Prediction of tumor volumes using an exponential model

Artit C. Jirapatnakul[a], Anthony P. Reeves[a], Tatiyana V. Apanasovich[b],
Matthew D. Cham[c], David F. Yankelevitz[c], and Claudia I. Henschke[c]

[a]School of Electrical and Computer Engineering, Cornell University, Ithaca, NY;
[b]School of Operations Research and Information Engineering, Cornell University, Ithaca, NY;
[c]Department of Radiology, Weill Medical College of Cornell University, New York, NY

ABSTRACT

Measurement of pulmonary nodule growth rate is important for the evaluation of lung cancer treatment. The change in nodule growth rate can be used as an indicator of the efficacy of a prescribed treatment. However, a change in growth rate may be due to actual physiological change, or it may be simply due to measurement error. To address this issue, we propose the use of an exponential model to predict the volume of a tumor based on two earlier scans. We examined 11 lung cancers presenting as solid pulmonary nodules that were not treated. Using 5 of these with optimal scan parameters, thin-slice (1.0mm or 1.25mm) with same axial resolution, we found an error ranging from 1.7% to 27.7%, with an average error of 14.9%. This indicates that we can estimate the growth of a lung cancer, as measured by CT, which includes the actual growth as well as the error due to the technique, by the amount indicated above. Using scans with non-optimal parameters, either thick-slice or different resolution thin-slice scans, resulted in errors ranging from 30% to 600%, suggesting that same resolution thin-slice CT scans are necessary for accurate measurement of nodule growth.

Keywords: CT, pulmonary nodule, growth rate, measurement accuracy, computer-assisted diagnosis, exponential growth model

1. INTRODUCTION

Lung cancer is the most common cause of cancer death today; the American Cancer Society estimates that there will be 174,470 new cases of lung cancer and 162,460 deaths. Not only is it important to detect cancers early, but it is also necessary to be able to quickly and accurately assess treatment response. Current guidelines for the evaluation of the response to treatment in solid tumors include WHO and RECIST criteria. These criteria are based on the decrease in diameter of a tumor; partial response is defined by RECIST criteria as a decrease in size of 30%, while WHO criteria requires a decrease in the product of length and width of 50%.[1] However, both of these criteria use 2D measurements; in the case of RECIST, a 30% decrease in size corresponds to over a halving of volume. The threshold is set high partly to counter the effect of possible measurement error.

Aided by the recent development of high-resolution, multi-detector CT scanners, a criteria based on a decrease in volume might be able to more quickly detect a tumor response than either of the WHO or RECIST criteria. Volumetric measurements may be obtained manually by marking the boundary of a nodule on every slice it appears, but this is incredibly time consuming for a radiologist to perform. Automated volumetric measurement algorithms have been developed, but it is difficult to evaluate the accuracy of these algorithms. There is also the possibility that, for some cancers, a response may not manifest as a decrease in size, but only as a slowing in growth. In this case, relying on a decrease in volume would also fail to measure a response.

To address these issues, we suggest the measuring the change in growth rate. Growth rate has been used as an indicator of malignancy in the past,[2,3] but few papers have attempted to use the change in growth rate, as measured by automated methods, to assess treatment response. However, there have been many papers that have attempted to assess the accuracy of automated methods of nodule volume measurement. Measuring the accuracy of automated methods is difficult, due to the lack of ground truth of *in vivo* nodules. Previous studies have measured accuracy based on the use of phantoms or the consistency of measurements made on the same nodule. One such study by Kostis et al measured the volumes of 115 nodules determined to have no growth on two time scans.[4] The authors found up to a 27.4% volume change from one time to the next, with the percent volume change dependent upon the size of the nodule. Even though *in vivo* nodules were used in this study,

Medical Imaging 2007: Computer-Aided Diagnosis, edited by Maryellen L. Giger, Nico Karssemeijer,
Proc. of SPIE Vol. 6514, 65143A, (2007) · 1605-7422/07/$18 · doi: 10.1117/12.710371

stable nodules are often much easier to measure than malignant nodules, and the assumption that the stable nodules had no growth or decline may not have been true for all of the nodules. A study on inter- and intra-observer agreement using an automated method was performed in another study.[5] The authors concluded that a volume increase of 50% could be detected, since the 95% limit of inter-observer agreement, as calculated by using the Bland Altman method of analysis, was 25%. Other studies using commercial software packages have also suggested consistent volume measurements. A study by Revel et al[6] found that for the 54 nodules they examined, 96% of them had repeatable volume estimates and all of the doubling times corresponded with the diagnosis of the nodule. A recent study by Goodman et al[7] scanned the same nodule three times, 20 minutes apart, providing the best basis for measuring accuracy to date. Inter-observer variation was very low, but inter-scan variation was somewhat high, with a mean of 13.1% and confidence limits of ± 25.6%; however, these results are still in the same range as previously reported work using benign nodules. The drawback of studies based on consistency measurements is that there is the possibility that despite being consistent, the measurements could still be inaccurate–in other words, the measurements might exhibit low variance, but high bias. Another study assessed the accuracy of volumetric measurements through the use of phantoms;[8] the researchers found at most a 3% error in volume. Yet another study using phantoms determined that the nodule size and scanner/reconstruction parameters had a significant effect on the volume measurement error.[9] Although the result on phantoms is very good, it is unclear how similar a phantom is to an *in vivo* pulmonary nodule.

In this paper, we propose a method to measure the change in growth rate of a nodule using at least three time-separated CT scans in order to assess tumor response. We compare the volume of the nodule on the final scan predicted by the exponential growth model to the actual measured volume. A deviation in volume on the third scan would indicate a change in the growth rate of the nodule, which can be used to quantify the effect of treatment. In this paper, we examine the prediction errors of untreated cancers to see if this type of error measurement can be integrated into a predication model, which can then be used to help assess treatment response.

2. DATA

For this study, we selected cases with a known malignant, solid nodule with at least three time-separated scans of similar resolution; for thin-slice, we allowed a variation in slice thickness of 1.0 mm or 1.25 mm, but for larger slices, we did not allow any variation in the slice thickness. Cases fulfilling these criteria were difficult to obtain, since after the second scan, the radiologist typically has sufficient information about the nodule's growth rate to recommend biopsy or resection, and no additional scans are obtained.

In this paper, 11 lung cancers presenting as solid pulmonary nodules with at least three temporally separated scans were evaluated; these cases represent less than 1% of all the cases in our database. Of these 11 cancers, 5 had all scans being thin-slice (1.0 mm or 1.25 mm) CT scans, 3 had scans being different thickness thin-slice CT scans, and 3 had all scans being thick-slice (5.0 mm) CT scans. The nodules were all confirmed to be malignant by biopsy or histology of resected tissue. Nodules ranged in size on initial scan from 3.29 mm to 10.7 mm. Scans were obtained with either a GE Medical Systems LightSpeed Ultra, LightSpeed QX/i, or HighSpeed CT/i scanner. The same scanner was used for all scans of each nodule.

3. METHOD

Our proposed method consists of two primary steps. In the first step, the nodule is segmented on each scan using an automated method, and the volume computed from the segmented nodule. In the second step, the volume of the nodule on two sequential scans is compared to establish a growth rate. This growth rate is used to estimate the nodule volume on the final CT scan, and the error between the estimated volume and actual volume is computed. These steps are shown in the flowchart of Figure 1 and further described in the sections below.

3.1. Nodule Segmentation

Accurate computation of the growth rate of a nodule requires accurate volumetric segmentation on each time-separated CT scan. In this paper, segmentation is performed using an algorithm previously developed by Reeves

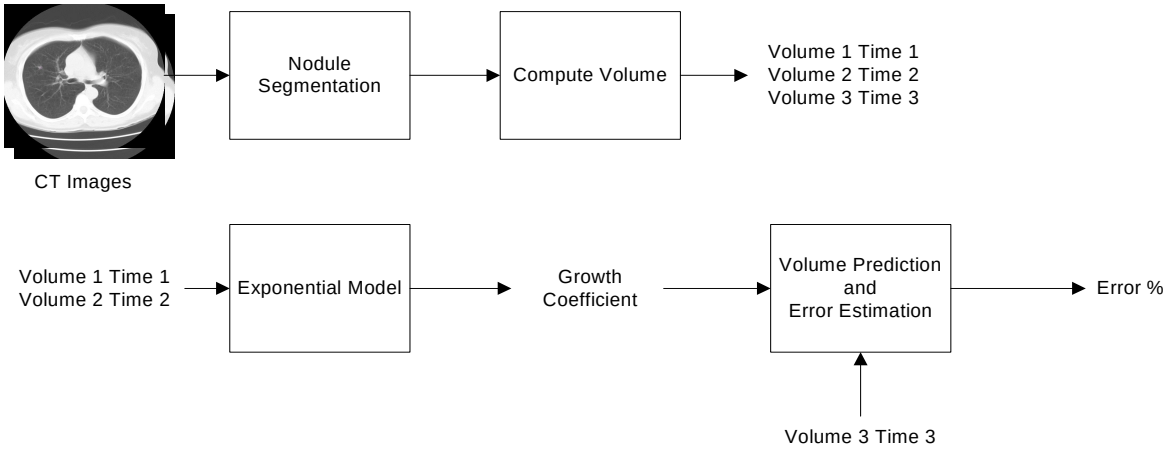
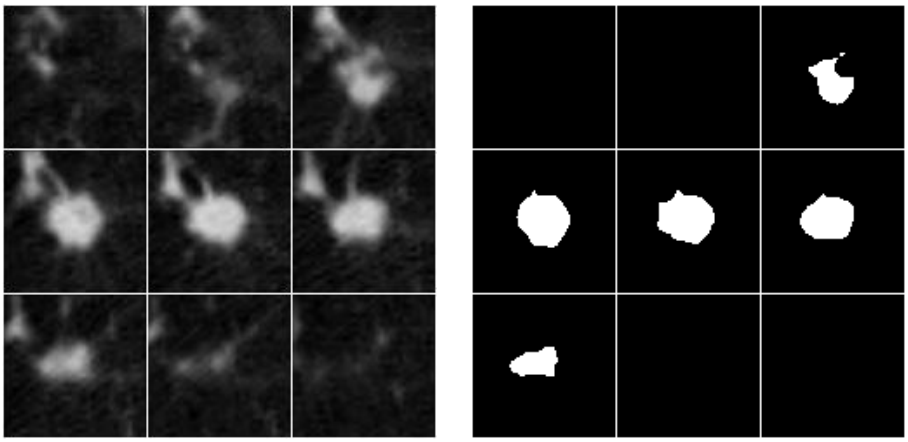


Figure 1. Flowchart of volume prediction and error estimation system. The nodule is first segmented on each CT image, and the volume computed from the segmented image. This results in three different volume measurements and times. Two of the volume measurements, along with the time interval, are then used to compute the growth rate. Finally, the growth rate and final time interval are used to predict the volume of the nodule on the last scan; this predicted volume is compared to the final volume of the actual nodule, and an error estimate is computed.



(a) (b)

Figure 2. Segmentation of nodule, starting with a) region of interest and resulting in b) binary segmented image. Volume is calculated by summing the non-zero voxels in the binary segmented image.

et al.[10] The first step in the algorithm is to determine an approximate size and location for the nodule in the CT image. A method using an initial user-specified seed point in conjunction with template functions is used. Based on the approximate size and location, a region of interest (ROI) is selected around the nodule, as shown in Figure 2a. The ROI is resampled into isotropic space by trilinear interpolation and a threshold is applied to obtain a binary image. Morphological filtering using an algorithm by Kostis et al[11] is performed to remove any attached vessels, followed by a step to determine if the nodule is juxtapleural. If necessary, juxtapleural segmentation is performed using an iterative algorithm that separates the nodule from the pleural surface using a clipping plane.[10] The result of this algorithm is a binary segmented image of the nodule as shown in Figure 2b; the volume is computed by summing the non-zero voxels in this image.

Table 1. Initial size, predicted and actual volumes, and absolute percent volume error on last CT scan (LS) for nodules on thin-slice CT

Nodule	Size (mm)	Actual vol. on LS (mm^3)	Predicted vol. on LS (mm^3)	Absolute Error (%)
1	8.63	603.27	583.99	3.2
2	4.78	69.03	88.18	27.7
3	3.29	198.09	233.28	16.7
4	3.40	336.08	252.71	24.8
5	5.05	132.03	134.24	1.7

Table 2. Initial size, predicted and actual volumes, and absolute percent volume error on last CT scan (LS) for nodules on mixed thickness thin-slice CT

Nodule	Size (mm)	Actual vol. on LS (mm^3)	Predicted vol. on LS (mm^3)	Absolute Error (%)
6	8.10	236.58	307.79	30.1
7	7.35	182.38	312.82	71.5
8	10.00	649.59	914.52	40.8

3.2. Error Estimation

Following segmentation of the nodule on each of the CT scans, the growth rate for the nodule is computed based on two of the CT scans. To compute the growth rate, we assume that the growth model is exponential. This is model is generally accepted in the medical community, particularly for small nodules.[2,12] It is based on the observation that the number of tumor cells increases exponentially over time, and this has been supported through observed growth of tumor volume. Other papers[3,13,14] have also shown that the growth rate is often effective in the differentiation of malignant from benign nodules whether measured volumetrically or by 2D measurements. The growth model can be expressed by the following equation:

$$\frac{V_2}{V_1} = e^{\lambda \Delta t_{1-2}} \tag{1}$$

where V_1 represents the volume on the first CT scan, V_2 represents the volume on the subsequent CT scan, Δt_{1-2} represents the time interval between the first and second scans in days, and λ is the exponential coefficient. Given that we have nodules with three time-separated scans, we can estimate λ from the volume of the nodule on the first two scans.

Using this value of λ in conjunction with the volume of the nodule on the first scan, and the time separation between the first and last scans, we can predict the volume of the nodule on the final CT scan.

$$V_{3_{predicted}} = V_1 e^{\lambda \Delta t_{1-3}} \tag{2}$$

In the few cases where more than three scans were available, the last scan was used. The error between the actual and predicted volumes can be computed to estimate the measurement error.

$$\text{Error} = \text{abs}\left(\frac{V_{3_{predicted}} - V_{3_{actual}}}{V_{3_{actual}}}\right) * 100\% \tag{3}$$

4. RESULTS

The automated segmentation results for all 11 pulmonary nodules were manually reviewed to ensure correctness. For each nodule, the size on the first scan, based on the automatic segmentation, the actual and predicted volumes on the final CT scan, and absolute percentage error are listed in Tables 1, 2, and 3, for cancers on same resolution thin-slice CT, mixed resolution thin-slice CT, and thick-slice CT respectively.

For the first set of 5 cancers with thin-slice scans of matched resolution in Table 1, the error between the predicted volume and the actual volume ranged from 1.7% to 27.7%, with a mean error of 14.9%. The nodules

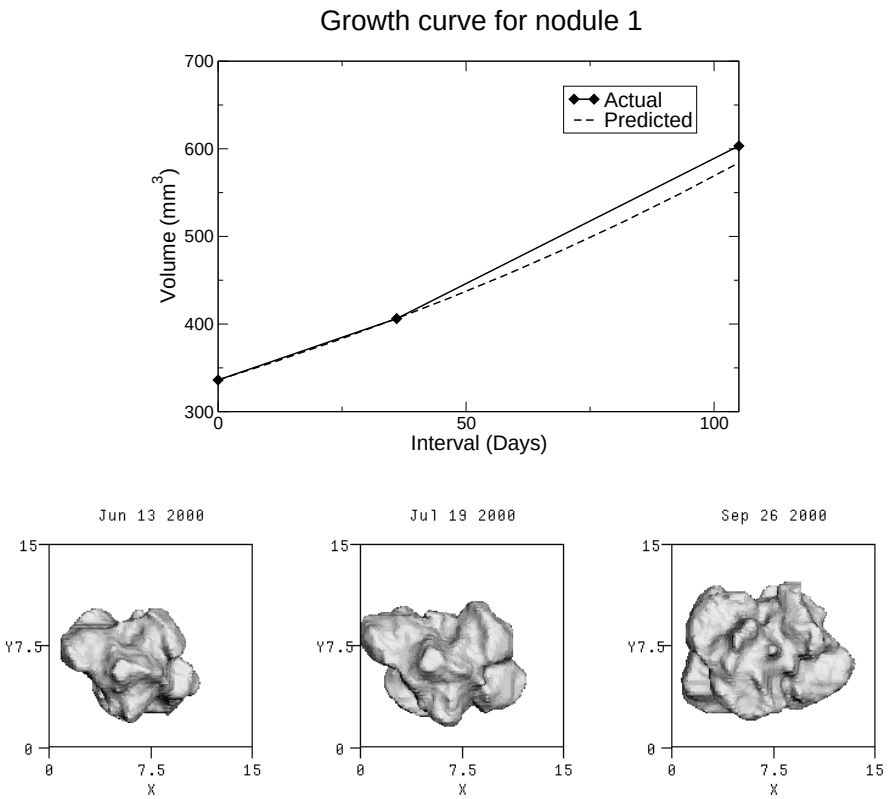


Figure 3. Actual and predicted growth curves for nodule 1 with 3% volume prediction error (top) and light-shaded visualizations of the nodule on each CT scan, axial view (bottom)

Table 3. Initial size, predicted and actual volumes, and absolute percent volume error on last CT scan (LS) for nodules on thick-slice CT

Nodule	Size (mm)	Actual vol. on LS (mm^3)	Predicted vol. on LS (mm^3)	Absolute Error (%)
9	8.49	945.44	5066.63	620.3
10	8.39	612.20	1009.13	64.8
11	10.72	1403.52	2200.93	56.8

with the largest initial size, nodules 1 and 5 had the lowest errors out of the 5 nodules. The actual growth curve for nodule 1 is plotted in Figure 3 along with the growth curve predicted from the exponential model. Light-shaded 3D visualizations are displayed for the nodule on each CT scan showing a steady growth. As the parameters for the model are estimated from the first two points, the curve predicted by the model goes through the first two points. The predicted volume on the final scan is within 3.2% of the actual volume. The nodule with the worst error, nodule 2, was very small on the final CT scan, with a volume of 69.03 mm^3 which corresponds to a size of 5.09 mm.

The second set of cancers, nodules 6 to 8 in Table 2, on a combination of 1.0 and 1.25 mm CT scans, had much larger errors. The errors for these nodules ranged from 30.1% to 71.5%, despite the larger size of these nodules as compared to the first set of nodules. We do see a similar trend of more accurate measurements on the larger nodules; the nodule with the highest error, 7, had the smallest volume of the three nodules. The actual and predicted growth curves are plotted for nodule 8 in Figure 4. One possible explanation for the error between the actual and predicted volumes is that the last scan had 1.00 mm slices, whereas the previous scans were all 1.25 mm. Note that even though this nodule has a long period of time between the second and third scans, the prediction error does not seem to be markedly different from the other nodules with shorter periods of time

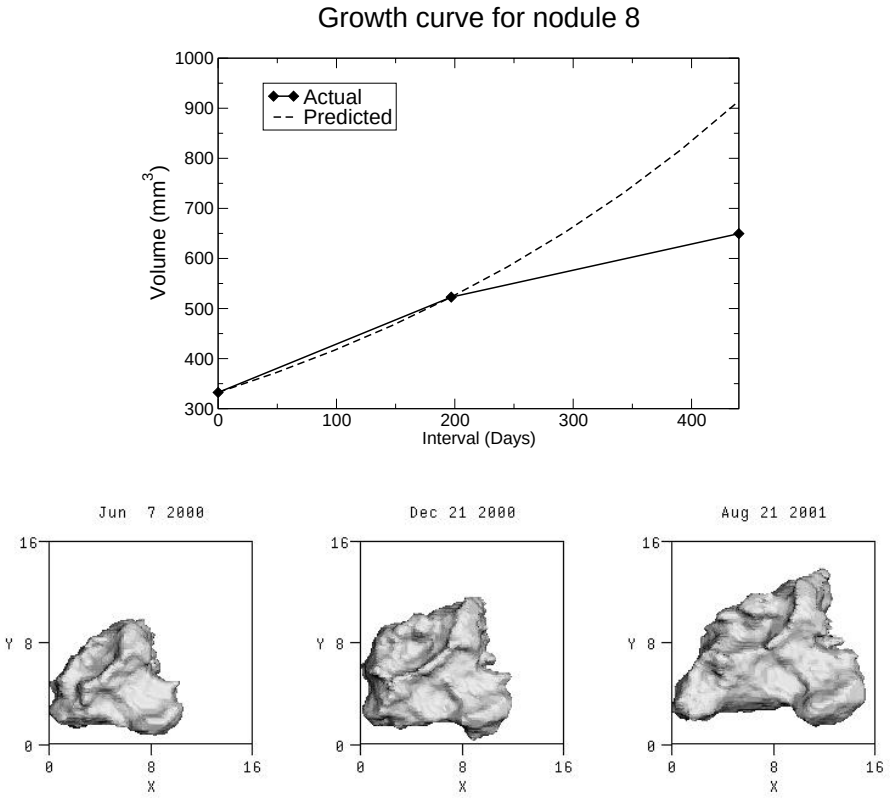


Figure 4. Actual and predicted growth curves for nodule 8 on thin-slice scans of different resolution with 41% volume prediction error (top) with light-shaded visualizations of the nodule on three different CT scans, axial view (bottom).

between scans, though we do not have enough data to assess this effect.

The third set of cancers, nodules 9 to 11 on thick-slice CT, whose results are listed in Table 3, exhibited even larger errors still. The range of errors was 56.8% to 620.3%. Despite the consistency of the slice thickness for these nodules, the 5.0mm slices did not have enough detail to enable accurate volume measurement for these nodules. For nodule 10, the actual and predicted growth curves are plotted in Figure 5. Given the size of the nodules, they were present on only 2 or 3 slices of the CT scan, which results in a great loss of detail as compared to what can be obtained with 1.25 or 1.0 mm slice CT scans. In the case of nodule 10, it is likely that the second volume measurement is greater than the actual volume of the nodule, which causes the exponential model to overestimate the volume on the final scan. Although two of these nodules are smaller than what is recommended for measurement using the RECIST criteria (twice the slice thickness, or 10 mm), cancers of these sizes are now being encountered more frequently. The cancer with the largest error, nodule 9, had a low measured volume on the first scan, as compared to the second scan, due largely to partial volume effects. Compounding the error is the fact that the patient was oriented differently on the third scan, possibly compressing the nodule and making it appear smaller on the scan.

5. DISCUSSION

The change in growth rate of a malignant nodule is a promising measure of the efficacy of cancer treatment. However, there are several obstacles in measuring this; although growth analysis of pulmonary nodules has been an extensively researched area, one question that has not been fully addressed is how to measure the error of automated volume measurement algorithms. In this paper, we used an exponential growth model as our surrogate ground truth and determined what the prediction error of the model would be for a variety of scans

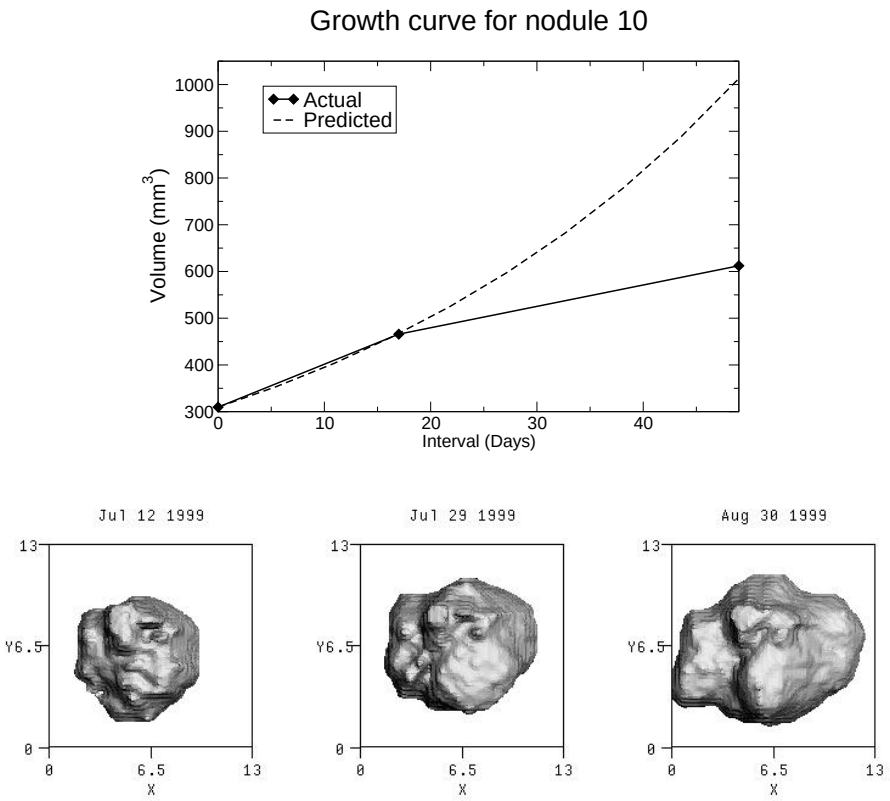


Figure 5. Actual and predicted growth curves for nodule 10 on thick-slice scans of the same resolution with 65% error(top) and light-shaded visualizations of the nodule on the three CT scans, axial view (bottom).

using different parameters. Our results indicated that the accuracy of our automated method was dependent upon three primary factors: slice thickness, consistency of slice thickness, and size of the nodule.

The most accurate measurements require thin-slice CT of 1.25 mm or less. This is now becoming more common as a result of the availability of multi-row scanners. Our results included two small nodules of 3.29 mm and 3.40 mm with low prediction errors, suggesting that volumetric methods should have at least three slices to obtain good measurements where at least one slice is not dominated by partial volume effects. For a 1.00 mm scan, this suggests that the smallest nodule that can be reliably measured is 3.00 mm. Additionally, the slice thickness, and ideally all scanner parameters, must be consistent across all scans used to determine growth rate. The effects of these two factors on measurement accuracy can be clearly seen in the differences of prediction error between the first set and the remaining two sets of nodules; with consistent thin-slice CT scans, measurement accuracy can be limited to under 30%, while inconsistent thin-slice CT scans more than double the percent volume error, and using thick-slice CT scans increases error to the point of being unusable. The final factor is the size of the nodule; larger nodules tend to have more accurate volume measurements, due to a lower percentage partial voxels.

The results of this paper are in agreement with past studies on measurement accuracy of stable nodules. Using consistent, thin-slice CT scans, we estimated a prediction error of up to 27.7% difference in volume. A study by Wormanns et al concluded that, based on inter- and intra-observer consistency measurements, volume changes greater than 50% could be measured using an automated method.[5] Another study by Kostis et al using stable nodules found up to a 27.4% change in volume from one scan to the next.[4] They also found that the volume change varied for nodules of different sizes, as we have also concluded from our results.

6. CONCLUSION

Assessing the response of lung cancer to treatment is important in both clinical practice and clinical trials. The results of this preliminary study using diagnosed lung cancers suggest that volume measurement of nodules using our automated method is within 27.7% of the volume predicted by the exponential growth model when thin-slice scans with consistent parameters are used. This result is in agreement with previous studies on the accuracy of automated volumetric measurements using stable nodules, suggesting that the exponential growth model is a suitable surrogate for ground truth. Deviations between the actual and predicted volumes that are greater than 27.7% would suggest a change in the growth rate of a nodule and thus indicate whether a given treatment is effective. Although it was difficult to find cancers with at least three time-separated scans in the screening database used for this study, in a clinical trial setting, finding cases with three scans should be easier – two scans may be taken to diagnose cancer followed by a third scan after the beginning of treatment. The method described in this paper of assessing treatment response based on the deviation of actual and predicted tumor volumes is promising, but further evaluation using a larger database of scans is necessary.

REFERENCES

1. P. Therasse, S. G. Arbuck, E. A. Eisenhauer, J. Wanders, R. S. Kaplan, L. Rubinstein, J. Verweij, M. V. Glabbeke, A. T. van Oosterom, M. C. Christian, and S. G. Gwyther, "New guidelines to evaluate the response to treatment in solid tumors," *J Natl Cancer Inst* **92**, pp. 205–216, February 2000.
2. V. P. Collins, R. K. Loeffler, and H. Tivey, "Observations on growth rates of human tumors," *American Journal of Roentgenology* **76**, pp. 988–1000, November 1956.
3. M. H. Nathan, V. P. Collins, and R. A. Adams, "Differentiation of benign and malignant pulmonary nodules by growth rate," *Radiology* **79**, pp. 221–231, August 1962.
4. W. J. Kostis, D. F. Yankelevitz, A. P. Reeves, S. C. Fluture, and C. I. Henschke, "Small pulmonary nodules: Reproducibility of three-dimensional volumetric measurement and estimation of time to follow-up CT," *Radiology* **231**, pp. 446–452, May 2004.
5. D. Wormanns, G. Kohl, E. Klotz, A. Marheine, F. Beyer, W. Heindel, and S. Diederich, "Volumetric measurements of pulmonary nodules at multi-row detector CT: In vivo reproducibility," *European Radiology* **14**, pp. 86–92, 2004.
6. M. Revel, C. Lefort, A. Bissery, M. Bienvenu, L. Aycard, G. Chatellier, and G. Frija, "Pulmonary nodules: Preliminary experience with three-dimensional evaluation," *Radiology* **231**, pp. 459–466, May 2004.
7. L. R. Goodman, M. Gulsun, L. Washington, P. G. Nagy, and K. L. Piacsek, "Inherent variability of CT lung nodule measurements in vivo using semiautomated volumetric measurements," *American Journal of Roentgenology* **186**, pp. 989–994, April 2006.
8. D. F. Yankelevitz, A. P. Reeves, W. J. Kostis, B. Zhao, and C. I. Henschke, "Small pulmonary nodules: Volumetrically determined growth rates based on CT evaluation," *Radiology* **217**, pp. 251–256, October 2000.
9. J. P. Ko, H. Rusinek, E. L. Jacobs, J. S. Babb, M. Betke, G. McGuinness, and D. P. Naidich, "Small pulmonary nodules: Volume measurement at chest CT – phantom study," *Radiology* **228**, pp. 864–870, September 2003.
10. A. Reeves, A. Chan, D. Yankelevitz, C. Henschke, B. Kressler, and W. Kostis, "On measuring the change in size of pulmonary nodules," *IEEE Transactions on Medical Imaging* **25**, pp. 435–450, April 2006.
11. W. J. Kostis, A. P. Reeves, D. F. Yankelevitz, and C. I. Henschke, "Three-dimensional segmentation and growth-rate estimation of small pulmonary nodules in helical CT images," *IEEE Transactions on Medical Imaging* **22**, pp. 1259–1274, October 2003.
12. S. Friberg and S. Mattson, "On the growth rates of human malignant tumors: Implications for medical decision making," *Journal of Surgical Oncology* **65**(4), pp. 284–297, 1997.
13. K. Usuda, Y. Saito, M. Sagawa, M. Sato, K. Kanma, S. Takahashi, C. Endo, Y. Chen, A. Sakurada, and S. Fujimura, "Tumor doubling time and prognostic assessment of patients with primary lung cancer," *Cancer* **74**, pp. 2239–2244, Oct. 1994.
14. M.-P. Revel, A. Merlin, S. Peyrard, R. Triki, S. Couchon, G. Chatellier, and G. Frija, "Software volumetric evaluation of doubling times for differentiating benign versus malignant pulmonary nodules," *American Journal of Roentgenology* **187**, pp. 135–142, July 2006.