Appendix E1

A nonsolid nodule is a combination of both soft tissue and air-contained spaces in partially aerated alveoli, as shown in Figures 1 and 2 in the text. Thus, the attenuation of the nonsolid nodule (D_N) at CT is a combination of the attenuation of soft tissue and air. Mathematically, the attenuation of the nodule can be represented by a linear combination of the attenuation of soft tissue within the nodule ($D_{N,ST}$) multiplied by the proportion of soft tissue ($P_{N,ST}$) and the attenuation of air ($D_{N,A}$) multiplied by the proportion of air ($P_{N,A}$) in the nodule. D_N (in Hounsfield units) is given by the following equation: $D_N = D_{N,ST} \cdot P_{N,ST} + D_{N,A} \cdot P_{N,A} = D_{N,ST} \cdot P_{N,ST} + D_{N,A}(1 - P_{N,ST})$.

Because the model consists of two components, the proportion of alveolar air in the nodule can be represented as the complement of the proportion of soft tissue, $P_{N,A} = 1 - P_{N,ST.}$ Solving for the proportion of soft tissue within the nodule, $P_{N,ST}$, we find that $P_{N,ST} = (D_N - D_{N,A})/(D_{N,ST} - D_{N,A})$.

Similarly, the nonneoplastic lung parenchyma consists of both soft tissue and air, and, thus, the proportion of soft tissue in lung parenchyma ($P_{L,ST}$) is given by the following equation: $P_{L,ST} = (D_L - D_{N,A})/(D_{L,ST} - D_{N,A})$, where D_L is the attenuation (in Hounsfield units) of the nonneoplastic lung parenchyma, $P_{L,ST}$ is the proportion of soft tissue in nonneoplastic lung, and the other variables are the same as previously defined. It is reasonable to assume that the attenuation of soft tissue is uniform, both in the nodule and in nonneoplastic lung, so that $D_{N,ST} = D_{L,ST} = D_{ST}$. Similarly, it is reasonable to assume that air in the nodule is the same as air in the trachea or outside of the lung (although minor differences owing to beam hardening may exist), so that $D_{N,A} = D_A$.

The difference in the proportion of soft tissue (P_{DIFF}) within the nonsolid nodule and the nonneoplastic lung parenchyma is due to tumor growing on the existing parenchyma and is given by $P_{DIFF} = P_{N,ST} - P_{L,ST} = (D_N - D_L)/(D_{ST} - D_A)$.

We consider that the CT attenuation of the nodule, D_N, can vary between that of nonneoplastic lung parenchyma, D_L, and pure soft tissue, D_{ST}. Nonneoplastic lung parenchyma varies between –800 and –900 HU and soft tissue between 40 and 60 HU. Air varies between –950 and –1000 HU. The values chosen are well-known typical values, but they can be varied and the same principals applied.

Table E1 provides the proportion of soft tissue within a nodule, $P_{N,ST}$, as a function of the attenuation of the nodule and soft tissue. For example, for the combination of D_N = –400 HU and D_{ST} = +60 HU or +50 HU, the proportion of soft tissue within the nodule, $P_{N,ST}$, is 0.57. For the same D_N when the soft tissue attenuation is +40 HU, then $P_{N,ST}$ = 0.58. Thus, for CT attenuation of soft tissue within reasonable limits of 40–60 HU, the proportion of soft tissue is essentially the same. We assumed in the above example that the attenuation of air, D_A, was –1000 HU. When we assume D_A is –950 HU, then $P_{N,ST}$ changes from 0.54 to 0.56.

Table E1. Proportion of Soft Tissue within Nodules as a Function of Nodule Attenuation and for Three Different Soft Tissue Attenuation Values

	Soft Tissue Attenuation (HU)		
Nodule Attenuation (HU)	60	50	40
−1000	0.00	0.00	0.00
−900	0.09	0.10	0.10
−800	0.19	0.19	0.19
−700	0.28	0.29	0.29
−600	0.38	0.38	0.38
−500	0.47	0.48	0.48
−400	0.57	0.57	0.58
−300	0.66	0.67	0.67
−200	0.75	0.76	0.77
−100	0.85	0.86	0.87
0	0.94	0.95	0.96
30	0.97	0.98	0.99
40	0.98	0.99	1.00
50	0.99	1.00	1.00
60	1.00	1.00	1.00

Note.—Data are the proportions of soft tissue within a nodule. The attenuation of air was fixed at −1000 HU.

Conversely, changes in the attenuation values for the nonsolid nodule, D_N, can vary considerably with corresponding changes in the proportion of soft tissue, $P_{N,ST}$. For example, given the attenuation of soft tissue, D_{ST}, of say +60 HU, and a D_N of −700 HU, the proportion of soft tissue within the nodule, $P_{N,ST}$, is 0.28. When the nodule attenuation, D_N, increases from −700 HU to −300 HU, there is an increase in $P_{N,ST}$ to 0.66; a further increase when the nodule attenuation is +40 HU results in an increase of $P_{N,ST}$ to 0.98.

Figure E1 shows the same relationship graphically for soft tissue CT attenuations of 40, 50, and 60 HU. It shows that the proportion of soft tissue within the nodule, $P_{N,ST}$ (y-axis), has a linear relationship with nodule attenuation, D_N (x-axis), for each of the three values for soft tissue attenuation. The figure also shows that the slope of the linear equation changes by approximately 1% when the attenuation of soft tissue changes by 10 HU. For example, the slope decreases by 1% when D_{ST} increases from 40 to 50 HU and decreases by another 1% when it increases from 50 to 60 HU. Conversely, the slope of the line increases by approximately 1% when the attenuation of air increases by 10 HU (from −1000 HU to −990 HU). Figure E1 also shows that for each 100-HU increase in

the CT attenuation of the nodule, there is a corresponding 10% increase in the soft tissue component.

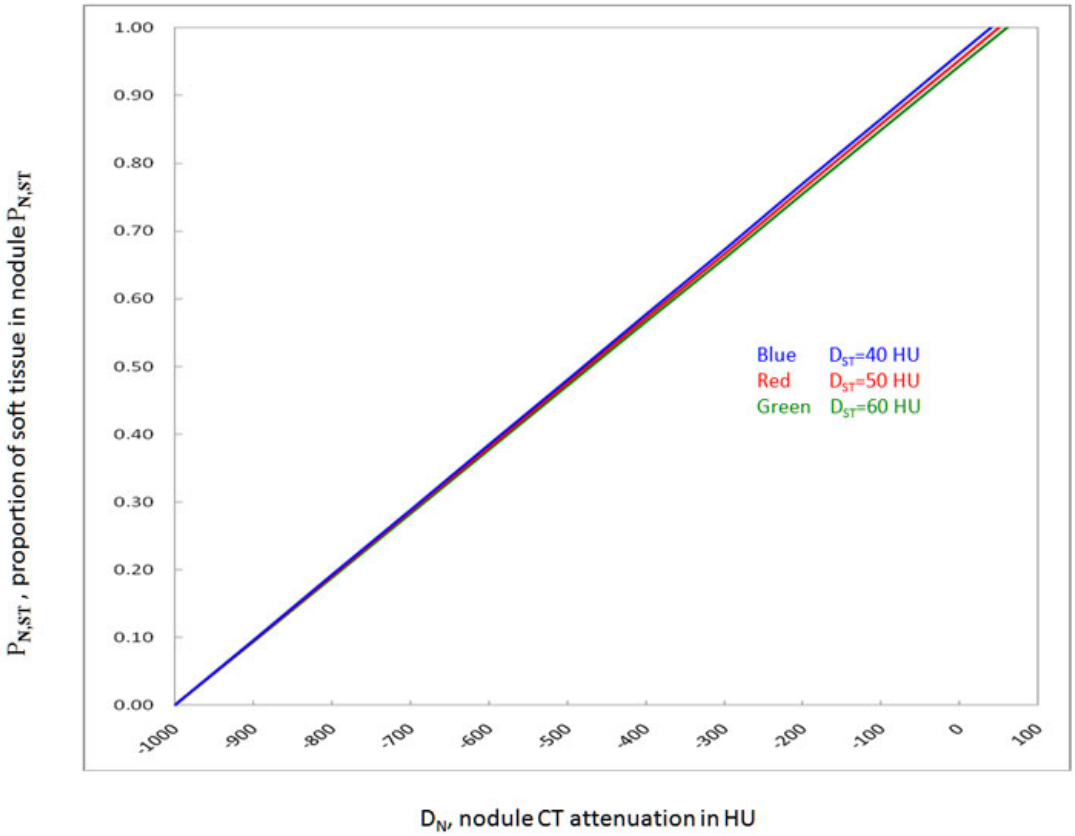

Figure E1: Graph shows the proportion of soft tissue within a nodule ($P_{N,ST}$) as a function of the measured nodule attenuation (D_N) for soft tissue attenuation values (D_{ST}) of 60, 50, and 40 HU.

Table E2 gives the proportion of tumor in the nodule, which is defined as the difference between the proportion of soft tissue in the nodule and that in the nonneoplastic lung, $P_{DIFF} = P_{N,ST} - P_{L,ST}$, for different attenuations of the nodule, D_N, and nonneoplastic lung, D_L. As the attenuation of nonneoplastic lung parenchyma changes from –800 HU to –850 HU to –900 HU for a given nodule attenuation, say D_N = –500 HU, there is a corresponding increase in the proportion of tumor from 0.29 to 0.34 and 0.38. When the nonneoplastic lung attenuation, D_L, is –800 HU and the nodule attenuation, D_N, changes from –500 to –200 HU, the proportion of tumor in the nodule, P_{DIFF}, increases from 0.29 to 0.58. When D_L is –900 HU and nodule attenuation changes from –500 to –200 HU, the proportion of tumor in the nodule increases from 0.38 to 0.67. The increase in the CT attenuation of nonneoplastic lung, say from –900 to –800 HU, reflects a decrease in the extent of emphysema. There may be other causes for decreased lung attenuation (eg, obstructive bronchiolitis), and attenuation values at thin-section CT may even be lower than –900 HU; however, the same principles apply.

Table E2. Differences in the Proportion of Soft Tissue within Nonsolid Nodules and Nonneoplastic Lung Parenchyma according to Nodule Attenuation and for Three Nonneoplastic Lung Attenuation Values

	Attenuation of Nonneoplastic Lung (HU)		
Nodule Attenuation (HU)	−800	−850	−900
−800	0.00	0.05	0.10
−700	0.10	0.14	0.19
−600	0.19	0.24	0.29
−500	0.29	0.34	0.38
−400	0.38	0.43	0.48
−300	0.48	0.53	0.58
−200	0.58	0.63	0.67
−100	0.67	0.72	0.77
0	0.77	0.82	0.87
30	0.80	0.85	0.89
40	0.81	0.86	0.90

Note.—Differences between the proportion of soft tissue within the nonsolid nodule and that in nonneoplastic lung parenchyma are due to tumor growing on the existing parenchyma. D_{ST} was fixed at 40 HU.

The relationship between P_{DIFF} and nodule attenuation is linear, as shown in Figure E2 for three different attenuation values in the nonneoplastic lung. For each attenuation value in the nonneoplastic lung, when the attenuation of the nodule D_N reaches its maximum value of soft tissue, P_{DIFF} does not reach 1.00 because the nodule does not consist entirely of tumor because by definition the background nonneoplastic lung is subtracted, that is, $P_{DIFF} = P_{N,ST} - P_{L,ST.}$

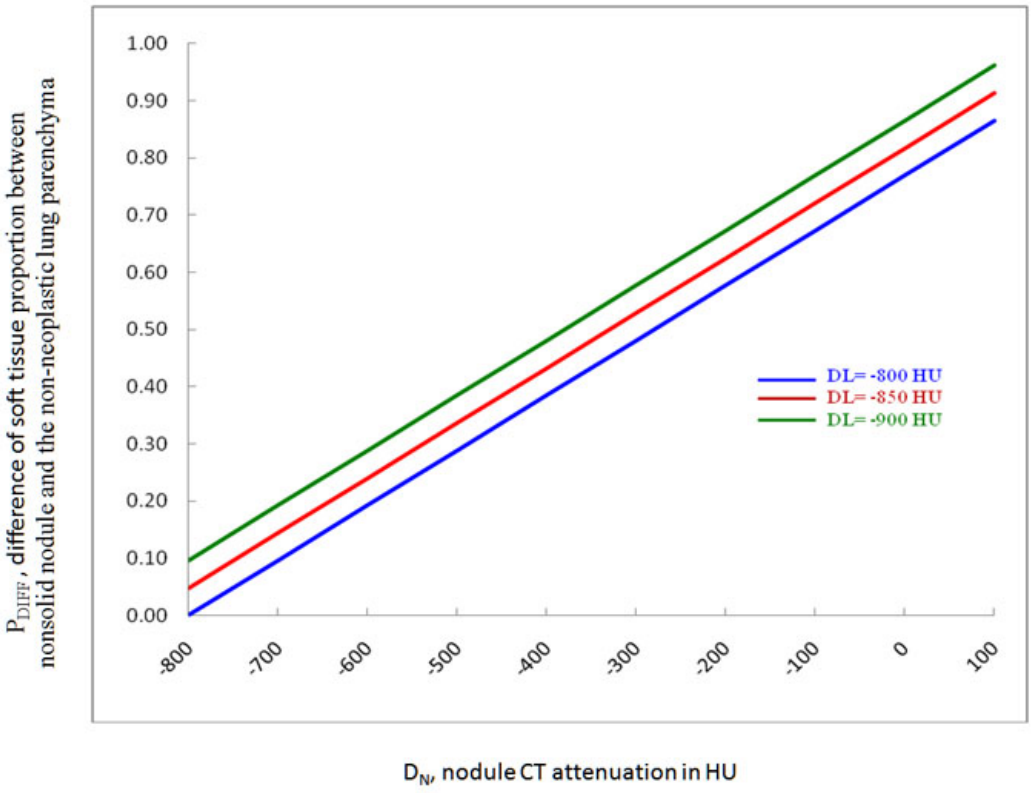

Figure E2: Graph shows the difference in the proportion of soft tissue within the nonsolid nodule and the nonneoplastic lung parenchyma (P_{DIFF}), which is due to tumor growing on the existing parenchyma, for different nodule attenuation values and for three different nonneoplastic lung attenuation (D_L) values (–800, –850, and –900 HU); D_{ST} was fixed at 40 HU.

Following the same steps that were used for CT images, the same can be done to estimate the proportion of tumor directly on the histologic images. This proportion, $P_{HN,ST}$, was calculated as follows: $P_{HN,ST} = (A_N - A_{NA})/A_N$, where A_N is the area of the nodule and A_{NA} the proportion of air contained within it.

Similarly, for the nonneoplastic lung, an ROI can be applied to each specimen and the air within the ROI automatically segmented and determined by the software. The nonneoplastic lung can also be assessed on the same histologic slide as the cancer. With this information, the proportion of soft tissue in lung, $P_{HL,ST}$, was calculated with the following equation: $P_{HL,ST} = (A_L - A_{LA})/A_L$, where A_L is the area of the ROI in the nonneoplastic lung adjacent to the tumor and A_{LA} the proportion of the area that is occupied by air.

The difference between the proportion of the soft tissue in the nodule and that in the nonneoplastic lung is defined as follows: $P_{H,DIFF} = P_{HN,ST} - P_{HL,ST}$. This value represents the increase in the proportion of the soft tissue due to tumor compared with nonneoplastic lung as determined from the histologic specimen.