Identification of asymmetric pulmonary nodule growth using a moment-based algorithm

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ABSTRACT

The growth rate of pulmonary nodules has been shown to be an indicator of malignancy, and previous work on pulmonary nodule characterization has suggested that the asymmetry of a nodule's shape may be correlated with malignancy. We have also observed that measurements in the axial direction on CT scans are less repeatable than measurements in-plane and this should be considered when making lesion size-change measurements. To address this, we present a method to measure the asymmetry of a pulmonary nodule's growth by the use of second-order central moments that are insensitive to z-direction variation. The difference in the moment ratios on each scan is used as a measure of the asymmetry of growth. To establish what level of difference is significant, the 95% confidence interval of the differences was determined on a zero-change dataset of 22 solid pulmonary nodules with repeat scans in the same session. This method was applied to a set of 47 solid, stable pulmonary nodules and a set of 49 solid, malignant nodules. The confidence interval established from the zero-change dataset was (-0.45, 0.38); nodules with differences outside this confidence interval are considered to have asymmetric growth. Of the 47 stable nodules, 12.8% (6/47) were found to have asymmetric growth compared to 24.5% (12/49) of malignant nodules. These preliminary results suggest that nodules with asymmetric growth can be identified.

Keywords: pulmonary nodule, moment analysis, asymmetric growth, computed tomography, zero-change, lung cancer

1. INTRODUCTION

Improvements in CT scanner technology have enabled radiologists to find and measure ever smaller nodules. Diagnosing these smaller nodules is often difficult. One of the most important indicators of the malignancy of a pulmonary nodule is its growth rate.[1,2] Growth assessment of pulmonary nodules on CT scans have shown that malignant nodules have a higher growth rate than benign nodules,[3,4] however, they all differ in the precise threshold used to identify malignant nodules. In some cases, a conclusive result can not be obtained from growth rate alone, and as a result, other features have been examined for diagnosing pulmonary nodules.

Studies on pulmonary nodule characterization have found that shape is often a positive predictor of malignancy. Aoyama et al computed the irregularity of a nodule's shape, as compared to an ellipse, as a feature in their characterization system.[5] Takashima et al suggested that the three-dimensional ratio of the extents of a pulmonary nodule is an indicator of malignancy.[6] Several other nodule characterization systems have used shape features, though they were not always used in the final system.[7–9] Previous work by our group has also made use of shape features computed using moments.[10]

Most previous work on nodule shape only measures shape on a single scan for the purpose of characterization. Very little work has been performed on measuring the change in nodule shape from one time to another, although there have been cancer growth models that take into account non-symmetric growth.[11] We make the assumption that malignant nodules, due to their fast growing nature, are more likely than stable nodules to exhibit asymmetric growth; if this assumption is true, measuring the asymmetry of a nodule's growth may improve the accuracy of diagnosis. To investigate this, we developed an algorithm to measure the asymmetry of the growth of a nodule using moment analysis. As past studies have shown that slice thickness has a significant

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effect on volume measurement,[12] this algorithm uses all the data in the image without directly computing an extent in the axial direction. The approach is described in Section 2 followed by results on several datasets of nodules in Section 3. Section 4 presents a discussion of the results and the paper is concluded in Section 5.

2. MATERIALS AND METHODS

The algorithm requires segmentation of the nodule prior to computing the moments. Segmentation of the nodule is performed using a semi-automated algorithm described by Reeves et al[13] that requires the manual specification of a seed point within the nodule. The segmentation algorithm determined the center and approximate size of the nodule, resampled the nodule into isotropic space, and performed vessel and pleural wall removal if necessary. The result of the algorithm is a binary image indicating which voxels belong to the nodule. Once the segmented image is obtained, the moments can be computed as described below.

2.1. Moments

Moment analysis has been used in for computer vision tasks varying from pattern recognition[14] to shape identification tasks[15] and nodule characterization algorithms.[10,16] The general equation for a moment of order $p+q+r$ for a 3D image is:

$$m_{pqr} = \sum_x \sum_y \sum_z x^p y^q z^r f(x,y,z)$$

where x, y, and z are the voxel coordinates and $f(x,y,z)$ is the intensity of the voxel. For a binary image, $f(x,y,z)$ is either 0 or 1. Note that this function is sensitive to the location of the region under consideration. This is undesirable since the same nodule in different locations should, for the purpose of growth analysis, result in the same value, assuming no change in size. This is addressed by using central moments, which have the following form:

$$\mu_{pqr} = \sum_x \sum_y \sum_z (x-\bar{x})^p (y-\bar{y})^q (z-\bar{z})^r f(x,y,z)$$

where $\bar{x} = \frac{m_{100}}{m_{000}}$, $\bar{y} = \frac{m_{010}}{m_{000}}$, and $\bar{z} = \frac{m_{001}}{m_{000}}$.

2.2. Asymmetric growth measurement

The goal in measuring asymmetric growth is to be able to quantify the degree of disparity between growth in various directions. Complicating this task is the anisotropic nature of most modern CT scanners; the in-plane resolution is typically higher than the axial resolution. As a result, we have observed that measurements made in the axial direction are less repeatable than measurements in-plane; however, we would like to still use all the available data.

To address this, our method makes use of image moments. The second-order central moments give the length of the axes of the ellipsoid of inertia of the nodule. Only the ratio of the moments corresponding to the in-plane directions is used to compute the asymmetry of the nodule growth. The difference of the moment ratio (DMR) of the second-order moments is determined according to the following equation:

$$DMR = \frac{\mu_{200}}{\mu_{020\,T2}} - \frac{\mu_{200}}{\mu_{020\,T1}}$$

Although only μ_{200} and μ_{020} are used in this equation, both of these are computed over all the pixels in the segmented region, thus making use of all the available data. Note that the DMR is invariant to nodule location and size.

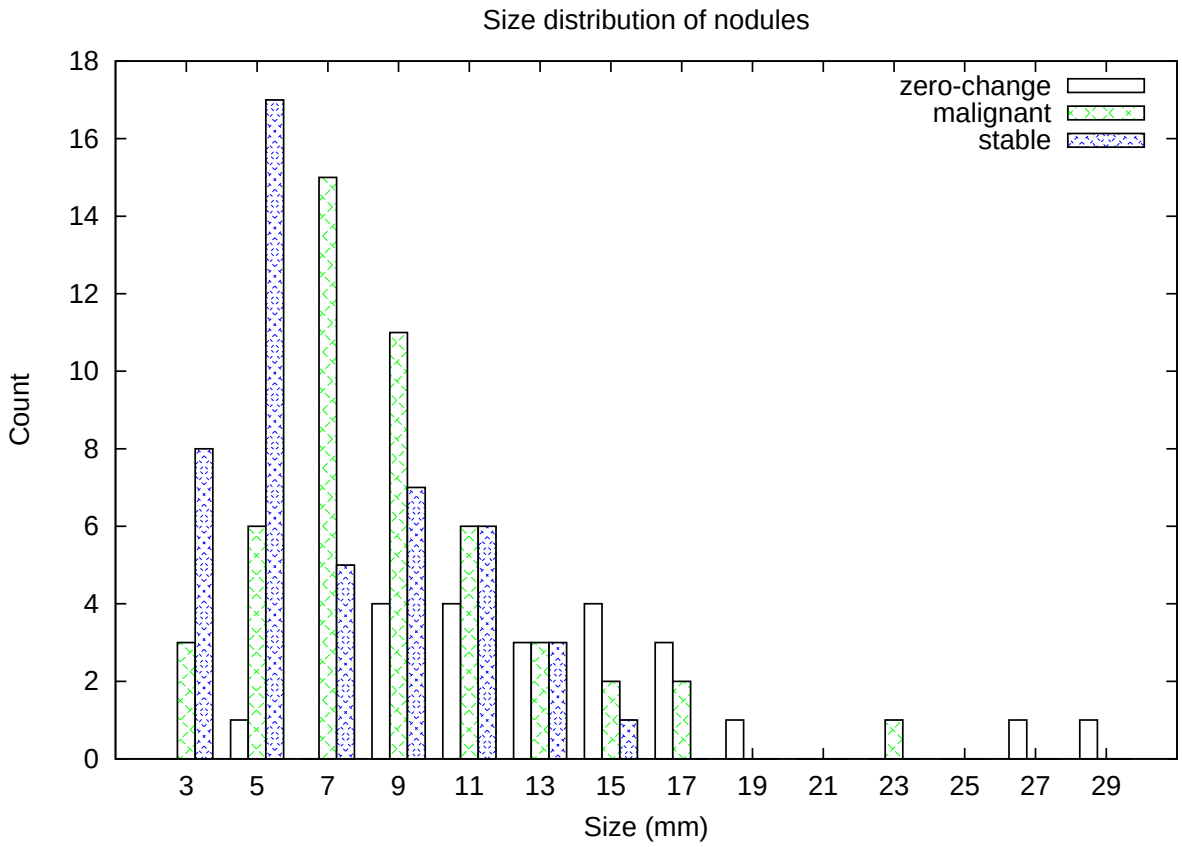

Figure 1. Size distribution of nodules in the zero-change, stable, and malignant datasets. The value along the x-axis indicates the middle size of nodules in the bin.

2.3. Experiment Design

As with all measurement methods, there is expected to be some uncertainty in the measurement of asymmetric growth by this moment-based method. Establishing the expected range of uncertainty is critical for correct interpretation of the results of the method. Thus, to establish what range of values is significant for measuring asymmetric growth, an experiment was performed using a zero-change dataset of nodules. Nodules in this dataset were imaged several times in the same session in the initial stages of a lung biopsy and thus should not have changed in size. Consequently, the nodules should not have any asymmetry between the two scans. The difference in moment ratios (DMR) was measured for the twenty-two nodules in this dataset, and the 95% confidence interval was established. DMR values within this interval could be expected for a nodule with no change between scans; any values of the DMR outside of this range were considered significant for the measurement of asymmetric growth.

Having established the range of significant values for the DMR, the method was applied to two datasets of solid pulmonary nodules. One dataset consisted of 47 stable pulmonary nodules, while the second dataset consisted of 49 malignant pulmonary nodules. The number of nodules with asymmetric growth was compared between the two datasets, and Fisher's exact test was used to determine whether there was a significant difference in the frequency of nodules exhibiting asymmetric nodule growth between the two datasets.

2.4. Data

There were three sets of nodules used in this study. The zero-change dataset was comprised of 22 cases with with multiple scans taken a few minutes apart in the initial stages of a lung biopsy so that there was no change in the

Table 1. Summary of image and scanner parameters for each dataset

	Zero-change	Stable	Malignant
Number of nodules	22	47	49
In-plane resolution (mm)	0.56 – 0.78	0.19 – 0.78	0.19 – 0.82
Slice thickness (mm)	1.25, 2.5, 5.0	1.0 or 1.25	1.0 – 5.0
kVp	120	120	120 or 140
Current (mAs)	40–250	40–330	40–300
Scanner model	GE LightSpeed QX/i or LightSpeed Ultra	GE LightSpeed Ultra, Pro 16 or VCT, HiSpeed CT/i, or Genesis	GE LightSpeed QX/i or Ultra, HiSpeed CT/i, or Genesis

nodule volume between the scans. All cases had a nodule of solid consistency, as determined by a radiologist, with at least two scans with a whole-lung field of view that included the entire nodule. In half of the cases, the scans were taken using the same slice thickness, with ten of the eleven cases at 1.25 mm slice thickness and one at a slice thickness of 2.5 mm. In the other half of the cases, scans were taken at different resolutions, with at least one scan at a slice thickness of 1.25 mm. In three cases, the second scan had a 5.0 mm slice thickness while eight had 2.5 mm. The mean size of the nodules in the dataset was 14.1 mm with a standard deviation (SD) of 5.6 mm. A plot of the size distribution of the nodules in this dataset is shown in Figure 1, and additional scan information is shown in Table 1.

The second dataset was comprised of 47 solid stable pulmonary nodules with at least two time-separated thin-slice (1.0 or 1.25 mm slice thickness) scans selected from the Weill Cornell Medical Center database. The consistency of the nodules was determined by a radiologist. The nodules were considered stable after two years of no clinically significant change or a negative biopsy result. In twelve cases, a different scanner was used for the second scan. The slice thickness was the same for both scans in all cases except one where the first scan had a slice thickness of 1.0 mm while the second scan was 1.25 mm. Additional scanner parameter information is given in Table 1. The nodules had a mean initial size of 7.0 mm with a SD of 3.3 mm with the distribution in Figure 1 and a median interval between scans of 425 days.

There were 49 solid malignant nodules in the third dataset selected from the Weill Cornell Medical Center database. The consistency of the nodules was established by a radiologist, and the malignant status was verified by a positive biopsy result. The mean initial size was 8.9 mm with a SD of 3.9 mm with the distribution shown in Figure 1. The median interval between scans was 98 days with a median growth index of 11.8% (doubling time 186 days). A majority of the nodules (32) were on thin-slice scans. A summary of scanner and image parameters are given in Table 1.

3. RESULTS

On the zero-change dataset, the average difference of the moment ratios (DMR) was -0.04 with a standard deviation of 0.21, resulting in a 95% confidence interval of (-0.45,0.38). DMR outside of this interval can be considered to be significant. For the stable nodules, only 12.8% (6/47) had a DMR outside the confidence interval above, signifying asymmetric growth. A larger percentage of malignant nodules, 24.5% (12/49), exhibited asymmetric growth. An example of a malignant nodule where the difference of the moment ratio was not significant and therefore does not exhibit asymmetric growth is shown in Figure 2. An example of a nodule where the DMR was outside of the confidence interval, thus exhibiting asymmetric growth, is shown in Figure 3.

4. DISCUSSION

Just as growth rate is an important indicator of malignancy, accurate measurement of the asymmetry of a nodule's growth may also have implications on the diagnosis of an indeterminate pulmonary nodule. Although many studies on characterization have attempted to quantify irregularities in nodule shape, few studies have looked at the growth rate pattern of nodules to asses whether there is even growth around the nodule. Due to the difficulty of manually measuring the amount of non-symmetric growth, evaluation of the algorithm was based

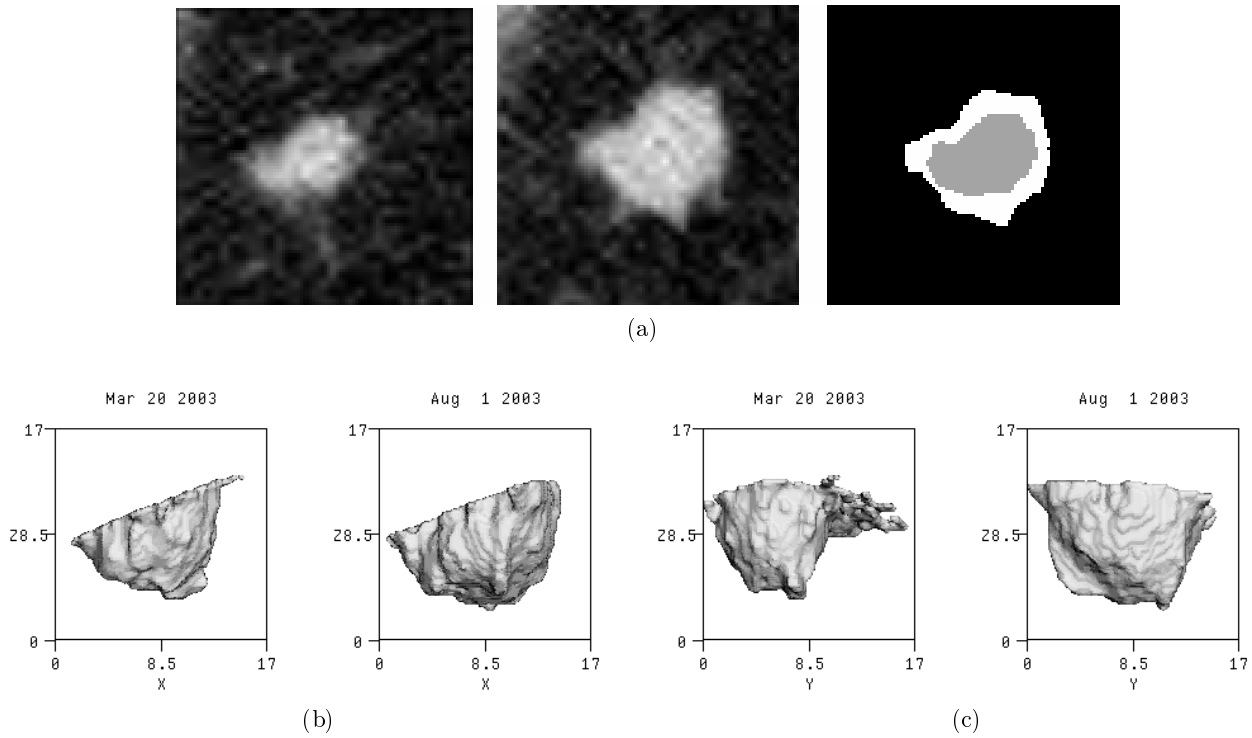

Figure 2. A malignant nodule not exhibiting asymmetric growth. a) Single slice through the nodule, scan at time 1 on the left, time 2 in the middle, and the segmented nodule region (T1: gray, T2: white). Light-shaded 3D visualizations of the nodule, b) coronal view and c) sagittal view.

on the assumption that malignant nodules are more likely to exhibit asymmetric growth due to their rapid rates of growth. As shown by Figures 2 and 3, visual review of the nodules identified by the moment-based method as having asymmetric growth agreed with the moment-based method for the majority of cases.

According to our automated method, only 12.8% of the nodules in the stable dataset exhibited asymmetric growth compared to the 24.5% of nodules in the malignant dataset. The odds ratio was 2.2, and this difference may be useful in differentiating benign from malignant nodules, but additional data is required – the p-value for Fisher's exact test was 0.11, which is not high enough to show significance. Comparing the actual difference in moment ratio (DMR) between the stable and malignant cases showed them to be fairly similar. For the stable cases, the average DMR was 0.07 with an SD of 1.39, while for the malignant cases, the average DMR was 0.13 with an SD of 1.15. This wider spread of DMR values for the stable cases compared to the malignant cases coupled with the lower number of cases outside of the established confidence interval further suggesting that the stable nodules with asymmetric growth are less likely to occur than in malignant nodules.

There were a few cases where significant asymmetric growth was measured but was not obvious in visual review. An example of a such a case is shown in Figure 4. This stable nodule had a DMR of 2.41, yet it is somewhat difficult to see any visible asymmetry to the volume change. However, this nodule had very little growth between the two scans, with a measured volume change of 6.5% over an interval of 877 days (doubling time of 9611 days) which corresponds to a size change of 9.54 mm to 9.74 mm. This size change is less than a voxel on a whole lung field of view CT scan; thus, any unevenness in the growth will likely be undetectable through visual observation.

Although the preliminary results of this method are promising, there a few remaining issues to address. The method is somewhat sensitive to the quality and repeatability of the segmentation – if there is a vessel located at one side of a nodule, whether the segmentation includes the nodule or not has a large impact on the DMR value. This could be ameliorated somewhat by using a function that weights the pixels at the center of the lesion

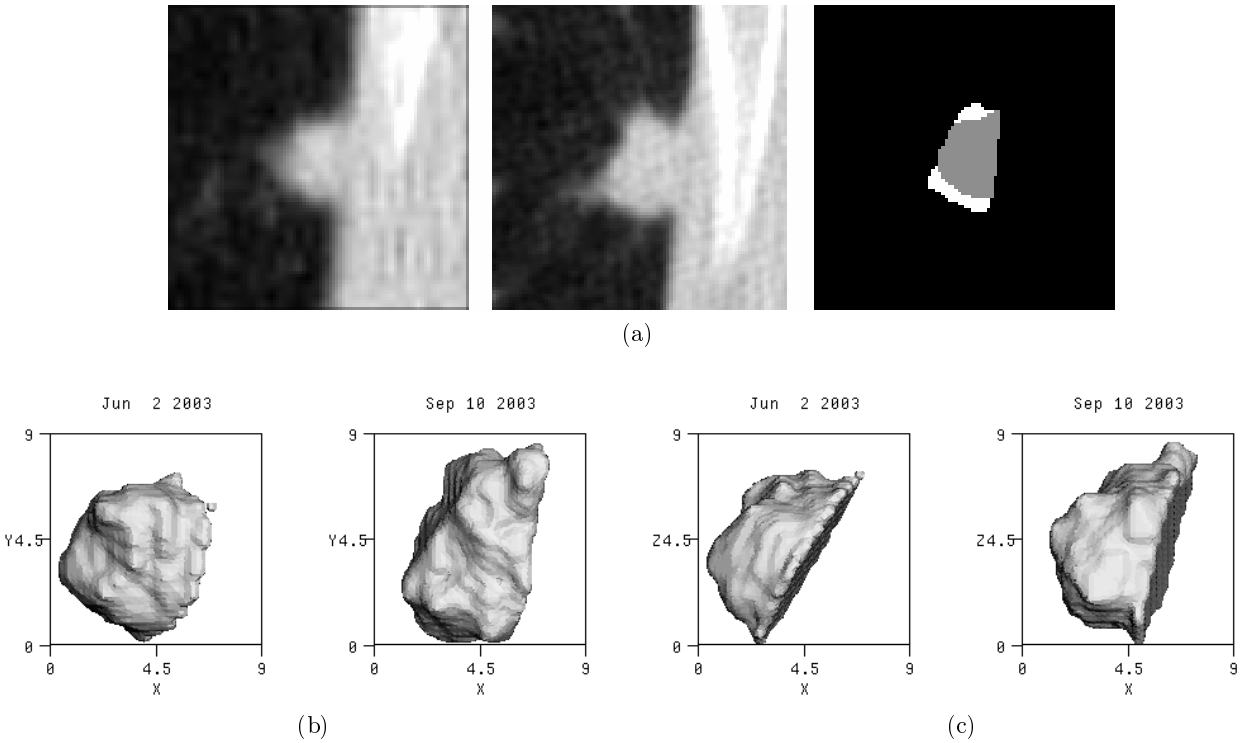

Figure 3. A malignant nodule exhibiting asymmetric growth, a) central slice of the nodule shown (left: T1, center: T2) with the segmented nodule regions on the right (T1: gray, T2: white). Light-shaded 3D visualizations the nodule, b) coronal view and c) sagittal view. Note that there is much more growth in the y direction than the other two directions.

more than the edges, but this may also reduce the sensitivity of the method. Sensitivity could be improved by taking into account differences in in-plane resolution, which is currently not addressed directly, especially on cases where one scan has a whole-lung field of view while the other scan is targeted. Note that our confidence interval is established on a zero-change dataset consisting of only scans with a whole-lung field of view, and it is unclear whether this confidence interval would be different for targeted scans. To address this, the zero-change dataset will be expanded to include additional cases.

5. CONCLUSION

A moment-based method to identify pulmonary nodules with asymmetric growth was presented. To establish what nodules had significant asymmetric growth, the 95% confidence interval for the difference of moment ratios (DMR) was established on a zero-change dataset, and nodules with a DMR outside this confidence interval were considered to have significant asymmetric growth. Using this method, 13% of stable nodules and 25% of malignant nodules were found to have asymmetric growth. Nearly twice as many malignant nodules as stable nodules were found to have asymmetric growth, suggesting that asymmetric growth may be an indicator of malignancy.

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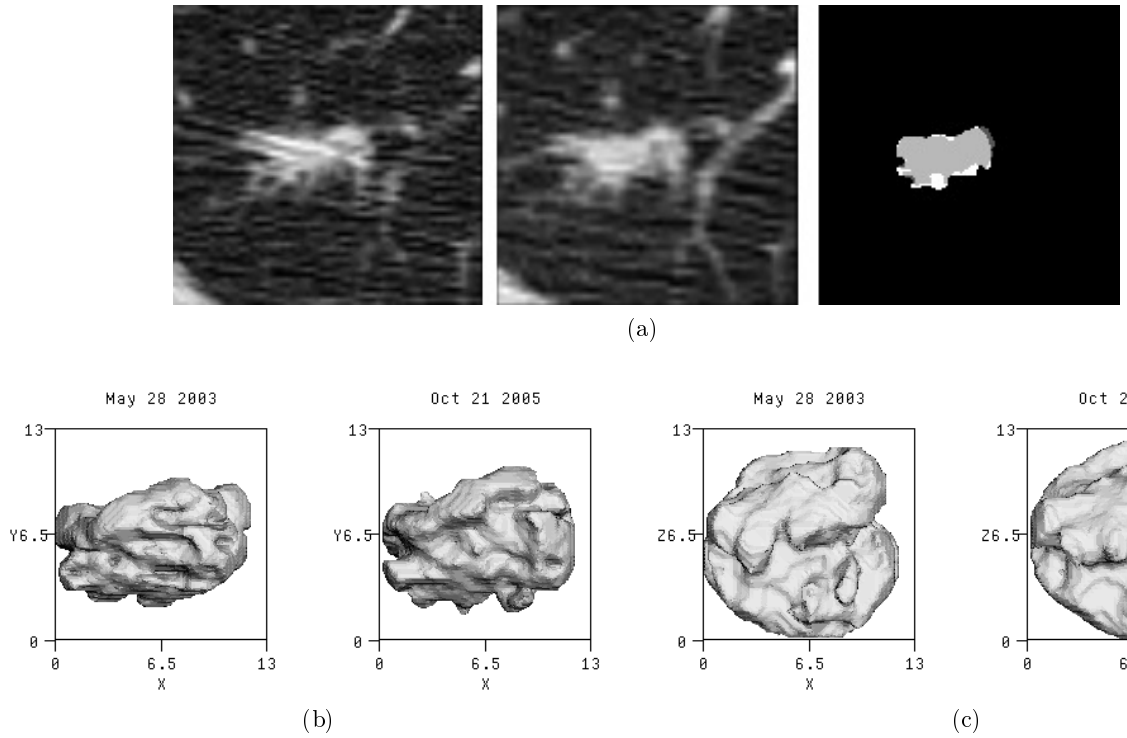

Figure 4. A stable nodule which had a difference of moment ratio consistent with asymmetric growth, but with no asymmetric growth visible. A central slice through the nodule on is shown in a) left for T1 and center for T2, with the overlapped segmentation shown on the right (T1: gray, T2: white). Light-shaded 3D visualization for b) axial and c) coronal views.

is an inventor on a pending patent owned by PneumRx related to biopsy needles, serves as a medical advisor to them, and holds an equity interest in PneumRx.

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