Final Yttrium-90 Microsphere Brachytherapy Medical Events Analysis
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Charge: To investigate the apparent trend in medical events involving yttrium-90 (Y-90) microsphere brachytherapy over the past 6 years, including the greater rate of medical events with glass microspheres than with resin microspheres.

Introduction:
At the April 15-16, 2013 Spring Meeting of the Advisory Committee for the Medical Uses of Isotopes (ACMUI), a subcommittee was charged with investigating the apparent increase in medical events involving Y-90 microsphere brachytherapy.

Over the past several years, the use of yttrium-90 (Y-90) microsphere brachytherapy has grown in popularity as a treatment option for hepatic malignancies but has also experienced an increase in the number of reported medical events (MEs). The subcommittee has been asked to explore the apparent increase in MEs over the past few years and ascertain if the trend is real, and if real what might be the underlying causes. The subcommittee has been asked to compare the two existing commercially available systems (TheraSphere® glass microspheres (Nordion Inc.) and SIR-Spheres® resin microspheres (Sirtex Medical Limited)) for ease of use, potential design flaws, and related aspects that might explain the apparent trend.

To begin, we present a table provided by NRC staff:

FY	% Incidence TheraSphere®	% Incidence SIR-Spheres®	**Total % Incidence**
2007	2.34%	0.21%	0.53%
2008	unknown	Unknown	0.13%
2009	0.30%	0.17%	0.23%
2010	0.10%	0.08%	0.09%
2011	0.29%	0.13%	0.20%
2012	0.36%	0.18%	0.26%
TOTAL	0.29%	0.13%	0.26%

A few points and comments can be made about the data presented:

1. Aside from 2007, neither type of microsphere demonstrated a medical event rate exceeding 0.36% in any given year.

2. For TheraSphere®, the ME rate has gone from 0.10% to 0.29% to 0.36% during the interval from 2010-2012. During the same period, the ME rate for SIR-Spheres® has gone from 0.08% to 0.13% to 0.18%. Thus one might conclude that in the period from 2010 to 2012, there appears to be an upward trend in ME incidence for both glass and resin microspheres. However, when

including data available from 2007 and 2009, this upward trend appears questionable since 2007 was the highest year for both glass and resin microspheres.

3. For TheraSphere® glass microspheres, 2009, at 0.30% was essentially the same as 2011 at 0.29%; for SIR-Spheres resin microspheres, 2009, at 0.17% was essentially the same as 2012 at 0.18%. For both microspheres, 2007 demonstrated the highest ME rate on record. Specific data from 2008 were not available because the type of microsphere used was not provided in the event report in NRC's Nuclear Material Events Database (NMED).

4. Given the available data, it may be impossible to state with certainty that there is a statistically significant increased number of MEs during the past six years.

General observations:
Focusing on 2011-2012 (the two years in which there appeared to be an increased incidence of MEs compared to years prior and the years that largely have prompted this investigation), if one ignores the unenlightening miscalculations and wrong lobe injections, the vast majority of medical events were underdoses due to flow problems.

The causes of the flow problems were varied with no single cause predominating. This would appear to indicate a process that is complex and somewhat susceptible to error. The TheraSphere® process appears to fit this description, with many things required to go right for it to work properly. TheraSphere® employs an excellent checklist approach, without which one might speculate that there would be more MEs. The equipment is delicate, and perhaps not ideally designed, but to change any of it might require an FDA process. The SIR-Spheres® apparatus, however, is no more robust and one could argue that the set-up and procedure may be even more involved. It could be that with no assessment of residual activity for SIR-Spheres®, the users are unaware of problems. Alternatively, as SIR-Spheres® users are more accustomed to reaching stasis and stopping the procedure prematurely, this could also lead to users being unaware of technical problems.

Because SIR-Spheres® and TheraSphere® went through different FDA approval pathways, initially TheraSphere® was only used for primary liver cancer (hepatocellular carcinoma (HCC)). Now, like SIR-Spheres®, it is being used to treat colorectal (and other) hepatic metastases, which typically includes patients that have previously received chemotherapy and other treatments. The number of MEs reported prior to 2011 was nearly the same for each manufacturer; however, the discrepancy between the two is more pronounced in 2011 and 2012. The subcommittee is aware that up to two TheraSphere® vials can be used for one patient. Thus, mathematically, the TheraSphere® ME denominator has the potential to be up to half of the number provided by the manufacturers to NRC staff, which would thereby double the incidence rate of MEs and causes an even larger discrepancy for TheraSphere®. A substantial change in the numbers, however, is unlikely.

Specific observations:
There are challenging aspects of the TheraSphere® system, such as the clamp used on the delivery tube before the administration that crimps the line (often requiring re-rounding before delivery) and a somewhat complicated delivery apparatus. Much of the complexity in the device is there specifically to *prevent* problems during delivery.

Over the last two years, the most common problem was microsphere settling due to low flow rates. This has occasionally happened due to a crimped line, but not often. The reported reasons for the slow flow were:

* Low flow due to pause
* Clumping
* Leaking of priming line and reduced pressure
* Needles inserted at an angle
* Possible defective catheter
* Hemostat caused deformation of tube and limited flow
* Slow flush due to small arteries
* "Dose seemed harder to push"
* Low flow rate NOS
* Piece of septum within vial impeded flow
* Clamp not fully opened
* Stasis due to vascular spasm, small/fragile vessels slowed delivery or malfunction of delivery system

The question of training was raised in several of these MEs but the subcommittee is aware that training is often used as an explanation when other explanations are not found. It should again be noted that Nordion Inc. provides an excellent training program.

SIR-Spheres® likewise has a complicated delivery apparatus, with three-way stopcocks and switching between the delivery and flush/arteriogram modes. Their reasons for incomplete delivery in the past two years were:

* Occlusion of catheter due to microcatheter (catheters < 2.8 French)
* Procedure halted because of patient pain (this should not be listed as a ME)
* Slow delivery that led to settling
* Microspheres stuck to septum because the bottle was shipped upside down

For neither type of microsphere was simple stasis (which should not be reported as an ME anyway) an issue. There were typical human errors, such as wrong patient, wrong lobe or misread prescriptions with both devices.

In several cases (low flow due to pause; leaking of priming line and reduced pressure; hemostat-deformed tube and limited flow; low flow rate NOS; not using appropriately sized catheters), the licensees indicated that inadequate training might be at the root of the problem.

Regarding the microspheres sticking to the septum due to an inverted bottle during shipping, the vendor was made aware and has agreed not to ship them where microspheres could settle on the septum of the vial.

One subcommittee member pointed out that compared with a permanent implant prostate seed brachytherapy procedure or a high-dose-rate brachytherapy cervical treatment, Y-90 microsphere brachytherapy is no more complex nor patient-dependent. However, another subcommittee member has pointed out that the precision of microsphere brachytherapy dosimetry is severely limited by the fact that unlike macrobrachytherapy, this procedure (which is more akin to radiopharmaceutical therapy) suffers from gross imprecision and comparisons to macrobrachytherapy and external beam radiation therapy are meaningless. None of this dosimetric uncertainty has anything to do with the events. However, the technical aspects of Y-90 microsphere brachytherapy are also far more complex and involved than simple parenteral

radiopharmaceutical therapy. Y-90 microsphere brachytherapy is considered "manual brachytherapy" but is licensed under 10 Code of Federal Regulations (CFR) 35.1000.
In 2011, in addition to Authorized Users (AUs) with traditional 10 CFR 35.300 and 400 training and experience, interventional radiologists with appropriate training, education and experience became eligible to serve as AUs.

Conclusions:
In summary, the subcommittee was not able to conclusively identify an obvious root cause for the apparent trend towards the increased incidence of MEs with Y-90 microsphere brachytherapy nor was it obvious why one product has been involved in more MEs than the other. Recommendations such as different clamps and different syringes can be made, but the subcommittee is aware that making significant changes could entail a significant change in the overall approach. Such radical recommendations, which could potentially introduce additional failures, do not appear warranted at this time. It remains possible that the apparent trend is, in fact, simply a non-statistically significant deviation from background in a procedure that has a low baseline medical event rate. Another observation is that the particular MEs reported (mostly underdoses) have generally not had serious clinical consequences, especially in cases where repeat treatment has been offered to provide full final dose to the patients. Rather than being of major clinical significance, these MEs appear to be of the type that serves the purpose of alerting NRC of a possible trend that someday could become clinically important, and provoking action, as in the form of this report. The subcommittee will continue to monitor the reported events and make recommendations, as appropriate.

The ACMUI unanimously approved this report on June 18, 2013.