Computers in Biology and Medicine 71 (2016) 57–66

Contents lists available at ScienceDirect

Computers in Biology and Medicine

journal homepage: www.elsevier.com/locate/cbm

Fully automated classification of bone marrow infiltration in low-dose CT of patients with multiple myeloma based on probabilistic density model and supervised learning

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ARTICLE INFO

Article history:
Received 11 August 2015
Accepted 1 February 2016

Keywords:
Multiple myeloma
Classification
Low-dose CT
Bone marrow CT
Femur

ABSTRACT

This paper presents a fully automated method for the identification of bone marrow infiltration in femurs in low-dose CT of patients with multiple myeloma. We automatically find the femurs and the bone marrow within them. In the next step, we create a probabilistic, spatially dependent density model of normal tissue. At test time, we detect unexpectedly high density voxels which may be related to bone marrow infiltration, as outliers to this model. Based on a set of global, aggregated features representing all detections from one femur, we classify the subjects as being either healthy or not. This method was validated on a dataset of 127 subjects with ground truth created from a consensus of two expert radiologists, obtaining an AUC of 0.996 for the task of distinguishing healthy controls and patients with bone marrow infiltration. To the best of our knowledge, no other automatic image-based method for this task has been published before.

1. Introduction

Multiple myeloma is a clonal plasma cell disorder that results in infiltration of bone marrow and osteolytic lesions of the skeleton. The diagnosis and staging of multiple myeloma are based on blood and urine tests, bone marrow biopsy and imaging (radiography, CT, PET-CT and MRI) [1,2]. The treatment is commonly initiated when the disease becomes symptomatic, usually by skeletal involvement, which can be detected by imaging.

Computer aided diagnostic tools exist for other types of cancer such as breast [3], lung [4] or large bowel cancer, and also for other manifestations of multiple myeloma, such as osteolytic lesions [5] and spine bone lesions [6].

There are non-imaging automatic methods to diagnose multiple myeloma using gene expression profiles of plasma cells [7,8] or biomarkers from blood serum samples [9]. This test is routinely used for screening but is by itself not sufficient for the diagnostics.

We are not aware of an automatic image based tool targeting multiple myeloma related to bone marrow infiltration detection in long bones. This task is currently performed manually by radiologists [10,11]. An automated image analysis method suggested in this study has the potential to accelerate the analysis, improve its reproducibility and reduce the radiologist's workload.

We have chosen CT for the following reasons: Compared to 3D imaging methods, plain radiography is insensitive to the detection of bone marrow infiltration [12–14]. MRI performs best of all imaging methods, especially in the vertebral column [15–17]. However, compared to CT, MRI is slow, more burdensome, expensive and less available. The value of PET is incremental, consisting of the assessment of increased metabolic activity in the tumoral mass [18,19].

In this work, we use a multidetector CT which offers a good trade-off between the cost, acquisition speed and diagnostic performance [20]. We have used a low-dose CT with hybrid iterative reconstruction technique [21,22] in order to reduce the radiation dose to the patient. However, such images are noisier than in standard dose CT which makes the automatic analysis more challenging.

Bone marrow infiltration is difficult to assess in axial skeleton by CT due to the presence of calcium in cancellous bones unless spectral decomposition is performed [23]. Therefore, we chose to evaluate bone marrow infiltration in the medullary cavity of long bones that has low calcium content and in adults it should contain predominantly low density fat. We chose the femur (thigh bone) as it is the largest cortical bone in humans.

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http://dx.doi.org/10.1016/j.compbiomed.2016.02.001
0010-4825/

1.1. Proposed method overview

First, the bone marrow is segmented (Section 2.1) and femurs are identified (see Fig. 1 for a flow chart). Infiltrated bone marrow appears bright. However, the density itself cannot be used to reliably detect the lesions, as there are other features of the same density such as the red bone marrow, inhomogeneity of the yellow bone marrow, non-neoplastic lesions (bone infarction), and artifacts (beam hardening artifact and image noise). Multiple myeloma presents multiple foci of bone infiltration that may coalesce (Fig. 2).

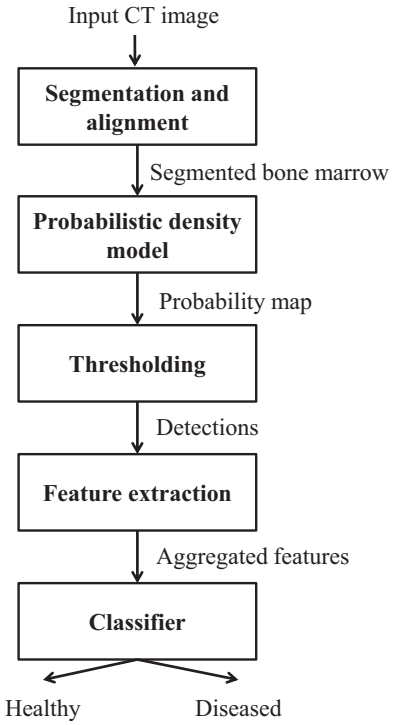

Fig. 1. Flow chart of the proposed method to classify CT images of femurs.

In addition, the lesion appearance is very variable and the number of positive cases available for training is limited. To address these issues, we do not attempt to model the appearance of the lesions. Instead, we create a probabilistic, spatially dependent model of bone-marrow density in healthy femurs. High density voxels, which may be related to the infiltrated bone marrow, are detected as outliers of this model. A set of global, aggregated features is calculated, representing all detections. In turn, these features are used to classify each subject as either healthy or diseased.

2. Methods

2.1. Bone marrow segmentation

We start by obtaining a binary mask $\mathbf{M_c}$ of the cortical (compact) bone by thresholding at 250 HU. (See Fig. 3.) In each *xy* 2D slice, we find the bone marrow mask $\mathbf{M_{bm}}$ (Fig. 3 top-right, *xz* slice shown) using connected component analysis [24], as a region enclosed by pixels in $\mathbf{M_c}$. The two biggest 3D connected components of $\mathbf{M_{bm}}$ correspond each to the bone marrow mask $\mathbf{M_f}$ of a single femur, which are processed separately. This method is simple and fast, yet sufficiently robust – we could successfully segment all subjects in our dataset.

2.2. Femur alignment

We align the femurs vertically, by performing the principal component analysis (PCA) [25] on the 3D coordinates of the femur bone marrow voxels $\mathbf{M_f}$. A bounding box enclosing $\mathbf{M_f}$ is rotated

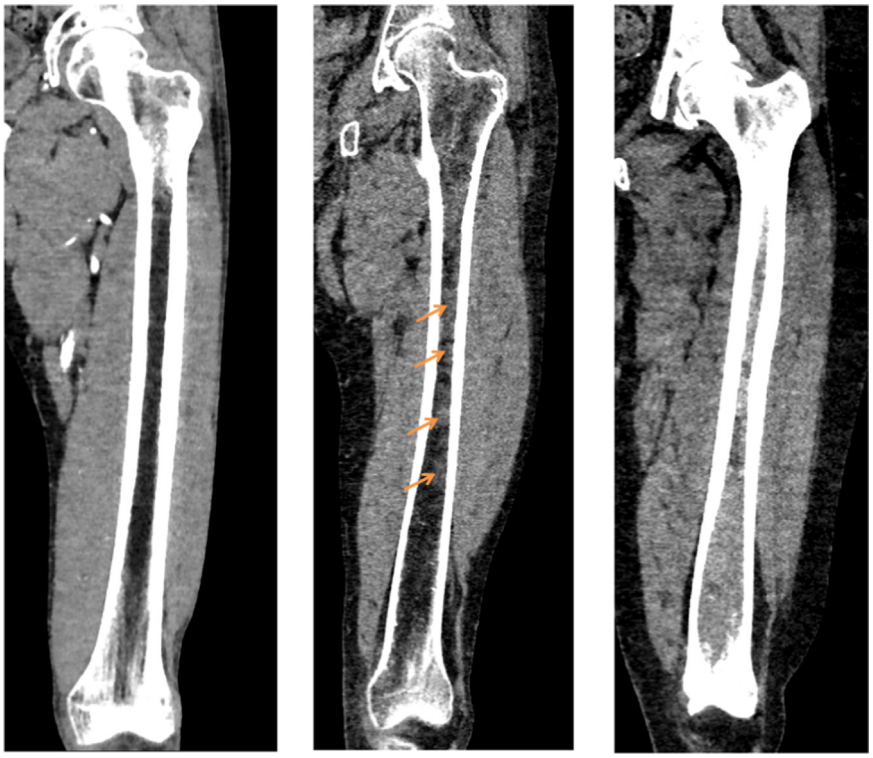

Fig. 2. Healthy femur with fatty bone marrow (left), femur with islets of bone marrow infiltration (middle) and femur coalescing diffuse bone marrow infiltration (right).