**QUANTITATIVE CHARACTERIZATION OF METASTATIC DISEASE IN THE SPINE AND DEVELOPMENT OF AN AUTOMATED TRACKING TOOL**

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INTRODUCTION

Spinal metastases are in 90% of prostate, 75% of breast, 45% of lung, and 30% of renal terminal cancer patients1. Computed tomography (CT) imaging has been used to evaluate clinical treatments for spinal metastases, however, in a restrictively qualitative fashion. Reliable diagnosis of tumor burden and progression through serial CT images is hindered by the subjective and inconsistent nature of visually contouring regions of interest (ROIs) from stacks of 2D images viewed at non-standardized grayscale mappings2. Attempts at quantification that simply calculated mean densities over an ROI also fail to elucidate the true severity and spatial distribution of spinal metastases.

The objective of this study was two-fold: (1) to establish an objective method to quantitatively characterize the extent and spatial distribution of metastatic disease in the bony spine; and (2) to develop an automated clinical research tool for tracking metastatic progression in the spine over time. It was hypothesized that these goals can be achieved through histogram analysis of vertebral density distributions using 3D reconstructions of serial CT scans.

METHODS

32 healthy vertebrae (sampled from 7 patients and spanning vertebral levels T5 to L5) were metastatically involved (sampled from 6 patients, 8 thoracic, 3 lumbar) were studied. A research protocol standardized serial patient CT scans (initial, 4month) of T6-L5 spines from a GE Lightspeed Plus CT Scanner at 120kVp, 1.25mm slice interval, and 2.5mm slice thickness. Standard reconstructions, featuring enhanced contrast resolution, were found to be optimal for differentiating small density differences between metastatic tissue and normal bone. The variation in reconstructed diameters (DDFOV 18 to 24cm) was compensated for by down-sampling all scans to a common pixel spacing of 0.4680/0.468 mm2, using a Lanczos resampling algorithm, which was determined through cadaveric phantom studies to have an accuracy of 98% (Amira 3.1.1. TGS, Berlin). To achieve an effective histogram concurrence of 97%, scans to be quantitatively compared were limited to a radiation exposure difference of <3000mAs.

 Entire trabecular regions (inside of the cortical shells) within the vertebrae bodies (VBs) were analyzed, chosen because vertebral bodies are involved in 80% of spinal metastases due to extensive vasculature and greater volumetric size than posterior elements1. The trabecular bone regions were segmented by atlas-based deformable registration programmed in ITK. Voxel intensity distribution histograms of the VBs (histogram plots of voxel counts over tissue density (x-ray attenuation) in Hounsfield Units (HU)) were used to characterize both healthy and tumorous vertebrae (Amira). Histograms were compared using one-way repeated measures ANOVA (p<0.05). Histogram intersection4, H(IM), was also used as a similarity measure in comparing histograms, I and M, by summing the overlap of voxels over n bins. Least-squares curve-fitting of histograms was performed using Matlab (Mathworks, Natick); the accuracy of a regression curve was measured by its RMS and H(IM) against histogram data. Fits on healthy vertebral levels from patients were used to predict the ideal healthy histogram for adjacent diseased vertebral levels within the same patient.

Tumors were segmented as connected areas with voxel intensities between specified thresholds (magic wand tool, Amira). The tested lytic and blastic thresholds were all defined as functions of the predicted healthy Gaussian µ and σ, as opposed to fixed absolute thresholds. The segmented tumorous regions were then removed from the distributions of the normalised VBs 11 non-fitting Gaussians to the remaining healthy voxels, the ideal segmentation thresholds were then determined as those that best restored the Gaussian uniformity of the remaining distributions.

Once a methodology for characterizing spinal metastases using histogram analysis was established, an automated tool implementing the method, scripted in Tool Command Language, was developed for tracking tumor progression over time. The tool takes two serial CT scans as DICOM format as inputs; the tool registers landmark-based, surface-aligning, and image-matching modules from Amira. ROIs are segmented from user-identified healthy and metastatic vertebral levels, using an atlas-based deformable registration program (ITK, NLM, Bethesda). Finally, 3D visualizations and histograms of segmented metastatic regions are generated with quantitative analyses.

RESULTS

Histograms of healthy vertebrae were found to be Gaussian distributions (avg. RMSD = 30 voxel counts), as expected statistically for a uniform material. Gaussian regression curves f(x)=A α exp(-(x-µ)/σ2) could thus be fitted to the histograms, where µ is the mean, σ is the standard deviation, and A α scales to segmented healthy VB volumes. The Gaussian µ ranged from 120 to 290HU within our tested sample, presumably due to differences in age and activity. However, the histogram data sets were not significantly different (p>0.8) across intra-patient vertebral levels T5-L5. Consequently, taking the same µ and σ from a nearby healthy vertebra, the original healthy Gaussian histograms of currently metastatic levels can be predicted through a simple scaling of VB volumes (V J: f(x)=A α exp(-(x-µ)/σ2), A α=A 2 V N H). Ideal lytic and blastic segmentation thresholds were determined to be µ- σ and µ+2σ respectively. While the histograms of metastatic VBs were non-Gaussian (RMSD of 56 voxels), subtracting from them the tumorous regions segmented accordingly would restore the Gaussian nature of the distributions (avg. RMSD of 24 voxels).

Histograms of metastases segmented using these optimized thresholds can be used to quantitatively characterize metastatic involvement in terms of: (1) lytic/ blastic volumes from areas under the curves; (2) severity of the pathologic involvement from the distribution and range; (3) tumor progression over time or treatment effects by taking the difference between the initial and sequential scans (Figure 1).

The performance of the scripted tracking tool was evaluated. The runtime of the automated portion averaged 8min 5sec ± 42sec over 5 repeated runs on a 3 GHz Pentium 4 machine with 1 GB RAM. Using conservative atlases for ROI segmentations, metastatic volumes could be consistently determined (standard deviation <0.75% of ROI volume).

DISCUSSION

By using thresholds relative to the mean and standard deviation of adjacent vertebra inter-patient variability in bone quality can be accounted for. However, the proposed lytic and blastic segmentation thresholds of µ-σ and µ+2σ were only validated for the CT scanning parameters stated above. Current research is underway to investigate whether different scanning parameters can resolve density differences between osteolytic structures and healthy trabecular bone more distinctly on CT images. Achieving this would necessitate a new definition of the lytic threshold, but would improve segmentation accuracy and precision. The method for histogram analysis presented does provide a quantitative assessment of disease; however, clinical interpretation is still crucial in verifying tumor volume results, since CT intensity-based analysis does not distinguish between tumor-induced bone formation, over-corrective healing and calcifying treatment effects.

In summary, our proposed histogram-based method for characterizing spinal metastases shows great potential in extending the quantitative capacity of CT-based radiographic evaluations. The development of a user-friendly tool for this purpose will encourage tracking of metastatic progression and treatment effectiveness in clinical research applications.


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**Fig 1. Histograms of Metastatic Vertebrae: Quantifiable characteristics are tumor volume/severity (left) and tumor progression (right).**

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