

ACMUI FINAL REPORT ON YTTRIUM-90 (Y-90) MICROSPHERE BRACHYTHERAPY MEDICAL EVENT CRITERIA

September 29, 2014

SUBCOMMITTEE MEMBERS

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CHARGE TO THE SUBCOMMITTEE

PROXIMATE CHARGE: To determine whether and under what conditions and circumstances deposition of intra-arterial Yttrium-90 (Y-90) microspheres in the gastrointestinal (GI) tract constitutes a medical event, specifically as regards notation of such prior expectation in the Authorized User's (AU) written directive. Attendant with this charge is the development of recommendations for any changes to current NRC Licensing Guidance for Microsphere Brachytherapy Sources and Devices (2008, Revised 2012)²³ to conform with current state of medical practice and to provide regulatory relief as needed.

EXPANDED CHARGE: At the discretion of the subcommittee, to determine whether any remediable constraints on authorized users unrelated to GI deposition of Y-90 microspheres are present in the NRC Regulatory Guidance with attendant recommendations for possible guidance change.

SUBCOMMITTEE PROCESS

The subcommittee and its Chair were appointed by ACMUI Chair, Bruce Thomadsen at the regularly scheduled ACMUI meeting, May 8-9, 2014. Discussions and deliberations were conducted by email and teleconference (June 24, 2014). This report has been approved unanimously by the ACMUI members of the subcommittee as of August 4, 2014.

SUMMARY OF SUBCOMMITTEE RECOMMENDATIONS

- **Specification of an “acceptable” GI tract and lung dose/activity in the written directive prior to performance of the Y-90 microsphere embolization procedure should NOT be required. Instead, a total treatment activity of Y-90 microspheres to be infused/administered should be the required compliance measure.**

- **GI irradiation from Y-90 microsphere brachytherapy should be considered a known risk of the procedure as it is in large part dependent on the practice of medicine, recognizing that**
 - **Pre-therapy assessment and/or preparation of the vascular embolic pathway has been accomplished to minimize or eliminate Y-90 microsphere passage to the GI tract in the judgment of the performing physician(s);**
 - **the placement of the infusion catheter tip at the time of Y-90 microsphere infusion is in alignment with the prior preparation;**
 - **once injected into the vascular pathway to the treatment target at the catheter tip, flow of the microsphere brachytherapy sources and their sites of final implantation are entirely dependent on the patient’s unique vascular anatomy and blood flow dynamics.**

- **Lung irradiation from Y-90 microsphere brachytherapy should also be considered a known risk of the procedure, recognizing that**
 - **Pre-therapy prediction of lung shunting of Y-90 microspheres is routinely assessed using Tc-99m MAA imaging**
 - **Based on that assessment, lung irradiation can be managed through clinical judgment by either titrating the total administered therapeutic activity to reduce lung doses or by not performing the procedure if the degree of shunted lung activity is unacceptably excessive. These determinations are largely based on currently established treatment guidelines.**
 - **Once injected into the vascular pathway to the treatment target at the catheter tip, flow of the microsphere brachytherapy sources and their sites of final implantation are entirely dependent on the degree of arteriovenous shunting to the lung.**
 - **In general, actual pre-therapy doses to the lung are not calculated nor are post-therapy doses recalculated.**

- **Implantation of the microsphere brachytherapy sources is considered to be in accordance with the written directive, if**
 - **The total administered/infused activity does not vary from the activity prescribed in the written directive by 20% or more;**
 - **Except in situations in which the activity administered is limited by termination of the procedure due to stasis.**

- **These recommendations should be incorporated into NRC guidance for Y-90 microsphere brachytherapy.**

- **The NRC staff, in consultation with ACMUI, compose and disseminate explanation of these recommended revisions in a manner best suited to both the NRC as well as to AUs and other stakeholders tasked with compliance.**

INTRODUCTION

Y-90 labeled microsphere brachytherapy, also known as “radioembolization”, has emerged over the past decade as a widely used, safe and efficacious therapeutic modality for palliation of inoperable liver malignancies, both primary and metastatic. While the overall complication rate of the procedure is low, radiation-related gastric and duodenal ulceration after Y-90 radioembolization has been reported as an adverse event.^{9,11,13} Because such GI complications are an uncommon, but well-documented side effect of the otherwise beneficial medical use of this procedure, ACMUI decided to examine pertinent issues related to these GI complications, to reassess the appropriateness of NRC guidance provided to Authorized Users (AU) for medical event reporting and to determine the possible need for regulatory relief.

A brief review of published incidence rates of this complication based on physician-directed clinical diagnostic criteria raises an issue regarding how these clinical occurrence rates can be reconciled with a relative paucity of GI tract-related medical events reported on NMED using the activity/dose-based criteria provided by NRC Y-90 Microsphere Brachytherapy Licensing Guidance (2008, rev. 2012). More specifically, are the current NRC dose/activity criteria based on concepts of conventional brachytherapy for reporting of GI-related “medical events” appropriate for a clinical procedure that differs in significant ways from conventional brachytherapy, that requires significant physician medical expertise and judgment, and which has evolved considerably since its introduction in 2000? If these criteria are not appropriate, should NRC guidance be revised to align with the realities of current procedure protocols, given considerable limitations in AU ability to accurately determine the information required to comply with this guidance?

In this respect, several targeted tasks were undertaken by the subcommittee. These are

- Review of current state-of-the-art performance of Y-90 microsphere brachytherapy techniques in relationship to gastrointestinal complications.
- Review of medical event reporting criteria for Y-90 microsphere brachytherapy guidance to evaluate guidance alignment with the unique procedural characteristics of intravascular brachytherapy, with particular consideration of non-target tissue irradiation, specifically the GI tract, but also the lung.
- Determine the need for updating Y-90 microsphere brachytherapy guidance and propose specific recommendations, if any.
- Consider whether NRC should provide an explicative communication regarding Y-90 microsphere brachytherapy guidance to assist stakeholder understanding and compliance.

In order to address these tasks, a targeted review of relevant peer-reviewed literature pertinent to current Y-90 intravascular brachytherapy practice, including dosimetry methodologies and procedure protocols, was performed in order to provide sufficient background for subcommittee deliberations, conclusions and recommendations.

BACKGROUND

Y-90 Microsphere Brachytherapy: Rationale

There are limited conventional options for treating inoperable primary and metastatic liver neoplasms. Selective Internal Radiation Therapy (SIRT) with Y-90 brachytherapy provides a method to deliver high absorbed radiation doses to intrahepatic neoplasms while sparing adjacent non-target tissues through the percutaneous intra-arterial injection of micron-sized embolic particles loaded with an appropriate radioisotope. Such regional therapy takes advantage of the dual blood supply of the liver in which blood flow to the normal liver is primarily through the portal vein, while blood flow to liver neoplasms, both primary and metastatic, is primarily through the hepatic artery. Thus, microspheres selectively injected into the hepatic artery circulation largely localize within the tumor, rather than in the normal liver. Although this procedure is not curative, it does offer patients with attenuated survival expectancies possible extension of quality life. Currently, two Y-90 labeled microsphere brachytherapy devices are clinically available, TheraSphere[®], (glass microspheres 20-30 microns in diameter containing Y-90) and SIR-Spheres[®] (biocompatible polymer microspheres, 20-60 microns in diameter, containing Y-90).

Y-90 Microsphere Brachytherapy: Procedure Principles

Y-90 microsphere embolization is considered brachytherapy because each labeled microsphere lodges within the microvasculature of neoplastic tissue. Thus positioned, adjacent to malignant cells, each microsphere brachytherapy source delivers a dose to those cells with which it is in apposition. This procedure differs from unsealed source radiopharmaceutical treatment because the radioactive material never leaves the delivery device (microspheres) and is not metabolized. This technique differs significantly from conventional brachytherapy in that once injected into the arterial bloodstream, the ultimate location of the individual microsphere sources cannot be guaranteed or precisely predicted. Only regional distribution of the microspheres can be attempted and this can be complicated by unforeseen changes or variations in the vascular pathway or blood flow dynamics during or after injection. Thus, the ultimate distribution of the injected microspheres depends entirely on the individual patient's unique vascular anatomy and attendant pathophysiologic circumstances as well as on pre-therapeutic interventional alteration of the vascular pathway. In some ways, intravascular brachytherapy presents as a brachytherapy analogue of unsealed source therapy in that both the placement of the therapeutic agent as well as the regional doses to normal and abnormal tissues can be approximated but not guaranteed even under the best of circumstances because of the significant dependence on the unique circumstances of each individual patient at the time of intravascular administration. Even with the best of pretreatment planning, once injected, the clinical success of the therapeutic agent is beyond control of the treating physician. Thus, there must be an appreciation of a procedural point at which the final location of the microsphere brachytherapy sources can be estimated, but not controlled. Dosimetry planning to predict post-therapeutic doses to both target and non-target tissues and organs when performing Y-90 intravascular brachytherapy is also challenging and variations from the predicted doses to target and non-target tissues and organs are to be expected.

Y-90 Microsphere Brachytherapy: Current Procedure Protocols

Current radioembolization protocols involve numerous steps aimed at maximizing treatment of the patient's intrahepatic tumor(s) and minimizing potential complications, including Y-90 microsphere accumulation in non-target tissues such as the lungs and gastrointestinal tract (Appendix A). The ACR-SIR-ASTRO Collaborative Practice Guideline for Radioembolization with Microsphere Brachytherapy Devices (RMBD) for Treatment of Liver Malignancies (2008) has established that an absolute contraindication to proceeding with treatment includes patients in whom: "Technetium-99m MAA hepatic arterial perfusion scintigraphy demonstrates significant reflux to the gastrointestinal organs that cannot be corrected by angiographic techniques such as embolization."¹ Thus, an important first step in evaluating a potential candidate for microsphere brachytherapy is a pre-treatment arteriogram to map the anatomy of the main

hepatic arteries as well as branch arteries which supply the stomach, duodenum and pancreas (especially the left gastric and gastroduodenal arteries) and to identify any variant or aberrant arteries supplying these structures.

Once the vessels supplying the GI tract have been identified, selective angiointerventional embolization is performed to occlude vessel origins near the intended injection site which otherwise may be prone to misdirect microsphere embolization to the GI tract and thus deliver undesirable radiation exposure to these areas.⁸ It should be noted that prophylactic embolization of vessels during mapping angiography may not be necessary in all cases.¹⁷ Rather, the degree of pretreatment embolization may be tailored based on the treating physician's experience, vessel size, planned treatment location, and radioembolic device being considered.

After GI vessel occlusion is performed, as a measure of safety, a pre-therapy imaging dosage of technetium-99 MAA is administered through the catheter to predict the distribution of Y-90 microspheres during actual treatment. The biodistribution of Tc-99m MAA is primarily used to estimate the magnitude of hepatopulmonary shunting (the lung "shunt fraction"). If lung shunting is detected, it cannot be corrected through angiointerventional techniques. Instead, lung irradiation can be managed either through appropriate titration of the total administered therapeutic activity or non-performance of the procedure if shunting is found to be unacceptably excessive. The biodistribution of Tc-99m MAA is also used to assess the success of the GI vessel occlusions and to detect any possible residual passage of microspheres into the GI tract. Although the Tc-99m MAA procedure can indicate the propensity for Y-90 microsphere accumulation in the GI tract, it does not provide a reliable estimate of GI tract dosimetry.

If, after this evaluation, a patient is found to be an appropriate candidate (no Tc-99m MAA in the GI tract and acceptable or manageable hepatopulmonary shunting), Y-90 brachytherapy is performed, usually one to three weeks later. At the time of treatment, diagnostic visceral angiography is repeated immediately prior to therapy to ensure the continued success of previously performed vascular occlusions and to check for any previously undetected collateral vessels to the GI tract. Any occlusive failures are re-occluded and any newly identified collateral vessels are occluded. Once the therapeutic team has determined that the vascular bed has properly prepared and that no significant GI deposition of microsphere is expected in the judgment of the treating physicians, the activity of Y-90 microspheres calculated to deliver a predetermined absorbed dose to the tumor site, normal liver and the lungs is then injected under fluoroscopic guidance. This may be followed by same-day post-treatment bremsstrahlung imaging, ideally using SPECT or SPECT/CT, to determine biodistribution of the treatment dosage. Newer techniques employing Y-90 PET imaging are also under-development.

Y-90 Microsphere Brachytherapy: Gastrointestinal Complications

Mechanisms. Current evidence indicates that radioembolization-associated gastroduodenal ulceration results from inadvertent delivery (sometimes referred to as “shunting”) of microspheres to the microvasculature of the gastrointestinal tract, leading to direct radiation toxicity, which may also lead to radiation-induced gastroduodenitis, gallbladder inflammation and pancreatitis. Ischemia (local tissue oxygen deprivation) related to arterial embolization does not appear to play a primary role.^{9,11} As opposed to microsphere deposition in the lungs which is caused by abnormal communication between the hepatic arterial and venous systems (“arteriovenous shunting”) primarily through abnormal vessels within the tumor, deposition of microspheres in the GI tract is due to antegrade (forward) arterial flow of the microspheres from the infusion catheter tip in the hepatic artery through normal or variant branch arteries supplying the stomach, duodenum and pancreas. Microsphere deposition in the GI tract also may result from reflux or retrograde (backward) flow from the catheter tip into known or unrecognized branch arteries supplying the GI tract secondary to unanticipated changes in flow dynamics in vessels supplying the GI tract (backflow). Further, with tumors in the periphery of the liver such that the lesion lies adjacent to the GI tract, the radiation can produce GI tract injury.

Dose-Response. Importantly, dose-response thresholds for the GI tract with respect to inflammatory response and ulceration are as yet undefined for Y-90 microsphere therapy. Once the post-exposure radiation inflammatory process is initiated, the likelihood of the development of frank ulceration is unpredictable and likely varies with the magnitude of the local absorbed dose of misdirected radiation as well as the underlying comorbidities and inherent defense mechanisms of the individual patient. Clinically, radiation-induced gastroduodenal ulceration cannot be definitively differentiated from symptomatic ulcers resulting from other etiologies. Most patients with postprocedure gastroduodenal ulceration present with abdominal pain, often associated with nausea, vomiting, and anorexia, and as with GI ulcerations in general, can be accompanied by significant bleeding. Symptoms may develop from hours to months after radioembolization and diagnosis can be difficult. When appearing early after treatment, symptoms may be mistaken for the more common and nonspecific “post embolization syndrome” which is thought to be due to acute hepatic radiation toxicity and/or intended tumor lysis.

Diagnosis/Treatment. The time from the completion of the procedure to ulcer diagnosis varies widely ranging from under 1 month to over 9 months (mean of 4 months). Definitive diagnosis is made by endoscopic biopsy and the identification of microspheres in the ulceration. Radiation-induced ulcers are difficult to treat. Current medical therapy based on acid suppression has had limited success, and the evidence for the addition of antioxidants and anti-

inflammatory agents is still sparse. Surgical resection of the affected tissue is necessary in some patients.

Incidence of Gastrointestinal Ulceration. Initial reports on the complications of Y-90 brachytherapy suggested an incidence of gastrointestinal tract ulceration averaging 8 to 12% and as high as 20%.^{7,12,20} The early variable incidence of complications is likely related to a steep learning curve among the physicians performing intravascular brachytherapy, evolutionary variations of performance protocols as well as ongoing advances and improvements in the techniques employed. In a 2010 meta-analysis review of collective early reports from 32 institutions, the overall incidence of ulceration ranged from 0.0% to 28.6% with a weighted mean incidence of between 2.9% and 4.8%.¹³ Other analyses have shown similar results.¹² However, meta-analyses based on these data are not without significant limitations as acknowledged by their authors. Naymagon et al state that “this is a crude calculation since the included studies are diverse, ranging from prospective trials to retrospective chart reviews, and a number of these studies were carried out at the same institution, making it highly probable that the data sets overlap.” Murthy et al. noted that “these results are skewed by reports with the highest incidence of ulcers being published in studies with a small number of patients suggesting a learning curve for the procedure coupled with the potential of duplication of the same patients with this complication in multiple publications by the same group.” Further, the data included by Murthy et al. were from studies performed in the early phases of Y-90 microsphere brachytherapy development (2000 to 2007), prior to the many advances and improvements in radioembolization techniques subsequently introduced, when physician experience was limited. As a result, these calculated incidences of gastroduodenal ulcers as a complication of Y-90 microsphere brachytherapy may represent overestimates compared with the current state-of-the-art environment.

Other factors also play a role in obscuring the true incidence of Y-90 microsphere induced GI ulcerations including difficulty in definitive diagnosis such that: symptoms must rise to a significant threshold to incur the expense and inconvenience of performing endoscopic biopsy, especially since there are no specific medical treatments for such ulcers; mild ulcerations may not be clinically significant and not trigger further investigation for diagnosis; the local absorbed dose threshold for initiating ulceration may vary from patient to patient as may the necessary local concentration and distribution of the Y-90 microspheres and thus, not correlate with the degree of microsphere shunting; and ulcerations due to other causes, such as stress, may be mistaken for radiation-induced lesions. Thus, the precise gastroduodenal ulceration incidence in the present practice environment is unknown.

What is clear is that current protocols demanding a meticulous attempt to define the arterial anatomy on preliminary angiography, followed by preemptive coil embolization of all collateral

arteries supplying the gastroduodenal region significantly decrease GI complication rates.⁹ In a large, multicenter retrospective analysis, no ulcers were reported in patients who underwent routine embolization of regional vessels supplying the GI tract, including the gastroduodenal artery and the right gastric artery.¹⁴ Overall training, careful patient selection, meticulous pre-treatment assessment, and embolization of relevant vasculature greatly reduce complication rates.¹⁷

Y-90 Microsphere Brachytherapy: Procedure Dosimetry with special reference to non-target tissue volumes such as the GI tract and Lung

Historically, dosimetry for intravascular radioisotope therapies has been largely dependent on empirical or semi-empirical methodologies and more recently on more individualized or “partition-based” algorithms. In principle, Y-90 radioembolization planned by current predictive individualized dosimetry is less subject to dose calculation uncertainties experienced by semi-empirical Y-90 activity methods, such as body surface area techniques, and aims to optimize treatment efficacy of tumor with acceptable toxicity to non-target organs such as normal liver, the lungs and GI tract. Pretreatment dosimetry, however, requires a diagnostic embolization trial using the Tc-99m MAA distribution as a reference for post-treatment dose distribution, classically determined by bremsstrahlung imaging.¹⁵ Technically, two of the biggest challenges in reconciling pre- and post-treatment dosimetry in Y-90 brachytherapy involve the accuracy of Tc-99m MAA perfusion for predicting Y-90 microsphere biodistribution and regional absorbed doses and the adequacy of bremsstrahlung imaging for delineating post-therapeutic biodistribution.

Tc-99m MAA Imaging (Pre-Treatment Dosimetry). Centers performing radioembolization use the distribution of 99mTc-MAA to calculate the lung shunt fraction and to detect any extrahepatic deposition of activity. However, Tc-99m MAA is an imperfect surrogate for Y-90 microspheres.²² Due to physical and technical differences between Tc-99m MAA and Y-90 microspheres such as particle size, specific gravity, injected particle load, microembolization, tumor histopathology, tumor load, physiologic variances in hepatic blood flow and catheter placement, Tc-99m MAA can never exactly predict the post-procedure biodistribution of Y-90 microspheres. Therefore, predictive dosimetry simulated by Tc-99m MAA provides only a rough estimate of the tissue absorbed doses intended.⁵ Thus, calculated dose delivery and actual dose delivery may differ significantly despite the best efforts of the individuals planning and performing the therapeutic procedure.

Bremsstrahlung Imaging (Post-Treatment Dosimetry). Using bremsstrahlung imaging to map Y-90 microsphere biodistributions is also problematic.^{5,6} The microsphere biodistribution within the target arterial territory is dependent on the locoregional flow environment distal to the point of injection. This in turn is influenced by a myriad of inter-related biophysical variables

such as the catheter tip cross-sectional spatial location, injection rate and timing interval, proximity to branching daughter vessels, extent of shunting, cardiovascular status, particle load, timing with respect to the most recent use of contrast medium and microembolization.^{6,10} Such complexity means that technical success cannot be assumed without some form of post therapy imaging, which is accomplished with Y-90 bremsstrahlung imaging. Bremsstrahlung imaging, however, suffers from poor spatial resolution and provides only a crude representation of the microsphere biodistribution. While initially performed only with planar gamma camera imaging, in recent years single-photon emission computed tomography with integrated computed tomography (SPECT/CT) has been the modality-of-choice for post-radioembolization microsphere imaging.^{16,18} Even when SPECT/CT is performed qualitative assessment of activity within small tumors or low-activity non-target locations, such as the GI tract, is often suboptimal, unreliable, and misleading. Quantitative bremsstrahlung SPECT/CT also is inaccurate despite compensation techniques for attenuation, scatter, and collimator-detector response, rendering it unsuitable for dose-response analysis. Adequate sophisticated algorithms for scatter correction are not yet commercially available.³ PET/CT may facilitate more accurate quantification in the future based on improved spatial resolution, but is also not currently widely in use for this purpose.⁵

SUBCOMMITTEE FINDINGS, CONCLUSIONS AND RECOMMENDATIONS:

At the present time the precise incidence of gastroduodenal irradiation during Y-90 microsphere brachytherapy for intrahepatic neoplasms is not known and recent assessments of a Y-90 microsphere radiation-related gastroduodenal ulcer complication rates have limitations. While it is accepted that GI tract irradiation during Y-90 microsphere brachytherapy can cause gastroduodenal ulceration, there is no established dose-response correlation between the threshold criterion for GI tract dose/activity regulatory reporting and the occurrence of GI tract ulcerations. Consequently, a determination regarding under-reporting of such events cannot be made. In addition, the NRC does not require the reporting of GI ulcerations per se, thus, those occurring at dose/activity levels below the regulatory threshold for reportable events do not come to the attention of the NRC. Likewise, there are no data regarding the incidence of ulcerations in patients whose GI tract doses or activity exceed the regulatory reporting threshold. Further, while pre-therapy prediction of lung shunting of Y-90 microspheres is routinely assessed using Tc-99m MAA imaging, this prediction is used by the treating team to make a medical judgment on whether or not to administer the therapeutic activity and/or how to minimize lung dose if this therapy is administered. In general, actual pre-therapy doses to the lung are not calculated, nor are post-therapy doses recalculated. Thus, it is uncertain whether current guidance based largely on conventional brachytherapy principles and

procedures appropriately addresses the issues of GI and lung irradiation as medical events related to Y-90 microsphere brachytherapy.

Perhaps more important than the frequency with which GI or lung medical events during Y-90 microsphere brachytherapy are reported in accordance with current guidance, is whether the medical event reporting criteria in current guidance are appropriately aligned with current state-of-the-art performance of Y-90 microsphere brachytherapy, such that AU compliance is straightforward and not a potential impediment to reporting. The subcommittee consensus is that current guidance is not in alignment with the unique characteristics of intravascular radioembolic methodology and practice and could be improved. In this respect, the subcommittee deliberated the underlying issues in an attempt to arrive at reasonable conclusions and make recommendations that would serve to protect patients and preserve patient access to a valuable treatment and at the same time provide regulatory guidance to AUs that takes into account the present realities of the procedure and may provide regulatory compliance relief from any current inconsistencies. As a result the subcommittee examined current guidance with these issues in mind and arrived at the following conclusions and recommendations.

NRC Licensing Guidance, Microsphere Brachytherapy Sources and Devices, revised June 2012 states:

- (1) “The written directive should specify the maximum dose(s)/activity(ies) that would be acceptable to the specified site(s) outside the primary treatment site due to shunting (e.g. lung and gastrointestinal tract)”, and
- (2) “The licensee shall commit to report any event, except for an event that results from intervention of a patient or human research subject, in which: the administration of Y-90 microspheres results in a dose to an organ or tissue other than the treatment site that exceeds by 0.5 Sv (50 rem) to an organ or tissue and by 50 percent or more of the prescribed dose/activity expected to that site from the administration of Y-90 microspheres, if carried out as specified in the written directive.”

These requirements present several limitations in the setting of Y-90 brachytherapy using intravascular microspheres which include:

- (1) The requirement to specify an “acceptable” dose/activity to the GI tract in the written directive has no clinically relevant or consensus-derived benchmark. And,

the assessment of lung irradiation is used as part of the physician's medical judgment whether and how to administer this therapy.

- *A requirement to determine an acceptable pre-treatment dose or activity in the written directive has no established basis in a treatment scenario in which dose-response thresholds are unknown.*

Normal tissue radiation dose thresholds for Y-90 microspheres shunted to non-target viscera such as the stomach or duodenum are largely unknown, precluding informed decision-making regarding clinically acceptable doses/activity. This leads to considerable limitations for AUs wishing to comply with "acceptable" dose/activity predictions. Thus, even if an accurate pre-therapeutic dose could be calculated or estimated, it is not possible to predict its effects on an individual patient's GI tract.

- *A requirement to determine a pre-treatment dose to or activity in the GI tract or lung in the written directive is inconsistent with current medical practice guidelines addressing parameters of performance of Y-90 intravascular brachytherapy.*

Unlike manufacturer and general medical community consensus limits for absorbed dose thresholds to the lungs from shunting of Y-90 microspheres, no such accepted limits exist for Y-90 microsphere dose thresholds to the gastrointestinal tract. Current collaborative clinical guidelines and procedure protocols state that any significant dose to the GI tract should be unacceptable and that vascular pathways from the Y-90 microsphere delivery site (catheter tip) to the GI tract which have a high probability of delivery of microspheres to the GI tract should be eliminated through angiointerventional occlusion. If significant "shunting" of Y-90 microspheres to the GI tract is predicted by way of focal accumulation of technetium 99m MAA imaging, and this "shunting" cannot be resolved by offending vessel occlusion, the procedure should not be performed, except under extraordinary circumstances, usually determined by patient-physician risk-benefit consultation.

- (2) Under current reporting criteria in Y-90 microsphere licensing guidance²³, a reportable medical event occurs when there is a discrepancy exceeding certain thresholds between an acceptable dose/activity to a specified site outside the primary treatment site, in this case the GI tract or lung, as specified in the written directive, and the dose/activity actually delivered to the GI tract or lung. This requirement is problematic, however, when the limitations of current technologies and methodologies are considered.

- *A requirement for determination of pre- and post-treatment absorbed doses to the GI tract or lung is technically challenging even under the best of circumstances.* Predictions of precise GI tract and lung doses, especially bowel doses, simulated by Tc-99m MAA deposition are subject to variable accuracy due to limitations in the physical characteristics of MAA and its imaging, inaccuracies in non-target tissue volume determinations, and imperfections in dose calculations to the GI tract employing commonly used dosimetric methods. Furthermore, since post-therapy GI and lung dose determinations by Y-90 bremsstrahlung imaging are also problematic depending on the imaging modality employed, there would seem to be little value in comparing two problematic doses/activities (pre- and post-treatment doses/activities) to define a variation constituting a medical event.
- *A requirement to determine discrepancies between pre-therapeutic estimated acceptable activities/doses and estimated post-therapy doses to the GI tract and lung is after the fact and not meaningful to the technical success of the procedure. Further such calculations are not a routine part of procedure performance.* Treatment teams follow detailed protocols for prophylactic modification of the vascular pathway to the GI tract as well as established guidelines to mitigate lung doses due to angiointerventionally uncorrectable shunting. Once these strategies are implemented and the pre-determined activity of Y-90 microsphere devices is successfully injected according to the written directive, *such discrepancies are related to unexpected and unintended intravascular flow dynamics beyond the control of the AU and/or treatment team.*

Thus, determining what constitutes expected or acceptable Y-90 depositions in and consequently doses to the GI tract is problematic and raises doubt that the current guidance is being or can be appropriately utilized by AUs.

Given these reservations concerning the current guidance as well as the consensus of the subcommittee that (1) GI shunting represents a well-recognized risk of a very complex medical procedure which may occur in spite of comprehensive pre-procedural prophylactic maneuvers performed by and dependent upon the medical judgment of the AU and/or treatment team to eliminate or minimize it; and (2) as such, should be viewed as an unpredictable complication attendant to the otherwise acceptable practice of medicine. The question arises as to what should be considered an acceptable technical end-point to the procedure such that deposition

of Y-90 microspheres in the GI tract is classified as a known clinical complication, rather than as a reportable medical event?

In arriving at a proposed answer to this question, the following elements of the procedure were considered pivotal:

- Current treatment planning and pre-administration maneuvers to mitigate non-target distribution of Y-90 microspheres in the GI tract represent considerable due diligence for patient protection on the part of physicians performing this Y-90 microsphere embolization. At that point, the most appropriate site (administering catheter tip position) for safe and effective intravascular “implantation” of Y-90 microspheres to accomplish the pre-determined therapeutic plan has been determined. Once intravascular “implantation” is performed in accordance with the written directive, the ultimate location and distribution of the Y-90 microsphere brachytherapy sources is determined by individual patient intravascular flow dynamics.
- There is ample documentation in the peer-reviewed literature that current techniques have greatly reduced, and in some cases eliminated, serious GI complications such as gastroduodenal ulcerations in all but the most unexpected circumstances. Thus, it is not unreasonable to conclude that GI shunting should simply be considered a consequence of best medical efforts to prevent any shunting at all.
- Current consensus-derived procedure protocols dictate elimination of identified pathways of Y-90 microsphere passage to the GI tract and that significant reflux to the gastrointestinal organs that cannot be corrected by angiographic techniques be considered a contraindication to treatment. Once eradication of such pathways has been accomplished in the sole judgment of the interventional radiologist, and the Y-90 microsphere are infused into the intravascular space, the remainder of the procedure is dependent on unpredictable factors, including unexpected reflux of microspheres with retrograde flow into vessels supplying the GI tract, or antegrade flow through previously unidentified vessels. These situations can neither be predicted nor controlled, are known risks of the procedure made evident to the patient during informed consent, and are rightly considered elements of the practice of medicine.

In consideration of the foregoing, the conclusion of the subcommittee is that current Y-90 microsphere brachytherapy guidance be revised such that (1) only a specified total treatment activity (without reference to the GI tract activity) be required in the written directive; and (2) an acceptable implantation of Y-90 microspheres with respect to GI deposition occurs when the specified Y-90 microsphere total treatment activity enter the intravascular space at the catheter tip in accordance with the written directive.

Finally, given the impression of the subcommittee that the current NRC Y-90 microsphere brachytherapy guidance has been confusing to some AUs and to stakeholders, the subcommittee strongly recommends that NRC should provide an explicative communication regarding guidance and guidance revisions to assist understanding and compliance. Staff should determine the best vehicles to employ, but a Regulatory Issue Summary (RIS) and other methods of communication should be considered.

The report was unanimously approved by the ACMUI on September 29, 2014.

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Appendix A

Sample Y-90 Microsphere Brachytherapy Protocol⁸

