Advisory Committee on the Medical Uses of Isotopes
TELECONFERENCE AGENDA
Thursday, February 15, 2018
9:00 AM – 11:00 AM (ET)

OPEN SESSION

9:00 – 10:00 am
Discuss the Revised Draft Report of the ACMUI Nursing Mother Guidelines for the Medical Administration of Radioactive Materials

10:00 – 11:00 am
Discuss the Revised Draft Report of the ACMUI Physical Presence Requirements for the Leksell Gamma Knife® Icon™

Advisory Committee on Medical Uses of Isotopes (ACMUI)
Sub-Committee on Nursing Mother Guidelines for the Medical Administration of Radioactive Materials

Subcommittee Members:

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Introduction

Nursing or breast-feeding is the feeding of an infant from the female breast. Lactation is the process of milk production. Shortly after delivery and along with the initiation of supply and demand, the maintenance of lactation becomes relatively constant with a daily production of about 800 mL[1].

Milk production is influenced by many hormones, the most important being prolactin. The release of prolactin is dependent on the removal of milk from the breasts. Milk removal occurs with nursing and stimulates feedback mechanisms promoting the release of prolactin, and thus further milk production. When milk ceases to be removed from the breast, prolactin levels fall with a concomitant rise in "Feedback Inhibitor of Lactation," a protein which inhibits milk production. Complete cessation of milk production generally occurs about six weeks after the last breast-feeding.

At times, it is necessary to administer diagnostic or therapeutic radiopharmaceuticals to the nursing mother. Many of these agents appear in breast milk.[2] Therefore, the use of radiopharmaceuticals during nursing raises radiation exposure concerns for both the nursing infant and mother. For the nursing infant, this exposure comes internally, from the ingested radioactive milk, and externally, from exposure to the mother who is a radiation source in close proximity to the infant during nursing and child care. Consequently, the charge of this subcommittee is "To review the radiation exposure from diagnostic and therapeutic radiopharmaceuticals, including brachytherapy, to the nursing mother and child."

Current Guidance

Breast-feeding is not regulated. A nursing mother who has received unsealed byproduct material can be released by a licensee if the total effective dose equivalent to any other individual,

including her nursing child, is projected to not exceed 5 mSv (0.5 rem). If a nursing mother continues to breast-feed after receiving a radiopharmaceutical and the nursing child's radiation exposure could exceed an effective dose equivalent of 1 mSv (0.1 rem), written instructions must be given to the mother regarding the potential adverse consequences if breast-feeding is not interrupted or ceased as well as guidance on the discontinuation of breast-feeding (10CFR 35.75)[3].

Radiation Safety

The ALARA (As Low As (is) Reasonably Achievable) principle is the Nuclear Regulatory Commission's (NRC) guidance on radiation safety (10 CFR 20.1003). ALARA directs the licensee and individuals to take every reasonable effort to decrease ionizing radiation exposure as far below regulatory dose limits as practically possible. These instructions should be individualized to include the consideration of available resources and their value in achieving this radiation exposure goal. Many nuclear medicine procedures are elective, and for the nursing mother it may be possible to delay these exams to allow for the interruption or, in some cases, the cessation of breast-feeding[4].

Before radioiodine therapy, oral and written radiation precaution instructions must be provided to the nursing mother and, as needed, to the appropriate family and/or caretakers. All patient, family or caretaker therapy concerns and questions should also be addressed. This information must be given in a sufficient individualized time frame to allow for appropriate radiation safety preparation, and should be provided at least six weeks prior to the anticipated radioiodine procedure, thereby allowing the necessary time for the cessation of lactation.

Radiopharmaceuticals

Radiopharmaceuticals consist of two components: the radioisotope and the non-radioactive carrier targeted for a specific molecule or metabolic pathway.

Once administered, these agents circulate and undergo both radioactive decay of the radioisotope and biologic elimination of the carrier component. The elimination half-time associated with the combined physical decay and pharmacokinetic clearance is termed the effective half-life.

The physical decay or half-life is the time required for a given quantity of radioactivity to decrease to one half of its original activity solely as a result of radioactive decay. For a radionuclide, ten physical half-lives will account for 99.999% of its radioactive decay[5].

The biological half-life is the time required to reduce the amount of a given substance in an internal organ or the whole body to one half of its original value solely as a result of biological elimination. Five biological half-lives of most drugs account for 97% of a drug's clearance, and

presumably this clearance also applies to the radiopharmaceutical carrier component in breast milk[6].

Lactation and Breast-feeding Cessation

When a radiopharmaceutical is administered to a nursing mother who temporarily stops breast-feeding, it is advisable for her to breast pump during this "interruption period." The ongoing removal of breast milk from the breast will ensure that lactation will continue. Expression of milk will also facilitate the radiopharmaceutical's biologic elimination from the breast and therefore, an overall potential reduction in the radiation exposure to the maternal breasts.

During this interruption period, the mother may express and store her milk to be used after the milk is no longer radioactive, which is typically 10 physical half-lives of the radiopharmaceutical (i.e., ^{99m}Tc physical half-life is 6 hours, equating ten half-lives to 60 hours). Breast milk can also be expressed prior to radiopharmaceutical administration and used to feed the nursing child until breast-feeding can be resumed[7]. Alternatively, the nursing mother may choose to discard the expressed radioactive milk.

Nursing mothers should inform their healthcare provider of their breast-feeding status so that if a medical procedure involving radioactive material is contemplated, decisions can be made to maximize patient outcomes while minimizing the overall radiation risk to the nursing mother and infant[8].

Appropriate signage should also be posted in the nuclear medicine clinic/waiting room alerting women to notify the nuclear medicine staff before their procedure if they are breast-feeding.

Breast Milk and Drugs

When substances enter the maternal circulation, this vascular delivery allows for transfer of material from the glandular breast alveoli into maternal milk. Many factors control the regulation of this transfer and include the dramatic increase in blood flow to the lactating breast. Shortly after child delivery, a brief period of greater alveolar diffusion occurs which permits a higher level of antibodies, antibacterial factors and other substances to concentrate in breast milk. These diffusion factors are facilitated by low molecular weight, low protein binding and high lipid solubility of these substances[9].

Although the exact mechanism of radiopharmaceutical uptake into breast milk is unknown[10], a drug's concentration in the maternal circulation is generally proportional to its concentration in breast milk. In other words, higher serum levels generally result in a higher drug level in breast milk.

Radiopharmaceutical uptake by the breast is fairly rapid with peak concentrations at 3-4 hours after administration. It is of interest that studies on breast milk uptake have been highly variable for a given radiopharmaceutical and at different times within the same patient. The biological half-life however, appears less variable[11].

Radiation Exposure to the Maternal Lactating Breast from Diagnostic and Therapeutic Radiopharmaceuticals

Systemically administered radiopharmaceuticals will localize in variable amounts to all body tissues, including the breasts. In lactating breasts, enhanced uptake and secretion into breast milk may occur with certain radiopharmaceuticals and possibly their radioactive metabolites[12 13 14 15 16 17 18 19 20 21 22 23 24]. This greater uptake would result in an increased radiation dose to the lactating relative to the non-lactating breast. Due to the relatively high sensitivity of the female breast to radiation carcinogenesis[25], the enhanced radiation dose to the lactating breast warrants consideration. This section therefore addresses the radiation dose to lactating breasts and provides absorbed dose estimates for commonly used radiopharmaceuticals (Table 1).

The time-integrated activity (also known as the cumulated activity or residence time) in the lactating breast results from radiopharmaceutical secretion into breast milk and was estimated by Stabin and Breitz[26]. These investigators assumed a linear filling of milk into the breast to a milk volume of 142 ml over 4 hours and then instantaneous emptying at feeding or pumping. The breast absorbed dose was calculated by using the breast-to-breast S values for the Reference Adult female anatomic model of Stabin et al[27]. No attempt was made to model the effect of a temporary interruption of breast-feeding since the mother would likely express/pump milk from her breasts at regular intervals, and the net effect would be comparable to actual breast-feeding.

The 2- to 5-fold increase in breast mass that occurs during pregnancy and lactation was also considered. Due to individual variability, these changes were difficult to model with certainty. However, the overall effect of a larger lactating breast would be a decrease in the absorbed breast dose, since the radioactivity will be deposited over a larger mass. Stabin and Breitz used a standard breast mass (400 g for both breasts) which produced a conservative upper-limit breast dose estimate for most women and a reasonable though less conservative estimate for smaller breasts.

For ^{18}F-FDG , the individual breast activity, expressed as the standard uptake value (SUV), was measured by Hicks et al[28] in a series of oncology patients at one hour after ^{18}F-FDG injection. Since the biokinetics of FDG are well known, the one-hour SUV was assumed to reflect the maximum breast activity. Conservatively, the kinetics of FDG breast uptake were ignored (i.e., uptake was considered instantaneous) and elimination of activity was assumed to occur only by physical decay (i.e., ignoring the effect of actual breast feeding or pumping). Given the short physical half-life of ^{18}F (1.2 hours), the latter assumption is likely not overly conservative. The

^{18}F-FDG breast-to breast absorbed dose was calculated using the *OLINDA* computer program[29], again assuming breast-to-breast S values for the Reference Adult Female model[30]. The absorbed-dose estimates for the lactating breast thus corresponds to self-irradiation (i.e., breast-to-breast) values.

For the majority of radiopharmaceuticals, once in the maternal circulation, there is less than 10% excretion into breast milk, with most estimates at 0.3 to 5% of the administered activity[31]. Several authors have reported higher radiopharmaceutical concentrations and cumulative excretions in patients with greater milk production. Cumulative excretions greater than 10% have been reported only for ^{67}Ga-citrate and ^{131}I-NaI [32]. Consequently, except for ^{67}Ga-citrate and ^{131}I-NaI, the highest absorbed dose estimates to the lactating breasts for typical diagnostic administered activities are usually well under 1 rad (0.01 Gy). ^{67}Ga-citrate and ^{131}I-NaI are both actively secreted into breast milk, and result in notably higher absorbed doses to the lactating breast: 1.1 rad (0.011 Gy) for an administered activity of 5 mCi (185 MBq) of ^{67}Ga-citrate and 200 rad (2 Gy) for a therapeutic administered activity of 150 mCi (5,550 MBq) of ^{131}I-NaI. The exceptionally high ^{131}I-NaI dose to the lactating breasts is worrisome, and has led to recommendations for lactating women for whom radioiodine therapy is planned to discontinue breast-feeding six weeks prior to therapy[33 34]. This recommendation ensures the complete cessation of lactation, which minimizes radioiodine concentration in the maternal breast, and thus, the absorbed maternal breast dose.

Radiation Exposure: Nursing Child from Nursing Mother

The dosimetric analyses in this section assume that there is no interruption of breast-feeding following administration of the radiopharmaceutical to the mother.

(a) External Maternal Radiation to the Nursing Child

The most obvious mode of radiation exposure to a nursing child from radiopharmaceutical administration to the child's mother is ingestion of maternal milk containing radioactivity. In addition, the nursing child will be exposed externally from radioactivity in the mother, and this exposure may be significant given the close proximity of the mother and child during nursing and child care. Given the general lack of pertinent data in the literature, the external absorbed dose to the nursing child has been estimated by the following model calculations:

$$D_{\text{nursing child}}\big|_{\text{ext}} = D_{\text{nursing child}\leftarrow\text{maternal breast}}\big|_{\text{ext}} + D_{\text{nursing child}\leftarrow\text{maternal rem}}\big|_{\text{ext}} \quad (1)$$

where

$D_{\text{nursing child}\leftarrow\text{maternal breast}}\big|_{\text{ext}}$ = the external absorbed dose to the nursing child from activity in the maternal breast

and

$D_{\text{nursing child}\leftarrow\text{maternal rem}|\text{ext}}$ = the external absorbed dose to the nursing child from activity in the maternal remainder of body (assumed to be equivalent to the maternal torso).

The external absorbed dose to the nursing child from activity in the maternal breast, $D_{\text{nursing child}\leftarrow\text{maternal breast}|\text{ext}}$, and in theremainder of the mother's body, $D_{\text{nursing child}\leftarrow\text{maternal rem}|\text{ext}}$, can be calculated by Equations (2) and (3), respectively:

$$D_{\text{nursing child}\leftarrow\text{maternal breast}|\text{ext}} = \tau_{\text{maternal breast}} \bullet A \bullet \Gamma \bullet \frac{1}{r_{\text{breast-to-child}}^2} \bullet CF_{\text{point-to-line}|\text{breast}} \bullet 0.5 \bullet [1-\phi(\text{breast-to-breast})] \bullet E_{\text{nursing}} \quad (2)$$

and

$$D_{\text{nursing child}\leftarrow\text{maternal rem}|\text{ext}} = \tau_{\text{maternal rem}} \bullet A \bullet \Gamma \bullet \frac{1}{r_{\text{maternal rem-to-child}}^2} \bullet CF_{\text{point-to-line}|\text{maternal rem}} \bullet 0.5 \bullet [1-\phi(\text{maternal WB}\leftarrow\text{maternal WB})] \bullet E_{\text{nursing}} \quad (3)$$

where $\tau_{\text{maternal breast}}$ = the radionuclide residence time in the maternal breast (in h),

$\tau_{\text{maternal rem}}$ = the radionuclide residence time in the maternal remainder of body (in h),

A = the administered activity (in μCi),

Γ = the radionuclide specific gamma-ray constant (in R-cm^2/μCi-h),

$r_{\text{breast-to-child}}$ = the maternal breast-to-child distance (in cm), that is, the distance from the mid-line of the maternal breast to the mid-line of the nursing child,

$r_{\text{maternal rem-to-child}}$ = the maternal remainder of body-to-child distance (in cm), that is, the distance from the mid-line of the mother's torso to the mid-line of the nursing child,

$CF_{\text{point-to-line}|\text{breast}}$ = the point source-to-line source conversion factor for the breast,

$CF_{\text{point-to-line}|\text{maternal rem}}$ = the point source-to-line source conversion factor for the maternal remainder of body (corresponding to the maternal torso),

ϕ(breast-to-breast) = the breast-to-breast photon absorbed fraction,

ϕ(maternal WB-to-maternal WB)

= the maternal whole body (WB)-to-maternal whole body (WB) photon absorbed fraction,

and $E_{nursing}$ = the occupancy factor for nursing.

The radionuclide residence times in the breast milk, $\tau_{maternal\ breast}$, and in the maternal remainder of body, $\tau_{maternal\ rem}$, can be calculated by Equations (4) and (5), respectively:

$$\tau_{breast\ milk} = 1.44 \bullet F_{breast\ milk} \bullet \sum_{i=1}^{n} f_i|_{breast\ milk} \bullet (T_e)_i|_{breast\ milk} \quad (4)$$

and

$$\tau_{maternal\ rem} = 1.44 \bullet F_{maternal\ rem} \bullet \sum_{i=1}^{n} f_i|_{maternal\ rem} \bullet (T_e)_i|_{maternal\ rem} \quad (5)$$

where $F_{breast\ milk}$ = the cumulative fraction of the administered activity in breast milk,

$f_i|_{breast\ milk}$ = the fraction corresponding to component i of the exponential function describing the time-activity data for breast milk,

$(T_e)_i|_{breast\ milk}$ = the effective half-time of component i of the exponential function describing the time-activity data for breast milk,

$F_{maternal\ rem}$ = the fraction of the administered activity in maternal remainder of body,

$f_i|_{maternal\ rem}$ = the fraction corresponding to component i of the exponential function describing the time-activity data for the maternal remainder of body,

and $(T_e)_i|_{breast\ milk}$ = the effective half-time of component i of the exponential function describing the time-activity data for the maternal remainder of body.

Implicit in equations (2) and (3) is the assumption that the beta-particle contribution to the external dose from the mother to the nursing child is negligible; given the very short range of beta particles in tissue, this is a reasonable assumption. The factor, 0.5, in Equations (2) and (3) reflects the fact that radiations emitted from within the mother have an equal probability of traveling either towards or away from the nursing child. Furthermore, rather than modeling the maternal breast and torso as point sources, they have been modeled as line sources as described by Siegel et al[35]. This provides a more accurate approach to estimating the distance-dependence of the mother-to-child doses than the conventional point-source model.

(b) Internal Radiation Dose to the Nursing Child from Ingestion of Radioactive Milk

The second major pathway of radiation exposure to a nursing child resulting from radiopharmaceutical administration to the child's mother is the ingestion of radioactive maternal

milk. As already noted, generallyless than 10% of an administered radiopharmaceutical activity is excreted into breast milk; typical estimates range from 0.3% to 5% of the initial administered activity[36]. Higher cumulative excretions been reported only with ^{67}Ga-citrate and ^{131}I-NaI up to ~10 and ~25%, respectively[37]. Based on the cumulative fraction of the administered activity in breast milk and the half-time(s) of clearance from breast milk (Table 3), radiopharmaceutical residence times can be calculated using equation (4).

Assuming complete ingestion of the 142 mL (Stabin and Breitz[26]) of radioactive milk by the nursing child and ignoring the subsequent kinetics of absorption and clearance from the child, the whole-body residence time of the radiopharmaceutical in the child can be equated with its residence time in the breast milk, $\tau_{\text{breast milk}}$. An upper limit of the whole-body absorbed dose to the nursing child (specifically, for the Reference Newborn anatomic model) from ingestion of radioactive milk, $D_{\text{nursing child}|\text{int}}$, can then be derived using equation (6):

$$D_{\text{nursing child}}\big|_{\text{int}} = \tau_{\text{breast milk}} \bullet DF(WB \leftarrow WB)_{\text{newborn}} \qquad (6)$$

where

$DF(WB \leftarrow WB)_{\text{newborn}}$ = the whole body-to-whole body dose factor (in rad/mCi-h) for the Reference Newborn anatomic model.

Implicit in the dose estimates shown in Table 3 is that breast-feeding was *not* interrupted following administration of the radiopharmaceutical to the nursing mother.

(c) Total Radiation Dose to the Nursing Child

The total radiation doses to a nursing child for various radiopharmaceuticals administered to the mother, calculated by summing the respective external and internal radiation doses, are presented in Table 4; these represent the mean whole-body absorbed doses to the child. The calculated absorbed doses to the nursing child if breast-feeding were *not* interrupted uniformly exceed 0.1 rad (= 100 mrad), and thus the 100-mrem (1-mSv) maximum recommended dose limit for a nursing child.

Despite the conservative assumptions implicit in estimating the doses for ^{18}F-FDG and ^{99m}Tc-labeled radiopharmaceuticals, these doses only slightly exceed the 100-mrem dose limit. ^{67}Ga-citrate and ^{131}I-NaI doses, however, exceed the 100-mrem dose limit by more than an order of magnitude and with ^{131}I-NaI therapy by several orders of magnitude. Therefore, with the exception of ^{131}I-NaI and several other radiopharmaceuticals (See "Precautions for Nursing Mothers: Recommendations and Rationale" and Table 5 below), a brief temporary discontinuation of breast-feeding following maternal radiopharmaceutical administration is sufficient to maintain the nursing child's radiation dose below the 100-mrem (1-mSv) dose limit.

The magnitude of the radiation dose to the nursing child for ^{131}I-NaI, especially for therapy, reinforces the need for permanent discontinuation of breast-feeding for the current child following ^{131}I-NaI administration to the nursing mother. Breast feeding, however, is allowed for future pregnancies. The radiation dose to the nursing child's thyroid will be considerably higher than that to the whole-body (with the potential for damage to the child's thyroid), further reinforcing the need to cease breast-feeding for any ^{131}I administration.

For ^{67}Ga-citrate, the dose to the nursing mother's breast and the whole-body dose to the nursing child will be significant as well if breast-feeding is not discontinued (see Tables 2, 3 and 4). However, based on the dose estimates to the maternal breast (Table 1), and in contrast to the recommendation for a therapeutic administration of ^{131}I, discontinuation of breast-feeding *prior* to the administration of ^{67}Ga-citrate is not required. Following administration of ^{67}Ga-citrate, discontinuation of breast-feeding for a period of 4 weeks is recommended, which is consistent with the most conservative recommendation in the literature.

Radiation Exposure to the Nursing Child from Implanted Sources: Brachytherapy and Radioactive Seed Localization

Brachytherapy is used to treat breast cancer, especially in breast conservation surgery for early-stage cancer[38] [39] [40]. The purpose of brachytherapy is to deliver a localized boost dose to the lumpectomy bed after whole-breast radiation. Several brachytherapy treatments are usually required. After each treatment, the radioactive seed is removed and no radioactivity remains in the breast. Accordingly, except for suspending breast-feeding while the sources are in place, brachytherapy does not present any restrictions on breast-feeding.

Radioembolic therapy using ytrrium-90 (^{90}Y)-labeled microspheres (SirSpheres™, TheraSperes™) is used for treating unresectable liver tumors[41] [42]. Under fluoroscopic guidance the radiolabeled microspheres are infused intra-arterially to selectively treat tumors, thereby relatively sparing normal tissue. The ^{90}Y microsphere system is considered a medical device (i.e., a brachytherapy device) and is licensed under 10CFR35.1000 ("Other medical uses of byproduct material or radiation from byproduct material"). As a pure beta emitter, ^{90}Y does not cause a significant external radiation hazard from the resulting *bremsstrahlung*, which produces only a negligible external dose[43]. For lactating mothers who receive ^{90}Y -microspheres breast-feeding does not need to be interrupted, as the ^{90}Y does not enter the systemic circulation, breast tissue or breast milk. As noted, there is no significant external dose to the child (as only the potential source of external radiation from ^{90}Y is the very low-yield emission of *bremsstrahlung*).

The purpose of radioactive seed localization (RSL) is to preoperatively localize suspicious non-palpable breast lesions for surgical excision[44] [45]. RSL is an alternative to the traditional needle-

wire preoperative localization, wherein a non-radioactive percutaneous wire is placed into the breast to guide surgical excision of suspicious tissue.

The RSL seed(s) may be removed intra-operatively from the tissue specimen or more commonly, the tissue specimen containing the seed(s) is sent to Pathology for seed removal, analysis and documentation. Breast-feeding should be suspended while the seeds are in place. No radioactivity remains in the breast once all seeds have been removed and accounted for. Breast-feeding can be continued up to seed implantation and resumed immediately after seed removal.

Precautions for Nursing Mothers: Recommendations and Rationale

Existing recommendations for nursing mothers promulgated by the NRC[46], the International Commission on Radiological Protection (ICRP)[47], and others[48] are based on a maximum dose (i.e., dose equivalent) to the nursing child of 100 mrem (0.1 rem). As summarized in Table 5, the extant recommended precautions for nursing mothers are somewhat variable in terms of both the radiopharmaceutical and the time interval for breast feeding interruption following radiopharmaceutical administration to the nursing mother. The cited NRC and ICRP recommendations are the most current and up-to-date.

In formulating the current recommendations – listed in the last column in Table 5 – our Sub-Committee generally selected the most conservative existing recommendation, which was usually the longest interruption period for each radiopharmaceutical. To the extent that it is practical, expressed radioactive milk can be held for decay in storage for the same length of time as the recommended interruption period and then used for feeding the child. The Sub-Committee's recommended interruption periods apply not only to breast-feeding but also to the close physical proximity of the nursing mother to the nursing child (i.e., caressing or holding the child with a similar distance to the mother as for breast-feeding).

Specific Sub-Committee recommendations for the nursing mother include the following:

1. For ^{99m}Tc-labeled radiopharmaceuticals, rather than a radiopharmaceutical-specific interruption period, a single interruption period of 24-hours is recommended. Although this time interval may be longer than absolutely necessary for some ^{99m}Tc-labeled radiopharmaceuticals, it is compliant with the 100-mrem dose limit and simplifies the guidance, thereby avoiding confusion and reducing the likelihood of error.

2. For ^{18}F-FDG, all other ^{18}F-labeled and all gallium-68 (^{68}Ga)-labeled radiopharmaceuticals, a 12-hour interruption period is recommended. This conservative recommendation is cautious and simplifies safety instructions for patients and medical professionals. A 12-hour interruption period is recommended for ^{68}Ga for the following reasons: (a) a physical half-life comparable to that of ^{18}F, (b) the propensity of free

radiogallium to accumulate in breast milk and (c) the lack of relevant data on ^{68}Ga-labeled agents in nursing mothers.

3. For very-short-lived positron-emitting radionuclides used in imaging, carbon-11 (^{11}C) (physical half-life: 20.4 min), nitrogen-13 (^{13}N) (9.97 min), and oxygen-15 (^{15}O) (2.04 min), and generator-produced rubidium-82 (^{82}Rb) (1.27 min), no interruption in breast-feeding is recommended, since there is no significant activity remaining in the mother after the procedure is completed.

4. For iodine-123 in the form of NaI (^{123}I-NaI), an interruption period of 7 days is recommended. This is in marked contrast to the past, where complete cessation of breast-feeding for the current child was recommended. This older, more stringent ^{123}I-NaI recommendation was largely based on contamination (up to 2.5% of the total activity) with long-lived iodine-125 (^{125}I) (physical half-life: 60 days) that occurred with older methods of ^{123}I production[49]. Such contamination of ^{123}I with ^{125}I no longer occurs. Therefore, the restrictions on breast-feeding following ^{123}I-NaI administration to the nursing mother may be justifiably relaxed to an interruption period of 7 days.

5. For gallium-67 (^{67}Ga)-gallium-citrate, an interruption period of 28 days is recommended, which is consistent with the most conservative recommendations for ^{67}Ga in the literature. For indium-111 (^{111}In) labeled white cells an interruption period of 7 days and for thallium-201 (^{201}Tl-chloride) an interruption period of 14 days are recommended. These recommendations mirror that of the NRC in the Consolidated Guidance About Materials Licenses: Program-Specific Guidance About Medical Use Licenses, NUREG-1556, Vol 9, Rev 1, Appendix U, 2005.

6. For zirconium-89 (^{89}Zr), a 28-day (i.e., 4-week) interruption period was set equal to the maximum recommended interruption period for ^{67}Ga. The rationale for this recommendation are the comparable physical half-lives of ^{89}Zr (3.27 days) and ^{67}Ga (3.26 days), both ^{89}Zr and ^{67}Ga are radiometals and may share some common chemical properties, and lastly, there is a lack of relevant data on ^{89}Zr-labeled agents in nursing mothers.

   For lutecium-177 (^{177}Lu), based on the foregoing ^{89}Zr rationale and a longer physical half-life (6.65 days), an interruption period of 35-days (i.e., 5 weeks) is recommended for ^{177}Lu-labeled radiopharmaceuticals used *diagnostically*. For ^{177}Lu-labeled radiopharmaceuticals used *therapeutically*, much higher activities are administered, and thus, permanent cessation of breast-feeding for the current child is recommended.

7. For radium-223 (^{223}Ra) and all other alpha particle-emitting radionuclides, permanent discontinuation of breast-feeding for the current child is recommended. Alpha particles are densely ionizing, have high-linear energy transfer (LET) radiations that potentially incur far more significant biological effects than beta-particles, and are of particular concern in the young child in whom rapid growth and development are occurring. In the absence of relevant data and out of an abundance of caution, permanent discontinuation of breast-feeding for the current child is therefore recommended.

Subcommittee Recommendations for the Nursing Mother

Radiopharmaceutical	**Breast Feeding Cessation**
^{11}C, ^{13}N, ^{15}O, ^{82}Rb	None
^{18}F-labeled	12-hours
^{68}Ga-labeled	12-hours
^{99m}Tc-labeled	24-hours
^{123}I-NaI	7 days
^{111}In-leukocytes	7 days
^{201}Tl-chloride	14 days
^{67}Ga and ^{89}Zr	28 days
^{177}Lu, diagnostic	35 days
^{131}I-NaI	Stop breast feeding
^{177}Lu, therapeutic	Stop breast feeding
^{223}Ra and all alpha emitters	Stop breast feeding

Patient Information: Departmental Signage for Nursing Mothers

Nursing mothers undergoing a nuclear medicine or nuclear cardiology procedure may not be aware of the potential dosimetric impact of such procedures on themselves and their nursing child. It is important that nuclear medicine and nuclear cardiology facilities therefore alert nursing mothers that certain radiation safety precautions with respect to breast-feeding may be required before and after they receive a radiopharmaceutical. Analogous to the signage used to alert pregnant and potentially pregnant patients to possible hazards of nuclear medicine and radiological procedures, the following or equivalent signage should be prominently displayed in all patient areas of a nuclear medicine or nuclear cardiology facility: "If you are currently breast-feeding or plan to begin breast-feeding in the near future, inform the technologist, nurse or doctor immediately." Depending on the patient demographics in a particular facility, posting such signage in various foreign languages as well as in English should be considered.

Table 1

Radiopharmaceutical Absorbed Doses to the Lactating Breast

			Breast Absorbed Dose[50 51]			
	Administered Activity		Lowest Estimate		Highest Estimate	
Radiopharmaceutical	mCi	MBq	Rad	Gy	rad	Gy
^{18}F-FDG	10	370	1.2E-01	1.2E-03	2.0E-01	2.0E-03
^{51}Cr-EDTA	0.05	1.85	4.2E-07	4.2E-09	2.5E-06	2.5E-08
^{67}Ga-citrate	5	185	2.2E-02	2.2E-04	1.1E+00	1.1E-02
^{99m}Tc-DTPA	20	740	6.1E-04	6.1E-06	1.2E-02	1.2E-04
^{99m}Tc-DTPA aerosol	1	37	1.2E-05	1.2E-07	2.5E-04	2.5E-06
^{99m}Tc-DISIDA	8	296	2.0E-03	2.0E-05	6.0E-03	6.0E-05
^{99m}Tc-glucoheptonate	20	740	3.6E-03	3.6E-05	7.4E-03	7.4E-05
^{99m}Tc-HAM	8	296	8.5E-03	8.5E-05	2.3E-02	2.3E-04
^{99m}Tc-MAG3	5	185	3.0E-04	3.0E-06	6.0E-03	6.0E-05
^{99m}Tc-MAA	4	148	1.6E-03	1.6E-05	1.2E-01	1.2E-03
^{99m}Tc-MDP	20	740	2.7E-03	2.7E-05	3.8E-03	3.8E-05
^{99m}Tc-MIBI	30	1110	5.5E-04	5.5E-06	5.1E-03	5.1E-05
^{99m}Tc-PYP	20	740	4.2E-03	4.2E-05	2.2E-02	2.2E-04

^{99m}Tc-RBCs - in vitro labeling	20	740	9.3E-04	9.3E-06	1.6E-03	1.6E-05
^{99m}Tc-RBCs - in vivo labeling	20	740	2.5E-04	2.5E-06	1.1E-01	1.1E-03
^{99m}Tc-pertechnetate	30	1110	1.9E-03	1.9E-05	2.5E-01	2.5E-03
^{99m}Tc-sulfur colloid	12	444	3.2E-03	3.2E-05	4.6E-02	4.6E-04
^{99m}Tc-WBCs	10	370	1.1E-02	1.1E-04	1.5E+00	1.5E-02
^{111}In-WBCs	0.5	18.5	5.0E-04	5.0E-06	2.5E-03	2.5E-05
^{123}I-MIBG	10	370	-	-	2.7E-02	2.7E-04
^{123}I-NaI	0.4	15	-	-	4.7E-02	4.7E-04
^{123}I-OIH	2	74	5.5E-03	5.5E-05	5.8E-02	5.8E-04
^{125}I-OIH	0.01	0.37	-	-	8.5E-05	8.5E-07
^{131}I-OIH	0.3	11	5.0E-03	5.0E-05	3.2E-02	3.2E-04
^{131}I-NaI	150	5,550	-	-	2.0E+02	2.0E+00
^{201}Tl-chloride	3	111	2.4E-03	2.4E-05	4.1E-03	4.1E-05

Table 2

Estimation of the External Radiation Dose from the Mother to the Nursing Child Assuming No Interruption of Breast-feeding: Model Parameters

	^{18}F-FDG	^{67}Ga-citrate	^{99m}Tc "Worst case"	^{131}I-NaI
Photon energy (keV)	511	93, 185, 300	140	364
Physical half-life (h)	1.2	78.2	6.04	193
Specific Gamma-ray Constant, G (R-cm^2/mCi-h)[52]	0.0057	0.00080	0.00060	0.0022
Administered Activity (mCi), A - Assumed	10	5	30	5 (imaging), 150 (therapy)
Cumulative fraction of activity in breast milk, $f_{breast\ milk}$	0.040[53]	0.10[54]	0.05[55]	0.25[56]
Fraction of activity in remainder of body, $f_{maternal\ rem}$[57]	0.96	0.90	0.95	0.75
Maternal whole body-to-whole body photon absorbed fraction, f(maternal WB¬maternal WB)[58]	0.34	0.31	0.31	0.31
Maternal breast-to-breast photon absorbed fraction, f(Br¬Br)[59]	0	0	0	0
Effective half-time of activity in breast, $(T_e)_{breast\ milk}$ (h)[60]	1.2	78.2	6.02	10.4 (99%) 81.8 (1%)
Effective half-life of activity in maternal remainder of body, $(T_e)_{maternal\ rem}$ (h)[61]	1.2	78.2	6.02	38.4

Distance from mother's breast to nursing child, $r_{breast\text{-}to\text{-}child}$ (cm)[62]	7.5
Point source-to-line source conversion factor for maternal breast-to-child exposure, $CF_{point\text{-}to\text{-}line\|breast}$[63]	0.32
Distance from mother's torso to nursing child, $r_{maternal\ rem\text{-}to\text{-}child}$ (cm)[64]	15
Point source-to-line source conversion factor for maternal torso-to-child exposure, $CF_{point\text{-}to\text{-}line\|maternal\ rem}$[65]	0.54
Occupancy factor for nursing, $E_{nursing}$[66]	0.33

Table 3

Internal Radiation Dose to the Nursing Child from Ingestion of Radioactive Milk Assuming No Interruption of Breast-feeding: Model and Kinetic Parameters and Radiation Dose Estimates

Radiopharmaceutical	Assumed Administered Activity (mCi)	Cumulative Fraction Excreted in Breast Milk, ($f_{breast\ milk}$)	Effective Half-Time in Breast Milk, $(T_e)_i$ [1] hours	Residence Time in Breast Milk $t_{breast\ milk}$ [67] (µCi-h/µCi)	Reference Newborn Whole Body-to-Whole Body Dose Factor ($DF(WB \neg WB)_{newborn}$ [68] rad/µCi-h)	Newborn Whole-Body Absorbed Doses, $D_{nursing\ child|int}$	
						rad/mCi	rad/Administered Activity
^{18}F-FDG	10	0.04 [69]	1.2 [70]	0.048	2.44E-04	0.012	0.12
^{67}Ga-citrate	5	0.10 [71]	78.2 [72]	7.8	3.68E-05	0.29	1.4
^{99m}Tc, "Worst case"	30	0.05 [73]	6.02 [74]	0.30	2.16E-05	0.0065	0.19
^{131}I-NaI	5 (imaging), 150 (therapy)	0.25 [75]	10.4 (99%) [76] 81.8 (1%)	2.78	1.53E-04	0.43	2.2, 65

Table 4

Total Radiation Dose to the Nursing Child Assuming No Interruption of Breast-feeding

Radiopharmaceutical	Assumed Administered Activity mCi	Whole-Body Absorbed Dose to Nursing Child rad		
		External	Internal	Total
^{18}F-FDG	10	0.027	0.12	0.15
^{67}Ga-citrate	5	0.17	1.4	1.6
^{99m}Tc, "Worst case"	30	0.044	0.19	0.23
^{131}I-NaI	5 (imaging)	0.2	2.2	2.4
	150 (therapy)	5.3	65	70

Table 5

Recommendations for Cessation of Breast-feeding in Nursing Mothers Undergoing Nuclear Medicine Procedures

Radiopharmaceutical	NRC NUREG 1556 Vol 9 Rev 3, Appendix U	ICRP Publication 106, Annex D	Hazel and Breitz, J Nucl Med 41: 863-873, 2000	MSKCC Recommendations, 2017	Current ACMUI Sub-Committee Recommendations, 2017
All ^{11}C-labeled radiopharmaceuticals	Not included	No interruption	Not included	Not included	No interruption
All ^{13}N-labeled radiopharmaceuticals	Not included	No interruption	Not included	Not included	No interruption
All ^{14}C-labeled radio-pharmaceuticals, including ^{14}C-urea	Not included	No interruption	Not included	Not included	No interruption
All ^{15}O-labeled radiopharmaceuticals	Not included	No interruption	Not included	Not included	No interruption
All ^{18}F-labeled radio-pharmaceuticals, including ^{18}F-FDG	Not included	No interruption	Not included	12 h	No interruption
^{51}Cr-EDTA	No interruption	No interruption	No interruption	Not included	No interruption
^{67}Ga-citrate	1 month for 4 mCi, 2 weeks for 1.3 mCi, 1 week for 0.2 mCi	> 21 d	Complete cessation for current child for 5 mCi	21 d	28 d
All ^{68}Ga-labeled radiopharmaceuticals	Not included	Not included	Not included	12 h	12 h
^{81m}Kr-gas	Not included	No interruption	Not included	Not included	No interruption
^{82}Rb-chloride	Not included	Not included	Not included	Not included	No interruption
^{89}Zr-antibodies	Not included	Not included	Not included	21 d	21 d
^{99m}Tc-DMSA	Not included	No interruption	Not included		
^{99m}Tc-DTPA	No interruption	No interruption	No interruption		
^{99m}Tc-DTPA aerosol	No interruption	No interruption	No interruption		
^{99m}Tc-DISIDA	No interruption	No interruption	No interruption		
^{99m}Tc-ECD	Not included	No interruption	Not included		
^{99m}Tc-gluconate	Not included	No interruption	Not included		
^{99m}Tc-glucoheptonate	No interruption	No interruption	No interruption		
^{99m}Tc-HAM	Not included	No interruption	No interruption		
^{99m}Tc-MAG3	No interruption	No interruption	No interruption		
^{99m}Tc-MAA	13 h for 4 mCi	12 h	12 h for 4 mCi	24 h	24 h
^{99m}Tc-MDP	No interruption	No interruption	No interruption		
^{99m}Tc-MIBI	No interruption	No interruption	No interruption		
^{99m}Tc-PYP	No interruption	No interruption	No interruption		
^{99m}Tc-RBCs - in vitro labeling	No interruption	No interruption	No interruption		
^{99m}Tc-RBCs - in vivo labeling	6 h for 20 mCi	12 h	12 h for 20 mCi		
^{99m}Tc-pertechnetate	24 h for 30 mCi, 12 h for 12 mCi	12 h	4 h for 5 mCi		
^{99m}Tc-sulfur colloid	6 h for 12 mCi	No interruption	No interruption		
^{99m}Tc-tetrofosmin	Not included	No interruption	Not included		
^{99m}Tc-WBCs	24 h for 30 mCi, 12 h for 12 mCi	12 h	No interruption		

^{99m}Tc-WBCs	24 h for 30 mCi, 12 h for 12 mCi	12 h	No interruption		
^{111}In-antibodies	Not included	Not included	Not included	Not included	7 d
^{111}In-octreotide	Not included	No interruption	Not included	Not included	24 h
^{111}In-WBCs	7 d for 0.5 mCi	No interruption	No interruption	7 d	7 d
^{123}I-MIBG	24 h for 10 mCi, 12 h for 4 mCi	> 3 weeks	48 h for 10 mCi	7 d	48 h
^{123}I-NaI	No interruption	> 3 weeks	Complete cessation for current child	7 d	48 h
^{123}I-OIH	No interruption	12 h	No interruption	7 d	No interruption
^{124}I-NaI	Not included	Not included	Not included	Complete cessation for current child	Complete cessation for current child
^{124}I-antibodies	Not included	Not included	Not included	Complete cessation for current child	Complete cessation for current child
^{125}I-OIH	No interruption	12 h	No interruption	Not included	No interruption
^{131}I-OIH	No interruption	12 h	No interruption	Not included	Complete cessation for current child
^{131}I-NaI	Complete cessation for current child	>3 weeks to complete cessation for the current child	Complete cessation for current child	Complete cessation for current child	Complete cessation for current child
^{133}Xe-gas	Not included	No interruption	Not included	Not included	No interruption
All ^{177}Lu-labeled radiopharmaceuticals	Not included	Not included	Not included	28 d for diagnostic activity, Complete cessation for the current child for therapeutic activity	28 d for diagnostic activity, Complete cessation for the current child for therapeutic activity
^{201}Tl-chloride	14 d for 3 mCi	48 h	96 h for 3 mCi	14 d	14 d
All alpha particle-emitting radiopharmaceuticals, including ^{223}Ra-dichloride	Not included	Not included	Not included	Complete cessation for current child	Complete cessation for current child

References

[1] Fahey F, Zanzonico P, "Radiation Safety for Nursing Mothers Undergoing Nuclear Medicine Procedures", presentation, 49th Annual Conference of Radiation Control Program Directors, May 8-11, 2017.

[2] Kelly Mom Parenting Breastfeeding website

[3] US Nuclear Regulatory Commission Regulatory Guide 8.39: Release of Patients Administered Radioactive Materialsm, April 1997.

[4] Royal HD, Schwarz SW, Seigel BA: Case 17: Radiopharmaceutical Misadministration. In: Nuclear Radiology (Fifth Series) Test And Syllabus (Keyes JW, Brown ML, Miller TR, eds.), American College of Radiology, Reston, VA, 1998 pp 177-191.

[5] Chandra R Introductory Physics of Nuclear Medicine, 3rd edition. Philadelphia. 1990 p.34-37.

[6] Anderson PO Radiopharmaceuticals LactMed Update. Breastfeeding Medicine Vol 11(5):2016. Page 216-217.

[7] Ibid

[8] Ibid

[9] Anderson PO Radiopharmaceuticals LactMed Update. Breastfeeding Medicine Vol 11(5):2016. Page 216-217.

[10] Stabin MG, Breitz HB. Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings and Radiation Dosimetry. J Nucl Med 2000; 41:863-873.

[11] Ibid

[12] Ibid

[13] Hedrick WR, Di Simone RN, and Keen RL: Radiation dosimetry from breast milk excretion of radioiodine and pertechnetate. J Nucl Med. 27:1569-71, 1986.

[14] Mountford PJ and Coakley AJ: Breast milk radioactivity following injection of 99Tcm-pertechnetate and 99Tcm-glucoheptonate. Nucl Med Commun. 8:839-45., 1987

[15] Mountford PJ and Coakley AJ: A review of the secretion of radioactivity in human breast milk: data, quantitative analysis and recommendations. Nucl Med Commun. 10:15-27, 1989.

[16] Mountford PJ, Coakley AJ, and Hall FM: Excretion of radioactivity in breast milk following injection of 99Tcm- DTPA. Nucl Med Commun. 6:341-5, 1985.

[17] Ogunleye OT: Assessment of radiation dose to infants from breast milk following the administration of 99mTc pertechnetate to nursing mothers. Health Phys. 45:149-51, 1983.

[18] Robinson PS, Barker P, Campbell A, et al.: Iodine-131 in breast milk following therapy for thyroid carcinoma [see comments]. J Nucl Med. 35:1797-801, 1994.

[19] Rubow S, Klopper J, Wasserman H, et al.: The excretion of radiopharmaceuticals in human breast milk: additional data and dosimetry [see comments]. Eur J Nucl Med. 21:144-53, 1994.

[20] Rumble WF, Aamodt RL, Jones AE, et al.: Accidental ingestion of Tc-99m in breast milk by a 10-week-old child. J Nucl Med. 19:913-5, 1978.

[21] Sharma SC, Osborne RP, Jose B, et al.: Dose estimation to the infant from breast milk following intraperitoneal administration of chromic phosphate 32P for the treatment of early ovarian cancer. Health Phys. 47:452-4, 1984.

[22] Siddiqui AR: Accidental ingestion of Tc-99m in breast milk by a 10-week-old child [letter]. J Nucl Med. 20:799, 1979.

[23] Simon SL, Luckyanov N, Bouville A, et al.: Transfer of 131I into human breast milk and transfer coefficients for radiological dose assessments. Health Phys. 82:796-806, 2002.

[24] Castronovo FP, Jr., Stone H, and Ulanski J: Radioactivity in breast milk following 111In-octreotide. Nucl Med Commun. 21:695-9, 2000.

[25] BEIR, Health Effects of Exposure to Low Levels of Ionizing Radiation (BEIR VII). Biological Effects of Ionizing Radiation (BEIR) Committee, National Research Council. 2006, Washington, DC: National Academies Press.

[26] Stabin MG, Breitz HB. Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings and Radiation Dosimetry. J Nucl Med 2000; 41:863-873.

[27] Stabin M, Watson E, Cristy M, et al., Mathematical Models and Specific Absorbed Fractions of Photon Energy in the Nonpregnant Adult Female and at the End of Each Trimester of Pregnancy. 1995, Oak Ridge National Laboratoies: Oak Ridge, TN

[28] Hicks RJ, Binns D, and Stabin MG: Pattern of uptake and excretion of (18)F-FDG in the lactating breast. J Nucl Med. 42:1238-42, 2001.

[29] Stabin MG, Sparks RB, and Crowe E: OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med. 46:1023-7, 2005.

[30] Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce.

[31] Stabin MG, Breitz HB. Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings and Radiation Dosimetry. J Nucl Med 2000; 41:863-873.

[32] Ibid

[33] Luster M, Clarke SE, Dietlein M, et al.: Guidelines for radioiodine therapy of differentiated thyroid cancer. Eur J Nucl Med Mol Imaging. 35:1941-59, 2008.

[34] Fact Sheet: Guidelines for Patients Receiving Radioiodine I-131 Treatment. Available from: http://snmmi.files.cms-plus.com/FileDownloads/Patients/FactSheets/Radio_.pdf.

[35] Siegel JA, Marcus CS, and Sparks RB: Calculating the absorbed dose from radioactive patients: the line-source versus point-source model. J Nucl Med. 43:1241-4, 2002.

[36] Stabin MG, Breitz HB. Breast Milk Excretion of Radiopharmaceuticals: Mechanisms, Findings and Radiation Dosimetry. J Nucl Med 2000; 41:863-873.

[37] Ibid

[38] Polgar C and Major T: Current status and perspectives of brachytherapy for breast cancer. Int J Clin Oncol. 14:7-24, 2009.

[39] Smith BD, Arthur DW, Buchholz TA, et al.: Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys. 74:987-1001, 2009.

[40] Smith GL, Xu Y, Buchholz TA, et al.: Brachytherapy for accelerated partial-breast irradiation: a rapidly emerging technology in breast cancer care. J Clin Oncol. 29:157-65, 2011.

[41] Thomson W, Mills A, Smith N, et al.: Day and night radiation doses to patients' relatives: Implications of ICRP 60 (Abstract). Nucl Med Commun. 14:275, 1993

[42] Edeline J, Gilabert M, Garin E, et al.: Yttrium-90 microsphere radioembolization for hepatocellular carcinoma. Liver Cancer. 4:16-25, 2015.

[43] Zanzonico PB, Binkert BL, and Goldsmith SJ: Bremsstrahlung radiation exposure from pure beta-ray emitters. J Nucl Med. 40:1024-8, 1999.

[44] Jakub JW, Gray RJ, Degnim AC, et al.: Current status of radioactive seed for localization of non palpable breast lesions. Am J Surg. 199:522-8, 2010.

[45] Gray RJ, Pockaj BA, Karstaedt PJ, et al.: Radioactive seed localization of nonpalpable breast lesions is better than wire localization. Am J Surg. 188:377-80, 2004.

[46] NRC, Consolidated Guidance About Materials Licenses Program-Specific Guidance About Medical Use Licenses, Draft Report for Comment, NUREG-1556, Volume 9, Rev. 3, N.R. Commission, Editor. 2016: Rockville, MD.

[47] ICRP: Annex D. Recommendations on Breat-Feeding Interruptions. Radiation Dose to Patients from Radiopharmaceuticals. A Third Amendment to ICRP Publication 53. Annals of the ICRP. 38:163-165, 2008.

[48] Center MSKC, Policy and Procedure L1208 - Lactating Mothers Receiving Radiopharmaceuticals. 2017: New York, NY.

[49] Johns H and Cunningham J, The Physics of Radiology. 1974, Springfield, IL: Charles C Thomas. pp 276-277.

[50] Except for ^{18}F-FDG, the breast absorbed doses are taken from Stabin MG and Breitz HB: Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. J Nucl Med. 41:863-73, 2000. The ^{18}F-FDG breast absorbed doses were calculated based on the referenced data from Hicks RJ, Binns D, and Stabin MG: Pattern of uptake and excretion of ^{18}F-FDG in the lactating breast. J Nucl Med. 42:1238-42, 2001.

[51] For radiopharmaceuticals which only a single breast absorbed dose is available in the literature, the absorbed dose is listed in the "Highest Estimate" column.

[52] The specific gamma-ray constant, G, is the photon exposure rate (in R/h) at 1 cm from a 1-mCi point source in air.

[53] Hicks RJ, Binns D, and Stabin MG: Pattern of uptake and excretion of (18)F-FDG in the lactating breast. J Nucl Med. 42:1238-42, 2001.

[54] Stabin MG and Breitz HB: Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. J Nucl Med. 41:863-73, 2000.

[55] Ibid

[56] Robinson PS, Barker P, Campbell A, et al.: Iodine-131 in breast milk following therapy for thyroid carcinoma [see comments]. J Nucl Med. 35:1797-801, 1994.

[57] The fraction of activity in the maternal remainder of the body, $f_{\text{maternal rem}}$, equals 1 minus the cumulative fraction of activity in breast milk.

[58] Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce.

[59] It is conservatively assumed that the maternal breast does not attenuate any of the photon radiation emitted from the breast.

[60] For short-lived ^{18}F and ^{99m}Tc, the effective half-time in breast milk, (Te)breast milk, is conservatively equated with the respective physical half-life. For ^{131}I, the bi-exponential time-activity function with the effective half-times listed is referenced in Robinson PS, Barker P, Campbell A, et al.: Iodine-131 in breast milk following therapy for thyroid carcinoma [see comments]. J Nucl Med. 35:1797-801, 1994.

[61] For short-lived ^{18}F and ^{99m}Tc, the effective half-time in maternal remainder of body, $(Te)_{maternal\ rem}$, is conservatively equated with the respective physical half-life. For ^{131}I, the whole-body biological half-time in a post-thyroidectomy thyroid cancer patient was assumed to be 2 days (or 48 hours).

[62] The distance from the mother's breast to the nursing child, $r_{breast\text{-}to\text{-}child}$, corresponds to the assumed approximate distance from the mid-line of the mother's breast (i.e., for the Reference Adult Female anatomic phantom) to the mid-line of the child (i.e., the Reference Newborn anatomic model). This is the sum of the one-half of the "a" parameter value, $1/2 \cdot 5$ cm =2.5 cm, tabulated for the Reference Adult Female and the "B_T" parameter value, 2.5 cm, for the Reference Newborn referenced in Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce.

[63] In order to model the maternal breast activity as a line source, rather than a point source, a conversion factor is required to appropriately adjust the inverse-square dependence on distance of the point-source dose rate. This conversion factor depends on the length of the line source, which is 5 cm for the breast line source, and the distance from the line source, which is $r_{breast\text{-}to\text{-}child}$ = 7.5 cm for the mid-line of the nursing child.

The length of the breast line source is equated with parameter "c" tabulated for the Reference Adult Female anatomic model referenced in Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce.

The conversion factor is taken from Siegel JA, Marcus CS, and Sparks RB: Calculating the absorbed dose from radioactive patients: the line-source versus point-source model. J Nucl Med. 43:1241-4, 2002, Table 1.

[64] The distance from the mother's torso to the nursing child, $r_{\text{maternal rem-to-child}}$, corresponds to the assumed approximate distance from the mid-line of the mother (i.e., for the Reference Adult Female anatomic phantom) to the mid-line of the child (i.e., the Reference Newborn anatomic model). This is the sum of the "B_T" parameter values, 5 and 10 cm res[ectively to include conversion factor referenced in Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce.

[65] See Note 63. For the point source-to-line source conversion factor for the maternal torso-to-child exposure, the length of the line source is 63 cm for the maternal torso and the distance from the line source is $r_{\text{mother-to-child}} = 15$ cm. The length of the maternal torso line source is equated with parameter "C_T" tabulated for the Reference Adult Female anatomic model referenced in Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce.

[66] An occupancy factor for nursing, E_{nursing}, of 0.25 conservatively assumes that the child will actually be nursing for 6 hours out of each day (24 hours).

[67] $$\tau_{\text{breast milk}} = 1.44 \bullet F_{\text{breast milk}} \bullet \sum_{i=1}^{n} f_{i|\text{breast milk}} \bullet (T_e)_{i|\text{breast milk}}$$

[68] Cristy M and Eckerman K, Specific absorbed fractions of energy at various ages from internal photon sources (I-VII). Oak Ridge National Laboratory Report ORNL/TM-8381/V1-7. 1987, Springfield, VA: National Technical Information Service, Dept of Commerce. Whole body-to-whole body dose factors, DF(WB¬WB)newborn, were taken from the OLINDA computer program in Stabin MG, Sparks RB, and Crowe E: OLINDA/EXM: the second-generation personal computer software for internal dose assessment in nuclear medicine. J Nucl Med. 46:1023-7, 2005.

[69] Hicks RJ, Binns D, and Stabin MG: Pattern of uptake and excretion of (18)F-FDG in the lactating breast. J Nucl Med. 42:1238-42, 2001.

[70] Ibid

[71] Stabin MG and Breitz HB: Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. J Nucl Med. 41:863-73, 2000.

[72] Ibid

[73] Stabin MG and Breitz HB: Breast milk excretion of radiopharmaceuticals: mechanisms, findings, and radiation dosimetry. J Nucl Med. 41:863-73, 2000.

[74] Ibid

[75] Robinson PS, Barker P, Campbell A, et al.: Iodine-131 in breast milk following therapy for thyroid carcinoma [see comments]. J Nucl Med. 35:1797-801, 1994.

[76] Ibid

Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Use of Isotopes (ACMUI)

Subcommittee on

Physical Presence Requirements for the Leksell Gamma Knife® Icon™

February 1, 2018

Subcommittee Members:
Ronald Ennis, M.D.
John Suh, M.D. (Chair)
Laura Weil

NRC Staff Resource: Sophie Holiday

Charge to subcommittee: To propose the appropriate physical presence requirement for the Leksell Gamma Knife® Icon™ radiosurgery unit.

Subcommittee Process

The subcommittee and its Chair were appointed by ACMUI Chair, Phil Alderson, at the regularly scheduled ACMUI meeting April 26, 2017. This subcommittee was formed after a presentation on April 26, 2017 by Elekta, Inc. requesting emendation of the Title 10 Code of Federal Regulations (10 CFR) 35.1000 licensing guidance for the Leksell Gamma Knife® Icon™ to allow the authorized user (AU) to be physically present in the department during patient treatment and immediately available to come to the treatment room to respond to an emergency based on the very small number of medical events (MEs) that have occurred with modern Gamma Knife® units. The initial report was presented on September 12, 2017 at the ACMUI meeting. This is an updated report based on feedback from the last ACMUI meeting in September 2017.

Summary of Subcommittee Recommendations

- The AU and authorized medical physicist (AMP) need to be physically present during the initiation of all treatments. This allows independent confirmation that the correct plan is being used for treatment and that the correct site is being treated during the initiation of treatment.

- The current physical presence requirements for the AU be modified by allowing the AU to be present in the department during treatment, which is defined for the Icon™ as within a two minute walk to the console area, and immediately available to come to the treatment room. An AMP needs to be physically present during the entire treatment. While we recognize the NRC does not have regulations for nursing or auxiliary staff, we

recommend as a best practice that appropriately trained nursing or auxiliary staff be present at Gamma Knife treatment to respond to any immediate medical needs. It should be the responsibility of the AU to determine the necessary training and experience required of the nursing staff.

- If there is an interruption of treatment secondary to medical or mechanical issues, the AU must return to Gamma Knife® Icon™ console to evaluate the patient and/or to review any mechanical issues. The AU must be present to ensure the correct site is being treated prior to re-initiation of treatment.

- At the conclusion of treatment, the AU must be present at the Icon™ console to discuss and review any treatment or patient issues with the patient, physicist, and nurse.

Introduction

Gamma stereotactic radiosurgery is a very effective and well established treatment for patients with various benign and malignant brain tumors, vascular malformations and some functional disorders such as trigeminal neuralgia. The shielded unit utilizes 192 or 201 Cobalt-60 (Co-60) sources that simultaneously converge to a central target in the brain by the use of different sized collimator channels that are positioned around the patient's skull. The first Gamma Knife® in the United States was installed at the University of Pittsburgh in 1987 (Model U). Over the next 12 years, the model B and model C units were introduced. These three systems, licensed under 10 CFR 35.600, (Models U, B and C) have tungsten collimators that are external to the Co-60 sources and are placed on the treatment unit manually. All these units required frame-based immobilization and have fixed beam geometry to maximize reliability and minimize quality assurance checks.

In 2006, the Perfexion™ unit was introduced. Unlike the model U, B, and C units, the collimators are inside the treatment unit with sources that can be shielded while the treatment helmet is being switched to another size collimator, which can decrease treatment times and manual intervention by the treatment team. The Perfexion™ also uses five different positions (16 mm, 4 mm, off, 8 mm, and home, which is an off position) to turn the beam on and off. These sectors allow for rapid change (within 1 second) of the collimators of each sector. Along with engineering differences that would not meet the provisions under 10 CFR 35.600, the NRC decided to license the Perfexion™ under 10 CFR 35.1000. In 2016, the Icon™ system was introduced, which allowed for treatment with a thermoplastic frameless mask unlike the Perfexion™ unit. In addition, the Icon™ unit has a cone-beam computed tomography (CT) which provides stereotactic reference for patient setup and high definition motion management for mask-based treatments. Since the introduction of the Gamma Knife® in 1987 in the United States, the use of gamma stereotactic radiosurgery has greatly increased in the United States. Based on information from Elekta, there are 77 Perfexion™ units and 22 Icon™ units. Worldwide, over 1 million patients have been treated with the Gamma Knife®.

Given the many advances in gamma stereotactic radiosurgery, the delivery has become more efficient allowing for treatment of multiple patients each day and treatment of multiple targets in a single session, which have increased the treatment times for some patients. Given the

evolution of the Gamma Knife® over the past decade from the Model C to Perfexion™ and now Icon™, the physical presence requirements were examined by the subcommittee.

Current Physical Presence Requirement

In October 2002, the NRC modified the regulations in 10 CFR Part 35 to include a section[1] regarding gamma stereotactic radiosurgery to include the requirement that "For gamma stereotactic radiosurgery unit require an Authorized User with appropriate training and experience in radiation oncology and Authorized Medical Physicist to be physically present throughout all patient treatments involving the unit." This regulation provided for an appropriate response to an emergency and to ensure that the correct dose of radiation is delivered to the patient. The term[2] "physically present" was defined as "within hearing distance of normal voice".

The NRC issued a Regulatory Issue Summary (RIS) to clarify the definition of "physically present" as a result of an event at one of the Gamma Knife centers. The RIS (RIS-2005-23)[3], "Clarification of the Physical Presence Requirement During Gamma Stereotactic Radiosurgery Treatment," stated that this meant speaking in a normal conversational tone and not a raised voice. As a result, a distance of 20 feet may not be close enough to adequately hear and respond to an emergent situation. This also ensures the correct dose of radiation was delivered.

Rationale for change

The current definition ensures that an emergent situation will be addressed immediately by the AU and that the correct dose is delivered. The AU has the knowledge and appropriate training to ensure the safe and effective delivery of stereotactic radiosurgery. The current physical presence definition is not ambiguous and ensures the AU is present for the all the critical portions of the procedure, able to address any medical issues that may arise during treatment, and verify the correct dose will be delivered to the target(s). The AU will have the competency to recognize and respond to any aberration of treatment and ensure response times within seconds if needed.

Medical issues during the Gamma Knife® treatment may include pain from the frame, nausea, vomiting, and seizure. Incorrect dose of radiation may result secondary to system failure which could be software, hardware, or combination of both. As serious medical issues and/or significant aberrations in treatment can result in reportable MEs, rules regulating physician presence exist to ensure patient safety.

Over the past ten years of NMED, there are 12 reportable events involving the Perfexion™. Of the 12 Perfexion™ reportable events, only a minority were identified during treatment. The Icon unit has significant enhancements over the Perfexion™ unit. Specifically, three features are important: 1) the option of treatment with a thermoplastic frameless mask rather than a frame, 2) ability to perform integrated stereotactic cone-beam computed tomography (CT) which provides stereotactic reference for patient setup, and 3) high definition motion management for mask-based treatments. These enhancements re-open the question regarding the physical presence requirements of the AU for the entire treatment. A review of the 12 events for Perfexion™ reveals that none of these events would have escaped detection on an Icon unit using

the thermoplastic frameless mask and high definition motion management for mask-based treatments even if the AU was not physically at the console and could have been rapidly and effectively addressed as long as the AU was immediately available.

Proposal by Elekta, Inc. on April 26, 2017 for Gamma Knife® Icon™

1. *We will have an Authorized User and Authorized Medical Physicist physically present during the initiation of all treatments involving the unit.*

2. *We will have an Authorized Medical Physicist physically present throughout all patient treatments involving the unit.*

3. *We will have an Authorized User physically present in the department during patient treatment and immediately available to come to the treatment room to respond to an emergency.*

Recommendations

Based on the extremely low number of MEs with the Perfexion™ unit coupled with the modifications with the Icon™, the subcommittee recommends modifying the current physical presence requirements for the Icon™ unit. The major differences between the Icon™ versus the Perfexion™ are: 1) treatment with a thermoplastic frameless mask rather than invasive frame for some patients; 2) ability to perform integrated stereotactic cone-beam computed tomography (CT) which provides stereotactic reference for patient setup; and 3) high definition motion management for mask-based treatments which allows for online adaptation. Although we respect the proposal by Elekta, Inc., we believe their proposal needs to be more stringent to ensure safe and accurate delivery of gamma stereotactic radiosurgery. Physical presence would utilize a similar definition used by Section V, Summary of changes of the 2002 revised 10 CFR part 35 in the *Federal Register*[4]. The following recommendations remain consistent with federal regulations and requirements governing physician supervision from the Centers for Medicare and Medicaid Services and federal regulations.

1. AU and AMP be physically present during the initiation of all treatments involving the Icon™ unit.

   This will allow independent confirmation that the correct plan is being used for treatment and that the correct site is being treated at the initiation of treatment. This will also allow the authorized user to be part of the universal timeout, which should help prevent the wrong plan from being delivered or the incorrect side from being treated initially.

2. AMP be physically present throughout all patient treatments involving the unit.

   The physical presence of an AMP is essential for the safe and accurate delivery of gamma stereotactic radiosurgery. The addition of a medical physicist would ensure that

any software, hardware, or combination of software/hardware failure be recognized immediately and addressed promptly.

The current physical presence requirements for the AU can be modified by allowing the AU to be close enough to the to the console to respond quickly to any issue that arises which is defined as within a two minute walk to the Icon™ console area, **and** immediately available to come to the treatment room. An AMP needs to be physically present during the entire treatment.

In addition to the AU and AMP, as a matter of good practice, we recommend that appropriately trained nursing or auxiliary staff be present at Icon™ treatment to respond to any immediate medical needs. It will be the responsibility of the AU to determine the necessary training and experience required of the nursing staff, who will be present throughout the procedure.

3. If there is an interruption of treatment secondary to medical or mechanical issues, the AU must return to Gamma Knife® Icon™ console to evaluate the patient and/or to review any mechanical issues. The AU must be present to ensure the correct site is being treated during re-initiation of treatment.

4. At the conclusion of treatment, the AU must be present at the Icon™ console to discuss any treatment or patient issues with the patient, physicist, and nurse.

The AU will be physically present close to the console, which is defined in this report as *within 2 minutes from the console area*, during patient treatment **and** immediately available to furnish assistance and direction throughout the performance of the procedure. Specifying time rather than presence in the department mitigates any misinterpretation of the regulations which has happened in the past[5]. This definition would be more stringent than the American Society for Radiation Oncology white paper.[6]

The subcommittee felt that a time, rather than distance, ought to be used to define "physically present in the department." Depending on the configuration of the department, distance may not be easily measured, i.e., the department may be located on multiple floors, not necessarily in close proximity. In addition, the subcommittee believes that 'physically present' in the department can be ambiguous especially if the Gamma Knife® center is distant from the radiation oncology department or if the Gamma Knife® is not present within the radiation oncology department such as a neurosurgery department or free standing center. Since a medical physicist would be physically present for the duration of treatments, medical and software/hardware incidents could be addressed during the 2 minute interval before the AU would arrive.

Summary:

The subcommittee recommends that for the Leksell Gamma Knife® Icon™:

- The AU and AMP need to be physically present during the initiation of all treatments. This allows independent confirmation that the correct site is being treated, confirm that

the correct plan is being used for treatment and particularly important for functional cases, all of which are components of the universal time outs. It also provides an opportunity to visualize the movement of the treatment table to the correct position via treatment room cameras.

- The current physical presence requirements for the AU be modified by allowing the AU to be within a 2 minute walk of the console area **and** immediately available to come to the treatment room after initiation of treatments. An AMP needs to be physically present by the console area during the entire treatment. (i.e., at the console or within normal hearing voice) of the AU.
- If there is an interruption of treatment secondary to medical or mechanical issues, the AU must return to Gamma Knife® Icon™ console to evaluate the patient and/or to review any mechanical issues. The AU must be present to ensure the correct site is being treated during re-initiation of treatment.
- At the conclusion of treatment, the AU must be present at the Gamma Knife® Icon™ console to discuss any treatment or patient issues with the patient, AMP and nurse.

We believe that the recommendations would allow for the safe and effective delivery of gamma stereotactic radiosurgery while allowing the AU more flexibility to be available for other medical issues, other than those requiring personal supervision, in a radiation oncology department if warranted. We also believe that the recommendations will allow the licensee to determine if an ME has occurred, would allow the regulator to inspect and regulate a Gamma Knife® center, would not unfavorably encroach on the practice of medicine, and are consistent with regulations governing physician supervision. As a subcommittee, we believe it is inappropriate for the AU to be more than a 2 minute walk from the console under any circumstance as the AU needs to be immediately available and needs to ensure the correct radiation dose is delivered. In addition, we recommend that the AU work with their radiation safety officer to determine how long it will take for the AU to return to the Gamma Knife® Icon™ console area from another location at which he/she wishes to work. The center will need to determine best method to contact the physician as paging a physician can take time. Since any change can be subject to interpretation, it is important that each Gamma Knife® center determine what area would be within 2 minutes of the console. Ultimately, each AU will need to decide if he or she wishes to adopt the revised physical presence proposal or maintain the current physical presence rules, which is more stringent.

Given the proposed change, it is imperative that a culture of safety and quality with checks and balances at every level exists to ensure that the safest and most effective care is delivered to patients while simultaneously protecting the public. Licensees are encouraged to continue to audit and monitor their programs and adopt best practices including a high reliability system approach[7] to mitigate MEs.

Respectfully submitted, February 1, 2018
Subcommittee on Physical Presence Requirements for Leksell Gamma Knife® Icon™,
Advisory Committee on the Medical Uses of Isotopes (ACMUI),
Nuclear Regulatory Commission (NRC)

References

1. 10 CFR 35.615(f)(3).

2. Section V, Summary of changes of 2002 revised part 35 in Federal Register (67 FR 20355)

3. NRC-issued Regulatory Issues Summary (RIS) 2005-23- October 2005

4. 42 C.F.R. § 410.32

5. Mastroianni A, McCaffrey JF. Target tumors, not yourself: A review of False Claims Act allegations against radiation oncologists. Appl Radiat Oncol 4(2): 14-21, 2015

6. Solberg TD, Balter JM, Benedict SH, et al. Quality and safety considerations in stereotactic radiosurgery and stereotactic body radiation therapy: Executive summary. Pract Radiat Oncol 2:2-9, 2012.

7. Reason J. Human error: models and management. BMJ 32:768-770, 2000