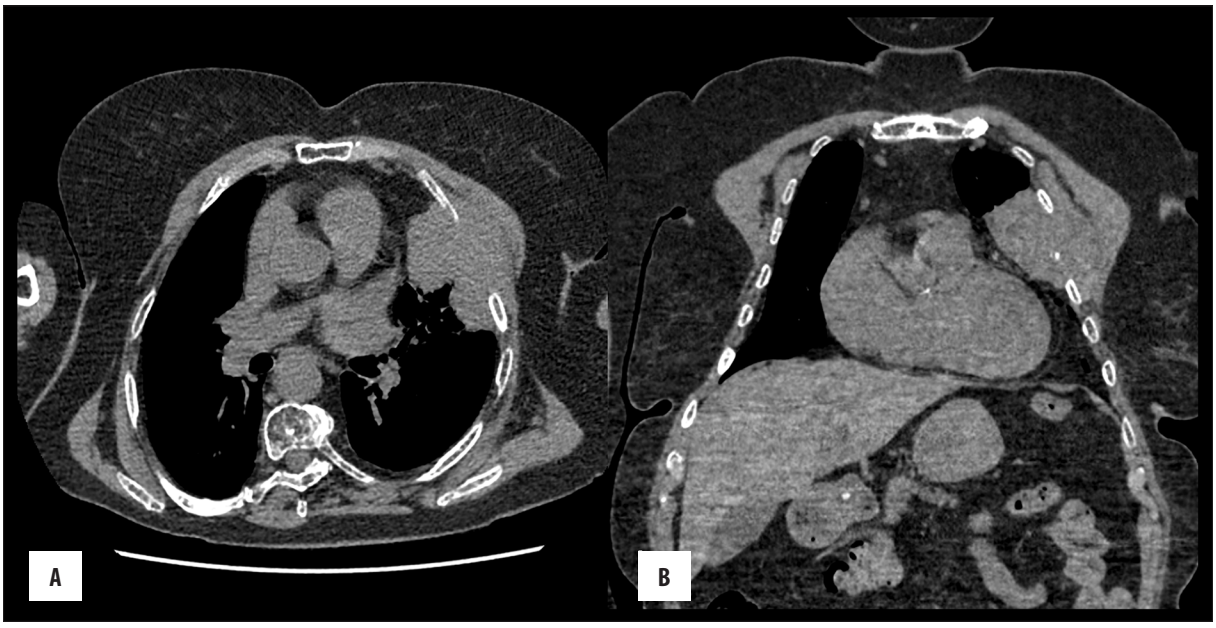

Figure 6. (**A**) Axial image and (**B**) coronal reconstruction, extraosseous infiltration.

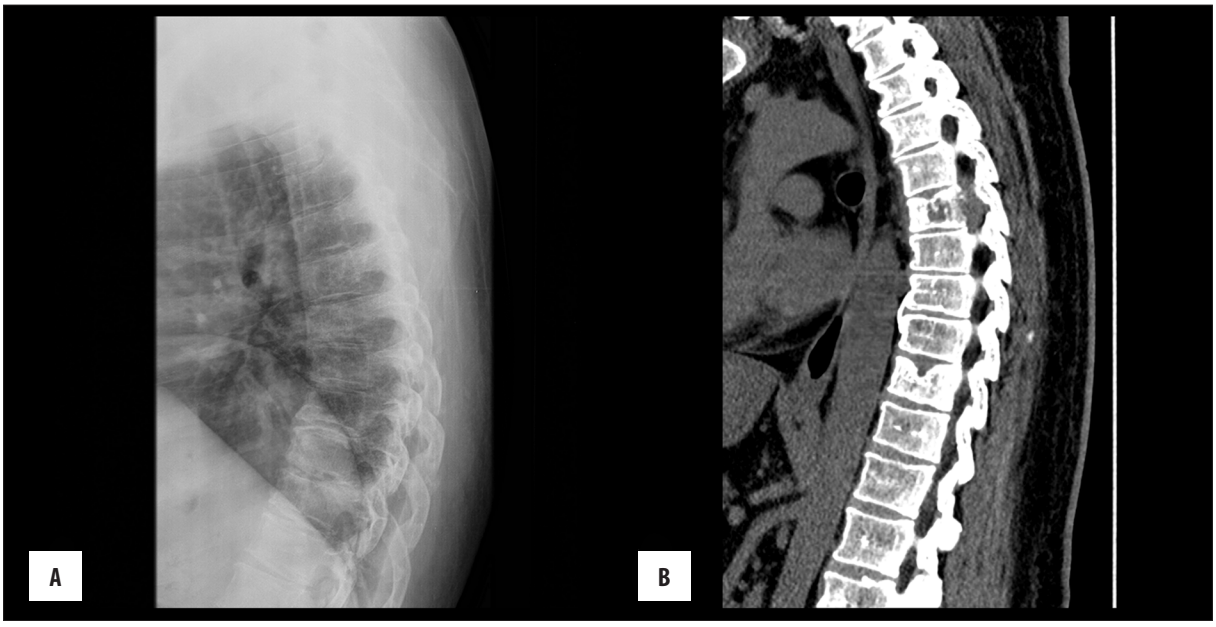

Figure 7. (**A**) X-ray and (**B**) CT sagittal reconstruction, vertebral lytic focus and spinal canal infiltration visible only on CT.

It should be also emphasized that WBLDCT was much faster and more convenient to patients, as compared to the set of radiographs that require special positioning for every projection. Using our 80-row scanner, final scanning after preparation of a scanning plan lasted only 12–15 s.

Discussion

Radiography is still the main imaging tool in MM patients; however, CT has promising characteristics and this modality could replace radiography as a screening test for lytic lesions and as a basic imaging tool for follow-up studies and treatment monitoring.

Horger et al. [8] were the first to explore whole-body CT protocols in MM patients. These protocols had lower radiation exposure related to imaging of the skeletal system, but at the same time preserved both sensitivity and image detail. Following their pioneering work, the use of WBLDCT in MM has become a standard practice in many European hospitals, and many studies confirmed the advantages of this technique [8–17].

Horger also found that WBLDCT can monitor treatment response [9] and shows bone marrow abnormalities correlated with haematological parameters [10].

Spira [11] found that WBLDCT correlates with haematological parameters during ongoing treatment.

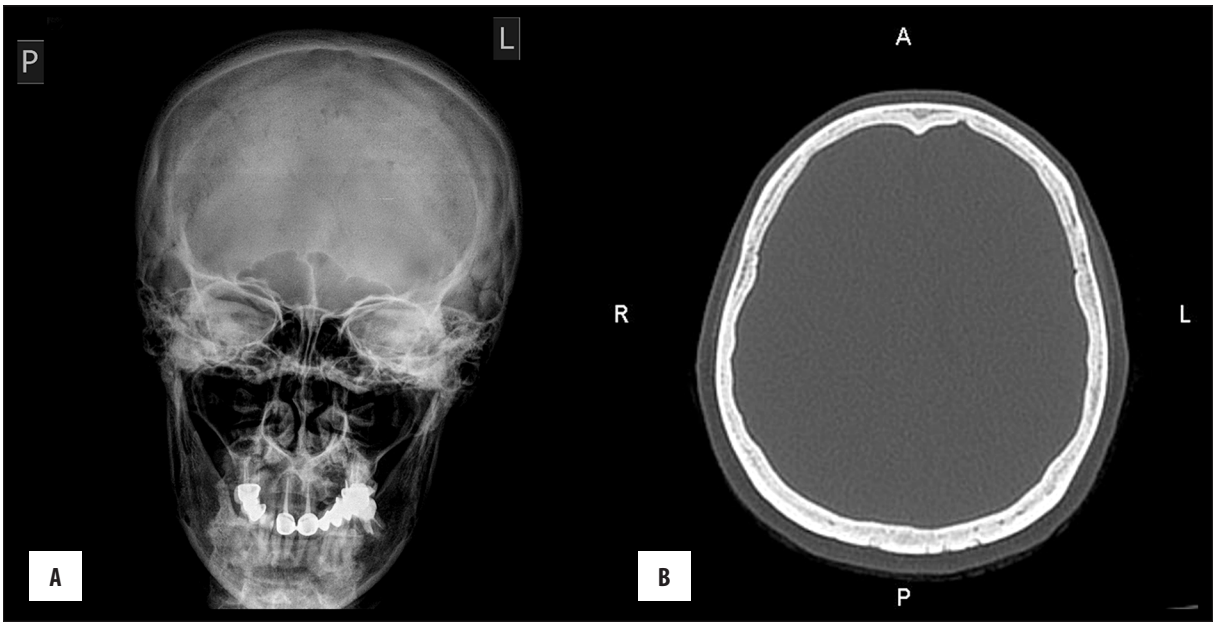

Figure 8. (**A**) X-ray and (**B**) CT axial image, suspicion of lytic lesions on skull radiograph that on CT turned out to be arachnoid granulations fovea.

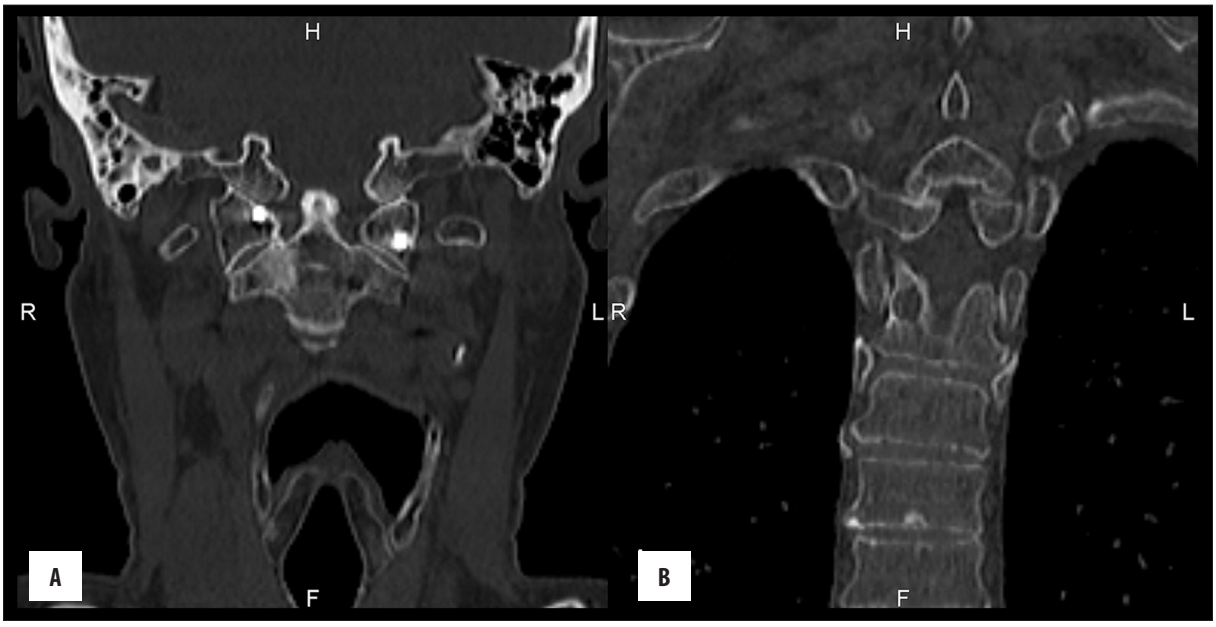

Figure 9. (**A**) CT coronal reconstruction, solitary bone plasmacytoma of C2 after treatment, (**B**) CT coronal reconstruction, new focus in another location confirming MM.

Kropil [12] and Princewill [13] proved a much higher detection rate of lytic bone lesions by body region in WBLDCT in comparison to WBXR.

Gleeson [14] found that WBLDCT correlates with WBMRI and has superior detection over WBXR.

However, in Poland, WBLDCT in MM patients is performed in few centres and the number of Polish publications on this method is very limited [18].

Our WBLDCT protocol parameters are similar to the most commonly used values in the WBLDCT studies published so far; tube voltage – 120 kVp [8–11,13,15], current tube-time product – 86mAs (70 mAs in [9–11], 90 mAs in [16], or 100 mAs in [13]).

Consequently, the radiation dose in our protocol (max. CTDIvol 7.4 mGy) is comparable to the values obtained in studies described above (from 4.1mGy [13] to 9.4mGy [16]).

The radiation parameters obtained in our WBLDCT (max. CTDIvol 7.4 mGy and DLP 660–810 mGy×cm) are much lower than typical values in the Whole-Body Trauma Protocol used in our Emergency Department (max. CTDIvol 50–60 mGy, DLP 2400–3000 mGy×cm).

Thus, it is possible to perform CT examinations of good quality that show typical MM features using much lower radiation dose in comparison to standard CT protocols. However, it must be emphasized that WBLDCT is not a tool to detect every possible pathology in the scanned regions. Because of that, we decided to include in every WBLDCT report a standard text defining that the procedure is a tool dedicated to skeletal assessment in MM patients.

The range of dose reduction should be reasonably justified. Many of MM patients are treated with radiotherapy that uses doses about a thousand times larger than the diagnostic doses in CT. Furthermore, because of the older age of most patents and their limited survival time, the period in which radiation-related complications can appear is much shorter compared, for example, to the increasing group of young otorhinolaryngological patients diagnosed by means of CT because of sinusitis.

There are publications presenting WBLDCT performed with current tube time product as low as 14 mAs [14]. In our opinion, such low values cannot ensure sufficient image quality. Furthermore, in a few of our obese patients, the current tube time product used (86 mAs) turned out to be too small, resulting in too high level of image noise. Therefore, in such cases it is advisable to increase the current tube time product to about 100 mAs.

In most modern CT scanners it is possible to use X-ray dose modulation systems, both in the Z axis and in the XY plane, to achieve dose reduction. In our Toshiba Aquilion PRIME, the SURE Exposure system can tailor the tube current along the longitudinal (Z) direction of the patient to account for variations in size and density and additionally can modulate the tube current in the axial (XY) plane to account for variations in shape and density. The level of dose reduction is defined by the level of noise expected and maximal/minimal values of tube current.

In all our WBLDCT examinations, we used constant values of tube current, similarly to other authors [8–16]. However, we plan to incorporate SURE Exposure in our WBLDCT protocol to obtain an even greater dose reduction.

Conclusions

It is possible to perform CT examinations of good quality that assess typical multiple myeloma features at much lower radiation doses in comparison to standard CT protocols.

WBLDCT can potentially increase diagnostic accuracy, relative to radiography, in multiple myeloma patients.

This pilot study should be followed by a larger study with a greater statistical power and quantitative measures.

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