Radiation Exposure During Catheter Ablation of Atrial Fibrillation

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Background—The purpose of this study was to determine the radiation exposure during catheter ablation of atrial fibrillation (AF) using the pulmonary vein (PV) approach.

Methods and Results—The study included 15 patients with AF and 5 patients each with atrial flutter and atrioventricular nodal reentrant tachycardia (AVNRT) who underwent fluoroscopically guided procedures on a biplane x-ray system operated at a low-frame pulsed fluoroscopy (7.5 frames per second). Radiation exposure was measured directly with 50 to 60 thermoluminescent dosimeters (TLDs). Peak skin doses (PSDs), effective radiation doses, and risk of fatal malignancies were all computed. Mean fluoroscopy durations for AF procedures were 67.8±21 minutes in the right anterior oblique (RAO) and 61.9±16.6 minutes in the left anterior oblique (LAO) projection, significantly different from that required for atrial flutter and AVNRT. The mean PSDs measured with the TLDs were 1.0±0.5 Gy in the RAO and 1.5±0.4 Gy in the LAO projection. The lifetime risk of excess fatal malignancies normalized to 60 minutes of fluoroscopy was 0.07% for women and 0.1% for men.

Conclusions—The relatively small amounts of the patient’s radiation exposure in this study, despite the prolonged fluoroscopy durations, can be attributed to the use of very-low-frame pulsed fluoroscopy, the avoidance of magnification, and optimal adjustments of the fluoroscopy exposure rates. The resulting lifetime risk of fatal malignancy is within the range previously reported for standard supraventricular arrhythmias. (Circulation. 2004;110:3003-3010.)

Key Words: catheter ablation ■ radiography ■ radiation

Catheter ablation of atrial fibrillation (AF) has evolved as an effective treatment option for patients with symptomatic drug-refractory AF.1–5 Most series have reported long-term efficacy varying from 60% to 95%.1–5 Widespread adoption of this procedure has been limited in large part because of the well-described potential for acute complications, including cardiac tamponade, pulmonary vein (PV) stenosis, and stroke.3–5 Another potential but less easily recognized complication associated with this procedure results from the delayed effects of radiation received by patients as the result of prolonged fluoroscopy times. These risks include acute and subacute skin injury6,7 as well as radiation-induced cancer and genetic abnormalities.8–13 This is of particular concern because of the complex nature of this procedure, typically involving double transseptal catheterization, PV angiography, and extensive radiofrequency (RF) application.3–5,14 The purpose of this study, therefore, was to determine the amount of radiation received by patients undergoing catheter ablation of AF by use of a PV approach. To put this degree of radiation exposure in context, we also determined the radiation exposure received by a comparison group of patients who were undergoing catheter ablation of atrioventricular nodal reentrant tachycardia (AVNRT) and atrial flutter. Particular attention was focused on precisely defining the amount and distribution of the fluoroscopy exposure rates. The resulting lifetime risk of fatal malignancy is within the range previously reported for standard supraventricular arrhythmias.

Methods

Patient Characteristics
The patient population included 15 patients referred for catheter ablation of AF by use of the PV approach. AF was paroxysmal in 10 and persistent in 5 patients. Also included in the study as control...
Electrophysiology Testing and RF Ablation

Catheter ablation was performed by use of the double transseptal approach. Contrast venography of all PVs was performed. A 64-pole basket catheter was used to map the PVs. PV potentials were targeted with RF energy. RF was also applied to the cavitricuspid isthmus. The approach used for AF ablation did not differ regardless of whether a patient had paroxysmal or persistent AF. RF ablation of atrial flutter and AVNRT was performed in the standard manner.

Fluoroscopic System and Radiation Measurement

Ablations were performed on a biplane fluoroscopy system (BICOR HS, Siemens Medical Systems). The system was set to pulsed mode at 7.5 frames per second. The image intensifier diameter of 23 cm was used for all subjects. Collimation and magnification were not used during the procedure. The x-ray beam size on the back of the patient’s skin surface was 12 cm in diameter for the right anterior oblique (RAO) and left anterior oblique (LAO) projections. Tube potential ranged from 70 to 109 kV peak (kVp) and tube current of 1 to 10 mA with maximum output of 8.7 R/min as measured at 30 cm from the image intensifier. The half-value layer (HVL) was 4.1 and 4.8 mm of aluminum at 80 kVp, respectively, for anteroposterior (RAO) and lateral (LAO) planes. Physics evaluations were performed at the onset of the study and every 6 months thereafter to ensure proper operational conditions. The radiation dose distribution on subjects was measured by use of thermoluminescent dosimeter (TLD) sensors. The TLD sensors were single-element TLD-100 lithium fluoride (LiF) nominally 3 x 3 x 1 mm in size (Landauer, Inc), calibrated to diagnostic energies (70 to 140 kVp). Individually wrapped TLD sensors were placed in the pockets of a custom-made vest (Figure 1A) and positioned on the back of the patient. We refer to this as the “TLD vest.” Depending on patient size, between 50 and 60 TLDs were distributed at regular intervals (3 to 5 cm) to cover the entire region (Figure 1B) facing the fluoroscopy source. In addition, 2 TLD sensors were taped to the center of the collimator on each x-ray tube, because the system lacked any type of online dose monitors. To verify that the radiation field was covered completely by TLDs during the ablation procedure, Ready-Pack (Kodak X-Omat) film was placed behind the vest. The top and bottom parts of the vest edges were marked with a pen on the film for later verification.

The patients’ demographic information is recorded in Table 1. The patient’s anteroposterior and lateral thickness in the chest region was measured with a caliper. During the ablation procedure, the source–to-image intensifier distance (SID) and source-to-skin distance (SSD) were recorded along with the tube angulations (Table 1). We adjusted the LAO and RAO angulations anatomically in accordance with the patient’s orientation of the interventricular septum. As a result, there is a slight variation in the RAO and LAO angulations between patients. The voltage (kVp), current (mA), and total fluoroscopy duration for each plane were recorded.

### TABLE 1. Patient Demographic Information and Procedure Parameters

<table>
<thead>
<tr>
<th>Demographic Particulars</th>
<th>AF</th>
<th>Atrial Flutter</th>
<th>AVNRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of subjects</td>
<td>15 (10 m, 5 f)</td>
<td>5 (4 m, 1 f)</td>
<td>5 (3 m, 2 f)</td>
</tr>
<tr>
<td>Age, y</td>
<td>56±11 (39–78)</td>
<td>70±7 (62–77)</td>
<td>56±11 (39–78)</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>82±12 (64–108)</td>
<td>80±7 (70–89)</td>
<td>89±29 (61–132)</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.8±0.1 (1.6–2.0)</td>
<td>1.7±0.2 (1.5–1.9)</td>
<td>1.8±0.1 (1.7–1.8)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>26±2 (23–32)</td>
<td>27±4 (21–30)</td>
<td>28±8 (22–42)</td>
</tr>
<tr>
<td>AP thickness, cm</td>
<td>20.1±2.5 (16–24)</td>
<td>21.6±3.1 (18–25)</td>
<td>22.6±6.1 (16–30)</td>
</tr>
<tr>
<td>Lateral thickness, cm</td>
<td>30.7±3.3 (25–36)</td>
<td>32.2±1.3 (31–34)</td>
<td>32.8±4.3 (28–39)</td>
</tr>
<tr>
<td>Procedure parameters</td>
<td>RAO</td>
<td>LAO</td>
<td>RAO</td>
</tr>
<tr>
<td>SID, cm</td>
<td>87±2</td>
<td>95±3</td>
<td>88±1</td>
</tr>
<tr>
<td>SSD, cm</td>
<td>47±3</td>
<td>47±3</td>
<td>46±5</td>
</tr>
<tr>
<td>Angulation, degrees</td>
<td>34±8</td>
<td>54±7</td>
<td>42±9</td>
</tr>
<tr>
<td>Peak voltage, kVp</td>
<td>76±7</td>
<td>89±6</td>
<td>83±9</td>
</tr>
</tbody>
</table>

Data are mean±SD (range).
Estimation of Deterministic Risk From Radiation Exposure

The TLD sensors from subjects and collimator were sent out for analysis (Landauer, Inc). The risks for radiation-induced skin injuries were calculated by 3 methods. The “direct method” measured radiation exposure with the TLD sensors placed on the subjects by use of the TLD vest. The maximum value for each projection is tabulated as peak skin dose (PSD). The “extrapolation method” is the dose measured with the TLD sensors positioned on the collimator and extrapolated to the subject’s skin surface on the basis of measured SSD. The “estimation method” was based on fluoroscopic times and technical parameters such as kVp, mA, SSD, SID, and others recorded for the procedure.

Estimation of Carcinogenic Risk From Radiation Exposure

Organ doses were computed for average men and women by the organ-dose methodology. For men, an HVL of 4.0 mm Al was assumed, corresponding to a 90-kVp beam with 4.0 mm Al total filtration. For women, an HVL of 3.5 mm Al was used, corresponding to 80 kVp with a total filtration of 3.9 mm Al. Three different sets of organ doses were calculated on the basis of the radiation estimates derived with the direct, extrapolation, and estimation approaches as described earlier. Once estimated organ doses had been computed for each subject, the effective doses were computed by use of International Commission on Radiological Protection 60 tissue-weighting factors. The risk of a fatal malignancy in specific tissues was obtained from organ-dose data by use of risk estimates compiled in the Biological Effects of Ionizing Radiation Committee Report. The risk of fatal cancers was also estimated from the total effective dose using an average lifetime risk factor of 4% per Sv.

Statistical Analysis

All variables are given as mean±SD. ANOVA was used to determine the significance level of differences in several parameters with regard to the ablation target. Bonferroni’s method was used for post hoc comparisons in ANOVA. A value of P<0.05 was considered statistically significant. All statistical analyses were performed using STATA software, version 8.0 (STATA Corp). Radiation doses are expressed in standardized international units.

Table 2. Mean and SD of Fluoroscopy Durations for Each Procedure in the Two Projections

<table>
<thead>
<tr>
<th>Projections</th>
<th>Fluoroscopy Duration, min</th>
<th>AF</th>
<th>Atrial Flutter</th>
<th>AVNRT</th>
<th>P, ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAO</td>
<td>67.8±21.6</td>
<td>18.1±4.5*</td>
<td>12.6±4.6*</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>LAO</td>
<td>61.9±16.6</td>
<td>11.5±6.8*</td>
<td>4.6±2.4*</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Combined (RAO+LAO)</td>
<td>129.7±36.7</td>
<td>29.7±10.5*</td>
<td>17.1±6.7*</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

There were no significant differences between atrial flutter and AVNRT in both projections. *P<0.001 for post hoc comparison between the ablation target and AF using Bonferroni’s test.

Results

Ablation Results

Catheter ablation was acutely successful, with complete electrical isolation of all PVs in each patient undergoing ablation of AF. Ablation was also acutely successful in each of the patients undergoing ablation of atrial flutter or AVNRT. There were no complications.

Fluoroscopy Time

Shown in Figure 2A and summarized in Table 2 are the fluoroscopy durations. The total fluoroscopy duration received by patients undergoing ablation of AF was at least 4-fold greater than during ablation of atrial flutter and at least 8-fold greater than during ablation of AVNRT.

Radiation Exposure

The PSDs as measured with the TLD vest are shown in Figure 2B. The mean PSD received by patients undergoing AF...
Ablation (1.00 ± 0.5 and 1.48 ± 0.37 Gy in the RAO and LAO projections, respectively) was at least 3-fold greater than that received by patients undergoing ablation of atrial flutter and AVNRT. Despite prolonged fluoroscopy times during AF ablation, only 1 exceeded the 2-Gy threshold dose required for the onset of radiation-induced skin injuries.20 Despite this, no patient in our study had any clinical evidence of radiation skin injury. The higher PSD in the LAO compared with the RAO projection is because of the orientation of the x-ray tube, resulting in a longer attenuation path for the x-ray beam in the LAO than in the RAO projection.

The skin dose distribution for a typical AF ablation procedure as measured with TLD sensors is shown in Figure 3A. The Ready-Pack direct exposed film (Figure 3B) verified the positioning of the TLD sensors within the x-ray field and demonstrates that the radiation entered the skin covering a small region on the back of the subject ≈16 × 10 cm in the RAO projection and 14 × 15 cm in the LAO projection. In Figure 3A, the fluoroscopic duration was 77.6 minutes in the RAO and 76.5 minutes in LAO, and the corresponding PSDs were 0.90 and 1.67 Gy in the RAO and LAO projections, respectively.

In addition to direct measurements of skin doses by use of the TLD vest, the skin doses were also estimated by the extrapolation and estimation methods described previously. The mean skin doses during AF, atrial flutter, and AVNRT ablation in both the RAO and LAO projections are summarized in the top part of Table 3. The absorbed skin doses as estimated by the extrapolation method overestimated by 72% and 66% for the RAO and LAO projections, respectively, compared with direct method. The absorbed skin doses as estimated by the estimation method overestimated by 57% and 108% for the RAO and LAO projections, respectively, compared with direct method. An excellent correlation between the 3 methods was observed in both the RAO and LAO projections (Figure 4).

Cancer Risk

The effective radiation doses calculated on the basis of the PSD measured with the TLD vest as well as the extrapolation and estimation methods is tabulated in the bottom part of Table 3.

Estimates of organ doses and the associated lifetime risk of excess fatal malignancies per 1 000 000 patients undergoing RF catheter ablation of AF is shown in Table 4. Data for risk estimates normalized to 60 minutes of fluoroscopy are based on the BEIR V report for leukemia, breast, lung, and stomach cancers using estimated doses to the organs.18 Radiation exposures received during catheter ablation may also result in other types of fatal cancers, such as bone or liver; however, the incidence would be much lower than for those included in Table 4.

Discussion

Major Findings

The purpose of the study was to evaluate radiation exposure during catheter ablation of AF. There are several important findings of this study. First, the results demonstrate that catheter ablation of AF by use of a PV approach is associated with markedly prolonged fluoroscopy duration. In this study, ≈1 hour of fluoroscopy exposure was delivered to patients in both the RAO and LAO projections. A second finding is that skin radiation exposure peaks at small regions 3 to 5 cm in diameter in the LAO and RAO projections. Despite similar fluoroscopy durations in both projections, we found that radiation dose was greater in the LAO than in the RAO projection, primarily because of a longer attenuation path for the x-ray beam entering in the LAO projection. Third, despite very long fluoroscopy times of up to 99 minutes in one projection, the resulting PSD approached the threshold for acute skin injury (2 Gy) in only 1 of 15 patients. Fourth, although approaches used to estimate radiation exposure result in a 50% to 100% overestimation of true radiation exposure, a good correlation exists between the skin dose
measured directly with TLD sensors on the skin and the extrapolated dose based on a limited number of TLDs attached to the collimator of the x-ray tube and the estimated dose based on technical factors. Finally, the estimated lifetime risk of a fatal malignancy after PV ablation using a modern low-frame pulsed fluoroscopy system is relatively low.

Fluoroscopy Exposure
The duration of fluoroscopy for patients undergoing catheter ablation of AF exceeded that of patients undergoing catheter ablation of atrial flutter or AVNRT by >4-fold. This finding most likely reflects 2 main factors. First, ablation of AF is far more complex compared with ablation of atrial flutter and AVNRT, requiring a double transseptal puncture and extensive mapping and ablation. Second, ablation of AF is a relatively new procedure, whereas ablation of atrial flutter and AVNRT has become extremely routine. The amount of fluoroscopy received by patients undergoing catheter ablation of AF in the present study (LAO, 67.8 ± 21 minutes; RAO, 61.9 ± 16.6 minutes) is greater than but in a similar range to that previously been reported (57 ± 30 minutes), which is smaller than the range previously reported. This difference can probably be attributed to the experience with AF ablation at the center at the time these studies were performed, as well as the fact that our ablation approach was somewhat more extensive, requiring both isolation of all 4 PVs and creation of a cavitricuspid isthmus ablation lesion.

Radiation Exposure
Skin injuries are well-recognized complications for catheter ablation procedures. Acute radiation-induced skin injury is subdivided into first-, second-, and third-degree reactions. The threshold for transient erythema and epilation is 2 to 3 Gy. In our study, only 1 of 15 patients reached a PSD of 2 Gy, despite prolonged fluoroscopy durations. This finding is striking and speaks to the effectiveness of the systems that use several technologies, such as last image hold, pulsed fluoroscopy, and additional filters to reduce radiation exposure. This also explains why radiation skin damage is an extremely rare complication of ablation procedures. In our study, the mean PSD for catheter ablation of AF was 1.00 ± 0.5 Gy (RAO) and 1.48 ± 0.37 Gy in the LAO projections, respectively. To date, only 1 previous study by Macle et al has reported radiation exposure for patients undergoing ablation of AF. They reported a median radiation exposure nearly 1000-fold lower than reported in our study (0.0011 versus 1 Gy [RAO] and 1.48 Gy [LAO]). Although it is difficult to reconcile these differences, the most likely basis for this is the differing approaches to the measurement of radiation. In the present study, a large number of TLDs with a TLD vest was used to measure PSD, whereas Macle et al used a single electronic personal dosimeter positioned on the anterior chest at the level of the xiphoid process. It is therefore highly likely that the single electronic dosimeter was not at the focal point of the radiation beam and therefore greatly underestimated the true PSD.
Radiation field may not be fully covered by dosimeters, and therefore, a complete reading may not be provided. This limitation was overcome in this study by placing a radio-graphic film (Ready-Pack) behind the vest. The exposure on the film ensured that the TLDs were well within the radiation field.

Methods to Determine Radiation Exposure
A variety of methods for measurement or estimation of radiation exposure during catheter ablation procedures has been used. Calkins et al.⁹ and Koovor et al.¹¹ used 6 and 41 TLDs, respectively, attached to the skin for direct recording of radiation exposure. A third study by Rosenthal et al.¹² used fluoroscopy times and technical factors of the x-ray equipment for estimation of radiation exposure. We refer to this method as the estimation method and used this calculation to compare with the direct and extrapolation methods. Yet another approach was used in studies by Lindsay et al.¹⁰ and Perisinakis et al.,¹³ in which fluoroscopy time was recorded in the individual projections during ablation, and in a separate step, an anthropomorphic phantom was loaded with dosimeters and radiated with the fluoroscopy parameters found in the human studies.

In our study, the estimation method overestimated the skin dose by 57% in the RAO and by 108% in the LAO projection compared with the direct method. However, the direct method is very time-consuming and costly because of the large numbers of TLDs needed to cover the complete skin area potentially irradiated during the ablation procedure. We therefore introduced the extrapolation method. This method uses 2 TLDs placed at the center of the x-ray tube collimator. We demonstrated that there is a significant correlation between direct PSD measurements as obtained by analysis of all 50 to 60 TLDs and the extrapolated radiation doses obtained from readings from the 2 TLDs on the collimator of each x-ray tube. In the absence of online dose monitors, this method, which can be used to estimate PSD exposure quickly and inexpensively, may be of clinical value, particularly in patients undergoing complex ablation procedures such as AF ablation, but also among those patients undergoing repeat procedures in a relatively short period of time.⁸

Radiation-Induced Cancer
Radiation-induced cancer is an important delayed risk associated with diagnostic and therapeutic procedures that require fluoroscopic imaging. This is of particular concern after procedures, such as ablation of AF, that require prolonged fluoroscopy guidance. The additional lifetime risk for a fatal malignancy associated with ablation of AF was 0.15% for female patients and 0.21% for male patients in our study. The respective risk normalized to 60 minutes of fluoroscopy was

![Figure 4. Correlation between absorbed skin dose measured directly with TLD sensors vs absorbed dose derived from extrapolation and estimation method for (A) RAO projection and (B) LAO projection.](http://circ.ahajournals.org/)

TABLE 4. Additional Lifetime Risks for Excess Fatal Malignancies per 1 000 000 Patients Undergoing AF Procedures

<table>
<thead>
<tr>
<th>Estimated Organ Doses, mSv</th>
<th>Risk in Present Study*</th>
<th>Risk per 60 Minutes of Fluoroscopy*</th>
<th>Estimated Organ Doses, mSv</th>
<th>Risk in Present Study*</th>
<th>Risk per 60 Minutes of Fluoroscopy*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>10.14</td>
<td>71</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Active bone marrow</td>
<td>12.02</td>
<td>96</td>
<td>44</td>
<td>16.97</td>
<td>187</td>
</tr>
<tr>
<td>Lungs</td>
<td>81.79</td>
<td>1227</td>
<td>566</td>
<td>122.45</td>
<td>2326</td>
</tr>
<tr>
<td>Stomach</td>
<td>6.35</td>
<td>184</td>
<td>85</td>
<td>10.71</td>
<td>182</td>
</tr>
<tr>
<td>Total</td>
<td>18.74</td>
<td>1518</td>
<td>700</td>
<td>27.25</td>
<td>2099</td>
</tr>
</tbody>
</table>

* Increased number of malignancies (additional lifetime risk) among 1 000 000 patients undergoing atrial fibrillation procedures.

Risk estimation was based on the PSDs measured directly with TLD sensors.
0.07% for female and 0.1% for male patients. Organs contributing most to the total risk were lungs, stomach, and active bone marrow in all patients and, in addition, breast tissue in female patients. The risk for a fatal malignancy resulting from ablation of AF in this study is slightly greater, although within the range previously reported to result from ablation of standard types of supraventricular arrhythmias (0.03% to 0.26%). It is reassuring that despite markedly prolonged fluoroscopy durations, the advances in techniques to reduce radiation exposure have allowed the risk of a fatal malignancy resulting from catheter ablation to remain at this low level.

Study Limitations

There are several limitations in this study. First, catheter ablation of AF was performed without electroanatomic mapping systems. Ablation of AF guided by electroanatomic mapping systems has been reported to require significantly less fluoroscopy exposure. Second, as pointed out previously, this series of patients was among the first 100 patients to undergo catheter ablation of AF at our institution. As reported previously by Knight et al., reductions in procedure and fluoroscopy duration can be anticipated after the first 70 AF ablation procedures. Third, dose-area-product (DAP) meters were not available on the system. DAP meters are available on new interventional systems. These monitors record fluoroscopy times and provide an estimate of radiation exposure (dose–area product [cGy-cm²]), which is the total radiation dose multiplied by the radiation field area. Although this parameter correlates with total patient radiation exposure, it provides little information about the PSD, which is the cause of skin injuries. Modified versions of the DAP meters are now available that provide cumulative dose at the center of the beam, which correlates more closely with PSD. We believe that these monitors will be better suited to assess risk for skin injuries, because the user can keep track of the cumulative dose to the patient’s skin surface in any projection. In fact, the Food and Drug Administration is considering mandating such a real-time dose display on fluoroscopy units under the new regulations currently under review. In the absence of DAP, we placed 2 TLDs on each of the collimators and extrapolated to the skin surface, which correlated with the direct measurements. The correlation shown in our study between these measurements and PSD supports the potential clinical usefulness of on-line DAP monitors.

Clinical Implications

The results of this study demonstrate that catheter ablation of AF requires several orders of magnitude greater fluoroscopy duration and radiation exposure than conventional catheter ablation procedures. This finding, together with the fact that repeat ablation procedures are commonly required among AF patients, should compel electrophysiologists to make every attempt to minimize radiation exposure. Radiation exposure to a patient can be minimized by reducing fluoroscopy time, by using low-frame pulsed fluoroscopy, and also by reducing the rate of radiation exposure. Fluoroscopy time, as well as the need for biplane fluoroscopy, can be reduced significantly with the use of electroanatomic mapping systems. The increasing availability and familiarity of electrophysiologists with the systems are likely to have a major impact on fluoroscopy time. The relatively small amounts of a patient’s radiation exposure in this study, despite the extremely prolonged fluoroscopy durations, can be attributed in large measure to the use of extremely low (7.5 frames per second) fluoroscopy rates, the avoidance of magnification, and optimal adjustments of the fluoroscopy unit to minimize exposure rates. The results of this study also validate the effectiveness of methods that estimate or extrapolate patient radiation exposure. Although each of these methods results in a 50% to 100% overestimation of actual patient radiation exposure, their excellent correlation with actual patient radiation exposure speaks to their potential clinical role.

References

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