REPLY: We thank our fellow researchers for their interest in our recent publication. The variable-threshold methods described in several studies are novel ways to determine gross tumor volume (GTV) for treatment planning with ^{18}F-FDG PET (*1–3*). We agree that care must be taken in implementing this new technology, especially in the case of lung tumors for which no true gold standard for review of tumor volumes has been defined.

In our review of 20 peripheral non–small cell lung cancer lesions without atelectasis, we believed that the GTV defined by reports 50 and 62 of the International Commission on Radiation Units and Measurements was the best surrogate for a gold standard (*4,5*). The decision to model PET tumor volume on CT tumor volume for a one-to-one correlation defines the minimum volume to be treated using PET. We recognize that volumes defined for smaller tumors with PET may be a representation of tumor motion rather than tumor biology. The significance of this possibility has not yet been determined. Clinical judgment must be used in extending these findings to individual treatment plans, including cases with atelectasis or small tumors.

As we previously stated, Poisson distribution of pixel intensity does make the use of maximum SUV a somewhat less reliable starting point for tumor delineation. Maximum SUV, however, is an important biologic tumor parameter and yields essential information. Consider the scenario of a case of lung cancer with adjacent atelectasis. PET may be most helpful in the atelectatic lung when CT-based GTV is difficult to determine. An iterative process as described by Black et al. (*2*) may be useful in this scenario. However, the mild to moderate ^{18}F-FDG uptake within the inflamed, atelectatic lung may alter the mean SUV and cause the inclusion of excess normal tissue.

Black et al. (*2*) described an alternate method for delineating PET-based GTV based on mean SUV derived from experiments involving stationary spheres. Although stationary spheres filled with ^{18}F-FDG may serve as an adequate model for tumors without significant motion during treatment, Caldwell et al. (*6*) have shown that such spheres are inadequate for modeling tumors throughout respiratory motion. Furthermore, the limitation of a mean SUV of greater than 2 would have excluded half the tumors in our study. Models derived from stationary spheres should not be applied to clinical management of the respiratory system or of other systems subject to significant motion. Any model based on spheres must be examined with scrutiny because tumor heterogeneity is difficult to model.

For these reasons, our clinically derived model based on GTV generated from CT seems a more robust method to determine tumor extent on PET. Our current recommendations are to contour the lung tumor using 4-dimensional CT and to use ^{18}F-FDG PET to clarify tumor versus no tumor or to clarify the distinction of tumor from surrounding atelectasis.

REFERENCES

1. Biehl KJ, Kong F-M, Dehdashti F, et al. ^{18}F-FDG PET definition of gross tumor volume for radiotherapy of non-small cell lung cancer: is a single standardized uptake value threshold approach appropriate? *J Nucl Med.* 2006;47:1808–1812.
2. Black QC, Grills IS, Kestin LL, et al. Defining a radiotherapy target with positron emission tomography. *Int J Radiat Oncol Biol Phys.* 2004;60:1272–1282.
3. Daisne J, Duprez T, Weynand B, et al. Tumor volume in pharyngolaryngeal squamous cell carcinoma: comparison at CT, MR imaging, and FDG PET and validation with surgical specimen. *Radiology.* 2004;233:93–100.
4. International Commission on Radiation Units and Measurements. *ICRU Report 50: Prescribing, Recording, and Reporting Photon Beam Therapy.* Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.
5. International Commission on Radiation Units and Measurements. *ICRU Report 62: Prescribing, Recording, and Reporting Photon Beam Therapy (supplement to ICRU Report 50).* Bethesda, MD: International Commission on Radiation Units and Measurements; 1999.
6. Caldwell CB, Mah K, Skinner M, Danjoux CE. Can PET provide the 3D extent of tumor motion for individualized internal target volumes? A phantom study of the limitations of CT and the promise of PET. *Int J Radiat Oncol Biol Phys.* 2003;55:1381–1393.

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DOI: 10.2967/jnumed.106.038398

Hepatitis C Virus Infections from Contaminated ^{99m}Tc-Sestamibi

TO THE EDITOR: I wish to bring to your notice a recent report by Patel et al. (*1*) in the *Journal of the American Medical Association* that describes an outbreak of acute hepatitis C virus (HCV) infection among 16 patients who underwent myocardial perfusion studies at 3 unaffiliated clinics in late 2004.

The outbreak was initially brought to the attention of a local health department in Maryland when 2 older adults with no recognized risk factors for HCV were diagnosed as having acute HCV infection approximately 1 mo after undergoing myocardial perfusion studies. Both patients were injected with ^{99m}Tc-sestamibi prepared by the same nuclear pharmacy. This nuclear pharmacy also prepared radiopharmaceuticals for other health care facilities in Maryland. Subsequently, additional cases of acute HCV infection developed among 14 other patients who also had received ^{99m}Tc-sestamibi prepared by this nuclear pharmacy.

The report indicated that all 16 infected patients received ^{99m}Tc-sestamibi drawn from a single vial (vial 1) and were the only patients to have received doses from this vial. The source of the HCV was traced to a patient whose blood had been processed for white blood cell (WBC) radiolabeling in the same nuclear pharmacy the day before the suspected contaminated ^{99m}Tc-sestamibi was prepared. The source patient was a nursing home resident with a history of HCV, hepatitis B virus, and HIV infections. Nine of the 16 infected patients had sufficient HCV RNA for quasispecies analyses, which showed the HCV sequences to be nearly identical (97.8%–98.5%) to those from the source patient.

Even though the source patient was coinfected with HIV, there was no evidence that HIV transmission occurred in any of the 16 HCV-infected patients. Patel et al. (*1*) surmised that the absence of HIV transmission may be due to the lower stability of HIV, compared with HCV, in a room temperature environment or to the antiretroviral treatment that the source patient had received in the past.

Although the specific cause of this catastrophic HCV transmission was not identified in the article, the authors speculated that a

syringe or multidose saline vial contaminated during the WBC radiolabeling process may have been used inadvertently in the preparation of ^{99m}Tc-sestamibi. However, there are several unclear issues with regard to the reported event. If specific deficiencies in the preparation and dispensing of radiopharmaceuticals can be identified, correcting them may effectively prevent any similar unfortunate event from happening again.

The viability of dried or stored HCV has been tested in chimpanzee infectivity studies, which have shown that HCV in dried plasma at room temperature remains infectious for 16 h or longer (*2*). In the case discussed by Patel et al. (*1*), blood was drawn from the source patient approximately 15 h before the preparation of vial 1, and the 16 patients were administered the "blood-contaminated" ^{99m}Tc-sestamibi between 6 and 8 h later. According to the authors, these findings suggest that "HCV at room temperature can remain infectious to humans for at least 21 to 23 h." To substantiate this claim, I think that Patel et al. should conduct a simulation experiment by placing a contaminated syringe and saline vial at room temperature for 21–23 h and then evaluating the viability of HCV.

According to records of the nuclear pharmacy under investigation, 5 additional vials of ^{99m}Tc-sestamibi were batched with vial 1, and all vials were prepared 1 min apart. If a contaminated syringe or multidose saline vial was shared and used during the preparation of 6 vials, it is unclear why only patients who received ^{99m}Tc-sestamibi from vial 1 had anti-HCV antibodies and HCV RNA. Although not every patient injected with ^{99m}Tc-sestamibi from vials 2 through 6 was tested for anti-HCV antibody and HCV RNA, it would be important for these patients to be tested because of the high likelihood of HCV transmission if the authors' hypothesis is correct.

The nuclear pharmacy performed the WBC radiolabeling procedure in a designated blood room adjacent to the main room. However, it is not clear why the pharmacist who performed the above procedure had "to leave the blood room carrying the blood-derived preparation to use a hood in the main room where ^{99m}Tc-sestamibi and other sterile radiopharmaceuticals were prepared." The pharmacist should be able to complete all of the procedures for ^{111}In-oxine labeling of WBCs in the blood room (*3*). It does not seem likely that the pharmacist brought the blood-derived preparation back and forth between the blood room and main room several times to use the "shared" saline vial during the middle of the radiolabeling process (i.e., steps 11 and 13 of a 21-step procedure) (*3*). Did the pharmacist bring the final preparation of ^{111}In-oxine–labeled WBCs to the main room for the radioactivity assay because of lack of a dose calibrator in the blood room? If so, the measurement of radioactivity with a capped syringe should not be the cause for the outbreak of acute HCV infection. Did the pharmacist bring the syringes or saline vials used during the WBC radiolabeling procedure to the hood located in the main room for future use (e.g., preparation of ^{99m}Tc-sestamibi)?

Did the pharmacist dilute the syringe dose of ^{111}In-oxine–labeled WBCs with saline in the main room hood and leave the used saline vial in the hood around 1 pm, October 14, 2004? Was any sterile drug prepared in the main room hood between 1 pm, October 14, and 1:05 am, October 15? If not, did the other pharmacist involved in the preparation of ^{99m}Tc-sestamibi, who started at 1:05 am, October 15, discard any unwrapped syringes and used saline vials or bags in the hood before the above preparation process?

The report indicates that the individual doses of ^{99m}Tc-sestamibi were drawn on October 15 by pharmacy technicians, whereas the reconstitution of vial 1 was conducted by a pharmacist. Did the pharmacy technicians withdraw these prefilled unit doses in the same laminar flow workstation where vial 1 was prepared by the pharmacist? Or were the doses withdrawn in a separate room or workstation?

I believe that the specific cause that led to this unfortunate HCV infection incident can be reasonably identified if answers to these queries or related information is available.

The report indicated that saline was drawn from "multidose bags or vials" for dilution during the preparation of ^{99m}Tc-sestamibi or for washes of the separated cells. The commercial multiple-dose vial of saline is a bacteriostatic solution that contains 0.9% benzyl alcohol as a preservative, but it should not be used in the preparation of ^{99m}Tc-labeled compound because of its negative effect on labeling efficiency. If, as mentioned in the report, saline vials or bags were designated for a single use only, it is incorrect for these products to be used multiple times. Furthermore, it is inappropriate and bad practice to reuse the unwrapped syringe.

The proposed revisions to U.S. Pharmacopeia General Chapter <797>, titled "Pharmaceutical Compounding—Sterile Preparations," states that "...[if] the manipulation of a patient's blood-derived or other biologic material [is required] (e.g., radiolabeling a patient's or a donor's white-blood cells), the manipulations must be clearly separated from routine paths and equipment used in CSP [compounded sterile product] preparation activities, and they must be controlled by specific standard operating procedures to avoid any cross-contamination" (*4*).

Even though the Nuclear Pharmacy Compounding Guidelines from the American Pharmaceutical Association do not include specific information on the risk of blood-borne pathogen contamination of compounded radiopharmaceuticals, they do state that U.S. Pharmacopeia General Chapter <1206>, titled "Sterile Drug Products for Home Use" (the former version of <797>), should be used as guidance for the compounding of radiopharmaceuticals in high-risk category II, which includes radiolabeled WBCs (*5*).

REFERENCES

1. Patel PR, Larson AK, Castel AD, et al. Hepatitis C virus infections from a contaminated radiopharmaceutical used in myocardial perfusion studies. *JAMA.* 2006;296:2005–2011.
2. Krawczynski K, Alter MJ, Robertson BH, Lu L, Spelbring JE, McCaustland KA. Environmental stability of hepatitis C virus (HCV): viability of dried/stored HCV in chimpanzee infectivity studies. In: *Program and Abstracts of the 54th Annual Meeting of the American Society for the Study of Liver Disease.* Philadelphia, PA: W.B. Saunders; 2003.
3. Indium In 111 oxyquinoline solution [package insert]. Arlington Heights, IL: Amersham Health Medi-Physics, Inc.; 2002.
4. U.S. Pharmacopeia Web site. <797> Pharmaceutical Compounding: Sterile Preparations. Available at: http://www.usp.org/pdf/EN/USPNF/PF797.pdf. Accessed February 23, 2007.
5. American Pharmacists Association Web site. Nuclear Pharmacy Compounding Guidelines. Available at: http://www.aphanet.org/AM/Template.cfm?Section=Search&section=APPM&template=/CM/ContentDisplay.cfm&ContentFileID=217. Accessed February 23, 2007.

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DOI: 10.2967/jnumed.107.040485