Theoretical Limitations in the Immunodiagnostic Imaging of Cancer with Computed Tomography and Nuclear Scanning

S. David Rockoff, David J. Goodenough, and K. Robert McIntire

Department of Radiology, The George Washington University Medical Center, Washington, D. C. 20037 [S.D.R., D.J.G.I., and The Laboratory of Immunodiagnosis, National Cancer Institute, NIH, Bethesda, Maryland 20205 [K.R.M.]

Abstract

In order to help assess the feasibility of using immunologically tagged agents to render tumors detectable with current computed tomographic and nuclear scanners, mathematical formulations were developed to determine the theoretical limits of tumor detection relative to size and depth of the lesions.

The results of our analysis suggest that visualization with computed tomography of a tiny tumor (1 sq mm, cross-sectional area) would require binding in the order of $2 \times 10^5$ iodine atoms/antigenic site, while imaging of a very large (900-sq mm) tumor would require approximately $10^4$ atoms/site. Very low energy scanners might reduce these discouraging estimates by an order of 10².

The immunological imaging of tumors with nuclear scanning appears quite feasible from our formulations, as has been demonstrated by others clinically. Small (1-sq cm) and deep (≥5-cm) tumors appear detectable with uptake ratios of the order of 5 or higher, which seem to be attainable currently. Smaller and deeper tumors require much higher uptake ratios to be detected.

The problem of detecting a tumor with a radiological imaging system is related to the characteristics of the imaging system as well as the physical and biological parameters of the tumor as compared to normal tissue. In the simplest case, one may hope to detect intrinsic physical differences such as density. However, it may be necessary to augment any such physical differences by using biological differences such as uptake ratio, and it is to this detection that most efforts in immunodiagnosis have been directed.

In this particular paper, mathematical formulations and some data from our laboratory will be used to address 2 questions: (a) the feasibility of using immunological tagging agents to render tumors detectable with state-of-the-art CT scanners; and (b) more to the subject of this workshop, what are the smallest tumors theoretically detectable using immunodiagnostic methods with present-day nuclear medicine camera imaging systems.

Immunological Approach to Tumor Imaging with CT Scanners

In the diagnostic energy range, the linear attenuation coefficient (μ) is comprised of 2 processes, the photoelectric effect and Compton interaction. The photoelectric effect (PE) is proportional to the approximate cube of the atomic number of the material ($Z^3$), directly proportional to the electron density ($N_e$), and inversely proportional to the cube of the energy ($E^3$):

$$\mu_{pe} \propto \frac{Z^3}{E^3} N_e$$  \hspace{1cm} (A)

where

$$N_e = \left( \frac{Z}{A} \right) \rho N_0$$

in which A is atomic weight, $\rho$ is density, and $N_0$ is Avogadro’s number.

Compton interactions (c) are proportional to the electron density of the material and change only slowly with energy [roughly as the inverse of energy, $F(E)$].

$$\mu_c \propto F(E) \cdot N_e$$  \hspace{1cm} (B)

In CT, we may examine how an effective linear attenuation coefficient changes as a function of energy, atomic number, or electron density. If we are dealing primarily with Compton interactions, the change in linear attenuation coefficient between materials will be a function only of their respective densities. Moreover, it has been shown empirically by Phelps (5) and Rutherford (7) that the CT number output for many substances is directly linear with respect to electron density. However, in CT, we are dealing with a polyenergetic source of radiation rather than a monoenergetic source. Comparison of the X-ray spectral distribution (Chart 1) with the attenuation coefficients of bone, muscle, and fat, shown in Chart 2, indicates that there may be a significant attenuation due to the photoelectric effect.

Thus, the total of the X-ray attenuation coefficients in CT will be a complicated combination of the photoelectric effect and Compton interaction occurring at each energy, and the measured attenuation coefficient in CT scanning will be the value of $\mu$ at each X-ray energy weighted by the relative intensity of that energy to the total energy spectrum.

In practice, the CT number (CT) is usually scaled to the difference of each effective linear attenuation coefficient of the reference material (ref)

$$CT = K \frac{(\mu - \mu_{ref})}{\mu_{ref}}$$  \hspace{1cm} (C)

where $K$ is an empirical constant. The EMI Mark I head scanner used water (w) as a reference material; thus, the EMI number (EMIw) was given by:

$$EMI_{w} = K \frac{(\mu - \mu_{w})}{\mu_{w}}$$  \hspace{1cm} (D)

1 Presented at the UICC Workshop on Radioimmunodetection of Cancer, July 19 to 21, 1979, Lexington, Ky.
2 The abbreviations used are: CT, computerized tomography; SNR, signal-to-noise ratio.
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\[ C_{CT} = \frac{\mu_s - \mu_b}{\mu_s - \mu_L} \]  

where \( \mu_s \), \( \mu_b \), and \( \mu_L \) are the respective effective linear X-ray attenuation coefficients for the signal (S), the background (B), and the lower window setting (L), (3).

For CT, the noise fluctuation \( \sigma_{CT} (\mu) \) can be considered as:

\[ \sigma_{CT} (\mu) \sim K' \frac{D^{1/2} h^{1/2}}{A^{1/2}} \]  

where \( K' \) is an empirical constant, \( D \) is dose, \( p \) is pixel width, \( A \) is the area of interest, and \( h \) is the slice thickness.

In terms of some viewed image, with light transmission \( T \) through the background region, the relative noise fluctuation level \( \frac{\sigma(T)}{T} \) is expressed as:

\[ \frac{\sigma(T)}{T} = \frac{K'(h p A D)^{-1/2}}{\mu_s - \mu_L} \]  

and

\[ C_{CT} = K'(h p A D)^{1/2} (\mu_s - \mu_b) \]

In terms of tagging a tumor with cold iodine, we may use empirical data developed by Gado et al. (1) which relate the increased lucency of the iodinated medium (\( \Delta CT \)) to the iodine content (IC), expressed in terms of mg/100 ml. This relationship is essentially given by:

\[ \Delta CT \approx \frac{IC}{8} \]

Then, using Equation G, for dose levels on the order of 2 rads, the state-of-the-art CT scanners have a standard deviation of noise level \( \sigma(CT) \) given by:

\[ \sigma(CT) \approx \frac{3}{\sqrt{A}} \]

where \( A \) is the area (sq mm) of the signal being searched. If we assume that the SNR is

\[ \text{SNR} = \frac{\Delta CT}{\sigma(CT)} \]

must be on the order of 1 to 5 for adequate detection (2), then, depending on dose and resolution levels of the CT scanner, one may assume for current CT scanners an approximate relationship of:

\[ \text{SNR} = \frac{1}{24} IC \sqrt{A} \]

and therefore

\[ IC \sim \frac{24(\text{SNR})}{M/A} \]

If we take limiting cases of 1 sq mm and 900 sq mm for \( A \) and a conservative SNR of 5, then, when \( A \) is 1 sq mm,

\[ IC = 24 (\text{SNR}) = 120 \]
and, when \( A \) is 900 sq mm,

\[
\text{IC} = \frac{24}{30} \text{(SNR)} = 4
\]

Then, one can calculate the number of iodine atoms \((N_t)\) per mg of iodine by:

\[
N_t = \left( \frac{1 \text{ mg}}{127 \times 10^3 \text{ mg}} \right) 2(6.02 \times 10^{23}) \quad \text{(M)}
\]

or \( \sim 10^{19} \) iodine atoms/mg of iodine.

Assume that there are approximately \( 10^{11} \) cells/100 ml of tissue (9). Therefore, in terms of IC, for each mg of iodine per 100 ml of tissue, one has approximately \( 10^8 \) iodine atoms/cell.

Using the estimate of approximately \( 5 \times 10^4 \) sites/cell (9), one must bind approximately \( 2 \times 10^3 \) iodine atoms/cell site in order to achieve an iodine concentration of 1 mg/100 ml.

It seems therefore very pessimistic to expect that small signals of area 1 sq mm could be detected by immunological approaches by conventional scanners under conventional dose levels because one would need on the order of \( 2 \times 10^5 \) atoms bound/site, even neglecting deleterious "volume-averaging" effects of such small tumors. Even large tumors (e.g., 900 sq mm) would require on the order of \( 10^9 \) atoms bound/site.

It should also be noted that the nonlinear effects of "volume averaging" are more severe than generally appreciated. The contrast reduction is dependent not only on the percentage of the slice thickness occupied by the tumor (\( h \)), but also by its spatial extent (\( x \)), such that:

\[
\mu_{\text{eff}} = \mu_2 - \frac{1}{x} \ln \left[ 1 + \frac{h}{h} (e^{x\mu_1} - 1) \right]
\]

\[
\text{(N)}
\]

where \( \frac{h}{h} \) is a fraction of \( \mu_1 \), and \( \frac{h}{z} \) is a fraction of \( \mu_2 \).

It should be noted, however, that very-low-energy scanners (e.g., 30 to 40 keV) that could preferentially enhance the photoelectric attenuation characteristics of high Z elements in conjunction with high dose levels (e.g., 100 rads) if radiation dose were not important (as in \textit{in vitro} specimens) might reduce these estimates by an order of 100 or more.

**Immunological Approach to Tumor Imaging with Nuclear Scanning**

Assume essentially the same model for an isolated tumor sitting at depth \( d \) in an otherwise uniform box of radioactivity and that the tumor has an uptake ratio of \( U \) compared to the background.

A first-order formulation of SNR for a parallel-hole nuclear-medicine camera system may be developed. For a box of depth \( L \), it can be shown that the count density \((C_d)\) expressed as counts per sq cm over the uniform background is given by:

\[
C_d = \phi C \int_0^L e^{-\mu z} dz, \quad \text{(O1)}
\]

\[
C_d = \frac{\phi C}{\mu} [1 - e^{-\mu}] \quad \text{(O2)}
\]

or

\[
\phi C = \frac{\mu C}{(1 - e^{-\mu})} \quad \text{(O3)}
\]

where \( c \) is the background radioactivity concentration, \( \phi \) is the system sensitivity (efficiency), and \( \mu \) is the linear x-ray attenuation coefficient of the radioactive solution.

An important aspect of modeling signal detection theory is the assumption of the criterion for selection. In this case, the criterion for detection is that the net difference in counts between the effective signal (e.g., tumor area \((A_{\text{eff}})\) and an equivalent area of background will be sufficiently different to be imaged as an abnormal area of uptake with state-of-the-art scanners.

It is relatively easy to show that, as a small radioactive source of volume \( V \), situated in air, is moved away from the camera face, the total detected (integrated) counts due to the source stay relatively constant. It is also noted, as expected, that the effective area of the image of the source (point spread function) becomes correspondingly larger.

Therefore, it follows that, if one assumes that the overall effective area of integration for a finite tumor source is obtained by convolving or cascading the camera blur function \((A')\) with the actual area of the tumor signal \((A_\lambda)\), one has:

\[
A_{\text{eff}} = [A(\lambda)^2 + (A')^2]^{1/2} \quad \text{(P)}
\]

Moreover, if one assumes that \( A_{\text{eff}} \) is large enough so that the net integrated signal strength is determined primarily by \( \phi \) in conjunction with \( \mu, c, \) and \( V \), then, considering the displacement of the background activity by the signal activity, the net activity is \((U - 1)cV \), and the total net counts in \( A_{\text{eff}} \) due to the lesion \((C_{\text{lesion}})\) are assumed to be:

\[
C_{\text{lesion}} = \phi [U - 1] cV e^{-\mu d} \quad \text{(Q)}
\]

Then, a measure of the SNR in \( A_{\text{eff}} \) is given by:

\[
\text{SNR} = \frac{|U - 1| cV e^{-\mu d}}{\sqrt{C_0 A_{\text{eff}}} \quad \text{(R1)}}
\]

\[
\text{SNR} = \frac{|U - 1| \mu \sqrt{C_0 V} e^{-\mu d}}{A_{\text{eff}} (1 - e^{-\mu L})} \quad \text{(R2)}
\]

In terms of state-of-the-art camera performance, one may assume a Gaussian spread function composed of degradation intrinsic to the crystal itself and geometric (collimator) effects. If one estimates the intrinsic \( (\sigma_i) \) and geometric \( (\sigma_g) \) effects as:

\[
\sigma_i \sim 2 \text{ mm} \quad \text{(S1)}
\]

\[
\sigma_g \sim 3 \text{ mm} \left( \frac{d + t}{t} \right) \quad \text{(S2)}
\]

where \( d \) is the distance of the (point) source and \( t \) is the collimator thickness, then the overall \( \sigma' \) due to camera degradation alone is given by:

\[
\sigma' \sim (\sigma_i^2 + \sigma_g^2)^{1/2} \quad \text{(T)}
\]

Then, if one assumes a Gaussian-shaped tumor signal and a value for the tumor signal as \( \sigma_s \), then:

\[
A_{\text{eff}} = 4\pi\sigma^2 = 4\pi(\sigma_i^2 + \sigma_g^2 + \sigma_s^2) \quad \text{(U)}
\]

Thus,

\[
\text{SNR} = \frac{\mu |U - 1| (C_0)^{1/2} V e^{-\mu d}}{(1 - e^{-\mu L})^{1/2}} \quad \text{(V)}
\]
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Chart 3. Computed uptake ratios needed for imaging of various size tumors in a 30-cm-thick patient at count densities \( C_B \) of 100, 1,000, and 10,000 at depths \( d \) ranging from the surface (0 cm) to 15 cm. \( A \), area of tumor.

\[
U = \frac{\text{SNR} \sqrt{A_{\text{eff}} (1 - e^{-a t})}}{\mu \sqrt{C_B \cdot V e^{-a d}}} + 1 \tag{W}
\]

One can note that, in the case when \( a \) and \( a_0 \) become small compared to \( a_0 \) (e.g., at large distances \( d \)), then the \( A_{\text{eff}} \) is proportional to \( d^2 \).

One may then solve for the value of \( U \) necessary to image various size tumors at various depths considering the following parameters:

Assume as constants:

- SNR = 5
- \( \mu = 0.15 \text{ cm}^{-1} \)
- \( a = 0.2 \text{ cm} \)
- \( a_0 = 0.3 \left( \frac{d + t}{t} \right) \text{ cm} \)
- \( t = 3 \text{ cm} \)
- \( V = \frac{4}{3} \pi (2a_0)^3 \text{ cu cm} \)
- \( L = 30 \text{ cm} \)

Solve Equation V for \( U \) using the following variables:

- \( A_s = 0.25, 1.0, 2.0, 4.0 \text{ sq cm} \)
- \( d = 0, 5, 10 \text{ cm} \)
- \( C_B = 100, 1,000, 10,000 \text{ counts/sq cm} \)

In Chart 3 are plotted the results of the above calculations. The resultant graphs show predicted uptake ratios for the indicated signal sizes \( A_s = 4\pi a_0^2 \) and count densities. It should be noted that a Gaussian-shaped signal with a standard deviation of \( a_0 \) can be thought of as a circular signal with a radius \( 2a_0 \). Therefore, a tumor size represented by \( a_0 = 2 \text{ cm} \) has a diameter of approximately 8 cm.

It should also be noted that a rather stringent SNR of 5 was used in solving for \( U \). This SNR is a conservative value and has been thought in excess of levels deemed clinically useful (8). As SNR relaxes, one would expect lower values of \( U \). However, while it is possible that lower SNR levels could be clinically applicable, it was thought reasonable to use a value of 5 for the present calculations.

It is apparent from Chart 3 that, for small tumors \( A = 0.25 \text{ or } 1.0 \text{ sq cm} \), deep tumors \( d \geq 5 \text{ cm} \), and/or low count densities \( C_B \leq 1000 \), there is a challenging requirement on the uptake ratio, tending to be over 5.

In data from our laboratory (Table 1) in which a sensitive assay for immunoglobulin binding to intact cells developed by us was utilized (6), the anti-carcinoembryonic antigen reactivity between certain cancer cells and normal cells approached an uptake ratio of 4. In addition, in discussions at this workshop, Dr. Bale quoted from his experiments uptake ratios varying from 4 to 8 and higher, Dr. J. P. Mach quoted uptake ratios of 4 or 5, and Dr. Goldenberg stated that he had found uptake ratios of 10 to 14 for anti-carcinoembryonic antigen localization in tumors.

The difficulty of successfully detecting very small tumors at great depths remains a challenging problem in light of current levels of uptake ratio for parallel-hole camera systems. Our analysis shows the importance of developing focused camera...
Table 1  
Assay of anti-carcinoembryonic antigen\(^a\) activity against human cells  

<table>
<thead>
<tr>
<th>Cell</th>
<th>Mean anti-carcinoembryonic antigen activity (N = 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td></td>
</tr>
<tr>
<td>Normal lung</td>
<td></td>
</tr>
<tr>
<td>Normal liver</td>
<td></td>
</tr>
<tr>
<td>Normal kidney</td>
<td></td>
</tr>
<tr>
<td>Normal spleen</td>
<td></td>
</tr>
<tr>
<td>Normal leukocytes</td>
<td></td>
</tr>
<tr>
<td>Normal lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Lung cancer 160</td>
<td>20.7</td>
</tr>
<tr>
<td>Lung cancer 172</td>
<td>14.5</td>
</tr>
<tr>
<td>Lung cancer 182</td>
<td>12.1</td>
</tr>
<tr>
<td>Lung cancer 200</td>
<td>22.3</td>
</tr>
<tr>
<td>Lung cancer 203</td>
<td>20.5</td>
</tr>
<tr>
<td>Lung cancer 205</td>
<td>13.3</td>
</tr>
<tr>
<td>Ovarian carcinoma (tissue culture)</td>
<td>15.0</td>
</tr>
<tr>
<td>Melanoma 91B</td>
<td>12.4</td>
</tr>
<tr>
<td>Melanoma 90</td>
<td>11.8</td>
</tr>
<tr>
<td>Metastatic breast 115</td>
<td>41.5</td>
</tr>
<tr>
<td>Metastatic osteosarcoma</td>
<td>11.9</td>
</tr>
<tr>
<td>Mouse</td>
<td></td>
</tr>
<tr>
<td>Small cell carcinoma lung A</td>
<td>13.2</td>
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<tr>
<td>Small cell carcinoma lung B</td>
<td>17.0</td>
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<tr>
<td>Small cell carcinoma lung C</td>
<td>12.7</td>
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<tr>
<td>Small cell carcinoma lung D</td>
<td>45.5</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>46.0</td>
</tr>
</tbody>
</table>

\(^a\) Partially purified, supplied by Dr. David Goldenberg.

and/or emission CT systems, where the depth dependence might be selectively minimized.

Acknowledgments

The authors would like to acknowledge helpful discussions with Dr. Frank Atkins of Walter Reed Army Hospital on the physical analysis of nuclear medicine camera systems. In addition, acknowledgment is made to Tim Lynch and Mark Selikson of The George Washington University Medical Center for technical assistance on the computer program for generation of theoretical data.

Addendum

Since formulation of the data in Chart 3, the spatial resolution (\(\alpha_0\)) of nuclear camera systems has improved by approximately a factor of 2, making the uptake ratios required to visualize small tumors approximately one-half that shown in Chart 3. Larger tumors are much less affected by the improvement in \(\alpha_0\).

References

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