

A Closer Look at the Latest NRC Patient Release Guidance

The Nuclear Regulatory Commission (NRC) in May 2008 issued new guidance to medical licensees relative to the post-radioiodine therapy release of individuals likely to come in contact with infants and/or young children (see the NRC press release reproduced on the facing Newsline page). A careful reading of the press release, the Regulatory Issue Summary (RIS) to which it refers, and the *Federal Register* notice on the denial of a public petition that provided the impetus for reviews leading to the RIS provides, as is often the case with the agency's "clarifying" efforts, more questions than answers. These questions are significant, because the answers are likely to influence patient release decisions for thousands of individuals each year. These questions fall into 2 broad categories: (1) the actual risks that can be reasonably associated with release of radioiodine-treated patients likely to come in contact with infants and/or young children; and (2) the interpretation of NRC guidance by licensees whose practices are regulated by the Commission or by Agreement States, which generally require that such guidance be implemented by licensees.

Doses and Risk to Infants and Children

On May 21, 2008, the NRC published in the *Federal Register* (73 FR 29445) its denial of a petition for rulemaking (PRM-35-18), filed in 2005 by Peter G. Crane, requesting that the NRC amend regulations that govern the medical use of byproduct material concerning release of individuals who have been treated with radiopharmaceuticals (1997 amendment to 10 CFR 35.75). Crane requested in the petition and subsequent amendments that the patient release rule be partially revoked because it allows patients to be released from radioactive isolation with more than the equivalent of 30 mCi of ^{131}I in their bodies. As part of the consideration process, the NRC received 14 comments supporting and more than 30 comments opposing the petition. Opposition comments included statements representing the viewpoints of physicians, medical physicists, and radiation safety officers, as well as professional organizations including SNM, the American Society of Therapeutic Radiation Oncologists, the American Association of Physicians in Medicine, the American Board of Nuclear Physicians, the American Thyroid Association, the Endocrine Society, the American College of Radiology, the National Association of Nuclear Pharmacists, the American Pharmacists Association, and the Council on Radionuclides and Radiopharmaceuticals.

The NRC concluded that "the issues raised in the petition do not justify a rule change." Among the issues cited by the petitioner was radiation exposure to children and infants coming in contact with patients released after ^{131}I treatment. In its denial of the petition for a rule change, the NRC explicitly expressed its support of the current requirements: "The NRC believes that the current NRC regulations provide adequate protection to family members and other members of the public. . . .NRC has determined not to change the rule to adopt a lower limit for children and infants."

Only 1 commentator (who otherwise opposed the Crane petition) cited in formal comments the 2004 recommendations of the International Commission on Radiological Protection (ICRP) (1) that doses to children be constrained to less than 1 mSv (100 mrem) and that doses to children from patient contamination "have the potential to be far greater than from external exposure." As a result of this comment, NRC considered the addition of an "alternative approach" that would assist patients in taking precautions to maintain the dose to children and infants as low as reasonably achievable (ALARA). New guidance was created to "stress the need to keep children and infants away from any possible sources of contamination" and to be "sufficiently flexible so that the patient's physician has the option of keeping the patient in the hospital for longer periods than currently required if the patient's living conditions warrant such a decision." (This latter statement makes little sense, because physicians have always had the flexibility and option to hospitalize patients based on the results of individualized evaluations and assessments.) The issuance of new guidance was necessary, according to the NRC, because current instructions, as provided in NUREG-1556, Volume 9 (2) (NRC-issued guidance for licensee compliance with 10 CFR 35.75), include precautions to reduce the spread of contamination but do not specifically caution against avoiding exposure of children to patient contamination.

Although on first glance this appears to be a reasonable approach, many nuclear medicine practitioners may be left asking: "So what's new?" The NRC noted in its denial of the Crane petition that many physicians reported that their routine practice is to carefully interview each patient, assess reported living conditions, and determine his or her ability to follow and understand radiation safety precautions at home—and then decide on release and outpatient treatments. Many of these physicians also stated that they

discuss with their patients arrangements to have any children in the households stay away from their homes during the initial week of their treatments, when patients' living conditions so warrant. These considerations are already an integral part of routine practice in radioiodine therapy. A recent article in *Health Physics* (3) and numerous other peer-reviewed publications specifically address efforts to minimize dose to children and the potential need to hospitalize some patients with living arrangements that may result in exposure that cannot reliably be maintained ALARA to children. Those of us in the nuclear medicine community are not only aware of the risk to children, but we are also instructing patients on how to maintain dose ALARA to them as well.

Therefore it is crucial to ask whether the guidance provides some new metric or useful data to assist the physician in making release decisions in radioiodine treatment. The NRC specifically stated in its denial of the Crane petition that it is difficult to "meaningfully estimate" the doses that may result from patient contamination. The factors involved in assessing such doses are largely indeterminate, and even assumptions are likely to be so much in error as to be meaningless. For example, the amount of iodine in the patient's saliva is highly variable even for patients receiving the same treatment, and the amount of saliva that may be ingested by contacts is dependent on the details of the family's living arrangements, family habits, and the age of the child and cannot be reliably estimated in assessing the dose to the child or the infant. Ingestion of any or any more than a few droplets of a patient's saliva would be difficult to imagine if patients are instructed to avoid kissing infants or young children for a specified time period. The NRC has also stated that internal and external doses are not minimized separately and that ALARA efforts should be directed at minimizing their sum (total effective dose equivalent [TEDE]). General practice and the professional literature (3,4) make it clear that the TEDE can be most effectively minimized through adequate patient instructions.

It is worthwhile to consider whether any new evidence supports raising the level of caution on the release of patients higher than that currently in practice. The NRC press release stated: "Concern has increased in recent years that contamination of infants and young children with saliva from a patient in the first few days following treatment may result in significant radiation doses to the child's thyroid." Yet in the next sentence the agency noted: "There have been no known incidents of infants or young children being contaminated in this way." That is, with thousands of patients treated with ^{131}I every year for more than half a century, not a single incident of infant or child contamination has been reported. Yet the NRC felt compelled to issue new guidance, despite significant anecdotal evidence that standard practice in the field is to provide more than adequate assessment and precautionary counseling of patients. The new RIS, although it seems innocuous, adds nothing to what most of us already do in terms of patient release.

In a 1997 regulatory analysis of the revised 10 CFR 35.75, Schneider and McGuire in NUREG-1492 (5) concluded that internal dose was insignificant compared with external dose. This analysis considered the available literature at the time, including 2 studies (6,7) regarding the intakes of individuals exposed to patients administered ^{131}I . These studies indicated that intakes were generally on the order of 1 millionth of the activity administered to patients and that internal doses were far below external doses. This belief was carried through most recently in NUREG-1556, Volume 9 (2), where an intake factor of 10^{-5} was used for added conservatism. However, in 2004 ICRP stated that contamination of infants and young children with saliva from a released patient treated with radioiodine therapy could result in significant doses to the child's thyroid and potentially raise the risk of subsequent radiation-induced thyroid cancer. Moreover, the ICRP stated that this internal dose has the potential to be far greater than the dose from external exposure. (Again in 2007, the ICRP Publication 103 contained the singular statement that "particular care should be taken to avoid the contamination of infants and children from patients treated with radioiodine"). The most obvious question the nuclear medicine community must ask is: Where are the new data on saliva and intake by children indicating that a radiation safety problem justifies ICRP concerns?

A 1992 study by Ibis et al. (8) and a 1993 study by O'Doherty et al. (9) are cited by the ICRP on this topic. One group looked at the salivary activity in patients treated for thyroid cancer and the other at patients treated for hyperthyroidism. The mean salivary activity in these patients was greatest at 24 h after treatment and ranged from 304 to 459 Bq/g of saliva/MBq administered activity in thyroid cancer patients and averaged a much lower 86.7 Bq/g/MBq in hyperthyroid patients. However, these articles were silent on what activity is likely to be ingested by others, and no evidence was found or provided to suggest that intake of saliva from individuals treated with ^{131}I is either likely or represents a major health problem. It is certainly important to know *likely* salivary activity concentrations, but these will not directly translate to child intakes and the associated radiation absorbed doses to their thyroids. Ibis et al. (8) also measured the activity on the toothbrushes of the studied patients and found levels ranging from 0.3 to 1.7 Bq/g/MBq, indicating that although the salivary activity is much higher, the activity transferred to the toothbrushes (perhaps a better surrogate than salivary activity to estimate likely activity intake by a child) was a factor of approximately 300 lower.

The ICRP presented the following most-likely-dose scenario to illustrate that internal dose is potentially much greater than the external dose. ICRP considered a hyperthyroid patient who received 555 MBq Na^{131}I . Based on the O'Doherty data, the salivary activity in this patient during the first day after therapy was estimated to be approximately 100 Bq/g saliva/MBq, or 55,500 Bq/g or mL of

saliva. If this patient did not follow instructions and an infant received 1 mL of saliva by being kissed by such a patient, the estimated thyroid dose would be about 24 mGy. If at this time, the child was also being held by the patient at a distance of 0.1 m for 1 h, the external dose to the child would be 0.2 mSv, much less than the internal dose. This scenario possibly led to the ICRP recommendation that released ^{131}I -treated patients be given the following instruction: "It is very important to avoid kissing your infant or child for a period of a few weeks as this can transfer radioiodine and result in an unnecessary risk to your child." Many things are wrong with this analysis and recommendation, but our biggest concern is that the assumed activity intake fraction by the infant is 10^{-4} , representing a factor of 100 higher than described by published data and even a factor of 10 higher than conservatively assumed by NRC in NUREG-1556, Volume 9. Also, it is important to question the likelihood that measurable quantities of saliva will be exchanged through a patient kissing a child (obviously patients should be instructed to refrain from open-mouth kissing; in situations in which this is actually highly likely there may be more serious issues involved than radiation dose).

We all agree that physicians should tell patients not to share utensils, toothbrushes, glasses, and other mouth-contact items with children (or anyone else for that matter). These are common sense recommendations that can be seen throughout the nuclear medicine literature. The NRC RIS (10), however, appears to go beyond common sense recommendations to imply that the best course of action may be to get infants and children out of the house or keep the patient in the hospital. The experienced nuclear medicine practitioner will probably continue with the same precautions and assessments as in the past, but many radiation safety officers and others may now be reluctant to authorize patient release. One radiation safety officer, as a result of this RIS, has already been documented as stating that any cooking by a released patient should be done with gloves. Such baseless actions and any others that may follow must be dealt with promptly by demanding to see data or any regulations requiring such unwarranted precautions. If not, patients may be unduly burdened for no legitimate reason, and this may lead to major impediments for the nuclear medicine community.

We must also consider whether this RIS could have a chilling effect on other potential therapies. Although the RIS is targeted only at oral Na^{131}I , these warnings could in practice be applied to restrict the release of patients undergoing other ^{131}I or radioisotope treatments, such as radioimmunotherapy (despite the much lower associated salivary activity).

Beierwaltes and Widman (11) astutely pointed out that the most important question is not whether contamination can be expected but whether such contamination can be expected to do harm (i.e., is significant risk involved). Beierwaltes and Widman and numerous others believe

the answer in the case of exposure to families is "no." Dickman et al. (12) studied 24,010 patients in Sweden who received diagnostic dosages of ^{131}I (<3.7 MBq) and were referred for reasons other than the suspicion of thyroid carcinoma. These patients received an average dose to the thyroid of 0.94 Gy. Thirty-six thyroid cancers were found, and 39.5 were expected. This study included about 2,700 patients under the age of 20 and about 380 under the age of 10 (the authors pointed out that their results applied primarily to adults because "few" patients who were <20 y old). Hall et al. (13) provided further details of the Swedish study, indicating that patients were followed for up to 40 y. Among the patients who were <20 y old at the time of the study (3 cancers found, 1.8 predicted), the thyroid cancer risk was found to be 2–10 times lower than that predicted from data from atomic bomb survivors. These researchers concluded that thyroid cancer risk was not related to the diagnostic radiation dose to the thyroid gland, the time since exposure, or the age at time of exposure. In another very large study, Hamilton et al. (14) prospectively studied 3,503 children and adolescents under the age of 20 (48% <10 y old, 24% ≤ 5 y old, and 7% <1 y old) who received diagnostic doses of ^{131}I to evaluate the risk of radiation-induced thyroid neoplasia. The exposed group was followed for a total of 93,442 person-years. Thyroid doses received by the exposed group ranged from <0.1 Gy to slightly >20 Gy, but the majority (slightly $>81\%$) received <1 Gy. A group of 2,594 children who were not exposed to radioactive iodine served as controls. The results failed to indicate a statistically significant difference between the control and exposed groups in terms of an elevated risk of malignant thyroid tumors or benign thyroid conditions. Finally, Hahn et al. (15) conducted a controlled study on 2,262 children referred for ^{131}I diagnostic thyroid scans in whom follow-up was possible in 35%. The mean thyroid dose was 1 Gy, and the relative risk for the exposed group for thyroid cancer was 0.86. Thus this study as well as all the others cited here found no evidence of increased risk of thyroid cancer after diagnostic administration of ^{131}I in childhood. It should be noted that the range of ^{131}I activities administered to small children was approximately 0.18–0.37 MBq.

These studies involved many thousands of children younger than 20 who actually received known quantities of ^{131}I for diagnostic purposes (although the number of infants <1 y old probably did not exceed 500). These children received actual ^{131}I intakes and associated thyroid absorbed doses much greater than those that we have previously discussed as potentially resulting from intake of any ^{131}I contamination from released radioiodine-treated patients. It is unlikely that large amounts of new data on this topic will be forthcoming, because ^{131}I is now infrequently employed for diagnosis (^{123}I and $^{99\text{m}}\text{Tc}$ are used). Nevertheless, the consistency of insignificant/negative findings related to ^{131}I in diagnostic dosages as a cause of thyroid cancer is persuasive.

The new NRC guidance given in the RIS (10), which is based on consideration of the ICRP recommendations (which emphasize direct contact and saliva as the major contamination routes), recommends that patients avoid direct as well as indirect contact with infants and young children for a specific time period (e.g., consider having children stay outside the home), have adequate living space at home for their exclusive use (e.g., bedroom and bathroom), and be provided with information on potential consequences, if any, of failure to follow these recommendations. The indirect contact recommendation is presumably related to sources of potential ^{131}I internal contamination that do not involve saliva and kissing, such as perspiration, breath, and urine, because infants and young children tend to crawl around, touch everything, and then put their hands into their mouths. However, no data support the proposition that radioiodine intake by infants or young children resulting from patient contamination can occur in an amount likely to cause an increased risk of thyroid cancer. Moreover, this new guidance appears to add an unnecessary regulatory burden on medical licensees that is not codified in the regulations. That is, patients can be released if, pursuant to 10 CFR 35.75(a), the 5 mSv dose limit is *not likely* to be exceeded (note that the requirement does not contemplate undocumented or anecdotal perception-based likelihood), and if, pursuant to 10 CFR 35.75(b), the licensee provides the released patient with instructions to maintain doses to others ALARA (not zero).

Guidance vs. Regulation

Over and above the issues raised by the new guidance that only reinforces current practice is the troubling NRC statement that issuance of the new guidance “will effect a change in practice” and do so “more quickly and efficiently than developing and implementing new regulations.” The reasons behind this assumption are astonishingly unclear. NRC guidance has no regulatory weight and requires no specific action. In fact, its adoption by licensees is purely optional. Yet it is unfortunately true that many if not most radiation safety practitioners immediately adopt and follow new NRC guidance as if it carried regulatory force.

Unrealistically conservative guidance and regulatory requirements for patient release violate the principle of optimization and place an undue burden on radionuclide therapy patients and their families. On one hand, many nuclear medicine practitioners might look at the new RIS and say, “I am already careful and conscientious, and this won’t affect the way I manage my patients—so it’s a no harm/no

foul development.” On the other, it seems important at a time of increasing public fears about radiation and the unfortunate possibility of a radiologic terrorist event to strongly question the release of new “guidance” (which many will accept as requisite) that comes from non-evidence-based concerns.

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