Zone of Transition: A Potential Source of Error in Tumor Volume Estimation¹

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Purpose:

To measure the width of the zone of transition (ZOT) between nonaerated solid tumor and surrounding nonneoplastic lung parenchyma and determine the extent to which ZOT influences computer-derived estimates of tumor volume based on computed tomographic (CT) images.

Materials and Methods:

This HIPAA-compliant study was approved by the institutional research board. The histologic slide containing the maximum tumor area was digitized for 20 consecutive patients with solid adenocarcinoma. The outer border of the tumor (A2) was marked; it included all lung parenchyma having any tumor cells. The inner border of the tumor (A1) was marked; it included only solid tumor where lung parenchyma was no longer preserved. Assuming two circles with areas of A2 and A1, the corresponding two radii, R2 and R1, were calculated. The average width of the ZOT was defined as R2 minus R1. The relationship between ZOT and tumor diameter on the CT images prior to surgery was assessed by using regression analysis. The relationship between ZOT and tumor volume was assessed by using a theoretical model of idealized spheres with varying diameters.

Results:

The mean width of the ZOT was 0.78 mm (median, 0.48 mm). The proportional effect of ZOT on tumor volume estimates decreased with increasing tumor diameter and increased with increasing width of ZOT. Correlation between ZOT and tumor diameter was not significant ($P = .87$).

Conclusion:

The average width of ZOT is about a single pixel width on a full field of view CT scan; thus, the ZOT can have a large effect on volume estimates, particularly for small tumors.

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Computer-aided growth assessment is becoming an increasingly important diagnostic tool in the evaluation of pulmonary nodules (1–3). This is especially true for nodules less than 1.0 cm in diameter for which there are known limitations in other diagnostic tests such as dual-modality positron emission tomography/computed tomography (CT) and percutaneous biopsy. For the purpose of estimating growth rates, absolute volume determination is less important than measuring the relative change in volume. Thus, when a computer-aided diagnosis (CAD) device chooses a boundary for its volume determination, as long as it is consistent in its approach, the effect of any bias will be minimized. Prior to the advent of multidetector CT scanners, nodule size was most frequently measured in either uni- or bidimensional manners for convenience owing to difficulty obtaining a complete set of thin-section images or because of lack of validated software tools that could reliably identify nodule boundaries. The advent of multidetector CT scanners allows for continuous thin-section, near-isotropic imaging and now has allowed for better visualization of tumor details and provided more accurate volumetric measurement, especially for solid nodules where the boundaries are more easily identified than for part-solid and nonsolid nodules (4–6).

CAD techniques have also improved and along with the higher quality CT data, these volumetric tools are increasingly being used in clinical practice. Nevertheless, precise volumetric measurement is still challenging due to multiple factors, including motion artifact; differences in

scanner performance (7–9); differences in the chosen scan parameters, such as section thickness, pitch, collimation, dose, reconstruction kernel, and field of view; and features of the nodule itself, such as vascular attachments, as well as challenges in accurately defining the interface between nodule and non-tumor-containing parenchyma (10).

This is certainly evident in histologic specimens of lung cancer, as the peripheral zone usually contains malignant cells as well as partially aerated preserved lung architecture. As a result, the CT attenuation within this peripheral zone is lower than the attenuation of its solid center but is still greater than that of the non-tumor-containing lung parenchyma. This may contribute to the variability in tumor volume estimation, in part because these tools rely on attenuation differences to define the border between the tumor and the surrounding non-tumor-containing lung parenchyma. We have termed this peripheral zone the zone of transition (ZOT) and, depending on the properties of the CAD algorithm and the resolution of the scanner, the amount of the ZOT that is incorporated into the boundary can lead to substantial variation in the volume estimate.

The purpose of this study was to measure the width of the ZOT between nonaerated solid tumor and surrounding nonneoplastic lung parenchyma and determine the extent to which ZOT influences computer-derived estimates of tumor volume based on CT images.

Materials and Methods

D.F.Y., A.P.R., and C.I.H. are named inventors on a number of patents and patent

applications relating to the evaluation of diseases of the chest including measurement of nodules. Some of these, which are owned by Cornell Research Foundation (CRF), are nonexclusively licensed to General Electric. As inventors of those patents, D.F.Y. and A.P.R. are entitled to a share of any compensation that CRF may receive from its commercialization of these patents. As of April 2009, C.I.H. signed away any financial benefit, including royalties and any other proceeds related to the patent or patent applications.

This study was approved by the institutional research board at Weill Cornell Medical College and was Health Insurance Portability and Accountability Act compliant. We retrospectively reviewed 20 consecutive patients (14 women and six men; mean age, 67 years $\pm$ 8.2 [standard deviation] in women and 66 years $\pm$ 3.3 in men) with surgically resected adenocarcinoma in whom the CT image prior to surgery was reported to show the nodule to be solid in consistency, the histologic slides showed no fixation artifacts, and a pathologic diagnosis of adenocarcinoma was confirmed by a senior pathologist (D.C.).

Histologic Specimens

The pathologic specimen for each patient had been prepared according to a standard protocol (11). For each patient, digitized images of the resected

Advance in Knowledge

- There is a thin transition zone of intermediate attenuation at the border between solid-appearing tumors and the non-tumor-containing lung parenchyma surrounding them; the width of this zone is in the range of a single pixel on a typical full field of view CT scan and can have a large effect on tumor volume estimates.

Implication for Patient Care

- When performing volumetric assessment of tumors, it is important to consider that there is an inherent degree of uncertainty associated with a given measurement that is partly related to anatomic features of the tumor, and this must be considered when estimating growth rates.

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Abbreviations:

CAD = computer-aided diagnosis
ZOT = zone of transition

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Guarantors of integrity of entire study, L.Z., D.F.Y., C.I.H.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, L.Z., C.I.H., A.P.R.; clinical studies, L.Z., C.I.H.; statistical analysis, L.Z., C.I.H., A.C.J.; and manuscript editing, all authors

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Figure 1

Figure 1: (a,c) Low-dose CT images of representative adenocarcinomas and (b,d) corresponding digitized pathologic images illustrate where inner and outer boundaries are drawn for outlining the ZOT. Although the shape of the nodule on pathologic specimens does not exactly match that on CT images, these images still illustrate that lung nodules have a variable zone of transition between tumor and peripheral normal lung tissue, even when they manifest as solid nodules on CT images.

pathologic specimens were acquired by using a microscope (Eclipse E400, with ImagePro software; Nikon, Melville, NY) at a magnification power of $\times 40$. With the digitized pathologic section that contained the maximum tumor diameter, the research fellow (L.Z.) manually drew two boundaries on the selected digitized image by using the software (Fig 1b, 1d). The outer boundary (A2) defined the tumor area that included all lung parenchyma that had tumor cells, while the inner boundary (A1) defined the tumor area that included only regions where the tumor was entirely solid and underlying lung parenchyma was not preserved. All digitized images and drawings were checked by a senior pathologist (D.C.).

Once the two boundaries were drawn for each of the 20 cases, the two areas, A2 and A1, were automatically calculated. For each tumor, we defined two circles, one having an area of A2 and the other of A1, and calculated the corresponding radius, R2 and R1, for each circle, respectively (Fig 2). The thickness of the ZOT in each case was then defined by the difference in the two radii. The mean and median values of R2 minus R1 for the 20 cases was then determined.

CT Imaging

CT scans obtained in each of the 20 patients whose adenocarcinoma was resected were examined. When more than one scan was available for a patient, the scan obtained at the time closest

Figure 2

Figure 2: By using circles with areas equivalent to the inner border, A1, and outer border, A2, of the ZOT, corresponding radii R1 and R2 can be derived. The average width of ZOT for a nodule was defined as R2 minus R1.

to surgery was chosen. All patients had undergone low-dose full field of view chest CT (GE Medical Systems, Milwaukee, Wis) (120 kVp, 40–80 mA) without intravenous contrast material. Section thickness ranged from 5 to 1.25 mm. Scanner models were as follows: Genesis Highspeed was used for a section thickness of 5 mm ($n = 9$), Lightspeed QX for 2.5 mm ($n = 4$), and Lightspeed Ultra for 1.25 mm ($n = 7$). The images were obtained in a single breath hold starting at the thoracic inlet and continuing through the upper abdomen. The corresponding width of the smallest pixel size in the x-y plane ranged from 0.57 to 0.78 mm. All cancers identified on CT scans were characterized as solid, with solid being defined as completely obscuring the underlying lung parenchyma. The solid appearance of the tumor was confirmed by experienced chest radiologists (D.F.Y., C.I.H.) during review of the CT images at a window width of 1500 and a window level of -650 . The CT image that contained the maximum tumor area was selected and the diameter was calculated as the average of the maximum tumor length and width (perpendicular to the length) (Fig 1a, 1c).

Tumor Volume Estimates

By using the average thickness of ZOT obtained above, we calculated the volumes: volume = $4/3\pi (d/2)^3$, for three idealized spherical nodules, each having diameter, d , of 5, 10, or 20 mm.

For each of these diameters, we arbitrarily defined the tumor boundary to include half of the ZOT. We then calculated the percentage change in volume for each nodule diameter in two ways, based on whether the nodule boundary (a) included the ZOT completely or (b) did not include any of the ZOT. For example, for a nodule with a diameter of 10 mm and ZOT equal to 2 mm, the nodule would have a radius that would be 5 mm, of which 4 mm is contributed by the solid tumor and 1 mm by the ZOT. If all of the ZOT is included, the radius would be 6 mm, and if none of the ZOT is included it would be 4 mm. The percentage volume change for the same nodule would be calculated by using the measurement that included half of the ZOT as the reference volume, 5 mm, and this would be compared with the 4 and 6 mm diameters. We then repeated this evaluation for three different thicknesses of the ZOT (the average, then twice and half of the average) for nodules with diameters ranging from 5 to 20 mm.

Statistical Analysis

Linear regression analysis was used to assess the relationship between the thickness of the ZOT and tumor diameter by using statistical software (SPSS version 13.0; SPSS, Chicago, IL). $P < .05$ was considered to indicate statistical significance.

Results

As determined by measurements from the histologic specimens of the 20 tumors, the mean and median ZOT was 0.78 mm and 0.48 mm, respectively (Table 1). The difference between the mean and median of ZOT is due to a single outlier. The ratio of ZOT relative to the tumor radius including the outer boundary ($[R2-R1]/R2$) ranged from 0.00 to 0.46 (mean, 0.15; median, 0.12). The tumor with 0.46 ratio was the outlier case and had a ZOT thickness of 3.78 mm.

Figure 3 illustrates the percentage change in the volume for idealized spherical nodules with diameters of 5, 10, and 20 mm. For each nodule we

Table 1

Area Bounded by Inner (A1) and Outer (A2) Border of Tumor, and Corresponding Radii, in 20 Cases of Adenocarcinoma

Parameter	Mean	Median	Maximum	Minimum
A1 (cm ²)	65.68	54.57	186.45	21.06
A2 (cm ²)	91.68	76.83	213.81	27.18
R1 (mm)	4.38	4.95	7.71	2.41
R2 (mm)	5.16	4.17	8.25	2.94
ZOT (mm)	0.78	0.48	3.78	0

Note.—The ZOT is the average difference of R2 minus R1 for each case.

assumed the ZOT was 0.78 mm, as this was the empirically determined value, and for illustrative purposes we chose the larger mean value rather than the median value. For each size nodule we determined the effect on volume by including either the entire ZOT or none of the ZOT (actual diameter was determined by including half of the ZOT as the actual boundary). For a nodule with a diameter of 5 mm, the volume change ranged from +54% to -40%, for the 10 mm nodule it ranged from +25% to -22%, and for the 20 mm nodule it ranged from +12% to -11%. In Figure 4, we showed the effect of varying the thickness of the ZOT on volume estimates by using half the empirically determined value and twice the value (0.39, 0.78, and 1.56 mm) for nodules ranging in size from 5 to 20 mm. For each size nodule and each thickness of the ZOT, we determined the effect on volume by including either the entire ZOT or none of the ZOT.

It can be seen that the potential effect on volume estimates for a given ZOT thickness increases with decreasing nodule size and that for any nodule size, the potential effect on volume estimates increases with increasing ZOT thickness.

For the 20 resected adenocarcinomas, the tumor diameter on the CT images ranged from 4.3 to 35 mm. The mean and median diameter was 12.8 and 11.0 mm, respectively (Table 2). No significant linear relationship (Fig 5, $P = .87$) was seen between the ZOT in histologic specimens and the tumor diameter on the CT scans.

Figure 3

Figure 3: Graph shows that percentage of volumetric measurement fluctuates around the “true” volume (assumed to be using a ZOT of 0.78 mm) for idealized spherical nodules with diameter of 5, 10, and 20 mm. The “true” borders of these nodules are assumed to be located in the middle of the ZOT (0% change). The percentage increase or decrease is greater for smaller tumors.

Discussion

We found that the width of the ZOT in 20 cases of adenocarcinoma manifesting as solid nodules on CT scans ranged from 0 to 3.78 mm (mean, 0.78 mm; median, 0.48 mm) and that this width was not significantly correlated with tumor size. This average value is approximately that of a single pixel width on a full field of view CT scan. The diameter of a pixel on a 40-cm field of view CT scan has a width of 0.78 mm. Thus, given the near isotropic capability of modern multi-detector row scanners, this pixel width approximates the thickness of the ZOT over the entire surface of the nodule.

Figure 4

Figure 4: Graph shows volumetric fluctuation around “true” volume (assuming ZOT of 0.78 mm) for three different values of ZOT (1.56, 0.78, and 0.39 mm) using twice and half the value of ZOT in determining the border for each nodule with given diameter. Volumetric fluctuation is dramatically larger with increased width of ZOT. Overall this effect decreases with increasing tumor diameter.

Table 2

Tumor Diameter in 20 Cases of Adenocarcinoma

Parameter	Diameter (mm)	Length (mm)	Width (mm)
Mean	12.8	14.2	11.5
Median	11.0	12.5	10.0
Maximum	35.0	35.0	35.0
Minimum	4.3	4.5	4.0

Note.—Diameter was calculated as the average of length and width (ie, perpendicular to the length) on the CT image that contained the maximum tumor area.

The effect of a single pixel width over the entire surface of a nodule can have a dramatic effect on volume estimates, particularly for smaller nodules. For example, a nodule measuring 5 mm in diameter (assuming that the correct diameter includes one-half the thickness of a ZOT), which has a volume of 65.4 mm³, can have a volume of 39.3 mm³ when no ZOT is included or a volume of 101.1 mm³ when the entire ZOT is included—either a reduction in volume of 40% or an increase of 54%. Overall, the proportional volume change, assuming the entire ZOT versus no ZOT, is

257% (101.1/ 39.3). This large volume change given the relatively small size of the ZOT is a result of the cubic relationship of tumor volume to its diameter; also, for smaller nodules, even a single pixel width can represent more than 10% of the diameter. While this can be a dramatic change for small nodules, its proportional effect lessens with increasing tumor size.

Although the proportional change in absolute volume was potentially quite large depending on the size of the nodule and how much of the ZOT was incorporated, this effect is somewhat minimized when estimating percentage change in nodule volume when scans obtained at different times are compared, as long as the algorithm includes the same proportion of the ZOT each time. In this way, any potential bias in a given volume estimation would be in the same direction for the two scans. Nevertheless, the amount of ZOT included still has an effect. To illustrate this, consider that the nodule grows from 5 to 10 mm (assuming the true diameter is the midpoint of the ZOT); if one excludes the entire ZOT, the calculated volume changes from 39.3 to 410.7 mm³, an approximate 10-fold increase (410.7/39.3).

Figure 5

Figure 5: Linear regression analysis of the average width of ZOT and the tumor diameter measured on CT images for 20 cases of resected adenocarcinomas showed no significant linear relation ($P = .87$).

If on the other hand, the entire ZOT is included, then the volume changes from 101.1 to 655.6 mm³, an approximate sevenfold increase (655.6/101.1). This example demonstrates that even when the software performs consistently, there still remains a difference in volume change estimates. Thus, the way change in volume over time is measured will depend on the way the boundaries are determined, even when the bias is in the same direction. However, these differences would be even further magnified if there were inconsistencies in software performance.

These findings are important when tumor volume estimates are performed by using computer-aided techniques. Such techniques typically use either a defined threshold or gradient of the Hounsfield units for determining a boundary between the tumor and the normal lung parenchyma. On the basis of the theoretical models, we have demonstrated that even small changes in the determination of this boundary can have a large effect on volume estimates. By evaluating the underlying pathologic findings in these adenocarcinomas we have demonstrated that there is a pathologic basis for a degree of uncertainty in choosing a boundary that on average is a pixel width. For those cases where the ZOT is larger than a single

pixel width there is the potential that the CAD algorithm may choose a boundary that deviates by more than a single pixel. Even in the absence of the ZOT there is still a gradient that will occur between the tumor border and surrounding lung owing to partial pixel values at the transition. Depending on how the algorithm chooses a boundary, the volume estimates can be quite different since a single pixel width over the entire surface of a small nodule represents a substantial portion of the volume.

A similar phenomenon occurs when estimating the size of the solid portion of a part-solid nodule. The primary difference being that for such nodules the radiologist has clearly identified the non-solid portion of the nodule as opposed to the “solid” nodules used in this study where the nonsolid ZOT was identified histologically and not reported radiologically. In these cases, the same type of decision must be made in determining the boundary between the solid and nonsolid portions of the tumor.

There are many different types of nodules that we could have chosen for this study, including those with much sharper edges, such as hamartoma. However, for this initial evaluation we were most interested in defining the ZOT for cancers and, in particular, for cancers that appear solid on the CT images, because this is the most common situation in which volumetric techniques are now being applied. We also chose for this initial evaluation to focus solely on adenocarcinomas, as they are now by far the most commonly detected peripheral solid lung tumor, and we wanted to characterize the ZOT for one type of cancer, understanding that it might be different for other types. We also did not evaluate any particular CAD device, since we wanted to better understand the sources of measurement uncertainty. The ZOT is only one contributing factor in how the software will be influenced in boundary determination.

We also showed that a ZOT as small as a single pixel width can have a large effect on volume estimates, and thus, techniques that allow for improved scanner resolution or use subvoxel interpolation based on attenuation gradients

may be advantageous in determining the boundary of a tumor. These techniques and their potential advantages in defining nodule boundaries because of the additional information provided in those voxels at the tumor boundary with volume averaging have previously been described (12–15). The ZOT represents an additional level of complexity beyond that of simple volume averaging as this represents an inherent property of the tumor and is unrelated to technical properties of the scanner. However, these techniques will allow for improved definition of the border between the solid portion of the tumor and the ZOT. When considering the evaluation of growth rates, it is important that the CAD software act in a consistent way on scans obtained at different times, as this will minimize any bias when looking at proportional differences. Ultimately, this is more important than absolute volume measurements. However, if there is a change in the ZOT as a tumor changes in size, this would have the potential to introduce another source of error into the volume estimate and to the subsequent change in size measurements derived from the volumes. While there is no way to be able to actually measure the ZOT at two time points, we were able to show that among adenocarcinomas manifesting as solid nodules there was no trend in terms of a change in the size of the ZOT, which suggests that its thickness does not change as the tumor changes in size and therefore does not add an additional source of measurement uncertainty. In the one outlier case with the much thicker ZOT, the nodule appeared solid on the CT scan, and the pathologic specimen showed that the ZOT contained areas of fibrosis and hemorrhage which likely accounted for the dense appearance on the CT scan but did not actually represent solid tumor.

A final consideration here is that there is no specific definition of what should be considered the “true” boundary of a solid tumor. Should it only be the portion that is actually solid, or instead include the entire ZOT or only a part of it? We have no specific answer at this time. But is worthwhile

to consider that the edge of the tumor represents the location where growth is the most active; thus, it should be considered an important component of the solid tumor.

This study had several limitations that should be considered when interpreting its results. We focused exclusively on adenocarcinomas that manifested as solid nodules on CT images, and there may be differences in the width of the ZOT in other types of tumors. In addition, it is not possible to determine whether ZOT remains constant as tumors change in size, since we cannot measure histologic findings for the same tumor at two time points. If this were to occur, it would add to additional uncertainty in volume assessment; however our data did not show a significant correlation between tumor size at CT and width of the ZOT in the histologic specimens, which suggests that ZOT is not dependent on tumor size and may not change as tumors grow. We also used only a single reader for measurements performed on the CT scan, as well as the histologic measurements. However, since we were only looking for broad trends the smaller changes that might be present as a result of interreader variability would not influence the results. Our main concern was to begin to understand the effect of the magnitude of the ZOT on tumor volume.

The ZOT was measured on resected specimens and could potentially differ between inspiration and expiration. This would manifest as a change in the thickness of the ZOT and affect volume measurements. However, given that this portion of the lung is already infiltrated with tumor cells, it is likely that the extent of change will be less than that of normal lung.

In summary, we demonstrated that small changes in boundary determination can have a large impact on volume estimates. While there are many technical factors that influence how a CAD algorithm chooses a boundary, we have now shown that there is an inherent pathologic basis contributing to this uncertainty, which we have defined as the ZOT. The interaction between the nodule size, thickness of the ZOT, and the

way in which the CAD algorithm functions can have a large influence on actual volume estimates. The effect increases with decreasing size of the tumor and increasing thickness of the ZOT, assuming the software does not fully distinguish this as nonsolid tumor. As the ZOT for solid adenocarcinomas was in the range of a single pixel width on a full field of view CT scan, it suggests methods to reduce measurement uncertainty will rely on improved resolution or subvoxel measuring techniques. Ultimately, a deeper understanding of these features will allow an estimate of the range of the measurement uncertainty, and consequently the range of proportional change in tumor size. Understanding these boundaries will allow for development of approaches to describe the degree of confidence for any given change in tumor size.

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