Original Investigation

Automated "Bone Subtraction" Image Analysis Software Package for Improved and Faster CT Monitoring of Longitudinal Spine Involvement in Patients with Multiple Myeloma

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Rationale and Objectives: The study aimed to assess the diagnostic benefit of a novel computed tomography (CT) post-processing software generating subtraction maps of longitudinal non-enhanced CT examinations for monitoring the course of myeloma bone disease in the spine.

Materials and Methods: The local institutional review board approved the retrospective data evaluation. Included were 82 consecutive myeloma patients (46 male; mean age, 65.08 ± 9.76) who underwent 188 repeated whole-body reduced-dose Multislice Detector Computed Tomography (MDCT) at our institution between December 2013 and January 2016. Lytic bone lesions were categorized as new or enlarging versus stable. Bone subtraction maps were read in combination with corresponding 1-mm source images comparing results to those of standard image reading of 5-mm axial and 2-mm multiplanar reformat reconstructions (MPR) scans and hematologic markers, and classified as either progressive disease (PD) or stable disease (SD or remission). The standard of reference was 1-mm axial CT image reading + hematologic response both confirmed at follow-up. For statistical purposes, we subgrouped the hematologic response categories similarly to those applied for CT imaging (progression vs stable/response).

Results: According to the standard of reference, 16 patients experienced PD and 66 SD at follow-up. Th sensitivity, specificity, and accuracy for axial 5 mm + 2 mm MPR image versus bone subtraction maps in a "lesion-by-lesion" reading were 97.6%, 92.3%, and 97.2% versus 97.8%, 96.7%, and 97.7%, respectively. The use of bone subtraction maps resulted in a change of response classification in 9.7% of the patients ($n = 8$) versus 5 mm + 2 mm MPR image reading from SD to PD. Bone sclerosis lesions were detected in 52 out of 82 patients (63.4%). The reading time was significantly lower with the software bone subtraction compared to standard reading ($P < 0.01$) and 1-mm image reading ($P < 0.001$).

Conclusion: Accuracy of bone subtraction maps reading for monitoring multiple myeloma is slightly increased over that of conventional axial + MPR image reading and significantly speeds up the reading time.

Key Words: Multiple myeloma; lytic bone lesions; pelvic bones; CT imaging; bone subtraction maps.

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INTRODUCTION

Multiple myeloma is a malignant hematologic disease of mature B cells with an often guarded prognosis. The disease is characterized by an overproduction of monoclonal immunoglobulins or light-chain molecules. One major feature is myeloma bone disease (MBD), which manifests as focal or diffuse generalized bone destruction. A misbalance of osteoblasts and osteoclasts function results in an overall increased osteoclast activity and subsequent bone resorption as well as disabled osteoblasts (1). As a consequence, these osteolyses do not heal in the majority of patients (2).

On first diagnosis, almost 80% of the patients with multiple myeloma present with lytic bone lesions (3), which due to an often high number and small size can pose a challenge for radiological detection. In particular at follow-up and during treatment, the determination of MBD progression can be time-consuming and potentially inaccurate.

In the last decades, post-processing techniques, such as multiplanar reconstructions and the use of thin-slice reconstructions, significantly improved lesion detection. In multiple myeloma, typically the axial skeleton is involved first as the disease predominates in regions of predominant red marrow. Typically, myeloma first involves the bone marrow, which follows bone destruction as the tumor nests enlarge and the dense trabecular architecture of the cancellous bone limits their expansion. Before bone destruction becomes evident on radiographs or even computed tomography (CT), magnetic resonance imaging proves superior for the detection of infiltrative medullary lesions. Nevertheless, CT can provide helpful information during or after therapy, specifically for the detection of residual abnormalities, which are concerning for localized relapse (4,5). Although many myeloma patients can be monitored reliably with hematologic parameters such as M-gradient, the non-secretory group of patients does not secrete paraproteins and is therefore difficult to monitor. In this group of patients, imaging plays an important diagnostic role. Moreover, progression of MBD is often not affected by chemotherapy even in responding patients (6). For this reason, the detection of changes occurring in the axial skeleton at follow-up is critical for accurate assessment of progressive disease. CT is the most accurate technique for imaging assessment of bone. Several new techniques have been tested in the last years with the goal to increase detection of bone changes during disease surveillance. Some researchers applied automatic detection of bone metastases in the thoracolumbar spine (7) and visualization of bone metastases with maximum intensity projection and surface-shaded display techniques (8,9). In a small animal myeloma model, Evans et al. tested a fully automatic image analysis method created to detect osteolyses in the cortical bone of the tibia (10).

We developed a new post-processing technique for the longitudinal assessment of bone that is based on the generation of difference maps through the subtraction of non-enhanced three-dimensional CT datasets that were acquired at different points in time. Therefore, the aim of this study was to compare the accuracy and time requirements of this new technique with visual comparison for the interpretation of CT datasets of the spine in patients with multiple myeloma.

MATERIALS AND METHODS

This retrospective study was approved by our institutional review board with a waiver of informed consent.

Subjects

The study cohort consisted of 82 patients (46 male; mean age 65.08 ± 9.76 years, range 38–81y) with multiple myeloma who were referred to our service between December 2013 and January 2016.

TABLE 1. Patients' Demographics

No. of Patients	$n = 82$	100%
Age, years, mean ± SD	65.08 ± 9.76	–
Range	38–81	–
Age at initial diagnosis, mean ± SD	61.21 ± 10.36	–
Male	46	56.09
Female	36	43.91
Durie and Salmon		
I	23	28.0
II	11	13.4
III	48	58.6
ISS		
I	42	51.2
II	13	15.8
III	27	33.0

ISS, International Staging System; SD, standard deviation.

All patients underwent a baseline and at least one follow-up whole-body reduced-dose multidetector CT study. The patients' age at initial diagnosis was 61.21 ± 10.36 years. All patients were followed by our hematology department, and underwent laboratory tests and clinical assessments.

Patients were classified into stage I ($n = 23$), stage II ($n = 11$), and stage III ($n = 48$) according to the Durie and Salmon classification (11). In addition, in accordance with the International Staging System (12), patients were classified into stage I ($n = 42$), stage II ($n = 13$), and stage III ($n = 27$). Patients' characteristics are shown in Table 1.

Based on hematologic diagnosis following myeloma, subtypes were registered: 34 of the patients had IgG kappa (41.9%) and 20 had IgG lambda (24.8%). Three patients had IgA kappa (3.6%) and three patients had IgA lambda (3.6%). Nine (11.1%) of the 82 patients had light-chain kappa and five (6.0%) had light-chain lambda. Two (2.4%) patients had a solitary manifestation, two had non-secretory myeloma, and another two had smouldering myeloma (each 2.4%). One patient had an extramedullary myeloma (1.2%) and another had POEMS (polyneuropathy, organomegaly, endocrinopathy/edema, M-protein, and skin abnormalities) (1.2%).

The patients were grouped into ongoing anti-myeloma treatment ($n = 22$, 26.8%), post-treatment imaging surveillance ($n = 29$, 35.4%), and no therapy ($n = 31$, 37.8%). The applied therapy regimens are shown in Table 2. All patients except those with smouldering myeloma and POEMS received bisphosphonates. Twenty-nine (35.3%) patients underwent autologous ($n = 21$) or allogeneic ($n = 8$) stem cell transplantation.

CT Image Protocol

A total of 188 CT examinations, consisting of 82 baseline CTs and 106 follow-up CTs, were available for final evaluation. Seventeen patients received two or more follow-ups. Mean