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Nuclear Material Events Database

Medical Events Involving Y-90 Microsphere Brachytherapy (Fiscal Year 2008-2017)

Thomas W. Smith, INL

Dante C. Huntsman, INL

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Idaho National Laboratory
Risk Assessment and Management Services
Idaho Falls, Idaho 83415

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Medical Events Involving Y-90 Microsphere Brachytherapy (Fiscal Year 2008-2017)

Introduction

Selective Internal Radiation Therapy (SIRT), also known as radioembolization, is a palliative therapy used to treat inoperable primary and metastatic liver tumors. This therapy involves the administration of millions of Yttrium-90 (Y-90) labeled microspheres into a patient's hepatic artery, typically via the femoral artery. The microspheres are transported by arterial blood flow to the liver. Although the microspheres are extremely small (about 25-32 microns), they are too large to pass through the capillary bed and become permanently trapped. This treatment exploits that liver tumors receive the majority of their blood flow from the hepatic artery, while normal liver tissue receives the majority of blood flow from the portal vein. Thus, the microspheres are preferentially deposited in the tumors.

Y-90 microsphere administration is a very complex treatment and presents many challenges to the medical treatment team. Difficulties include:

- Pre-treatment visualization of a patient's vasculature
- Determining doses anticipated to other sites such as the lungs or gastrointestinal tract
- Occluding any unwanted vascular pathways
- Positioning the catheter during administration
- Administering the microspheres with the appropriate flow rate
- Determining where the microspheres were actually deposited.

These treatments do not always occur exactly as planned. The Nuclear Material Events Database (NMED) contains 152 records of medical events, reportable to the NRC per the Code of Federal Regulations, involving Y-90 microspheres during the most recent 10-year period (Fiscal Year 2008-2017). This report provides an overview of those events.

The event data presented in this report are limited to reportable events that occurred between October 1, 2007, and September 30, 2017 (FY 2008-2017). The data were downloaded from the NMED on January 4, 2018. Because the NMED is a dynamic database that is updated daily, variations in data may be encountered over time. The FY 2017 data is most susceptible to change as subsequent updates and late reports are received.

The data is not normalized, meaning that the data only considers the number of reported events and does not directly account for external issues, such as changes in microsphere treatment equipment, procedures, or the number of treatments performed. For example, an increasing trend in the number of events could be caused by an increase in the number of treatments performed, the total number of which is not readily available and could not be considered in this analysis.

General Observations

The microspheres involved in the NMED events are of two different types: SIR-Spheres and TheraSphere. Table 1 displays some of the differences between the two types.

	SIR-Spheres	TheraSphere
Manufacturer	Sirtex	Nordion
Material	glass	resin
Mean diameter	32 micron	25 micron
Specific gravity	1.6 g/dL	3.6 g/dL
Activity per microsphere	75 Bq (2.0 nCi)	2500 Bq (67.6 nCi)
Number of microspheres per 3 GBq (81 mCi) vial	40 million	1.2 million
Supplied dose sizes	3 Gbq (81 mCi)	3 Gbq (81 mCi) 5 Gbq (135 mCi) 7 Gbq (189 mCi) 10 Gbq (270 mCi) 15 Gbq (405 mCi) 20 Gbq (540 mCi)
Dose preparation	Medical staff draws the applicable patient dose from the shipping vial (may not be the entire contents) and transfers it into an administration vial.	The entire contents/dose of the shipping vial is administered at a specific time in decay to achieve the applicable patient dose. The shipping vial is the administration vial.
Administration rate	Takes about 20 minutes Pulsed infusion alternating infusion/flush at ≤ 5 cc per minute	Takes about 5 minutes Continuous infusion at ≥ 20 cc per minute Followed by a minimum of three flushes at ≥ 20 cc per minute Infusion pressure ≤ 30 psi
FDA approval	2002 - Premarket approval to treat unresectable metastatic liver tumors from primary colorectal cancer.	1999 - Humanitarian device exemption to treat unresectable hepatocellular carcinoma

Table 1. Differences between SIR-Spheres and TheraSphere

Figure 1 displays the annual number and trend of 152 medical events involving Y-90 microsphere treatments that occurred during the 10-year period. The trend analysis determined that the data represent statistically significant increasing trends (indicated by the trend lines). Note that the increasing trends could be the result of an increasing number of microsphere treatments performed. That specific information is currently not available for this review of NMED data.

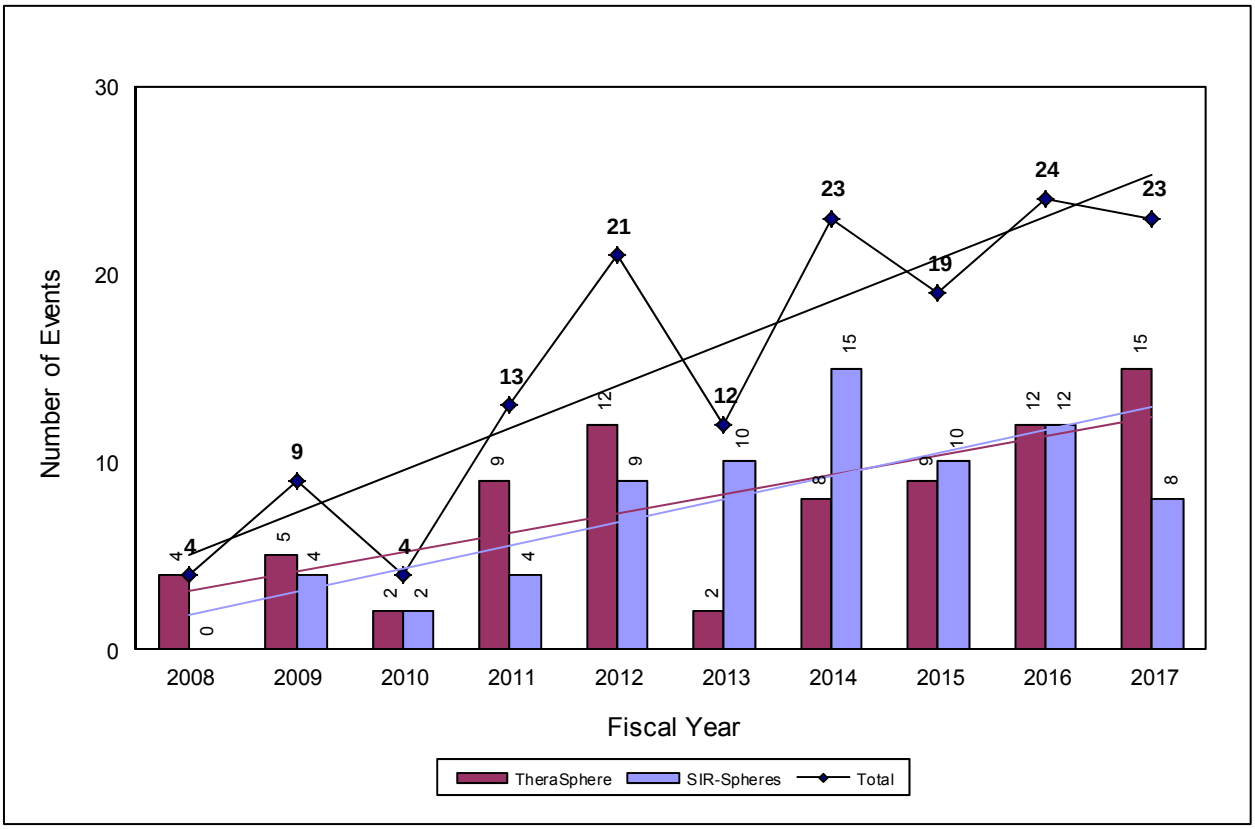

Figure 1. Medical Events Involving Y-90 Microsphere Treatments (152 total events)

The 152 events were almost evenly split between TheraSphere (78) and SIR-Spheres (74). The events actually involved 157 patients; one event affected five patients and another event affected two patients.

Ten of the 152 event abstracts noted that post-treatment patient imaging was used to map microsphere deposition; bremsstrahlung imaging, PET-MRI, etc. This does not signify that such scans were only performed 10 times. NMED event abstracts are summaries of events and do not contain all of the specific event details. Note that NRC does not require that post-treatment patient imaging be performed.

Figure 2 displays the event causes and Figure 3 displays the types of problems encountered (based on reporting requirements). Because this data is very similar between the TheraSphere and SIR-Sphere events, the differences are not highlighted here. Note that although each event has only one cause (Figure 2), the event may involve more than one type of problem (Figure 3). For example, an event where a portion of the microspheres intended for the liver were inadvertently deposited in the duodenum may be reported as less dose than prescribed for the intended site [10 CFR 35.3045(a)(1)(i)] and more dose than expected to the unintended site [10 CFR 35.3045(a)(3)].

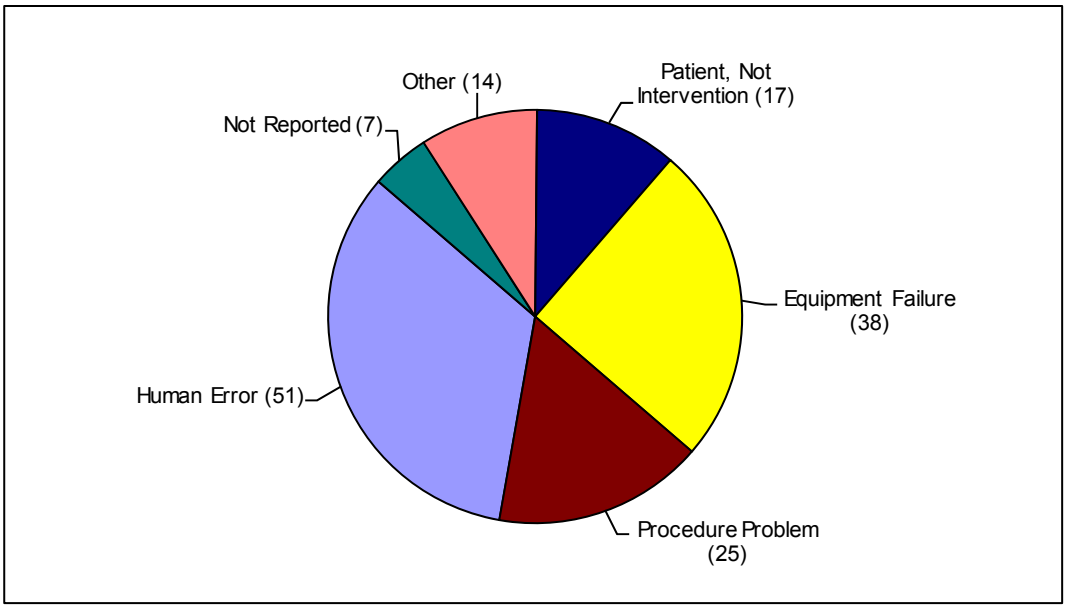

Figure 2. Event Causes

The Patient, Not Intervention data in Figure 2 represents events that do not result from patient intervention, yet are reported as beyond the control of the medical licensee. For example, an event where a non-intended site received microspheres due to a change in the patient's vasculature between the time the treatment was planned and the time it was performed.

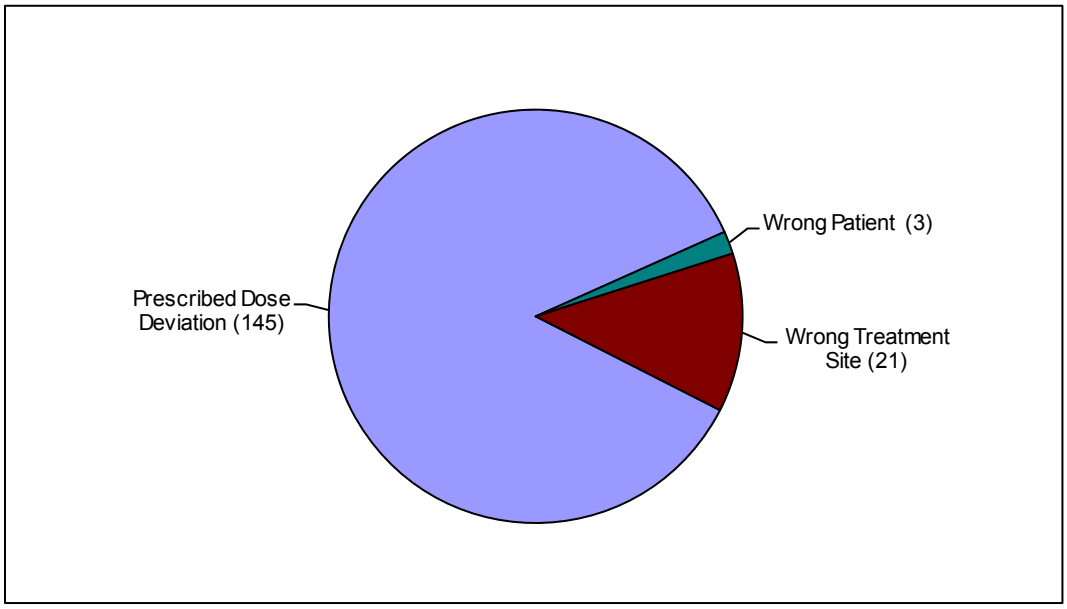

Figure 3. Event Problems (based on reporting requirements)

The Prescribed Dose Deviation data in Figure 3 includes both doses that were less than prescribed and doses that were more than prescribed.

For this report, events classified as Abnormal Occurrences (AOs) are considered to be significant.

The majority of the 152 events were not considered to be significant. Most (about 75%) involved doses to patients that were less than prescribed. A common theme among these events was that microspheres tend to settle out during the infusion procedure, either partially or totally clogging the delivery device/catheter, and never reach the artery. Sometimes, the doctor injecting the microspheres felt an increase in back pressure on the syringe indicating a resistance to flow (clog or stasis) and stopped the procedure. However, many times the medical team (perhaps including a manufacturer's representative) did not identify any abnormalities during a procedure, only to subsequently find from a post-procedure equipment radiation survey that a sizeable portion of the microspheres remained in the delivery device/catheter.

The manufacturers recognize the tendency for microspheres to settle out or clog the delivery device/catheter and have procedural steps/recommendations to help overcome this tendency. Such instructions include:

- TheraSphere - Ship and store the microsphere vial upright. Don't invert the vial prior to administration as this may cause microspheres to stick to the bottom of the vial septum. Just prior to administration, tilt the lead pot (shielding) in which the vial resides back and forth to 90 degrees to wet any microspheres on the vial septum, then tap the bottom of the lead pot firmly on a hard surface. Keep the infusion rate ≥ 20 cc per minute and immediately perform a minimum of three flushes.

- SIR-Spheres - Shake the shipping vial vigorously just prior to drawing off the patient's dose. The infusion procedure uses a slower (≤ 5 cc per minute) pulsing technique that alternates infusion and catheter flushing to help keep the microspheres suspended.

Some of the non-significant "less dose than prescribed" events resulted from equipment problems such as kinked or improperly sized catheters and fewer events from equipment leaks due to improper setup that resulted in prematurely stopping the infusion. Many NMED event abstracts mentioned that the delivery device/catheter was being sent back to the manufacturer (after an amount of time to permit radioactive decay) to determine why microspheres remained in the device/catheter. Other than kinked catheters, NMED records either do not contain the manufacturer's determination or the determination was inconclusive.

Significant Events - Abnormal Occurrences

Of the 152 events, 28 were considered to be significant (classified as AOs or potential AOs). Recent events are marked as potential AOs until they complete the NRC's formal AO determination process and are reported in NUREG-0090, *Report to Congress on Abnormal Occurrences*. Figure 4 and Table 2 display these events. The trend analysis indicates that the Total data represents a statistically significant increasing trend. The following appendices contain the NMED abstracts for the 28 AO events.

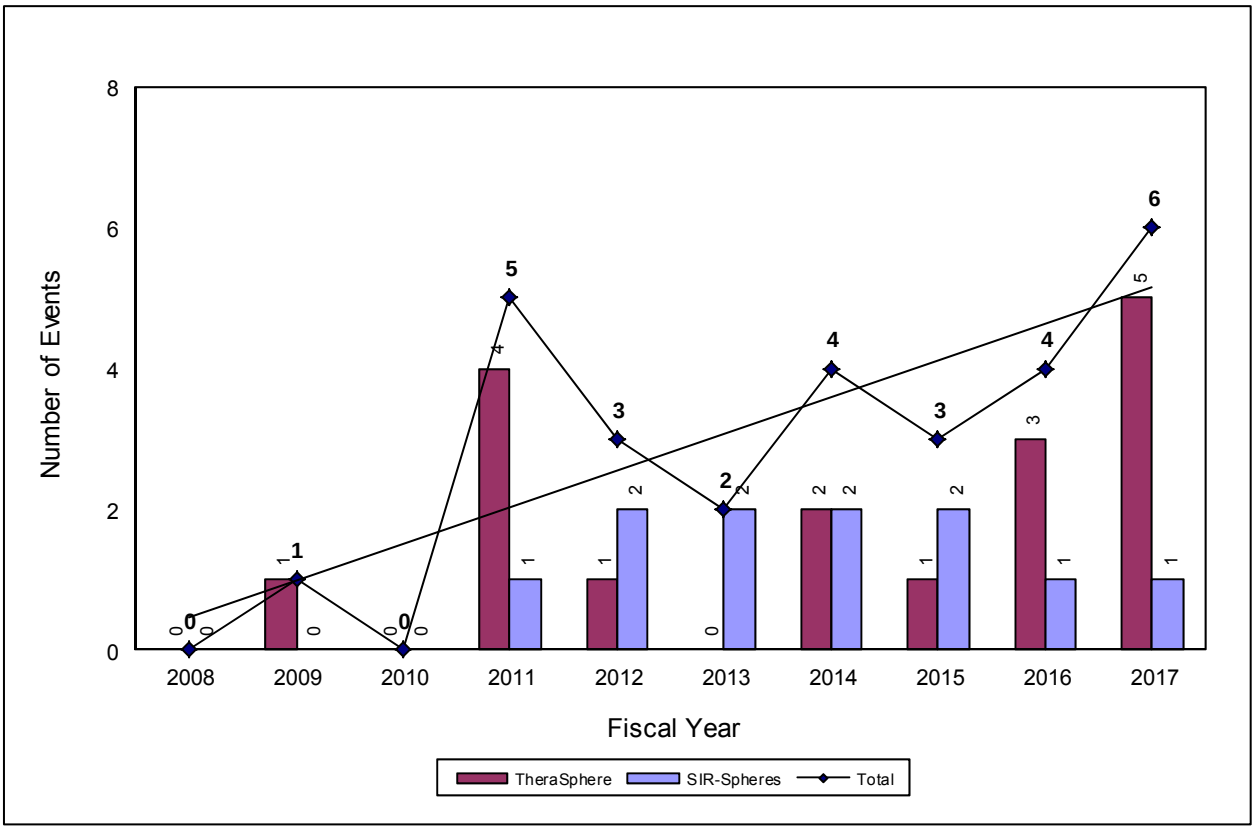

Figure 4. Abnormal Occurrences (28 total events)

Table 2. Abnormal Occurrences

	Fiscal Year										
	2008	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**Total**
TheraSphere	0	1	0	4	1	0	2	1	3	5	**17**
SIR-Spheres	0	0	0	1	2	2	2	2	1	1	**11**
Total	**0**	**1**	**0**	**5**	**3**	**2**	**4**	**3**	**4**	**6**	**28**

A review of the events revealed that they essentially fell into one of three categories displayed in Table 3.

Table 3. AO Event Categories

	TheraSphere	SIR-Spheres	Not Reported	Total
Dose to Unintended Site	10	7	0	**17**
Too Much Dose to Intended Site	5	3	1	**9**
Wrong Patient	2	1	0	**3**
Total	**17**	**11**	**1**	**29**

Note that the Table 3 data sums to 29 categories for 28 events. One of the TheraSphere events fell into two categories; a patient was infused to an unintended site using another patient's dose.

Figure 5 displays the causes of the 28 AO events. Because this data is very similar between the TheraSphere and SIR-Sphere events, the differences are not highlighted here.

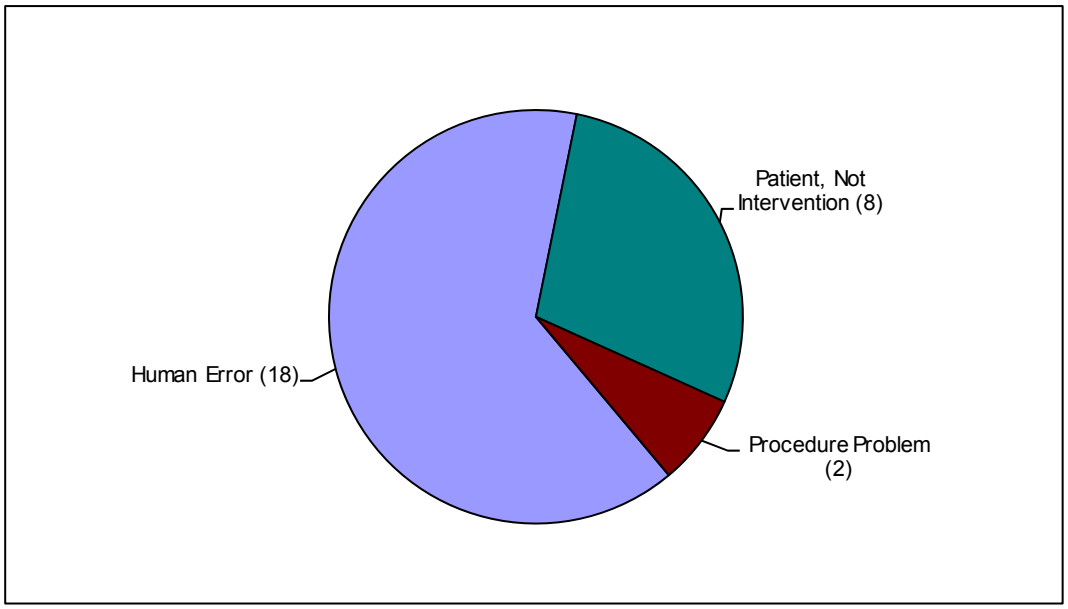

Figure 5. AO Event Causes

None of the events resulted from patient intervention. The Patient, Not Intervention data in Figure 5 represents events that do not result from patient intervention, yet are reported as beyond the control of the medical licensee. For example, an event where an unintended site received microspheres due to a change in the patient's vasculature between the time the treatment was planned and when it was performed. However, the majority of AO events were caused by factors within the licensee's control (Human Errors and Procedure Problems).

Dose to Unintended Site

The 17 events in this category include doses to the incorrect liver lobe, gastrointestinal tract, lungs, spleen, or kidney. Half of these events were caused by medical staff errors such as:

- Improper catheter placement. Some of these were simple mistakes such as placement in the wrong artery (left hepatic artery when the right was intended). In others, the catheter placement was not verified by imaging just before infusion.

- Catheter shifted position during treatment. This included an event where the fluoroscopy table moved, shifting the catheter, the placement of which was not re-verified. Other events stated that patient movement (perhaps even as slight as breathing) shifted the catheter. Note that it appears that these procedures are typically performed with the patient under mild sedation, but conscious and responsive; movement may occur.

The other half of the Dose to Unintended Site events resulted from the Patient, Not Intervention cause, which is beyond the control of the licensee. These include:

- Vasculature changes between the time the treatment was planned and when it was performed
- Temporary blood vessel contractions during infusion
- Unusual patient vasculature that resulted in unanticipated shunts or difficult catheter placement. In one event, the catheter could not be place properly, but because the disease was bilateral, the medical team went ahead with the treatment, knowing that the other lobe (unintended site) would need to be treated anyway.

The patient outcomes varied depending on which organ was the unintended site:

- Liver lobe (9 events). No negative complications were expected. These events were typically associated with bilateral disease; the unintended site (lobe) was either going to be treated or had already been treated.
- GI tract (6 events). Most of these events resulted in patient ulcers or increased susceptibility to ulcers. In one event, a patient was hospitalized about six months later with a duodenum lesion and ulcer.
- Lungs (1 event). Approximately five months after the event, the patient was hospitalized with Acute Respiratory Distress Syndrome-like symptoms with lung infiltrates consistent with radiation pneumonitis and passed away several days later.
- Spleen (1 event). The patient may experience permanent functional damage.
- Kidney (1 event). The patient did not experience any significant effect.

Note that the above sums to 18 unintended sites for 17 events; one event involved a dose to the GI tract and spleen.

Too Much Dose to Intended Site

The nine events in this category all resulted from medical staff errors. All but one event resulted from improper dose preparation (too much activity) that was not identified prior to infusion. The remaining event resulted when performing two separate infusions to the same patient; the vials were mixed up.

No unintended patient consequences were expected. Two events reported a small increased risk of atrophy.

Wrong Patient

The two events in this category both resulted from medical staff error. In these events, two patients were to be treated at the same facility on the same day. In one case, the medical staff mixed up the written directives and infused both patients with the other's dose. In the other event, medical staff mixed up the dose vials and infused one patient with the other's dose.

No unintended patient consequences were expected.

Appendix A
TheraSphere AO Events (17)

Recent events are marked as potential AOs until they complete the NRC's formal AO determination process and are reported in NUREG-0090, *Report to Congress on Abnormal Occurrences*.

Item Number 170399 (potential AO) - Washington University in Saint Louis reported that Y-90 microspheres (Nordion TheraSphere) intended for the left lobe of a patient's liver were administered to the right lobe. The patient treatment plan specified a radioembolization dose of 12,400 cGy (rad) to the left lobe on 8/18/2017, followed by radioembolization of the right lobe approximately one month later. The interventional radiologist and radiation oncologist authorized user signed off on the planning activity for the left lobe via the left hepatic artery on 8/2 and 8/3/2017, respectively. The authorized user completed the written directive to administer 1.74 GBq (47.03 mCi) of Y-90 microspheres. On 8/18/2017, the interventional radiologist placed the catheter in the patient's right hepatic artery, which supplies the right lobe. Medical personnel came to the operating room and a time-out procedure was performed where all parties confirmed the procedure, after which the treatment was administered. An interventional radiologist fellow who assisted in the procedure discovered the error later that day while writing up the patient notes and reviewing the treatment plan. He immediately notified the authorized user, who then notified the RSO. This event was caused by human error due to the interventional radiologist's confusion regarding the intent to treat the right lobe on a later date. The authorized user determined that 1.71 GBq (46.22 mCi) had been administered to the right lobe for an estimated dose of 6,100 cGy (rad). The patient and referring physician were notified of the medical event. Treatment of the left lobe was rescheduled and no harm to the patient is expected. Corrective actions included modification of the written directive time out procedure and personnel training.

Item Number 170357 (potential AO) - Mayo Clinic reported that a patient was administered 1.5 GBq (40.56 mCi) of Y-90 microspheres (Nordion model TheraSphere) to a 90 cc liver volume for ablation on 7/28/2017, instead of the prescribed 0.629 GBq (17 mCi). The liver received 80,780 cGy (rad) instead of the prescribed 34,000 cGy (rad). The microspheres were administered to the patient too early, before they decayed to the prescribed activity. The cause was an error by a scheduling nurse who used the pre-treatment plan rather than the final treatment plan. The physicist's pre-treatment calculations and a pre-administration time-out failed to identify the error. The physician was notified and contacted the patient. To prevent recurrence, the spreadsheet used to calculate patient dose was modified to include a check of the administration vial's calibration activity and date versus the prescribed activity and procedure date. The time-out procedure was also modified to confirm the proper activity prior to administration. Applicable personnel were trained on these changes. Mayo Clinic committed to provide a written report to the Florida Bureau of Radiation Control (BRC) before 8/11/2017. BRC is tracking the incident as number FL17-230.

Item Number 170294 (potential AO) - Providence Alaska Medical Center (PAMC) reported that a patient received 54,060 cGy (rad) to the right lobe of the liver, instead of the prescribed 11,000 cGy (rad), from a Y-90 microsphere (Nordion model TheraSphere) treatment performed on 6/14/2017. This event was caused by using the wrong calibration date (6/11/2017 instead of 6/4/2017) when ordering the source, resulting in a much higher activity. The source was surveyed with a dose calibrator prior to administration, but the abnormal results were not questioned. The patient's lung dose from lung shunting for this treatment was 2,576 cGy (rad), and 3,449 cGy (rad) cumulative; these values are within the 3,000 cGy (rad) and 5,000 cGy (rad) values, respectively, in the vendor's manual. The prescribing physician discussed the error with the patient. Corrective actions included personnel training and procedure modification to improve step-by-step implementation.

Item Number 170128 (potential AO) - Duke University Medical Center (DUMC) reported that a patient was administered a dose that was 94% higher than prescribed in the written directive during a liver embolization procedure on 2/24/2017. The prescribed activity was 1.05 GBq (28.37 mCi) of Y-90 microspheres (BTG Nordion model TheraSphere) but the administered activity was 2.05 GBq (55.35 mCi). The cause was human error at the DUMC radiopharmacy when converting the Y-90 activity from GBq to mCi. The patient was informed of the incident on 2/26/2017. The North Carolina Radiation Protection Section performed a reactive inspection on 3/2 and 3/17/2017. Corrective actions included procedure modifications, written directive revisions, and software updates to assist in unit conversions.

Item Number 170083 (potential AO) - Henry Ford Hospital reported that a patient prescribed to receive 6,000 cGy (rad) to the left lobe of the liver instead received 4,860 cGy (rad) to the left lobe and 3,650 cGy (rad) to the right lobe on 1/31/2017. This patient was known to have challenging anatomy and the only viable treatment location was a narrow window just distal to vasculature that supplies the right lobe of the liver. The interventional radiologist verified the catheter position multiple ways prior to the administration of 1.67 GBq (45 mCi) of Y-90 microspheres (Nordion model TheraSphere). The administration was performed with no apparent complications. However, Bremsstrahlung imaging following the administration showed that microspheres were present in both lobes of the liver. The referring physician and patient were notified of the incident. The licensee believes that the cause was either movement of the catheter from unnoticed patient movement (as subtle as breathing) or angiographically undetected reflux caused by the difference in flow dynamics between the microspheres and both the contrast agent and Tc-99M macro-aggregated albumin (MAA) used for treatment planning. This event caused no harm to the patient and no change to the patient's medical plans (the right lobe had been treated previously and was already essentially non-functional). A review of the event determined that no change in technique was advised and nothing could have been done differently. The NRC contracted a medical consultant, who concurred with the hospital's analysis..

Item Number 170074 (potential AO) - Washington University in Saint Louis reported that a patient was administered Y-90 microspheres (Nordion model TheraSphere) to the right lobe of the liver instead of the prescribed left lobe on 4/8/2016. The University planned to treat the patient's liver in two fractions. The first fraction involved treating the right lobe, which was successfully completed on 3/3/2016. The second fraction involved treatment of the left lobe, for which the written directive prescribed 4.15 GBq (112.16 mCi) for a dose of 11,700 cGy (rad). The catheter placement was confirmed by the interventional radiologist with an angiogram. The delivered activity was 4.07 GBq (110 mCi). Following administration of the second fraction, PET/MRI images were taken on 4/8/2016 and read on 4/16/2016. The images indicated that approximately 95% of the microspheres were deposited in the right lobe, with the remainder in the left lobe. The patient was notified of this event on 4/20/2016. The dose to the right lobe during the second fraction was 9,380 cGy (rad). When combined with the first fraction, the cumulative dose to the right lobe was 21,180 cGy (rad). The NRC contracted a medical consultant to review this event, who calculated the cumulative dose to the right lobe to be 21,200 cGy (rad). The University thought that the incident was not a medical event due to patient intervention (shifting the catheter tip location by breathing, coughing, or other movement). NRC Headquarters and Region III determined that the incident was a medical event on 1/30/2017 and requested that the University report the event. The patient remained under the care of the University, had no significant changes to liver function that were inconsistent with liver cancer, and had no abdominal pain. The left lobe of the liver was subsequently treated with chemotherapy. The University reviewed this event with applicable personnel to identify process improvement opportunities.

Item Number 160253 (AO) - University of California (UCLA) reported that a patient received a Y-90 microsphere dose (Nordion model TheraSphere) that was 88.6% more than prescribed on 6/16/2016. In addition to the incorrect activity, the incorrect liver lobe was treated. The patient received 4.02 GBq

(108.6 mCi) of Y-90, which resulted in a dose of 32,800 cGy (rad) to the right lobe. The patient was prescribed a dose of 12,000 cGy (rad) to the left lobe. The administered microspheres were intended for another patient's treatment scheduled for 6/17/2016. The patient was notified of the error and UCLA investigated the event. A two-month follow-up liver function test showed acceptable liver function in spite of this event. The cause of the event were inadequate procedures and insufficient training. These led to improper identification of the vial containing the correct dosage, improper verification of the calculated dosage by the preparing technician, and inadequate involvement by the AU to verify the radiopharmaceutical dosage before treatment. Treatment of the wrong lobe was attributed to displacement of the catheter after its insertion in the patient. The displacement was not detected because of a failure to verify catheter position during injection of the Y-90 to ensure that the catheter location remained constant. Corrective actions included developing and implementing a formal standard operating procedure for microsphere treatments, implementing multiple visual and written verifications, and incorporating additional imaging techniques to verify catheter placement.

Item Number 160185 (AO) - Spectrum Health reported that a patient received 3.28 GBq (88.65 mCi) of Y-90 microspheres (BTG International/Nordion model TheraSphere) to an incorrect segment of the liver. The patient had hepatocellular carcinoma and was prescribed to receive treatment to segments V, VI, VII, and VIII (right lobe) of the liver, with an estimated treatment volume of 1,290 ml. However, during treatment on 4/27/2016, the catheter moved (due to patient movement or breathing) and the microspheres were administered to a medial portion of segment IV (left lobe), with an estimated administered volume of 330 ml. The prescribed dose was 12,000 cGy (rad) to the segments in the right lobe, but segment IV received approximately 11,850 cGy (rad), as determined by post-administration Bremmstrahlung imaging. Segment IV was previously treated on 1/27/2016 and there was some residual cancer. The patient and referring physician were notified and the patient was rescheduled for treatment of segments V, VI, VII, and VIII at a later date. The administration procedure requires fluoroscopic imaging with a contrast agent immediately prior to connecting the microsphere treatment device to verify catheter position, but this step was not performed. No significant consequences to the patient are expected. Corrective actions included procedure modification to ensure that the catheter position is properly verified.

Item Number 150317 (AO) - Abbott Northwest Hospital (ANH) reported that a patient received 0.87 GBq (23.62 mCi) of Y-90 microspheres (BTG International/Nordion model TheraSphere) to the wrong lobe of the liver on 5/29/2015. The prescribed dose was 1 GBq (27 mCi) of Y-90 to the left lobe of the liver (segment 4) for a dose of 13,000 cGy (rad). However, the microspheres were unintentionally administered to the right lobe of the liver (segments 1, 5, 6, 7, and 8) for a dose of 4,370 cGy (rad). ANH was planning on treating the right lobe of the liver in the future. The patient and referring physician were notified of the event on 5/29/2015. The Minnesota Department of Health investigated the incident. The cause of the event was determined to be injecting the microspheres into the wrong artery. A contributing factor was the patient's small and similarly appearing vessels. Treatment will be given to the left lobe as originally planned. No adverse effect to the patient is anticipated. To prevent recurrence, ANH will have an image available from the panning angiogram with the vessels clearly labeled for reference during catheter placement for future treatments.

Item Number 140502 (AO) - University of Virginia (UVA) reported that a Y-90 microsphere (MDS Nordion model TheraSphere) treatment on 9/4/2014 resulted in doses to a patient's liver and lungs that differed from prescribed. The revised lung shunt fraction value was used to calculate the actual radiation dose to the lungs and LT liver lobe. Results revealed that the lungs received 3,450 cGy (rad), instead of the intended 370 cGy (rad). The LT liver lobe received 6,700 cGy (rad), instead of the prescribed 11,700 cGy (rad). The administered activity to the LT liver lobe was 821.4 MBq (22.2 mCi) and the lungs were administer 689.68 MBq (18.64 mCi). The patient was prescribed to receive a total of 1,499.61 MBq (40.53 mCi). The patient's family was notified. University staff investigated the root cause of the

incident. The Virginia Radioactive Materials Program (RMP) also investigated the incident. The cause was determined to be a liver to lung shunt from the left hepatic artery. The incident involved a complicated arteriovenous shunting pathway involving two shunts. The left hepatic artery was not assayed prior to treatment. Corrective actions included procedure modifications to determine the lung shunt fractions from both the left and right hepatic arteries. RMP requested that UVA hire an independent consultant to review the incident and corrective actions taken. The consultant agreed with corrective actions taken and had several recommendations. UVA saw the patient on 10/3, 10/7, and 10/24/14 and detected no symptoms of radiation pneumonitis or radiation lung injury. However, during the week of 2/2/2015, the patient was admitted to Lynchburg General with Acute Respiratory Distress Syndrome-like symptoms with lung infiltrates consistent with radiation pneumonitis. The patient required high oxygen and was very ill. The patient passed away over the following weekend; however, the cause of death and any potential association with the medical event are being evaluated.

Item Number 140147 (AO) - Emory University reported that a patient only received 0.8066 GBq (21.8 mCi) of Y-90 microspheres (BTG International/Nordion model TheraSphere, lot #4990036-36) to Segment IV of the left lobe of the liver instead of the prescribed 2 GBq (54.05 mCi) for an expected dose of 6,900 cGy (rad). Due to issues with hepatic arterial anatomy not previously anticipated, the medical team could not properly position the catheter. Because it was a bilateral disease that would eventually require the treatment of both lobes, they decided to move forward with the procedure. A post-delivery Bremsstrahlung scan revealed excellent coverage of Segment IV, with some minor coverage in the right lobe due to arterial anatomy. Approximately 0.81 GBq (21.8 mCi) was localized to Segment IV and 0.91 GBq (24.5 mCi) ended up in the right lobe. That resulted in doses of 2,783 and 3,128 cGy (rad), respectively. There was no significant extrahepatic activity seen. The authorized user intended to treat the right lobe next and the team reported that the treatment plan would be adjusted to take into account the diseased areas that were already treated. The patient and referring physician were notified. The event occurred due to an arterial aberration that caused the interventional radiologist to be unable to cannulate the artery. Corrective actions included requiring the authorized user to issue written directives to reflect the target organ as the entire liver versus a specific segment or lobe. They also instructed their medical team to require immediate notification of microspheres to extrahepatic organs above the acceptable levels of anticipated shunting.

Item Number 120096 (AO) - Intermountain Medical Center (IMC) reported that a patient prescribed to receive 5.31 GBq (143.6 mCi) of Y-90 microspheres (MDS Nordion model TheraSphere) for a treatment dose of 12,000 cGy (rad) to the right liver received another patient's dose. Two patients were at the IMC facility on 2/2/2012 to receive microspheres. The first patient received the second patient's intended dose of 1.77 GBq (47.8 mCi), for a delivered dose of 3,960 cGy (rad). Both patients' doses had been loaded into a shielded carrier, with patient specific markers (patients' initials) placed on each dose. At the time of the first patient's administration, the nuclear medicine technologist inadvertently selected the wrong microsphere vial. When IMC was preparing for the second patient's dose, the vial was surveyed and found to be much higher than anticipated. The error was identified prior to the second patient receiving treatment. IMC determined that the medical event would not have an effect on the first patient. Corrective actions included procedure modification to ensure patient identification, site being treated, dose to be administered, and correct identification on the dose vial prior to administration. The Utah Department of Environmental Quality, Division of Radiation Control, performed an onsite investigation.

Item Number 110402 (AO) - The University of Wisconsin (UOW) reported that a patient received 1.05 GBq (28.38 mCi) of Y-90 microspheres (MDS Nordion model TheraSphere) on 7/7/2011 to the wrong side of the liver as documented in the written directive. The patient was prescribed to receive 12,000 cGy (rad) using 1.04 GBq (28.11 mCi) to the left lobe of the liver for treatment of multinodlar hepatocellular cancer. A treatment plan was created for the left lobe, but during the procedure the right lobe was treated with the prescribed dose for the left lobe and received 4,180 cGy (rad). It was determined that the

interventional radiologist forgot about the conclusions to treat the patient's left lobe and completed the treatment to the right lobe. The error was not discovered until the patient returned to the facility on 8/8/2011. UOW determined that a double check of both the dose and the targeted organ should be performed in the interventional radiology procedure room. The Wisconsin Department of Health Services conducted an investigation on 8/12/2011.

Item Number 110133 (AO) - University of Michigan Hospital reported that a patient received a calculated dose of 15,940 cGy (rad) to the left lateral lobe of the liver instead of the prescribed 7,440 cGy (rad). An authorized user (AU) planned two liver infusion treatments for a patient with non-resectable hepatocellular carcinoma, using Y-90 microspheres (MDS Nordion model Therasphere). The first treatment to the right lobe and left medial segment of the patient's liver was successfully performed on 12/15/2010. The AU then ordered a 7,440 cGy (rad) dose to the left lateral lobe of the patient's liver. The medical physicist calculated a corresponding activity of 2.24 GBq (60.5 mCi) of Y-90 to be infused into the patient's left liver lobe. The treatment was performed on 3/9/2011. However, in determining the Y-90 activity needed, the physicist used the liver segment volumes for the right lobe and left medial segment instead of that for the left lateral lobe. Had the correct volume been used, the Y-90 activity would have been about one-third of that calculated. That error resulted in a dose of approximately 114.25% more than prescribed. The patient was notified of the event on 3/9/2011 and the physician was notified on 3/10/2011. No permanent medical damage to the patient's liver and no further loss of function is anticipated due to this event. This event was caused by inadequate communication between the prescribing physician and the medical physicist. Corrective actions included procedure modification to improve communication and documentation. The NRC contracted a medical consultant to review this event. The medical consultant concurred with the hospital's assessment.

Item Number 110052 (AO) - Eastern Regional Medical Center reported that a patient prescribed to receive 1.42 GBq (38.3 mCi) of Y-90 microspheres (MDS Nordion model TheraSphere) to the left lobe of the liver, received approximately 4.73 GBq (127.8 mCi) on 1/19/2011. As a result, the left lobe of the liver received 25,700 cGy (rad) instead of the intended 11,700 cGy (rad). The cause of the event was determined to be human error. There was a transcription error when preparing the order form. The error was not recognized upon receipt of the Y-90, because the received activity (as measured in a dose calibrator) was compared to the activity indicated on the order form rather than on the written directive. The Pennsylvania Department of Health conducted a reactive inspection on 1/25/2011. The incident may result in an increased risk of atrophy to the treated liver lobe. Corrective actions included generating a computer spreadsheet that populates fields based on initial calculations, written directive, order form, etc. In addition, several procedure modifications were implemented to ensure the correct dosage is ordered and received.

Item Number 100543 (AO) - Cleveland Clinic Foundation reported that a patient received dose to an unintended location during the administration of 3.959 GBq (107 mCi) of Y-90 microspheres (model TheraSphere) on 10/26/2010. Approximately three weeks prior to the treatment, the patient was scanned for extrahepatic shunting through injection of Tc-99m MAA into the hepatic artery. No shunting to the duodenum was identified during that test. A post-procedure scan for the Y-90 microsphere treatment identified significant activity in the duodenum. Initial estimates indicated that approximately 0.37 GBq (10 mCi), or about 10% of the microspheres, ended up in the duodenum. The estimated dose to the duodenum was calculated to be approximately 9,000 cGy (rad). The patient was hospitalized for observation and possible intervention as a result of dose to the duodenum. Some ulceration of the duodenum bulb was observed, but no evidence of perforation or bleeding was detected. The patient and referring physician were notified. Corrective actions included generating new procedures and modifying existing procedures.

Item Number 090732 (AO) - Greenville Hospital System reported that a therapy patient was administered 1.7 GBq (45.9 mCi) of Y-90 microspheres (MDS Nordion TheraSphere) instead of the intended 0.9398 GBq (25.4 mCi). The prescribed dose to the liver was 1,300 cGy (rad), but the delivered dose was 2,600 cGy (rad). The event occurred on 9/15/2009 during a procedure associated with a radioembolization brachytherapy treatment for liver cancer. The patient and the referring physician were notified on 9/17/2009. An investigation determined that errors occurred while preparing the treatment and while estimating the activity from the written directive. Upon medical follow-up, the patient had good tumor response with no adverse medical effects. Corrective actions included providing refresher training to involved staff members and procedure modification.

Appendix B
SIR-Spheres AO Events (11)

Recent events are marked as potential AOs until they complete the NRC's formal AO determination process and are reported in NUREG-0090, *Report to Congress on Abnormal Occurrences*.

Item Number 170034 (potential AO) - A medical facility in New York reported that a 61-year-old female patient received a medical misadministration on 12/29/2016, which involved liver treatment with Y-90 microspheres (Sirtex Medical model SIR-Spheres). The patient was prescribed an activity of 90.76 MBq (2.453 mCi) to a small lesion in her liver and 816.85 MBq (22.077 mCi) to a large lesion in her liver. Staff prepared two vials according to written directive and labeled each vial shield. They did not label the vials. During the first infusion of microspheres to the patient's small lesion, the technologist accidentally provided the vial that contained 816.85 MBq (22.077 mCi). The patient was administered those microspheres. When the second infusion of the patient's large lesion was requested, the same technologist determined that the vial that contained an activity of 90.76 MBq (2.453 mCi) remained unused. The misadministration was identified at that point. Medical personnel decided to infuse the large lesion with what was left in the first vial as well as what was in the second vial. The medical facility is investigating the administered radioactivity to each lesion. New York State Department of Health believes that a discrepancy meets reportable requirements. The medical facility implemented a requirement to perform a time-out prior to all treatments. The labeling requirements were revised to require that both the vial and vial shield be labeled. The labels will be read three times prior to administration. All pertinent staff received training on the revised protocols in January 2017.

Item Number 160284 (AO) - Medstar Georgetown Medical Center (MGMC) reported that a patient's written directive was not followed during a hepatic Y-90 microsphere treatment (Sirtex Medical model SIR-Spheres) administered on 5/19/2016. The error was discovered during a subsequent review of the patient's records in preparation for an additional hepatic treatment scheduled for 6/16/2016. The 5/19/2016 written directive prescribed radioembolization of the patient's right hepatic lobe with an activity of 1,076.7 MBq (29.1 mCi) for a dose of 3,213 cGy (rad). However, that treatment was delivered to the left hepatic lobe, during which stasis was reached after administering 868.76 MBq (23.48 mCi) and a resulting dose of 5,177 cGy (rad). During preparation for treatment of the left hepatic lobe on 6/16/2016, it was discovered that the 5/16/2016 treatment had been administered to the left lobe. The left hepatic lobe actually received 119.4% of the activity prescribed in the written directive scheduled for 6/16/2016, which listed 727.79 MBq (19.67 mCi) and a dose of 4,337 cGy (rad). The patient's right hepatic lobe was treated under a revised written directive on 6/16/2016. The patient was informed of this event on 7/5/2016. This event was caused by the failure to follow procedures. Procedure modifications were incorporated into the Radiation Medicine SIR-Sphere policy and each member of the team received instruction. MGMC tracked the event in their internal risk management system for further review and potential improvements to their program.

Item Number 150408 (AO) - University Hospitals of Cleveland (UHC) reported that a patient received 288.23 MBq (7.79 mCi) of Y-90 microspheres (Sirtex model SIR-Spheres) to the small bowel on 7/14/2015. The patient was prescribed to receive an activity of 758.5 MBq (20.5 mCi) to the right lobe of the liver for a dose of 7,800 cGy (rad). However, during administration the physician determined that the microspheres were not traveling to the liver and discontinued treatment. The small bowel received a dose of 3,600 cGy (rad). The involved physician was also the patient's referring physician. The patient was notified of the event. The patient experienced some abdominal pain approximately 3 weeks after the procedure. The patient was examined and admitted to a local hospital. A CT scan of the patient's abdomen and pelvis identified abnormal inflammation to a short segment of the small bowel, but no acute

perforation or ulcers. The patient was discharged, and the licensee spoke to the patient on 8/10/2015. At that time, the patient presented with some abdominal discomfort or pain, which was relieved by prescribed pain medications. The Ohio Bureau of Radiation Protection sent an inspector to the UHC facility to investigate. The cause of the medical event was determined to be that the fluoroscopy table may have been moved during the procedure, causing the microcatheter used to administer the Y-90 to change positions from the hepatic artery to the superior mesenteric artery. After the table and consequently the microcatheter were moved, a fluoroscopy of the patient was not performed, resulting in the licensee not identifying the relocated microcatheter in the patient's arteries before Y-90 SIR-Sphere administration. Corrective actions taken by UHC included procedure modifications and providing additional training to personnel.

Item Number 150326 (AO) - Riverside Medical Center (RMC) reported that a patient received 1.3 GBq (35.2 mCi) of Y-90 microspheres (Sirtex Medical model SIR-Spheres) to the wrong site during treatment of the liver for metastatic cancer lesions on 6/2/2015. When the patient was imaged immediately following the administration, the kidney was observed as the organ that had received the dose with no material evident in the liver. It was determined that the infusion catheter had been placed into the patient's renal artery, instead of the hepatic artery. This was the facility's first patient to undergo this treatment modality and the manufacturer's representative was present during the procedure. The patient was informed of the error and consented to a second dose of Y-90 microspheres, which was performed successfully. The patient was held overnight and routine collection and measurement of urine was performed prior to being discharged into the sewer system. Radioactivity was confirmed in the urine when measured with a GM counter near the surface of the container. No other contamination was noted in the patient's specially prepared room. The dose to the patient's liver was approximately 65 Gy (6,500 rad) from the second treatment. The dose to the patient's kidney from the misadministration was calculated by the manufacturer to be 1,345 Gy (134,500 rad). The patient was discharged the next day (6/3/2015) and received follow-up visits with the urologist and radiologist; no renal dysfunction or clinically significant radiation nephritis were observed. Corrective actions included developing a formal written checklist to be completed prior to each patient administration, having additional mapping imagines available for placement of the catheter, and a review of the catheter placement by a second physician prior to administration. The Illinois Emergency Management Agency investigated the incident.

Item Number 140249 (AO) - Cedars Sinai Medical Center (CSMC) reported that a patient received 1.59 GBq (43 mCi) of Y-90 microspheres (Sirtex model SIR-Spheres) on 4/30/2014, instead of the prescribed maximum dosage of 0.463 GBq (12.5 mCi). The event took place during the second phase of a liver treatment. The patient received 36,300 cGy (rad) instead of the intended maximum dose of 10,200 cGy (rad). An ambiguous written directive was misinterpreted by the radiopharmacist, who prepared an incorrect dosage. A delay in the arrival of the dosage, the fact that the patient was already anesthetized, and the patient's frail medical condition caused heightened stress and urgency to administer the dosage. This, combined with a vendor's inadequate implementation of a radiopharmaceutical software revision, resulted in the failure to follow all procedures and the defeat of normal checks and balances that should have identified the incorrect dosage. Both the patient and referring physician were notified. The patient has experienced no unintended medical effects due to this event, but will continue to be monitored. Corrective actions included procedure changes for creating written directives and scheduling patients, correcting the radiopharmaceutical software, and additional training for radiopharmacists and authorized users.

Item Number 140139 (AO) - Abington Memorial Hospital (AMH) reported that a patient treated with Y-90 microspheres (Sirtex model SIR-Spheres) received a dose to an unintended organ. On 8/15/2013, the patient was treated with 1,339.77 MBq (36.21 mCi) through the right hepatic artery with a prescribed dose of 10,700 cGy (rad). On 9/6/2013, the physician noted that the patient was experiencing intermittent abdominal pain. On 10/10/2013, the patient was administered 188.33 MBq (5.09 mCi) through the

proximal left hepatic artery and 179.45 MBq (4.85 mCi) through the distal left hepatic artery. On 2/24/2014, the patient was admitted due to severe anemia and suspected GI bleeding. On 2/27/2014, endoscopy revealed a duodenum lesion and an ulcer that had developed seemingly because of microspheres migrating to the stomach. A biopsy of the affected region revealed synthetic beads. It was determined that the synthetic beads were larger than normal microsphere size. The dose delivered to the liver was calculated to be 16,000 cGy (rad). The dose delivered to the stomach could not be determined, but a dose greater than 1,000 cGy (rad) is required for the pain and gastrointestinal bleeding experienced by the patient. The patient and referring physician were informed of this event. The cause of the incident was determined to be the migration of microspheres through an aberrant hepatic arterial vasculature supplying the stomach. To prevent recurrence, AMH reevaluated the microsphere procedure with the manufacturer's guidance. AMH and Pennsylvania Bureau of Radiation Protection (BRP) investigated the event.

Item Number 140094 (AO) - Cleveland Clinic Foundation (CCF) reported that a patient received dose to an unintended site during a procedure to treat liver metastases from colorectal cancer using Y-90 microspheres (Sirtex model SIR-Spheres) on 1/24/2014. The left liver lobe was treated as planned. The patient was also prescribed 925 MBq (25 mCi) to the right liver lobe for a dose of 47,670 cGy (rad) to the tumor and a resultant 1,297 cGy (rad) to the liver. The treatment to the right lobe was stopped when unanticipated shunting was identified (CCF used contrast between vial doses to verify proper delivery of the microspheres). The final activity delivered to the right lobe was 555 MBq (15 mCi) for a dose of 26,590 cGy (rad) to the tumor and 770 cGy (rad) to the liver. The shunting caused the duodenum to receive 21.46 MBq (0.58 mCi) for a dose of 1,100 cGy (rad). The referring physician and patient were notified of the incident on 1/24/2014. The patient is being monitored for the development of a duodenal ulcer. The licensee is treating the patient to minimize radiation damage to the duodenum and will continue to monitor the patient's condition. This event was caused by the development of collateral vessels around the tumor between the time of the initial patient treatment planning and delivery of the microspheres. The licensee was not able to identify the small change of vasculature with its routine checks at the time of the procedure. The Ohio Department of Health performed a reactive inspection on 2/20/2014. No corrective actions were taken for this event.

Item Number 130438 (AO) - Cleveland Clinic Foundation (CCF) reported that a patient received dose to the wrong organ during Y-90 microsphere (Sirtex model SIR-Sphere) treatment conducted on 5/9/2013. The patient complained of abdominal pain during treatment. The post-treatment scan was inconclusive regarding shunting to the stomach. The patient continued to complain of stomach pain and returned to CCF on 9/5/2013 for an endoscopy, which revealed ulcers in the potentially affected areas. The cause of this event was most likely the development of collateral vessels around the tumor between the time of the initial patient treatment planning and delivery of the Y-90 microspheres. CCF was not able to identify the small change of vasculature during routine checks at the time of the procedure. CCF determined that the gastric duodenum, an unintended treatment area, received 14.8 MBq (400 µCi) for a dose of 6,200 cGy (rad). The Ohio Department of Health conducted an onsite investigation on 10/8/2013. CCF was not cited for the incident.

Item Number 120103 (AO) - Abbott Northwestern Hospital reported that a patient received dose to unintended areas during a liver treatment on 2/2/2012 that involved 1.55 GBq (41.89 mCi) of Y-90 microspheres (Sirtex Medical model SIR-Spheres). The infusion procedure went according to plan. After accounting for normal loss within the delivery system, the final administered activity was 1.53 GBq (41.35 mCi). However, follow-up scans revealed that some of the microspheres were not in the liver. An investigation on 2/6/2012 determined that an estimated 10 to 15% of the microspheres were in the spleen, gastric fundus, and duodenum. The patient and the ordering physician were informed. Further investigation and SPECT CT imaging revealed that the liver received 83.9% of the administered activity for a dose of 53 Gy (5,300 rad), the gastric fundus received 5.8% of the administered activity for a dose of

44 Gy (4,400 rad), the spleen received 9.3% of the administered activity for a dose of 35 Gy (3,500 rad), and the duodenum received 1% of the administered activity for a dose of 35 Gy (3,500 rad). These dose estimates have uncertainties of at least 20% and local concentrations and doses may be significantly higher. Maximum concentrations per pixel in the SPECT images were as much as 50% higher than the average concentration. The Minnesota Department of Health (DOH) performed an onsite investigation on 2/6/2012. Abbott Northwestern's investigation was unable to identify any procedural failures or human errors that may have produced the event, but hypothesized that this may have been the result of temporary blood vessel contractions. This event may result in unintended permanent functional damage and some form of medical intervention is likely. The patient was administered the radio-protective pharmaceutical Amifostine and will be monitored weekly to determine the extent of damage to the unintended organs. The RSO will provide periodic updates regarding the status of the patient to DOH.

Item Number 120081 (AO) - Thomas Jefferson University Hospital (TJUH) reported that two patients received Y-90 microsphere (Sirtex Medical model SIR-Spheres) doses that were different than prescribed on 1/19/2012. Both patients were scheduled to be treated on the same day, close in time. The worksheets were switched and each patient received the other patient's dose. The first patient reached stasis before receiving the full amount and received a dose 35% above the prescribed dose. The first patient was administered 513 MBq (13.86 mCi) instead of the prescribed 381.1 MBq (10.3 mCi), for a dose of approximately 8000 cGy (rad). The second patient received 56% less than prescribed or 329.3 MBq (8.9 mCi) instead of the prescribed 751.1 MBq (20.3 mCi). The cause of the event was determined to be human error. To compensate, the second patient received a higher dose than planned during the next scheduled treatment. No adverse medical conditions are expected. Written procedures were developed and implemented to both minimize the chance of errors occurring in the microsphere dose preparation process and to identify/correct any such errors prior to administration. The Pennsylvania DEP conducted a reactive inspection.

Item Number 110144 (AO) - Abbott Northwestern Hospital reported that a Y-90 microsphere therapy patient was administered 1.66 GBq (44.82 mCi) instead of the intended 1.11 GBq (29.97 mCi) on 3/17/2011. This resulted in a dose to the liver of 4,610 cGy (rad) instead of the intended 3,080 cGy (rad). This event was discovered on 3/18/2011 when the radiation oncologist determined that the amount of Y-90 microspheres (Sirtex model SIR-Spheres) delivered was 150% of the prescribed dose rather than the intended 105%. An investigation determined that the medical physicist had not read the written directive correctly. Contributing factors to this error included difficulty discerning the prescribed activity on the written directive and the lack of a secondary check of the activity worksheet after manually transcribing the prescribed activity from the written directive. Corrective actions included implementing a new procedure, modifying the written directive to display the prescribed activity more clearly, and instituting a second check of the activity worksheet. The referring physicians and the patient were notified of this event. Because the patient's risk of radiation-induced liver disease slightly increased, she will receive follow-up testing to track her status.