

Optimized Mammary Lymphoscintigraphy Using Larger Colloid Particles

TO THE EDITOR: In their very interesting article on mammary lymphoscintigraphy, Valdés Olmos et al. (1) report on applying a single intratumoral injection for sentinel lymph node (SLN) identification. Only patients with an operable, palpable breast tumor were included in the study. The authors used ^{99m}Tc -labeled nanocolloid with a particle size of <80 nm. During the first 30 min, two to eight nodes were visualized in 61% of the patients. In our department we have recently begun using ^{99m}Tc -labeled human serum albumin colloid (Senti-Scint; MEDI-Radiopharma, Budapest, Hungary) with a particle size of 100–600 nm in a small volume of 0.5 mL and inject it subcutaneously above the tumor. The visualization rate of the SLN in 35 patients has been 94%, whereas in just three cases ($<10\%$) we observed more than one node in the first 60 min. We believe that this difference in visualization rate is not the result of the difference in injection sites. In accordance with De Cicco et al. (2) and Paganelli et al. (3), we suggest that larger particle size (which is often taken up by only one node) may be more suitable for SLN identification, which can be easily identified by the γ -ray-detecting probe during surgery, whereas the use of small particle size increases the risk of sampling non-SLNs during biopsy.

REFERENCES

1. Valdés Olmos RA, Jansen L, Hoefnagel CA, et al. Evaluation of mammary lymphoscintigraphy by a single intratumoral injection for sentinel node identification. *J Nucl Med.* 2000;41:1500–1506.
2. De Cicco C, Cremonesi M, Luini A, et al. Lymphoscintigraphy and radioguided biopsy of the sentinel axillary node in breast cancer. *J Nucl Med.* 1998;39:2080–2084.
3. Paganelli G, De Cicco C, Grana C, et al. Radioguided biopsy of the sentinel node in breast cancer: first results of a randomized trial [abstract]. *Eur J Nucl Med.* 2000;27:915.

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REPLY: The use of ^{99m}Tc -labeled nanocolloid for sentinel node lymphoscintigraphy in breast cancer has been extensively validated in the literature, as recently reviewed by Nieweg et al. (1). The wide use of this radiopharmaceutical is related to its particle size, which varies from 5 to 80 nm, enabling adequate migration from the injection site and lymph node uptake (2). In our study (3), in only 39% of the patients with lymph node visualization, a single lymph node was visualized during lymphoscintigraphy performed on the basis of a 20-min dynamic study followed by static images at 30 min and at 2 and 4 h. In 61% of the patients, two to eight lymph nodes were seen, not during the first 30 min, as stated by Mirzaei et al., but in the course of the 4-h study. By documenting lymph channel visualization and sequential lymph node filling, the sentinel node was identified in most of these patients. This was reflected by an average of about 1.5 removed axillary sentinel

nodes per patient. Furthermore, in this subgroup of patients, non-axillary drainage was evident in almost 20% of the cases. Further adjustment of the particle concentration and dosage of ^{99m}Tc -labeled nanocolloid increased the lymph node visualization rate to 99% (75/76 patients with breast cancer) (4). This approach led to significantly increased uptake in the sentinel node in relation to second-echelon lymph nodes and improved the lymph channel visualization rate to 53%.

The particle size of the radiopharmaceutical is the subject of much discussion. The use of large particles has been associated with insufficient penetration into lymphatic capillaries (2). Despite this fact, some groups prefer large-particle tracers to minimize the number of radioactive lymph nodes in the axilla. However, this also may lead to an underestimation of the number of sentinel nodes. By visualizing afferent lymph channels on scintigraphy and using blue dye during surgery, we have observed that the presence of two or more sentinel nodes in the axilla is not uncommon. As indicated by Alazraki et al. (5), the greater number of lymph nodes accumulating the radiotracer with smaller particle size should not be regarded as a problem because sequential imaging will help to differentiate between sentinel and secondary nodes in both axillary and nonaxillary locations.

Another important issue is the difference in injection site. Intratumoral and peritumoral administration of the radiotracer enables the mapping of both axillary and nonaxillary drainage, whereas subcutaneous or intracutaneous injection limits the study to the superficial mammary lymphatic system, which drains predominantly to the axilla. Because the detection of metastases in the internal mammary nodes may have prognostic significance and therapeutic implications, the staging of the internal mammary chain by lymphoscintigraphy and sentinel node biopsy may be important. Every node must be counted.

REFERENCES

1. Nieweg OE, Jansen L, Valdés Olmos RA, et al. Lymphatic mapping and sentinel lymph node biopsy in breast cancer. *Eur J Nucl Med.* 1999;26(suppl):S11–S16.
2. Wilhem AJ, Mijnhout S, Franssen EJJ. Radiopharmaceuticals in sentinel lymph-node detection: an overview. *Eur J Nucl Med.* 1999;26(suppl):S36–S42.
3. Valdés Olmos RA, Jansen L, Hoefnagel CA, et al. Evaluation of mammary lymphoscintigraphy by a single intratumoral injection for sentinel node identification. *J Nucl Med.* 2000;41:1500–1506.
4. Valdés Olmos RA, Tanis PJ, Hoefnagel CA, et al. Improved sentinel node visualization in breast cancer by optimizing the colloid particle concentration and tracer dosage. *Nucl Med Commun.* 2001:in press.
5. Alazraki N, Grant S, Styblo T. Is sentinel node staging for breast cancer standard care? The role of imaging. *Nucl Med Commun.* 1999;20:1089–1091.

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Clinical Skills in Conducting Research Studies on Clinical Applications of Oncologic PET

TO THE EDITOR: We read with great interest the article by Hara et al. (1), which was published in the September 2000 issue of *The Journal of Nuclear Medicine*. Although we agree with the

authors that the FDG uptake in metastatic mediastinal lymph node lesions could be less than that of the primary cancer, this does not preclude our accurate detection of these metastatic lesions. The authors wanted to illustrate their points in the article but had forgotten the clinical skills of interpreting clinical PET. If one scales down the intensity in Figures 3 and 4, one can readily see the lesions in the mediastinum by FDG. The only case they presented that is not obvious to us is in Figure 2, which the authors presented with the wrong image of FDG. They used nonattenuated corrected images instead of the corresponding images with attenuation correction, which is known to show higher intensity than that of the former images. The foregoing reasons may explain the low-end sensitivity of detecting mediastinal lymph nodes observed by the authors as reported previously (2). We bring up these issues to stress the importance of clinical skills in conducting research studies on clinical applications of oncologic PET.

REFERENCES

1. Hara T, Inagaki K, Kosaka N, Morita T. Sensitive detection of mediastinal lymph node metastasis of lung cancer with ^{11}C -choline PET. *J Nucl Med.* 2000;41:1507–1513.
2. Coleman RE. PET in lung cancer. *J Nucl Med.* 1999;40:814–820.

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REPLY: We read the comments by Wong and Dworkin regarding our article in *The Journal of Nuclear Medicine* (1). They pointed out that the FDG PET image in Figure 2 must be an emission image that was not properly corrected by the transmission data. We confirmed this fact by reappraising our logbooks and computer files (a transmission scan was not obtained in this particular case) and found no such negligence in other cases. We apologize for overlooking this. In addition, they stated that the skills of clinical interpretation compensate for the difficulty in detecting small tumors with FDG. We agree partially with their opinion but emphasize that the FDG image can be interpreted more easily if it is compared with the ^{11}C -choline image, as we have done on nearly 1,500 patients with tumors.

REFERENCE

1. Hara T, Inagaki K, Kosaka N, Morita T. Sensitive detection of mediastinal lymph node metastasis of lung cancer with ^{11}C -choline PET. *J Nucl Med.* 2000;41:1507–1513.

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“Yellow Eluate” from a $^{99\text{m}}\text{Tc}$ Generator

TO THE EDITOR: According to the package insert for the Ultra-TechneKow DTE generator (Mallinckrodt Inc., St. Louis, MO) (1), generator eluate should not be used if its appearance is discolored. One of the few unique features that has been imple-

mented with this new generation of $^{99\text{m}}\text{Tc}$ generators is the placement of a bright orange-color paper disk (13-mm diameter and 1-mm thickness) at the bottom of the column safe hole where the ^{98}Mo column is located. The so-called “molybdenum column integrity pigment disk” turns the eluate a light yellow color if the column is broken, cracked, etc. (2). If such a change in the color of the eluate occurs, this is an indication that the sterility of the generator system has been compromised (2). Therefore, any discolored eluate should be discarded (1).

Although the use of a pigment disk is an interesting idea, it may not be practical because the leaded glass used in either the elution shield or the syringe shield would also appear to be yellow in color. Thus, it would be quite difficult to detect a light yellow appearance of the eluate through the yellow leaded glass.

To facilitate the fractionated elution process, an ergonomically designed elution shield was introduced along with the Ultra-TechneKow DTE generator. Although this elution shield has been fitted with a light source to allow visual inspection of the elution process, the double-layer lead-glass windows (i.e., one layer on the elution shield and the other layer on the window ring of the auxiliary lead shield for the generator) make it difficult to notice any change in the appearance of the $^{99\text{m}}\text{Tc}$ eluate. If an all-metal canister such as a lead CAP-MAC or tungsten CAP-MAC (Capintec, Inc., Ramsey, NJ) is used to elute an Ultra-TechneKow DTE generator, it would be impossible to note any discoloration of the eluate unless the elution vial is removed from the vial shield. To reduce hand and eye exposure to the operator, both of these CAP-MAC canisters are designed to measure ^{99}Mo or $^{99\text{m}}\text{Tc}$ without exposing the operator to the unshielded elution vial. If it is necessary to remove the eluate vial from the CAP-MAC shield to observe the coloration of the $^{99\text{m}}\text{Tc}$ eluate, this undoubtedly defeats the purpose of using the CAP-MAC device.

During the past 4 y in which we have used the Ultra-TechneKow DTE generators in our institution, we have experienced one isolated incident of “yellow eluate.” Because we use the tungsten CAP-MAC device for eluting generators as well as for storing $^{99\text{m}}\text{Tc}$ eluate, the technologist, in this instance, initially did not notice the yellow coloration of the flawed eluate. However, the technologist was prompted to check the elution vial when the measured radioactivity of the eluate was found to be far less than that anticipated. The total eluted volume (approximately 10 mL) was satisfactory because a 10-mL elution vial was used; however, the eluate was yellow in color. To confirm that the generator eluate was defective (i.e., low activity and yellow appearance), a fractionation elution process (i.e., elution was terminated at approximately 45 s) was conducted using the same generator immediately afterward, and once again the collected eluate (approximately 7 mL) appeared yellow in color.

The generator was then returned to Mallinckrodt for further investigation. According to the report that I received from Mallinckrodt Inc. (R.R. Bartnick, written communication, November 1999), another elution of this generator was conducted at the Mallinckrodt facility, and the eluate obtained was slightly yellow in color. After this generator was dismantled at Mallinckrodt, a pool of yellow eluate was found inside the column safe hole, and it was later determined to be leakage from the generator column that had caused the eluate to turn yellow.

The aforementioned scenario is the only yellow eluate incident that we have noticed in our institution since we began to use the Ultra-TechneKow DTE generators in 1997. On average, we order four to seven new Ultra-TechneKow DTE generators (depending

on ^{99}Mo radioactivity amounts) every week. Therefore, in our experience, occurrence of the leakage problem with the Ultra-TechneKow DTE generator is very rare. However, four issues relative to the yellow eluate problem still must be addressed:

1. What is the incidence rate of yellow eluate since the Ultra-TechneKow DTE generator was first introduced to the United States market in July 1997? On the basis of our own experience, the occurrence rate of yellow eluate from an Ultra-TechneKow DTE generator appears to be very low.
2. Should visual inspection of each eluate obtained from an Ultra-TechneKow DTE generator be required? Currently, visual inspection of the $^{99\text{m}}\text{Tc}$ eluate is not listed as a required step either in the Ultra-TechneKow DTE package insert (1) or in the monograph for $^{99\text{m}}\text{Tc}$ -sodium pertechnetate injection in *U.S. Pharmacopeia 24 & National Formulary 19* (3).
3. Is the yellow appearance of eluate obtained from an Ultra-TechneKow DTE generator always associated with an amount of $^{99\text{m}}\text{Tc}$ radioactivity that is much less than that anticipated? If so, it may only be necessary to check the color of the eluate when the measured $^{99\text{m}}\text{Tc}$ activity is far below the normal value.
4. In the event that yellow eluate were used inadvertently in the preparation of a radiopharmaceutical for patient studies, would the pigment material used in the disk have any adverse effect on the patients involved, other than compromising the sterility of the $^{99\text{m}}\text{Tc}$ drug product (2)?

REFERENCES

1. Ultra-TechneKow DTE (technetium Tc 99m generator) [package insert]. Product code 880/887. St. Louis, MO: Mallinckrodt Inc.; January 2000.
2. Mallinckrodt Medical, Inc. *Ultra-TechneKow DTE Generator*. St. Louis, MO: Mallinckrodt Medical, Inc.; 1997:6.
3. United States Pharmacopeial Convention, Inc. Sodium pertechnetate Tc 99m injection. In: *U.S. Pharmacopeia 24 & National Formulary 19*. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2000:1598-1599.

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REPLY: We thank Dr. Hung for his comments regarding Mallinckrodt's Ultra-TechneKow DTE generator ($^{99\text{m}}\text{Tc}$ generator) and note his concerns over the appearance of the "yellow eluate" from one of the generators shipped to his facility.

Mallinckrodt Inc. is dedicated to providing products to the nuclear medicine community that are safe for both the customer and the patients that benefit from them. In this regard, Mallinckrodt's Ultra-TechneKow DTE generator is designed with features that ensure the delivery of a sterile drug product for either direct patient administration or use in an approved $^{99\text{m}}\text{Tc}$ radiopharmaceutical kit from various vendors. One of these features, as specified by Dr. Hung, is the inclusion of a dye-impregnated disk that is placed under the generator column in its shielding. The purpose of the disk is to provide the customer with a visual indicator in the event that the integrity of the sterile generator column has been compromised.

Should there be a loss of integrity in the column seals, generator eluate leaking out of the column would come in contact with the disk, extract the yellow-orange dye, and produce a colored solu-

tion. During the elution step, this colored solution would be drawn back into the generator column through the break in the seal and be collected in the eluate vial. When colored eluate is observed in the collection vial, it is an indication that the generator eluate has bypassed the sterile confines of the generator assembly and should no longer be considered to be a sterile drug product. The Mallinckrodt Ultra-TechneKow DTE generator is unique in this design, and we are unaware of a similar feature in $^{99\text{m}}\text{Tc}$ generators from other vendors.

Responses to the specific issues raised by Dr. Hung follow:

1. According to our records, the incidence rate of the yellow eluate appearing in Mallinckrodt's Ultra-TechneKow DTE generator since its 1997 launch in the United States has been <0.02%. As construed by Dr. Hung, the incidence of the yellow eluate is indeed very rare and affirms the overall integrity of this product for customer use.
2. It is true that visual inspection of the generator eluate is not specifically listed as a required step either in the Ultra-TechneKow DTE package insert (1) or in the monograph for $^{99\text{m}}\text{Tc}$ -sodium pertechnetate injection in *U.S. Pharmacopeia 24 & National Formulary 19* (2). As Dr. Hung pointed out, the package insert does state under the elution directions that the generator eluate should not be used if its appearance is discolored, which does imply that some type of visual check must be performed on the eluate before its use. Furthermore, according to the *U.S. Pharmacopeia* monograph for $^{99\text{m}}\text{Tc}$ -sodium pertechnetate injection (2), the material is expected to meet the requirements listed in the general chapter on injections, which specifies that all products intended for injection should be free of foreign matter and inspected for such. Good pharmacy practice and adherence to the ALARA (as low as reasonably achievable [radiation exposure]) principle may appear to be in conflict in this situation; yet, an inspection procedure that satisfies both the requirements for injectable materials and the ALARA principle can be readily implemented (e.g., by the use of mirrors behind lead shielding). In solution, the dye exhibits fluorescence under ultraviolet light, so an ultraviolet lamp may be useful to visualize the presence of the dye in the generator eluate.
3. The appearance of a yellow color in the generator eluate is not entirely indicative of a low $^{99\text{m}}\text{Tc}$ yield. A low $^{99\text{m}}\text{Tc}$ yield may occur in conjunction with a discolored generator eluate if, during the elution process, solution in contact with the dye disk outside the column is drawn into the generator fluid path to a greater extent than generator eluent is drawn through the column that contains the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ load. Conversely, a normal $^{99\text{m}}\text{Tc}$ yield can occur with a discolored generator eluate if the generator eluent is drawn through the column to a greater extent than dye-containing solution is drawn into the generator system. Furthermore, it is known that low $^{99\text{m}}\text{Tc}$ yields can occur in generator eluates that are clear and colorless because such losses are chemical in origin and may be related to the oxidation state of the $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ on the generator column.
4. The toxicity of the dye in the pigment disk is unknown; therefore, any solution containing this dye should not be administered to humans.

In conclusion, we believe the addition of the dye-impregnated disk in Mallinckrodt's Ultra-TechneKow DTE generator is an

important safety feature for this product, which helps ensure that patients receive a drug product that is safe.

injection. In: *U.S. Pharmacopeia 24 & National Formulary 19*. Rockville, MD: United States Pharmacopeial Convention, Inc.; 2000:1598–1599.

REFERENCES

1. Ultra-TechneKow DTE (technetium Tc 99m generator) [package insert]. Product code 880/887. St. Louis, MO: Mallinckrodt Inc.; January 2000.
2. United States Pharmacopeial Convention, Inc. Sodium pertechnetate Tc 99m

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