



SIR-Spheres[®]

Training Program

Physicians and Institutions

SIRTEX MEDICAL LIMITED
PO Box 760, North Ryde NSW 1670
Australia

Tel: +61 2 9936 1400
Fax: +61 2 9936 1404

SIRTEX MEDICAL Inc
1401 N. Western Ave
Lake Forest, Illinois 60045
USA

Tel: +1 847 482 9023
Fax: +1 847 234 2115

www.sirtex.com
Email: sirtex@sirtex.com

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OVERVIEW

The purpose of this training program from Sirtex Medical (Sirtex) is to prepare users for practical training. Practical training and assessment is discipline specific. This program provides data on:

- Requirements for personnel and facilities.
- Product
- Clinical properties and use of the device, including patient selection and dosimetry.
- Calculation and preparation of individual radiation doses.
- Implant procedures, potential post-op reactions and suggested management.
- Radiation safety
- Product ordering

The training program is predicated on the demonstrated expertise of the participants entering the program. As such, the program is provided for physicians in a position to use or recommend SIR-Spheres microspheres clinically, appropriately licensed personnel who prepare patient doses of radiation and radiation safety officers responsible for radiation issues in institutions and treatment centers. For these practitioners, this training program utilizes existing knowledge and experience in radioactive implant therapy and the application of their background to the specifics of this particular device.

Additional data is provided for nurses and ancillary healthcare workers involved in the process, such as|

- Patient nursing care
- Implantation room set-up

Note to U.S. Physicians: Some of the use of SIR-Spheres discussed herein has not been approved by the Food and Drug Administration and is provided to U.S. physicians for educational purposes only. Your attention is directed to the U.S. prescribing information for SIR-Spheres which may be obtained from the Sirtex Medical office, any member of staff or from the website at www.sirtex.com .

FACILITIES

SIR-Spheres microspheres are only available to facilities appropriately approved for handling of therapeutic levels of radioactivity for medical use, or for handling of brachytherapy devices. Such facilities are licensed in the USA under the provisions of the Nuclear Regulatory Commission, as per Title 10 of the Code of Federal Regulations Part 35. Licenses must be appropriate to cover the process.

In other jurisdictions, the relevant Euratoms in the EEC and Radiation Regulations in various other localities apply.

SIR-SPHERES MICROSPHERES PRODUCT INFORMATION

1.1 Structure & Function

1.1.1 *Physical Characteristics*

SIR-Spheres microspheres consists of biocompatible microspheres designed to be between 20-60 μ m (microns) in diameter, containing yttrium-90, a high-energy pure beta emitting isotope with no primary gamma emission. The upper size limit of the microspheres allows delivery to the tumors via the hepatic artery. The lower size limit prevents the microspheres passing from the arterial circulation, through the tumor vasculature and into the venous circulation. The microspheres remain trapped within the vasculature of the tumors and deliver a radiation dose to the surrounding tissue. The microspheres do not degrade and remain permanently implanted. They are not retrievable unless the tumor is resected at a later stage. The microspheres are biocompatible but have demonstrated a mild dermal sensitivity in an animal model. This has not been demonstrated in humans.

The microspheres are supplied for single patient use with an activity of 3GBq \pm 10% at the calibration time and date. SIR-Spheres microspheres are suspended in pyrogen free water for injection to a total of ~5ml per 3GBq. This allows the activity required for implantation into individual patients to be measured as a volume. The device is supplied with a decay graph to allow for estimation of the remaining activity of the product on arrival. This should be separately verified. The device forms a suspension of microspheres in the water for injection. Each device is moist heat sterilized and single use only.

SIR-Spheres microspheres are 3GBq (\pm 10%) of activity as a single dose device from which the individual patient dose is calculated and drawn. The activity of the microspheres, rather than their weight or volume, determines the number of microspheres delivered to any individual patient. The total radiation required by a patient is dependent on the extent of tumor tissue and is at the discretion of the treating physician.

1.1.2 *Properties*

Yttrium-90 is a pure beta emitting isotope. The properties are:

Half-life 64.1 hours

Energy of beta particles:

Maximum	2.27MeV
Mean	0.93MeV

Range:

Maximum in air	9621mm
Maximum in tissue	11mm
Mean in air	3724mm

Mean in tissue 2.5mm

Effective treatment time when isotope is applied to infinity = 92.4 hours

In a therapeutic application of decay to infinity, 94% of the radiation dose is delivered in 11 days

Fractional Bremsstrahlung yield:

At maximal energy (2.27MeV)

In air	0.0089
In water	0.0081
In bone	0.0110

At mean energy (0.93MeV)

In air	0.0037
In water	0.0034
In bone	0.0043

The fractional Bremsstrahlung yield may be roughly estimated from the following formula:

$$f = \frac{E_T \cdot Z}{3000}$$

where f = fractional Bremsstrahlung
 Z = atomic number
 E_T = transitional energy of the beta particles

1.2 Calibration

SIR-Spheres microspheres are intended for use on the day of calibration. At the date and time of calibration, the activity in the vial matches the activity printed on the label (3GBq ±10%). The microspheres may be used for up to 24 hours after calibration. Beyond 24 hours, the number of microspheres required to provide sufficient activity increases by approximately 30% and this may exceed the vascular capacity of the tumors in some patients.

Calibration for the day of use means that the microspheres will be more active on arrival at the treatment centre, particularly if they arrive the day before. Microspheres are typically manufactured from 45 to 48 hours before calibration to allow time for shipping. The calibration time, date and reference time zone is on the label.

The time zones for labeling include New York (east coast) time for the USA, Greenwich Mean Time for Europe and Sydney (east coast) times for the Asia/Pacific area. This means, for example, that in the USA, a device labeled as 3GBq at 1800 hours New York time will be at 3GBq at 1700 hours in

Chicago, 1600 hours in Denver, and 1500 hours in Los Angeles. These time adjustments need to be made when calculating the activity of SIR-Spheres microspheres and preparing patient doses.

SIR-Spheres microspheres are not recommended for implantation before calibration time and date.

1.3 Regulation

SIR-Spheres microspheres are regulated and approved in all major markets (USA, EU and Australia) by therapeutic goods legislation as a **medical device**. The product is classified in the USA as a Class III product, and in EU and Australia as an AIMD (Active Implantable Medical Device). Copies of all certification may be obtained upon request.

See Section 8.1 of this manual for information on radiation regulation.

1.4 How to Order SIR-Spheres Microspheres

1.4.1 Certification

SIR-Spheres microspheres are used in restricted medical institutions that hold the appropriate license to handle SIR-Spheres microspheres. These institutions have radiation safety officers trained in radiation safety issues and authorized users trained specifically in the principles and use of SIR-Spheres microspheres. Individual patient doses of SIR-Spheres microspheres may be prepared at the medical institution or at a licensed nuclear pharmacy. These facilities also have appropriately licensed personnel trained in the preparation of doses of SIR-Spheres microspheres.

1.4.2 Ordering

SIR-Spheres microspheres are provided on an individual patient order basis. This requires the order to be placed in advance of anticipated need. Typically 7 to 10 days should be allowed between placing an order and availability of the SIR-Spheres microspheres.

Ordering can be done via fax to the company or via email, once a treatment centre or individual doctor has been certified and an account established.

Delivery can only be made to licensed premises with an authorized user of SIR-Spheres microspheres. SIR-Spheres microspheres is only available from Sirtex or its authorized distributors. More detail on licensing is available in Chapter 8, Section 8.4.1 of this document.

SIR-Spheres microspheres are being monitored in clinical practice by post-market vigilance. Post marketing data, incident reports or complaints may be supplied to Sirtex at any time, via direct contact, telephone or electronic contact.

SELECTIVE INTERNAL RADIATION THERAPY (SIRT)

1.5 Principles of Therapy With Yttrium-90 Microspheres

SIR-Spheres microspheres are radioactive microspheres. The intended use of these microspheres is to implant them into malignant hepatic tumors via a catheter placed into the hepatic artery. The microspheres lodge preferentially within the vasculature of liver tumors, with minimal amounts lodging in the normal liver parenchyma and smaller amounts again distributing to other organs, particularly the lung. The microspheres, when implanted into the liver tumors, deliver tumoricidal doses of radiation.

SIR-Spheres microspheres exploit the dominance of hepatic arterial blood flow to tumor tissue. Hepatic tissue receives the majority of blood flow from the portal vein, with very little from the hepatic artery. Conversely, flow to tumor tissue is almost exclusively from the hepatic artery. By placing the microspheres via the hepatic artery, they are preferentially delivered to tumor tissue while sparing healthy tissue.

The vascularity of small tumors tends to be uniform, but as tumor size increases, the blood supply predominantly services the actively growing rim of the tumor, with the centre becoming a necrotic core of predominantly avascular tissue. The microspheres will distribute to the actively growing rim and provide radiation with an average range of 2.5mm. This will irradiate the majority of viable cells in the identified tumor and micro-infiltrations in the tissue immediately adjacent to the tumor. There will be minimal radiation to the core of large tumors, hence the inability to ensure complete tumor cell death. The core may harbor viable cells despite the necrosis.

1.6 Clinical experience

Over 2,000 people have now been treated with SIR-Spheres microspheres at 84 locations in 11 countries across the globe. The largest treating countries are the USA, Australia, New Zealand, and Hong Kong, with treatment experience rapidly growing in Germany, Spain and the UK. Treatment has been predominantly for liver metastases derived from Colorectal Cancer in Western Countries and for Hepato-Cellular Carcinoma in the Asian countries.

1.7 Patient Selection

1.7.1 Assessment Criteria Summary

Patient selection is critical to providing a benefit with acceptable risk. SIR-Spheres microspheres should only be used for patients with liver cancer not suitable for surgical resection with curative intent. In addition, the liver should be the dominant site of disease, as SIR-Spheres microspheres provide regional treatment. Patients will also require detailed assessment before considering

treatment to ensure that the microspheres will be delivered to the tumor in sufficient doses to treat the tumor, while sparing the normal liver and other organs unacceptable radiation doses.

Assessment consists of determination of:

- resectability
- extent of disease in the liver
- presence and extent of extra-hepatic disease
- hepatic vascular anatomy
- arteriovenous shunting
- liver function
- renal function (if chemotherapy is proposed)
- general ability of the patient to tolerate implanted radiation.

As many of these assessments are radiological, most units treating patients with SIR-Spheres microspheres prefer to perform a preliminary radiological work-up including:

- hepatic angiogram
- combined angiogram/CTA scan
- embolisation of the gastro-duodenal or other artery that might result in inadvertent delivery of SIR-Spheres microspheres, and
- MAA nuclear medicine SPECT scan.

This allows proper planning for the delivery of SIR-Spheres microspheres at the scheduled time.

1.7.2 *General*

In addition to the specialized assessments outlined, patients should be assessed for general well-being.

Routine liver function, renal and hematological testing is normally performed as part of the monitoring protocol for any ongoing chemotherapy. Baseline measurements are generally required to assess toxicity. These general markers also indicate overall health status and the patient's potential to tolerate radiation treatment.

The patient should be generally well and considered fit to undertake radiation therapy. Patients unwell from their cancer, concurrent chemotherapy or other non-malignant disease may not tolerate radiation therapy.

1.7.3 *Hepatic Vascular abnormalities*

The most common vasculature abnormalities are discussed in Chapter 5 of this document.

1.7.4 *Arteriovenous Shunting*

A feature of the neoplastic vasculature within tumors is the formation of arteriovenous anastomoses or shunts. Such shunts are more common in primary liver tumors than in metastatic disease from large bowel; however, there will always be a degree of shunting or breakthrough from the arteriolar to the venous circulation. Shunts allow microspheres to directly enter the venous return by bypassing the terminal arterioles in the tumor. This will deposit the shunted microspheres into the lung, resulting in potential radiation damage.

At low levels, the amount of radiation shunted to the lung is clinically benign and acceptable in relation to the potential benefit in any given patient. The degree of shunting to the lung must be assessed before considering use of SIR-Spheres microspheres. The determination of the amount of radiation that will shunt to the lung may require that there be a modification to the radiation implanted and, at a certain level, precludes use of SIR-Spheres microspheres. Patients with >20% pulmonary shunting should not be treated. See Table in Section 4.3 of this document for further information.

Radiation damage to the lung is cumulative. Repeated use of SIR-Spheres microspheres may lead to radiation pneumonitis. This is particularly likely with large doses of radiation to primary tumors, which generally have greater lung shunting than metastatic tumors.

The percentage of shunting to the lungs is determined from a nuclear medicine scan using technetium-99m labeled on macroaggregated albumin (99m TC-MAA) for imaging. The Tc-MAA is injected via catheter placed in a similar manner to that which will be used to deliver the SIR-Spheres microspheres, that is, either a trans-femoral catheter or surgically implanted catheter plus port placed into the hepatic artery at the time of the pre-treatment angiogram. The patient is positioned under a gamma camera and the regions of interest are defined as the liver and lungs. The activity of MAA particles that pass through the liver and lodge in the lungs can then be calculated.

The amount of MAA that has escaped through the liver and lodged in the lungs can then be expressed as the percent lung shunting. Normally this is less than 10% in patients with metastatic disease arising from the colon or rectum. If the percent lung shunting is more than 10% then the amount of SIR-Spheres microspheres delivered to the patient must be reduced.

The technique for performing a nuclear medicine breakthrough scan is in Appendix 1 of this document.

1.7.5 *Hepatic and Renal Status*

While accepting that patients are likely to have abnormalities in their hepatic function as a result of their disease, the liver must be sufficiently robust to tolerate radiation treatment. Patients need to have adequate liver function as reflected by a normal serum albumin and clotting factors, together with a normal bilirubin. Radiation treatment to the liver will result in further short-term abnormalities in liver function, in particular transient, but possibly significant, increases in alkaline phosphatase (AP) and aspartate transaminase (AST). These abnormalities should subside within a few weeks. Continued monitoring of liver function tests is recommended to determine the outcome of treatment. This includes monitoring for stabilization in liver function tests due to control of disease, as well as

monitoring for continued disturbances that may indicate absence of patient benefit or treatment related toxicity.

Renal status must be adequate to accommodate any concurrent chemotherapy that may be administered as part of the treatment plan.

1.8 General Recommendations from Assessments

Patients in whom the liver tumors are resectable should not receive SIR-Spheres microspheres. Exceptions to this include patients with disease elsewhere, such as the lung, in which case resection is not for cure and would not generally be of benefit. In such patients, the liver cancer should be the significant site of disease and represent the most immediate life-threatening event. The use of SIR-Spheres microspheres to provide regional treatment to a single organ is questionable in patients with widely disseminated disease. The decision on the potential benefit of treatment in such cases rests with the treating doctor.

Hepatic vascular anatomy that is anomalous should be examined with care. Selective placement of the catheter may overcome accessory vessels and allow reliable placement of the microspheres. It is important to identify accessory or replacement vessels, in particular a gastro-duodenal artery arising from the main hepatic artery distal to the origin of the left hepatic artery. This vessel is difficult to visualize and, if present, may deliver microspheres to the gastrointestinal tract. This anomaly occurs in perhaps 10% of patients and if present, the gastro-duodenal artery must be occluded before implanting SIR-Spheres microspheres. Alternatively the catheter should be placed well into the right and left hepatic arteries separately. If there is an inability to take either of these options, the patient must not receive SIR-Spheres microspheres.

A number of patients will have tortuous vasculature that will preclude accurate and reliable placement of the catheter. Any circumstance that reduces the ability to reliably deliver SIR-Spheres microspheres to the desired location precludes use of the microspheres in that patient.

The percent lung shunting may alter the activity that can be safely implanted commensurate with acceptable risk of radiation pneumonitis. The following recommendations apply:

<i>Percent Lung Shunting</i>	<i>Activity of SIR-Spheres microspheres</i>
<10%	Deliver full amount of SIR-Spheres
10% to 15%	Reduce amount of SIR-Spheres by 20%
15% to 20%	Reduce amount of SIR-Spheres by 40%
>20%	Do not give SIR-Spheres microspheres

The reduction in the activity implanted should be considered in light of the radiation dose that may be received by the tumor. In some patients, a reduction in activity of 20% may ensure the safety of the lung, but no longer provide sufficient radiation to the tumor. This will depend on the bulk of tumor being treated and the tumor to normal ratio of SIR-Spheres microspheres deposition.

This can be determined from the nuclear medicine breakthrough scan, in which the amount of MAA in the liver can be quantified into that in the tumor and that in the normal liver. This may be difficult

to determine in some patients with diffuse and/or metastatic disease, but can be clearly defined in many cases of primary disease. Details of these determinations are covered under *7.1 Dose Calculations* in the Implant Technique, see Chapter 7 of this document.

1.9 Normal Routine for Patients Receiving Treatment

The following provides a typical outline of the normal routine for patients being considered for treatment with SIR-Spheres microspheres.

Liver metastases are diagnosed, either by discovery at surgery or as part of screening in the management of primary cancer at another site, typically the bowel, other abdominal organs, breast or skin. Alternatively the cancer is a primary in the liver.

The patient undergoes standard staging for extent of disease in the liver and extra-hepatic dissemination. This involves a standard battery of tests, particularly of liver and renal function, tumor markers, chest X-rays or CT scans and other imaging suggested by symptoms or history.

At this point the decision on resectability or otherwise of the liver cancer, and the relative merits of doing so in light of extra-hepatic dissemination, can be made.

Non-resectable patients with limited extra-hepatic disease are potential candidates for treatment with SIR-Spheres microspheres.

The initial work-up for staging provides many of the data regarding patient suitability for treatment, particularly general well-being, liver status, and extent and location of disease. At this stage, the patient will have an angiogram to determine the suitability of the hepatic vasculature and a technetium scan to determine the extent of lung shunting. These are both generally performed via a transfemoral catheter, placed in the hepatic artery. If both of these parameters are suitable, then the patient can be treated.

At this stage, a decision on use of concurrent or sequential chemotherapy can be made. This may be as an adjunct to SIR-Spheres microspheres, as many chemotherapeutics are radio-sensitizers. Use of chemotherapy and the specific chemotherapy to use is the decision of the treating doctor, but is subject to regional regulatory restriction. Please refer to the Package Insert for the indications for use, which describes the method and type of chemotherapy approved in various jurisdictions.

In terms of the patient procedures, the decision to use chemotherapy and the mode of administration determines whether the patient will have a catheter with access port implanted into the hepatic artery or a temporary transfemoral catheter placed. The catheter will need to be implanted to accommodate regional chemotherapy, and SIR-Spheres microspheres can be implanted via this catheter. If systemic chemotherapy or no chemotherapy is intended, then a transfemoral catheter can be placed for the implant and removed immediately after the procedure.

For patients receiving regional chemotherapy, a surgical procedure for implanting the port is required. In cases where regional chemotherapy to the liver is anticipated, the catheter and port may be implanted as part of earlier procedure, such as removal of the primary tumor from the bowel.

For patient receiving no chemotherapy or systemic chemotherapy, a second angiogram is required on the day of implant to guide the placement of the transfemoral catheter.

If the microspheres are to be implanted via a transfemoral catheter, the procedure takes place in a catheter suite or laboratory to accommodate the placement of the catheter. The procedure takes approximately an hour from starting to place the catheter until it is removed.

It is recommended that a SPECT scan of the upper abdomen per performed immediately after implantation of SIR-Spheres microspheres. The SPECT scan will detect the Bremsstrahlung radiation from the yttrium-90 SPECT scan to confirm the placement of the microspheres in the liver. This is recommended, but in the event of acute, significant abdominal pain, this should be done to check for microspheres in other abdominal organs.

Patients are removed to a recovery room for approximately one hour before being transferred to the ward. Patients may stay over-night for observation or to comply with local radiation regulations. Day patients may proceed home as instructed by their doctor. Patients having the transfemoral procedure should remain supine for approximately 6 hours after the procedure to reduce complications with the transfemoral artery puncture wound. Alternatively, dedicated arterial wound closures may be used.

1.10 Preventing Gastritis through Appropriate Assessment

The SIRT complication of gastritis is seen as a problem with many centers. The incidence occurs more commonly when there is not a lot of familiarity in administering SIRT, and is therefore considered to be training and experience-related. It is common in new users and rarely seen with experienced hands.

1.10.1 *How it occurs*

Gastritis happens when microspheres get into the stomach/duodenum. This can only occur by the microspheres passing to the gut through small arteries that take origin from around the hepatic hilum. This can occur when the microspheres are inadvertently injected into small arteries that are either;

- a) misinterpreted by the user as an artery and thinks it is just another left sided liver artery supplying blood to the left lobe of the liver, when it is actually going to the gut (this is very common). The main culprit is a right gastric artery that takes origin from the left hepatic and it is not recognized as or considered to be a small artery supplying the left lobe of the liver; or
- b) the user does not know the aberrant artery is present because it was not seen on the angiogram. In about 15% of patients there can be other small vessels that are very small

and hard to see on an angiogram and which pass from the liver to the gut. These are the cause of most of the problems with gastritis.

1.10.2 *How to avoid it*

The question is why does the user not see these small vessels as in (b) above on the angiogram?

When doing the initial angiogram to assess patients, a catheter is placed in the main hepatic artery and contrast injected to look at all the vessels. On the basis of what is seen, a plan is formulated as to where to inject the SIR-Spheres microspheres.

There has been a move in angiography to use the least amount of contrast as possible. This might be good for patients but it is extremely inappropriate for SIR-Spheres microspheres. If a small amount of contrast (eg 8mls over 3 seconds) is used then large arteries will be seen very clearly. However, in order to see the small arteries that pass from the liver hilum to the stomach and duodenum, it is necessary to load up the arteries with contrast and this means giving a **lot of contrast**. For instance it is necessary to inject something like 3-4ml/sec for 5 seconds (a total of 15-20mls of contrast in one angiogram run). If a lot of contrast is injected over a long period such as 5 seconds then all the small arteries will fill with contrast and can then be seen.

It is highly likely that the cases where there gastritis occurs, yet the angiogram looks acceptable, that this is a result of the angiogram not demonstrating these small arteries that go to the stomach/duodenum. If they are not seen then the Interventional Radiologist is going to say they were not there. However, they would be shown to be there if a large forceful bolus of contrast had been used.

It is important to ensure that all IRs use a lot of contrast as shown above with the initial angiogram assessment of patients. After the initial angiographic assessment the IR can use whatever is wanted because the only time a lot of contrast is used is when they are trying to look for the small arteries that are the cause of gastritis.

1.11 Use of Chemotherapy with SIR-Spheres microspheres

1.11.1 *Indications for Use*

SIR-Spheres microspheres are indicated for the treatment of unresectable metastatic liver tumors from primary colorectal cancer with adjuvant intra-hepatic artery chemotherapy (IHAC) of FUDR (Floxuridine).

Surgery is normally the preferred option for suitable patients with resectable disease, as this offers the best prognosis. SIR-Spheres microspheres have been used to shrink large tumors to a stage where they become resectable.

1.11.2 *Technique*

Most chemotherapeutics are radio-sensitisers, therefore simultaneous use of SIR-Spheres microspheres and the chemotherapeutic is desirable. SIR-Spheres microspheres are generally implanted during a course of chemotherapy, often the second cycle. This allows the patient's tolerance to chemotherapy to be established before adding the radiation and for treatment with chemotherapy to commence while the order is placed and the device manufactured. Cycles of chemotherapy are generally continued according to clinical need and the patient tumor response

The chemotherapies used concurrently with SIR-Spheres microspheres are floxuridine (FUDR) given regionally (hepatic artery chemotherapy – HAC), or 5-fluorouracil (5-FU) given systemically together with leucovorin. More recently, systemic irinotecan has been used with SIR-Spheres microspheres, either alone or in combination with 5-FU and leucovorin. These regimes are still under evaluation. Studies on Oxaliplatin with SIR-Spheres microspheres as single or combination chemotherapy are underway, but have yet to be completed.

Regional chemotherapy together with the radiation provides intense therapy to liver tumors. This mode of chemotherapy would be an option for patients with disease confined to the liver. The high extraction ratio of FUDR by the liver leaves only small amounts in systemic circulation. This reduces the systemic toxicity of the chemotherapy, but also reduces the ability to effectively treat any extra-hepatic disease. A further disadvantage is the requirement to implant a catheter into the hepatic artery and connect it to a port. For up to 12 days a month, the patient must use a pump containing the FUDR, which may be external or implanted and the therapy is delivered via the catheter to the liver. This is cumbersome and intense therapy, but may provide additional benefit for patients with confined disease. If patients were to receive regional chemotherapy, then SIR-Spheres microspheres would be delivered via the catheter and port implanted for the chemotherapy.

An alternative is systemic chemotherapy with 5FU, leucovorin, irinotecan or other approved chemotherapeutic regimes. This provides less intense liver chemotherapy but as there are substantial circulating levels, extra-hepatic disease may be treated. There is currently less experience with systemic chemotherapy and SIR-Spheres microspheres published. The systemic circulation of the drugs may increase side effects of the chemotherapy, but for patients with extra-hepatic metastases, this may be a better option. The combination of radiation and chemotherapy addresses the liver disease, and the circulating chemotherapy the distant disease. In this scenario, the SIR-Spheres microspheres would need to be implanted via a transfemoral catheter, which would be removed after the implantation procedure.

1.11.3 *Contraindications*

SIR-Spheres microspheres are contraindicated in patients who have

- had previous external beam radiation therapy to the liver,
- ascites or are in clinical liver failure,
- markedly abnormal synthetic and excretory liver function tests (LFTs),
- greater than 20% lung shunting of the hepatic artery blood flow determined by Technetium MAA scan,
- pre-assessment angiogram that demonstrates abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, pancreas or bowel,

- disseminated extra-hepatic malignant disease,
- been treated with capecitabine within the two previous months, or who will be treated with capecitabine at any time following treatment with SIR-Spheres microspheres,
- portal vein thrombosis.

1.11.4 *Warnings*

- Inadvertent delivery of SIR-Spheres microspheres to the gastrointestinal tract or pancreas will cause acute abdominal pain, acute pancreatitis or peptic ulceration.
- High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis.
- Excessive radiation to the normal liver parenchyma may result in radiation hepatitis.
- Inadvertent delivery of SIR-Spheres microspheres to the gall bladder may result in cholecystitis.

1.11.5 *Precautions*

There are no studies on the safety and effectiveness of SIR-Spheres microspheres in pregnant women, nursing mothers or children.

Due to the radioactivity of this device and the significant consequences of incorrect placement of the microspheres, doctors should not implant this product without adequate training in the handling and implantation technique for this device.

Sirtex Medical recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres microspheres. The SPECT scan will detect the Bremsstrahlung radiation from the yttrium-90 to confirm placement of the microspheres in the liver.

All persons handling, dispensing and implanting this device must be familiar with and abide by all Local, State and Federal regulatory requirements governing therapeutic radioactive materials. Accepted radiation protection techniques should be used to protect staff when handling both the isotope and the patient.

Some patients may experience gastric problems following treatment with SIR-Spheres microspheres, but H-2 blocking agents may be used the day before implantation and continued as needed to reduce gastric complications.

SIR-Spheres microspheres demonstrated a mild sensitization potential when tested dermally in an animal model.

1.11.6 Previous Treatment Regimes

1.11.6.1 External Beam Radiation

SIR-Spheres microspheres should not be implanted into patients who have had previous external beam radiation therapy to the liver.

1.11.6.2 Other chemotherapy

There are currently no safety data pertaining to the use of CPT11 (irinotecan, camptosar) or oxaliplatin in the period before, or within several months after, treatment with SIR-Spheres microspheres.

1.11.7 Liver Status

1.11.7.1 Liver Function Tests

SIR-Spheres microspheres should not be used in patients who have ascites or are in clinical liver failure. SIR-Spheres microspheres are contraindicated if pre-assessment investigations demonstrate markedly abnormal synthetic and excretory liver function tests.

1.11.7.2 Portal Vein Thrombosis

Portal vein thrombosis precludes all forms of embolic therapy and is a contraindication for SIR-Spheres microspheres.

1.11.7.3 Degree of Lung shunting

SIR-Spheres microspheres are directly contraindicated in patients with greater than 20% lung shunting (determined by the nuclear medicine break-through scan) as an unacceptably high dose of radiation will be shunted from the liver to the lung.

1.11.7.4 Hepatic Vascular Anatomy

SIR-Spheres microspheres are contraindicated in patients with abnormal vascular anatomy that would result in significant reflux of hepatic arterial blood to the stomach, bowel, pancreas or other abdominal organs. Furthermore, if the pre-assessment angiogram and MAA nuclear medicine scan demonstrates significant reflux of hepatic arterial blood to the stomach, pancreas or bowel, SIR-Spheres microspheres should not be implanted. See Chapter 5 of this document for more information.

1.11.8 Other Considerations

1.11.8.1 Extra-Hepatic Disease

As SIR-Spheres microspheres provides local radiotherapy to the liver, their place in the management of patients with disseminated or extra-hepatic disease is questionable in the absence of an ancillary treatment regime for the distant disease.

1.11.8.2 Overall Patient Well-being

SIR-Spheres microspheres are contraindicated in patients not sufficiently well to undertake the implantation procedure. If patients are to have a port implanted, they must be medically fit for this

surgical procedure. Patients unwell from their cancer or other non-malignant disease require appropriate assessment before considering SIR-Spheres microspheres as an option.

1.11.8.3 Pregnancy/Children

Women of childbearing age requiring SIR-Spheres microspheres should be treated when non-pregnancy can be ascertained. Safety in pregnancy and childhood has not been established and SIR-Spheres microspheres should not be implanted into these patients.

1.11.9 Other

Inadvertent delivery of SIR-Spheres microspheres to the gastrointestinal tract or pancreas will cause acute abdominal pain, acute pancreatitis or peptic ulceration.

High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis

Excessive radiation to the normal liver parenchyma may result in radiation hepatitis.

The patient may emit low levels of radiation for several weeks, therefore care must be taken with pregnant women and children in close proximity to the patient.

This device is permanently implanted and cannot be retrieved. There is no evidence to date that the decayed microspheres remaining in the tumor or liver cause adverse reactions.

This product is radioactive. US CFR Title 10 of the Code of Federal Regulations Part 35, the European Euratoms and other regional and state regulations regulate use of this device. These regulations must be followed when handling SIR-Spheres microspheres (See Section 8.1).

1.12 Product Incidents And Post-Operative Adverse Effects

1.12.1 Reporting

We request that all product incidents be reported to the company. Sirtex encourages reports of all events, whether serious or not. Small details that may be relevant to the event should be included. Adverse events should be reported as they occur. Events may be reported by telephone to any Sirtex personnel, in hard copy, fax or via the Sirtex web site www.sirtex.com.

In addition, Incident Report Forms are available from Sirtex. Serious Adverse Event forms are provided for in all Clinical Trial documentation. As much detail as possible should be supplied on this form. Incidents or Serious Adverse Events may constitute a reportable item under the provisions of medical device reporting, vigilance or other reporting legislation and must be reported within short time frames to maintain regulatory compliance. All reports should be sent to Sirtex as soon as possible, which allows faster corrective and preventive actions (if necessary) to avoid repetitive

incidents. It will also allow the company to fulfill its reporting obligations to regulatory authorities. Incidents or adverse events may also be reported directly to regulatory bodies, however, if you report directly, we do request that you please inform Sirtex simultaneously.

1.12.2 *General*

When the patient is treated with the proper technique, without excessive radiation to any organ, the common adverse events after receiving SIR-Spheres microspheres are fever, transient decrease in hemoglobin, mild to moderate abnormality of liver function tests – specifically a mild increase in SGOT, alkaline phosphatase and bilirubin, abdominal pain, nausea, vomiting, and diarrhea.

The majority of adverse events are grade 1 and 2 toxicity, as assessed by the UICC toxicity grading scale. The adverse events experienced by patients receiving combination therapy of SIR-Spheres microspheres with chemotherapy are similar to patients receiving chemotherapy alone.

Most patients develop a post-operative fever that starts immediately after implantation of SIR-Spheres microspheres and can last from a few days to a week. The fever does not necessarily indicate sepsis but may be related to the embolic effect of the microspheres and the acute toxic effects on the tumor. If there is any suspicion of bacterial infection, investigate and treat appropriately.

Many patients experience nausea that may last up to several weeks and this may occasionally be severe enough to require anti-emetic medication that should be continued until the symptoms subside.

Many patients experience significant abdominal pain immediately after administration of SIR-Spheres microspheres and may need pain relief with narcotic analgesia. The pain generally subsides within an hour or so, but patients may require oral analgesia for up to several days.

1.12.3 *Immediate, Serious Abdominal Pain*

1.12.3.1 *Possible Causes*

Immediate, excessive abdominal pain after implantation of SIR-Spheres microspheres may indicate that microspheres have been inadvertently delivered to other organs such as the pancreas, stomach or duodenum. (see also Section 4.6 of this document). This will result in acute pancreatitis or peptic or duodenal ulceration. A post-implantation nuclear scan will verify the placement of the microspheres. This is performed with a gamma camera, which will pick up the secondary Bremsstrahlung radiation from the yttrium-90. See Appendix 1.

1.12.3.2 *Acute Pancreatitis*

A yttrium-90 nuclear scan will determine if the microspheres have lodged in the pancreas or other organs, but additional tests such as serum amylase are also indicated if pancreatitis is diagnosed. If this were to occur the patient should be treated using best standard practice, including pain relief, and intravenous fluids.

1.12.3.3 Acute Peptic Ulceration

The development of acute peptic ulceration is suggested by the recognised symptoms of ulcer disease and diagnosed by endoscopy. If this were to occur the patient should be treated using best standard practice, including pain relief, gastric acid blocking drugs and intravenous fluids. Treatment is the same as for any cause of acute peptic ulceration.

1.12.4 *Delayed Serious Events*

1.12.4.1 Radiation Pneumonitis

High levels of implanted radiation and/or excessive shunting to the lung may lead to radiation pneumonitis. This may be suspected if patients develop a non-productive cough several days or weeks after the implantation of SIR-Spheres microspheres and is diagnosed by chest X-ray. Patients should be treated with systemic corticosteroids and supportive care until the disease has subsided.

1.12.4.2 Radiation Hepatitis

Excessive radiation to the normal liver parenchyma may result in radiation hepatitis. This can be difficult to diagnose, and may appear many weeks after the implantation of SIR-Spheres microspheres. It is suspected if there is unexplained progressive deterioration in liver function. The diagnosis can be confirmed by histologic examination of core liver biopsy. If the diagnosis is suspected or proven then patients should be treated with systemic corticosteroids and supportive care until the inflammation settles.

1.13 Radiation Dosimetry

1.13.1 *Point Source Beta Radiation*

There is no simple way to precisely know the radiation dose delivered to tumors, normal liver or adjacent organs when SIR-Spheres microspheres are implanted. This is because Y90 only emits pure beta radiation with limited penetration range in tissue. Mathematical calculations of the dose from a Y90 point source of beta radiation show that the dose is largely confined to a distance of 2-3 mm from the point source (see “Point Source Beta Radiation” in Appendix 4). The total dose at any particular position of interest in the implanted tissue can be found by summing together the contributions from all of the individual point sources in the vicinity. Hence, the deposited dose is highly dependent on the distribution of microspheres and this cannot be known with any great precision other than by microscopic examination of tissue after implantation has occurred (see, for example, *Campbell AM, Bailey IH, Burton MA, Tumor dosimetry in human liver following hepatic yttrium-90 microsphere therapy. Phys Med Biol 2001; 46: 487-498*). Such analyses do confirm that tumors receive a lethal dose of radiation whilst the average dose to normal tissue is well below harmful levels. However, this approach is clearly not appropriate for treatment planning purposes.

1.13.2 *MIRD and the Partition Model*

Within the liver, it is possible to estimate *a priori* an absorbed dose for the tumors and the normal liver in patients with distinct tumors that may be effectively considered as separate organs. This is achieved using the partition model, which is based on a modification of the MIRD theory. Discussion of the limitations of standard MIRD theory are given in Appendix 4 of this document and details of the partition model are given in Section 7.1.3. The partition model may be used in treatment planning.

1.13.3 *Empirical Models for Treatment Planning*

There are also empirical models for estimating the appropriate activity to administer to a patient prior to treatment. These are based on a large amount of clinical experience and can be adjusted to suit individual patient circumstances and characteristics. The empirical models can be used to determine the maximum activity that can be safely implanted subject to the limitations imposed by lung shunting and maximum tolerable dose to normal liver. However, they provide no information about actual dosimetry to tumor and normal liver. Details of the empirical models are given in Section 7.1.1.

1.14 Radiological Work-up Prior to SIR-Spheres Microspheres Implant

Most units treating patients with SIR-Spheres microspheres prefer to perform a preliminary radiological work-up including:

- hepatic angiogram
- combined angiogram/CTA scan
- embolisation of the gastro-duodenal or other artery that might result in inadvertent delivery of SIR-Spheres microspheres, and
- MAA nuclear medicine SPECT scan.

See also Section 4.6 of this document regarding preventing gastritis.

The radiologist must look carefully for small arterial branches and if in doubt, take whatever steps are necessary to ensure that SIR-Spheres microspheres is never implanted if there is any possibility that they might enter these small aberrant vessels. A small number of SIR-Spheres microspheres in the stomach or duodenum will cause severe inflammation. The options in this situation are:

- pass the catheter well beyond the offending artery;
- block the artery with a coil, gel, foam or other suitable device; and
- abandon the transfemoral procedure and have a surgeon implant a port into the hepatic artery and ligate the offending vessels.

HEPATIC VASCULAR ANATOMY

Many patients exhibit anomalies of hepatic vascular architecture. This raises two main concerns:

- firstly, vascular anomalies may prevent appropriate placement of the catheter into the hepatic artery for the delivery of SIR-Spheres microspheres;
- these anomalies can lead to microspheres lodging in excess amounts in the hepatic parenchyma or other organs such as the pancreas, gastro-duodenum or the stomach.

An angiogram is required to identify the detail of hepatic vascular anatomy. This angiogram must be assessed by a physician skilled in scan interpretation with a view to identifying any anomalous vessels leading to other organs. Such vessels may not be easy to see and should be deliberately sought. Clinical proctoring is provided and the issues concerning the identification of such vessels is addressed.

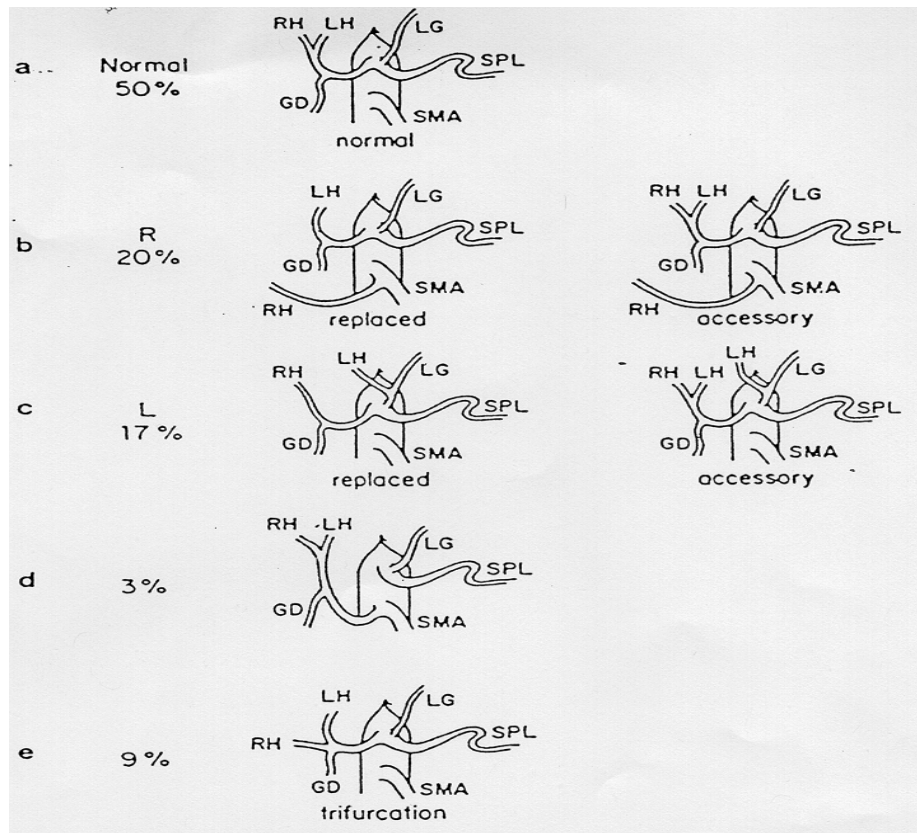
1.15 Variations in Arterial Blood Supply to the Liver

The following common anomalies in vascular supply must be noted:

- In 20% of patients there will be an **accessory right hepatic artery arising from the superior mesenteric artery** (see Diagram 1, 'b' below). This accessory right hepatic artery *will supply most of the right lobe of liver* and is easily demonstrated on an angiogram. If present, it must be accessed to deliver SIR-Spheres microspheres to the right lobe of the liver as well as the main hepatic artery; otherwise the radiation will not be delivered to tumors in the right lobe of the liver.
- In 17% of patients **an accessory left hepatic artery will arise from the left gastric artery** (see Diagram 1, 'c' below). This accessory left artery is usually difficult to demonstrate on an angiogram, and is often not recognized at the time of angiography. It is usually possible to get a co-axial catheter into this artery if it is necessary to deliver SIR-Spheres microspheres to the left lobe of the liver. If there is no tumor in the left lobe then it can be ignored.
- In a minority of patients **the gastro-duodenal artery arises from the same point as the bifurcation of the common hepatic artery into right and left hepatic arteries**. It is imperative that the SIR-Spheres microspheres not be delivered into the gastro-duodenal artery, as this will result in the SIR-Spheres microspheres lodging in the duodenum and pancreas with severe side effects. In this situation the gastro-duodenal artery should be either embolized to occlude it before delivering the SIR-Spheres microspheres into the hepatic artery, or alternatively the catheter can be passed separately into the right and left arteries and part of the SIR-Spheres microspheres implanted into each side.

VARIATIONS IN ARTERIAL BLOOD SUPPLY TO THE LIVER

Diagram 1



- (50%) In the normal setting the gastro-duodenal (GD) artery comes off the common hepatic artery proximal to the bifurcation into the right hepatic (RH) and left hepatic (LH) arteries. The left gastric (LG) and splenic (SPL) arteries come off the coeliac axis separately.
- (20%) When the right hepatic (RH) artery is replaced, the whole blood supply to the right lobe comes off the superior mesenteric artery (SMA). In the case of an accessory right hepatic artery, the vasculature off the coeliac axis is normal but there is an additional right hepatic artery off the superior mesenteric artery.
- (17%) When the left hepatic (LH) artery is replaced, the whole blood supply to the left lobe comes off the left gastric (LG) artery. In the case of an accessory left hepatic artery the vasculature of the common hepatic artery is normal but there is an additional left hepatic artery off the left gastric artery.
- (3%) In this situation the entire common hepatic artery arises from the superior mesenteric artery.
- (9%) A trifurcation occurs when the bifurcation of the left hepatic and right hepatic arteries occurs at the same spot as the take off of the gastro-duodenal (GD) artery.
- There are specific cases of an accessory right gastric artery originating from the left hepatic artery and passing in the gastro-hepatic omentum back to the lesser curvature of the stomach.

Note: In about 10% of patients there are small arterial branches that take origin from either the common hepatic artery or right or left hepatic arteries and pass back to the stomach and duodenum. These small arteries are not described in any of the normal anatomy texts and are easily mistaken for small liver arteries.

There are specific cases of an accessory right gastric artery originating from the left hepatic artery and passing in the gastro-hepatic omentum back to the lesser curvature of the stomach.

These abnormalities must be fully visualized to ensure that the majority of SIR-Spheres microspheres will be reliably delivered to the tumor. Furthermore, the presence of small arteries leading from the main hepatic arteries to other organs must be identified if present, and avoided or blocked during implant to prevent unintentional irradiation of abdominal organs. If the implanting physician cannot assure that the vascular anatomy will result in the required placement of microspheres, then SIR-Spheres microspheres should not be implanted.

1.16 Dealing with Abnormalities of Liver Vascular Anatomy

If there is a dual arterial supply to the liver, then each artery will have to be separately catheterized to implant the SIR-Spheres microspheres if there is tumor in both lobes. If there is tumor in only one lobe, then SIR-Spheres microspheres need only be implanted into that side of the liver. For example, if all the tumors were in the right lobe of the liver, and there was an accessory right hepatic artery arising from the superior mesenteric artery, then delivering the SIR-Spheres microspheres into this accessory right hepatic artery would deliver all the radiation to the tumor in the right lobe.

If there are separate right and left arteries and there are tumors in both lobes, then SIR-Spheres microspheres will need to be separately delivered into both arteries.

The radiologist must look carefully for these small branches and if in doubt, take whatever steps are necessary to ensure that SIR-Spheres microspheres are never injected if there is any possibility that they might enter these small aberrant vessels, as even a small number of SIR-Spheres microspheres in the stomach or duodenum will cause severe inflammation. The options in this situation are as follows:

- a) pass the catheter well beyond the offending artery,
- b) block the artery with a coil, or
- c) abandon the transfemoral procedure and have a surgeon implant a port into the hepatic artery and ligate the offending vessels.

These abnormalities must be fully visualized to ensure that all of the SIR-Spheres microspheres will be reliably delivered to the tumor. Furthermore, the presence of small arteries leading from the main hepatic arteries to other organs must be identified if present, and avoided or blocked during implant to prevent unintentional irradiation of abdominal organs. If the implanting physician cannot assure that the vascular anatomy will result in the required placement of microspheres, then SIR-Spheres microspheres should not be implanted.

DOSE PREPARATION PROCEDURE

1.17 Dose Calibrator Calibration

The most common dose calibrators in use are ion chambers. Capintec is a widely used brand, and the information in this section pertains to Capintecs. If other dose calibrators or other brands of ion chambers are used, the manufacturer's instructions regarding calibration for yttrium-90 sources should be consulted.

Published work and general experience suggests that a dial setting of 775 with a multiplication factor of 70, or a dial setting of 48 with a multiplication factor of 10 will give consistent readings for yttrium-90 sources between 1GBq and 3GBq over a range of volumes. These settings should be used initially and adjusted if necessary as a result of calibration activities. In general, if more than one dial setting and multiplication factor provide consistent and reliable measurements, one should be adopted as the standard.

The manufacturer of SIR-Spheres microspheres calibrates its ion chambers with secondary national standards. To calibrate the Capintec, the manufacturer's ion chamber measurement at time and date of manufacture is supplied with the first few, generally three (3) devices.

The device should be measured in the Capintec and the activity measurements compared (allowing for decay). Adjustments to the settings should be made to bring the measurement from the Capintec to $\pm 10\%$ of the manufacturer-supplied measurement. An alternative is to apply a correction factor. These settings should then be the standard used for activity measurements of SIR-Spheres microspheres.

At regular intervals it is advisable to recheck that calibration remains accurate. This can be easily achieved by requesting a manufacturer activity measurement with a device.

To ensure that calibration is meaningful, the other factors that can influence the activity measurements must be as consistent as possible for each measurement made in the Capintec. Potential areas of inaccuracy are:

- the activity measured
- the volume of the source
- the shape of the container holding the source
- the material of the container holding the source and
- homogeneity of the suspension.

The accuracy of measurement may be dependent on the range of activity being measured. At the suggested settings, measurements up to 3GBq are generally linear and consistent. If alternative settings are used, linearity and consistency should be confirmed.

The volume of the source may alter the accuracy of measurement due to self-shielding that can occur with short penetration beta emissions. A slight inaccuracy occurs between measurements taken on a 3GBq device and a confirmatory measurement of residual activity after a patient dose is withdrawn from the vial. This can be minimised by ensuring the microspheres are fully suspended at the time of each measurement. Allowing the microspheres to settle changes the effective volume of the source and contributes to unquantifiable self-shielding effects of water, air and the container.

The shape of the container should be consistent to minimise changes in the geometry of the source, and thus self-shielding effects. For this reason, the activity of the patient dose in the v-vial is confirmed by re-measuring the remaining activity in the shipping vial.

The container material also contributes to the activity measurement as the penetration through plastic is substantially greater than through glass. A correction factor for the container is not generally necessary for glass containers. This potential inconsistency is removed if all measurements for SIR-Spheres microspheres are taken in the shipping vial.

1.18 Dose Preparation

Preparation of the individual patient dose will be undertaken by a Sirtex-trained approved dispenser either within the medical institution using the SIR-Spheres microspheres or by a nuclear dispensing facility elsewhere. Results of data obtained from thermoluminescent detectors (TLD) worn by an operator preparing individual patient doses can be found in Appendix 8 of this document. TLDs were worn on the trunk, collar and fingers.

1.19 Preparation of an Individual Patient Radiation Dose

The patient specific activity (as determined by the doctor) is drawn from the shipping vial and placed into the v-vial. The v-vial is then placed into the acrylic v-vial holder and transported to where the patient will be treated. The v-vial holder is placed into the acrylic SIR-Spheres Delivery Box provided for this purpose and SIR-Spheres microspheres are delivered using the disposable SIR-Spheres Delivery Set.

1.20 Activity Calculations

The activity of the yttrium-90 must be determined by measurement using an appropriate dose calibrator, such as an ion chamber, on arrival or at the time of dose preparation. Confirmation that the correct activity has been drawn from the vial should also be directly verified by measurement. Drawn doses must allow for decay during the time between dose preparation and implantation. The decay table supplied with the device can be used for this purpose. The activity of SIR-Spheres microspheres implanted will usually be in the range of 1.5–2.5GBq.

1.21 Preparation Guidelines

The following guidelines are for preparing an individual patient radiation dose. All activity measurements should be conducted using fully suspended SIR-Spheres microspheres to avoid inconsistencies associated with self-shielding due to geometry changes.

A pictorial step-by-step dispensary poster is available upon request from Sirtex .

- All manipulations and handling of SIR-Spheres microspheres must be undertaken by trained staff approved to handle therapeutic radioisotopes.
- All handling of SIR-Spheres microspheres is undertaken using aseptic technique, standard radiation protection methods and equipment.
- The physician in charge of the patient must determine the activity required by the patient
- The activity of SIR-Spheres microspheres is calculated for the time of delivery into the patient using the decay table supplied with the device.
- The nuclear medicine technician or radio-pharmacist should verify the activity of the shipped dose using the institution's radiation measuring equipment.
- Using aseptic technique, the required amount of SIR-Spheres microspheres are removed from the shipping container and delivered into the v-vial.
- The yttrium-90 activity in the v-vial should be confirmed and corrected if necessary.
- If required additional water for injection should be added to bring the volume in the v-vial to a minimum of 3ml.
- The v-vial is placed into the v-vial holder, which is the dedicated acrylic shield.
- The v-vial holder containing the v-vial is transported to the patient treatment room.

1.22 Step-By-Step Example

The recommended method for preparing a patient specific radiation dose of SIR-Spheres microspheres follows. The procedure should be undertaken in a lead shielded or acrylic box if available, otherwise leave SIR-Spheres microspheres shipping vial in delivery lead pot during the procedure.

1. Invert the lead pot several times before opening the lead pot to re-suspend the microspheres, which will have settled during shipping.
2. Quickly open the pot and remove the shipping vial with tongs and determine the total activity using an appropriate ion chamber (dose calibrator).

NOTE: Accurate measurement requires fully suspended SIR-Spheres microspheres, so it is important to make all measurements quickly.

3. Return the shipping vial to the lead delivery pot and place it in the shielded work area. Replace the lid on the lead delivery pot.

4. Completely remove centre of aluminium crimp seal from sterile v-vial with forceps to expose septum and swab septum with an alcohol wipe.
5. Place sterile v-vial in the dedicated acrylic v-vial holder. This provides stability and shielding for the sterile v-vial. Place the v-vial holder near the lead pot containing the SIR-Spheres microspheres in the shielded working area.
6. Insert a short 25g needle through the septum of the v-vial until it just pierces the septum to create a vent. The v-vial is now ready to receive SIR-Spheres microspheres.
7. Determine the volume of SIR-Spheres microspheres to be withdrawn from the shipping vial to provide the required patient radiation dose.
8. Resuspend the SIR-Spheres microspheres by inverting the shipping vial several times. Remove lid from the lead delivery pot to expose SIR-Spheres microspheres shipping vial.
9. **Partially** remove centre of aluminium crimp seal from SIR-Spheres microspheres shipping vial with forceps to expose septum and swab septum with an alcohol wipe held in forceps. Do not fully remove crimp seal.
10. Insert a 25g needle through the septum of the shipping vial to create a vent, ensuring the needle is well clear of the contents of the shipping vial.
11. Use a shielded 5mL syringe with a 20-22g spinal needle at least 70mm long to puncture the septum of the shipping vial.
12. Re-suspend SIR-Spheres microspheres with vigorous mixing by quickly drawing up and expelling the SIR-Spheres microspheres in the shielded 5mL syringe at least six times.
13. Quickly draw up the volume of SIR-Spheres microspheres containing the calculated dose into the shielded 5mL syringe. Carefully remove the 20-22g needle from the shipping vial, recap the needle using forceps and set the dose aside.
14. To check the dose activity of the v-vial contents (patient specific dose), return the shipping vial to the ion chamber (dose calibrator) to verify (by measuring the difference).
15. If additional activity is required, repeat steps 12 to 14 above to obtain the correct patient dose as determined at item 7 above.
16. If the total volume in the shielded syringe is less than 3mLs, draw up enough sterile water for injection to make up to a total volume between 3 and 5mLs.
17. Insert the 20-22g spinal needle into swabbed septum of sterile v-vial and deliver the specific patient dose of SIR-Spheres microspheres from the shielded syringe into sterile v-vial. **Note: this step should be done ONCE only.**
18. Remove the vent needle from the v-vial; ensure lid of the v-vial holder is secure and the plug is in place.
19. Remove the vent needle from the shipping vial and replace the lid of the lead delivery pot.

SIR-SPHERES MICROSPHERES IMPLANT PROCEDURE

1.23 Dose Calculations

There are two methods for calculating the activity of SIR-Spheres microspheres to implant - Empiric and Partition.

1.23.1 *Empiric Method of Dose/Activity Calculation for Treatment*

1.23.1.1 Basic

The empiric method recommends a standard amount of activity which is varied only according to the size of the tumor within the liver. This technique has been applied in clinical trials when SIR-Spheres microspheres have been used in conjunction with hepatic perfusion chemotherapy with FUDR. The recommended activity to be implanted for varying degrees of tumor involvement of the liver is in the table.

Activity Recommendations

Estimated Degree of Tumor Involvement of the Liver	Recommended Yttrium-90 Amount for Treatment
>50%	3GBq
25-50%	2.5GBq
<25%	2GBq

The amount of yttrium-90 should be reduced according to the dose adjustment table in the Clinical Module if the percentage lung shunting is greater than 10%.

1.23.1.2 Body Surface Area (BSA) Method

A variant of the empiric method is to adjust the activity implanted according to the size of the tumor within the liver and the size of the patient. This technique has been applied in clinical trials in which SIR-Spheres microspheres have been used in conjunction with systemic chemotherapy using 5-fluorouracil and leucovorin.

Equation 2 is used to calculate the activity of yttrium-90 to be implanted. This equation requires:

- the patient's Body Surface Area (BSA) to be calculated from the patient's weight and height, using equation 1;
- the percentage of the liver that is replaced with tumor as calculated from the CT scan.

This will usually result in 1.3-2.5GBq of yttrium-90 being given to the patient.

Equation 1: Determination of BSA

- BSA is calculated from a weight/height chart

$$BSA \text{ (m}^2\text{)} = 0.20247 \times \text{height (m)}^{0.725} \times \text{weight(kg)}^{0.425}$$

Equation 2:

- *Activity of SIR - Spheres in GBq* = $(BSA - 0.2) + \left(\frac{\text{volume of tumour}}{\text{volume of tumour} + \text{volume of normal liver}} \right)$

The BSA method is recommended for patients having concurrent systemic chemotherapy or for particularly small patients.

Again, it should be noted that the calculated activity of yttrium-90 may have to be further reduced if the percentage lung shunting is greater than 10% as demonstrated by the Nuclear Medicine Break-through scan.

1.23.2 Partition Model for Calculation of Dose/Activity of SIR-Spheres microspheres

This method involves implanting the highest possible activity to the tumor while maintaining radiation dose to sensitive tissues such as the lung and the normal liver. Therefore this method provides the highest radiation dose to the tumor that is associated with protection of normal tissue from radiation damage.

For this method to be utilized, the following must be identified:

- the main tissue compartments, these being tumor, normal liver and lung;
- the amount of implanted activity that partitions to each of the compartments;
- pre-determined acceptable radiation doses to these compartments.

In clinical practice, the Partition Model can only be used where the tumor mass is localized in a discrete area within the liver and the tumor can be drawn as an 'area-of-interest' on a SPECT camera image. This is usually only possible for patients with Primary Hepatocellular Carcinoma (HCC) where there is often a large single tumor mass. In contrast, patients with metastatic disease usually have multiple areas of metastatic spread that often precludes drawing 'areas-of-interest' that define the tumor and normal parenchymal compartments. The lung compartment is readily identifiable.

Identification of the two liver compartments, the lung and the amount of implanted activity that partitions into each of them is determined by using a technetium-99m tracer dose injected via the hepatic artery. The distribution of the technetium-99m is a reliable clinical predictor of SIR-Spheres microspheres distribution and hence radiation dose to each compartment. This scan, the nuclear medicine break through scan, is performed in all patients to determine the percentage of the dose that shunts from the liver to the lungs, but also determines the distribution in the liver between the tumor and normal tissue. In the liver, this allows the tumor to normal ratio of activity to be determined

If the partition model is used, then the radiation dose to the normal liver parenchyma should not exceed 80Gray in patients with normal liver and 70Gray in patients with cirrhosis. The dose to the lung should not exceed 25Gray. The dose received by the tumor has no upper limit.

Use of the partition model requires two measurements to be made:

- measurement of the volume of tumor and normal liver determined from a CT scan and
- measurement of the proportion of technetium-99 labeled MAA activity that lodges in the tumor, normal liver and lung as determined from a gamma SPECT scan (nuclear medicine breakthrough scan).

The following equation is used to calculate the radiation dose received by an organ after SIR-Spheres microspheres have been delivered to that organ:

Note: All activities are in GBq and masses in g (grams).

Equation 3:

$$\text{Tissue Radiation Dose (Gy)} = \frac{49670 \times \text{Total yttrium-90 activity in organ or tissue (in GBq)}}{\text{Mass of the organ or tissue (in grams)}}$$

Therefore, to calculate the radiation dose received by the tumor, normal liver tissue or lung, we need to calculate the volumes of those tissue compartments, know the amount of yttrium-90 activity that will be implanted, calculate the T/N activity ratio (calculated as activity per unit mass of the organ or tissue) which is the ratio of the concentrations of SIR-Spheres microspheres in the tumor and normal liver compartments after they have been delivered into the hepatic artery and corrected for any SIR-Spheres microspheres that are shunted to the lungs as determined by the nuclear medicine breakthrough scan.

To determine the T/N ratio, Equation 4 should be used.

Equation 4: $T/N = r = (A_{Tumor}/M_{Tumor})/(A_{Liver}/M_{Liver})$

Where: T/N (r) is the tissue/normal ratio of the activity in the tumor and normal liver per unit mass of each of these compartments.

A_{Tumor} is the activity in tumor

M_{Tumor} is the mass of tumor

A_{Liver} is the activity in the normal liver

M_{Liver} is the mass of the normal liver

As some of the SIR-Spheres microspheres delivered into the hepatic artery will shunt into the lungs, a correction factor has to be made to account for activity that is lost into the lungs. If the total amount of yttrium-90 activity that is delivered is A_{Total} and the percent lung shunting = L, then the amount that goes to the lungs (A_{Lung}) is given by;

Equation 5: Lung activity (A_{Lung}) = $A_{Total} \times \frac{L}{100}$

Where: A_{Total} is the amount of yttrium-90 delivered to the patient and L is the percent lung shunting

The percent lung shunting is calculated from the nuclear scan and is:

$$\text{Percent lung shunting} = 100 \times A_{Lung} / (A_{Lung} + A_{Liver} + A_{Tumor})$$

Note: As the lung is largely filled with air, the CT scan cannot be used to measure the volume of the lung parenchyma, and hence an estimation of 1000cc is made. For the purpose of calculating tissue mass, all tissue densities are estimated at 1gm/cc.

If the lung mass is estimated to be 1000g, then the radiation dose to the lung can be calculated from Equation 3. The percent lung shunting can be calculated from the nuclear medicine break-through scan.

The tumor and normal liver radiation doses can also be simply calculated by first calculating the amount of yttrium-90 activity that remains in the liver (A_{Liver}) and tumor (A_{Tumor}) which is given by Equation 6.

Equation 6: $A_{Liver} + A_{Tumor} = A_{Total} - A_{Lung}$

The tissue radiation dose that will be delivered to the normal liver and tumor can be calculated from Equation 3. The nuclear medicine break-through scan is used to determine the activity ratio between tumor and normal liver. As the total $A_{Liver} + A_{Tumor}$ is known from Equation 6, and the activity ratio also known, the individual A_{Liver} and A_{Tumor} can easily be calculated. The volume and hence mass, of tumor and normal liver can be measured from a CT scan.

In practical terms, in order to calculate the total activity to be implanted, while keeping the radiation doses to organs within desired limits, the following equations should be used. The activity required should be calculated using the lung dose as the limiting factor, and then again using the normal liver dose as the limiting factor. The lower of the two activities calculated should be used.

To determine the activity implanted to accommodate a limiting lung dose:

Equation 7: $A_{Lung} = D_{Lung} M_{Lung} / 49670$

Equation 8: $A_{Total} = A_{Lung} 100/L$

Therefore:

Equation 9: $A_{Total} = \frac{D_{Lung} M_{Lung} 100/L}{49670}$

Where: D_{Lung} is the dose to the lung

M_{Lung} is the mass of the lung
 A_{Lung} is the activity to the lung
 A_{Total} is the total activity
 L = the percentage lung shunting

To determine the activity implanted to accommodate a limiting normal liver dose:

Equation 10:
$$A_{Total} = \frac{[D_{Liver} ((T/N M_{Tumor}) + M_{Liver})]}{[49670 (1-L/100)]}$$

Calculation of Tumor and Normal Liver Volumes

Tumor and liver volumes can generally be determined using the diagnostic package associated with the CT scanner. If an older scanner is used, the CT scan of the liver is performed using 10mm slices. The tumor and total liver areas are traced out for each slice of the CT scan. This is traced using a graphics tablet and the total areas multiplied by 10mm to give the volume of tumor and normal liver. These values are used in Equation 3 to determine tissue radiation dose.

1.24 SIR-Spheres Microspheres Implant Procedure

SIR-Spheres microspheres can be implanted via the hepatic artery in one of two ways, either via an implanted catheter with port, or transfemorally. Dedicated Delivery Apparatus must be used, providing a safe environment for the implant procedure. Use of the Delivery Apparatus is mandatory in the USA.

1.25 Use of the Delivery Apparatus

The Delivery Apparatus consists of a Delivery Set, a V-vial and the Delivery Box. A video and a pictorial step-by-step dispensary poster which shows the set-up and use of the Delivery Apparatus is available upon request from Sirtex.

The acrylic Delivery Box with the V-Vial holder acts to shield the operating room staff from beta radiation emitted by SIR-Spheres microspheres. The Delivery Set and V-Vial are used for the delivery of SIR-Spheres microspheres.

SIR-Spheres microspheres can be administered via the hepatic artery by one of two routes:

- a trans-femoral catheter , or
- an implanted hepatic artery port.

If a needle is used to puncture an implanted hepatic artery port, then the internal diameter of the needle must not be less than 0.65mm (i.e. gauge 20). If a port is used to deliver the SIR-Spheres

microspheres then it is absolutely necessary to be completely sure that the catheter is placed correctly so that the SIR-Spheres microspheres go only to the liver and not to any other organs, such as the duodenum or stomach. If a trans-femoral catheter is used then it should have as large an internal diameter as possible in order to prevent blocking. It may be preferable to use a micro-catheter but the operator must be aware that fine bore catheters may block unless the SIR-Spheres microspheres are delivered as a very dilute suspension. *Small bore catheters and needles may block with SIR-Spheres microspheres.*

The Stopcock Control Knob on the front of the Delivery Box makes it possible to operate the 3-Way stopcock of the Delivery Set without reaching into the box. The Stopcock Control Knob is limited to a one quarter turn when properly engaged. This limit is a safety feature designed to prevent the injection of SIR-Spheres microspheres into the Flushing Tube.

1.25.1 *Equipment Required*

Delivery Set, Delivery Box, including V-Vial Holder, V-Vial, SIR-Spheres microspheres, two 20ml syringes filled with water for injection. See also 8.9.11 for general equipment requirements.

1.25.2 *Assembly of Delivery Set in Delivery Box*

1. Dispense the required patient specific dose of SIR-Spheres microspheres from the shipping vial into the V-Vial. The volume of the patient specific dose should be 3-5mls. *If the total volume in the V-Vial is less than 3ml, add sufficient extra water for injection (NOT SALINE) to bring the volume to a minimum of approximately 3ml.*
2. Confirm that the dose of SIR-Spheres microspheres contained in the V-Vial is correct for the patient.
3. The Medical Physics or Nuclear Medicine technician or pharmacist drawing up the patient specific radiation dose should put the V-Vial into the V-Vial Holder and replace the screw cap on the acrylic V-Vial Holder.
4. Remove the sterile Delivery Set from the package and keep sterile. Take care not to take the caps off the two needles, as this will breach the sterile barrier.
5. Firmly place the 3-way stopcock into the bracket on the back wall of Delivery Box so that tube 'A' leads up, tube 'B' leads down and tube 'C' leads to the right
6. From inside the Delivery Box insert tubes 'A' and 'B' through the corresponding holes in the Delivery Box. The holes in the Delivery Box are color coded and marked with 'A' and 'B'. Tube 'C' with the needle attached is left in the box).
7. From inside the Delivery Box insert tube 'D' through Hole 'D' in the Delivery Box so that the needle stays inside the Delivery Box and the tubing passes outside.
8. Push the Stopcock Control Knob in so that the cupped end engages firmly onto the 3-way stopcock. Ensure that the Stopcock Control Knob is fully engaged to the handle of the 3-way stopcock so that it is limited to one-quarter turn by the small safety bar on the outside shaft of the Stopcock Control Knob. This requires the safety bar on the shaft of the stopcock Control Knob to be firmly seated in the limiting notch.

9. Remove the caps from the end of Flushing Tube 'B' and tube 'D' and attach 20ml syringes filled with water for injection (NOT SALINE) to the tubes 'B' and 'D' on the outside of the Delivery Box.
10. Prime all tubes with water for injection (see below). This is done with covers left on needles to maintain sterility.
 - 10.1. Note that there are one-way valves fitted to the tubes 'B' and 'D' to prevent any possibility of SIR-Spheres microspheres being injected back into either of the syringes.
 - 10.2. To enable flushing of all tubes with water for injection, partially disengage the Stopcock Control Knob to allow more than the limited one-quarter turn. This requires the safety bar on the shaft of the Stopcock Control Knob to be just free of the limiting notch, while still being engaged enough to control the 3-way stopcock handle.
 - 10.3. In order to prime the tube from the 3-way stopcock to the Long Needle (labeled 'C'), rotate the Stopcock Control Knob 90° counter clockwise (9 o'clock position) past the normal limit to allow water to flow through the 3-way stopcock into tube 'C'. *This is the only time it is recommended to disengage the Stopcock Control Knob by pulling it out slightly to allow full rotation.*
 - 10.4. Re-engage the Stopcock Control Knob fully so that it is limited to one-quarter turn.
11. Place the V-Vial Holder that contains the V-Vial with the SIR-Spheres microspheres into the Retaining Ring in the Delivery Box.
12. Swab the V-Vial septum and the sides of the hole in the top of the V-Vial Holder with alcohol. Care must be taken when inserting needles not to contaminate them. If contamination occurs, then discard Delivery Set and get a new one.
13. Remove cover from shorter needle (attached to the tube labeled 'D'). *This tube contains a one-way valve to prevent any SIR-Spheres microspheres flowing back into the delivery syringe.*
14. Insert the short needle 'D' through one side of septum and push it into the V-Vial all the way up to the hub. *It is important that this needle goes to the bottom of the V-Vial so that when water is injected it will swirl the SIR-Spheres microspheres into a thin suspension. The SIR-Spheres microspheres will be decanted from the top of the V-Vial. An excessively concentrated suspension of SIR-Spheres microspheres may cause clogging in the fine catheter.*
15. Remove cover from Long Needle (labeled 'C').
16. Insert the Long Needle through the V-Vial septum until it penetrates approximately 10mm below the surface of the water in the V-Vial containing the SIR-Spheres microspheres. *SIR-Spheres microspheres delivered to the patient must be decanted from the top of the V-Vial so the suspension remains dilute and does not clog the catheter.*
17. Remove cap on tube 'A' and connect tube 'A' to the patient, either via a surgically implanted hepatic artery port, or to a trans-femoral catheter. *It is preferable not to use another 3-way stopcock to the patient because the SIR-Spheres microspheres may deposit in the corners of the 3-way stopcock and become trapped.*

The apparatus is now ready for delivery of the SIR-Spheres microspheres.

When the apparatus is fully assembled, injecting water from the syringe on tube 'D' will cause the SIR-Spheres microspheres to swirl into a suspension and pass into tube 'C' and then into tube 'A' that is connected to the patient.

With the safety bar at the 3 o'clock position, deliver slowly from the Delivery Syringe (connected to tube labeled 'D' at a rate of approximately 5ml per minute. It is important to **deliver slowly** to reduce the possibility of SIR-Spheres microspheres refluxing back down the hepatic artery and into other organs such as the stomach or the pancreas. In order to achieve a slow delivery rate and to maintain the SIR-Spheres microspheres in suspension, the flow from the delivery syringe may be given in pulses of 0.25ml-0.5ml, separated by a pause. Use all 20ml of water for injection.

18. At all times observe the V-Vial and tubing to ensure that the SIR-Spheres microspheres are flowing properly and there is no leakage, blockage or air bubbles at the needle/septum interface. *If delivery of the microspheres is paused for any reason, continually flush lines with water for injection from tube B to prevent microspheres in the lines from settling out and blocking. If blockage does occur, it can be cleared by flushing water with the flushing syringe.*
19. When the whole 20mls in syringe 'D' has been delivered, there will still be some water and SIR-Spheres microspheres left in the V-Vial. In order to deliver this last remaining amount out of the V-Vial, push long needle to bottom of V- Vial, then inject air into tubing 'D' (Approx 8 – 10mls). This will cause all the remaining fluid to empty from the V-Vial.
Care must be taken to prevent air from entering the tubing going to the patient.
20. If using a transfemoral catheter, the specialist should periodically stop the delivery of SIR-Spheres microspheres and inject IV contrast through the Flushing Tube 'B' and perform fluoroscopy. This is an essential step to ensure that the catheter remains in the correct position in the hepatic artery at all times and also to ensure that no reflux is occurring back down the hepatic artery.
21. **It is absolutely essential to ensure that none of the SIR-Spheres microspheres are allowed to enter the gastroduodenal artery or other small arteries that pass from the liver to the stomach or duodenum. If there is any risk of this occurring then abandon the procedure.**
Note: only specialists who have received instruction from Sirtex Medical are to deliver SIR-Spheres microspheres.
22. When the delivery has been completed, the catheters are flushed and the tubing removed.

Directions for the use of the Delivery Apparatus are included with the Delivery Set. These directions should be read in their entirety prior to use and Sirtex recommends a practice run using a demonstration set (available from Sirtex) before the implantation procedure. The design of the Delivery Apparatus allows protection of staff and patient from radiation, and correct delivery of the microspheres.

The Delivery Apparatus should be set up in close proximity to the patient. The apparatus can be assembled on a steel tray and placed at the side of the patient.

1.26 Hepatic Artery Port Implantation

Generally this method of implantation would be used if the port were also to be used for other treatment, such as regional hepatic perfusion chemotherapy. This is commonly undertaken for patients with liver metastases and the chemotherapy is added to potentiate the effect of SIR-Spheres microspheres. The decision to use chemotherapy in addition to SIR-Spheres microspheres rests with the treating doctor. A surgeon who is totally familiar with this technique must undertake insertion of

the hepatic artery port. Attention to small surgical details can have a dramatic effect on the success or complications of the procedure.

There are several additional factors that should be noted if SIR-Spheres microspheres are to be implanted through a port. These include:

- The hepatic artery catheter should be placed into the arterial supply of the liver so that the catheter perfuses all the liver.
- There are frequently small arteries that pass from the common hepatic artery (and sometimes from the right and left hepatic arteries) to the stomach and the duodenum. These small vessels must be ligated at the time of inserting the port and catheter. Failure to ligate these small vessels may result in SIR-Spheres microspheres lodging in the stomach or duodenum at the time of SIRT and this may result in severe complications.
- The catheter is usually placed into the hepatic artery by inserting it through the gastro-duodenal artery, but may need to be placed into another artery.
- The diameter of the catheter should be at least 0.8mm. If smaller diameter catheters are used, they may block during the delivery of SIR-Spheres microspheres.
- The gallbladder may be removed to prevent SIR-Spheres microspheres from causing radiation necrosis of the gallbladder. This is most likely to occur with concurrent use of hepatic artery chemotherapy which frequently causes chemical cholecystitis.
- The patient must recover from any surgical operations before being treated with SIR-Spheres microspheres. These may include removal of primary cancer elsewhere, removal of the gallbladder or the implantation of the port and catheter.
- It is important to deliver the SIR-Spheres microspheres *slowly* into the hepatic artery. If this is done too quickly, the microspheres may reflux back down the hepatic artery and lodge in the pancreas, stomach or other organs. The catheter should be flushed at regular intervals during the delivery procedure to ensure the microspheres do not block the catheter.
- If a pump has been inserted, SIR-Spheres microspheres are implanted via the side port of the pump. In some types of pumps (eg Medtronic) the side port can only be accessed with a gauge 24 or smaller needle. Whilst SIR-Spheres microspheres can be injected through this small needle, there is an increased risk of the microspheres clogging the needle during injection. The operator should therefore inject a very dilute suspension of SIR-Spheres microspheres to prevent clogging of the needle.

If clogging does occur, it can usually be cleared by pulling back on the syringe and then injecting once more. This can only be done if SIR-Spheres microspheres are being injected into the side port directly from a shielded syringe. The Delivery Set can be used, but in the event of clogging, pull-back on the syringe (connected to Tube D) is not possible due to the one-way valves in the Delivery Set.

- If the pump does not have a separate side port, then it cannot be accessed to implant SIR-Spheres microspheres.

1.27 Trans-Femoral Implantation

The hepatic artery catheter is inserted via the femoral artery under X-ray guidance. If this is the preferred method of implantation, an experienced radiologist must perform the procedure.

The procedure for delivering the SIR-Spheres microspheres is similar to using a port, except that the femoral artery catheter is connected to the Delivery Set. Once the catheter has been correctly sited in the hepatic artery, the end of the catheter is connected to the SIR-Spheres microspheres Delivery Set that has been primed with water for injection. SIR-Spheres microspheres are then delivered into the trans-femoral catheter. The radiologist should periodically check the position of the catheter to ensure it remains correctly sited during the delivery procedure.

SIR-Spheres microspheres must be delivered slowly at a rate of no more than 5ml per minute as rapid delivery may cause reflux back down the artery into other organs. At the conclusion of the procedure, the catheter is removed and the patient returned to the ward for observation before discharge.

1.28 Radiological Placement of Catheter

As there are frequent arterial abnormalities in the blood supply to the liver, the radiologist must be familiar with these anomalies (see Chapter 5 of this document). If there are tumors in both lobes, every attempt should be made to deliver the SIR-Spheres microspheres into the main hepatic artery so that radiation is distributed to both lobes of the liver. If the tumors are limited to one lobe, the catheter can be selectively inserted into the lobar artery supplying only that lobe, thus sparing the normal lobe. This is an excellent method of delivering high radiation activity to the tumor while at the same time ensuring that one lobe of the liver is unaffected by the radiation.

It is essential that SIR-Spheres microspheres are not delivered to other organs, in particular the pancreas, stomach or duodenum. **The catheter that is inserted into the hepatic artery must be placed well distal to the gastro-duodenal artery in order to prevent SIR-Spheres microspheres going to the duodenum and stomach.** If there is any possibility of SIR-Spheres microspheres passing down the gastro-duodenal artery then the implant must not proceed. It is often preferable to block the gastro-duodenal artery with an intraluminal coil and/or gel foam or other agent to prevent SIR-Spheres microspheres from flowing to the duodenum. No harm will occur if the gastro-duodenal artery is blocked. **During the implant procedure, the radiologist must repeatedly check with fluoroscopy to make sure that SIR-Spheres microspheres are being delivered to the liver and that reflux is not occurring back down the artery as this will result in spillage into other organs such as the stomach and duodenum.**

Note: Virtually all complications from SIR-Spheres microspheres arise from the inadvertent injection of SIR-Spheres microspheres into small blood vessels that go to the pancreas, stomach or duodenum. If this is prevented then implantation of SIR-Spheres microspheres is a very safe procedure.

See also section 4.6 of this document regarding preventing gastritis.

1.29 Abnormalities of Liver Vascular Anatomy

Common anomalies in vascular supply are documented in Chapter 5 of this document. A Radiological work-up prior to the procedure is common.

1.30 Catheter Selection

1.30.1 Co-axial system

This is a safe, atraumatic approach with a high success rate and is the preferred method. Catheterize the coeliac axis with a simple single curved 5F non-tapered catheter, depending on the size of the artery.

Use a micro-catheter co-axially and the appropriate micro-guide-wires to catheterize the hepatic artery proper and its branches.

It may be preferable to use a micro-catheter but the operator must be aware that fine bore catheters may block unless the SIR-Spheres microspheres are delivered as a very dilute suspension.

Small bore catheters and needles may block with SIR-Spheres microspheres.

1.30.2 5F Catheter

This method is more traumatic than the co-axial system. Success rate of correct placement is lower as it is more difficult to accurately place the tip of the catheter in the exact position within the hepatic artery anatomy. Success depends on the hepatic artery anatomy, size and tortuosity. Size 4F catheters can be used, but 6F are too large and stiff.

Use a simple single curved 5F non-tapered catheter, depending on aorta size to catheterize the coeliac axis. Advance the catheter over an .035" guide-wire to the desired site. This catheter tip configuration is only suitable for some hepatic artery anatomy with larger diameter vessels.

Another useful catheter is a double curved catheter. The tip configuration is somewhat similar but it has an excellent modification to make it suitable for super-selective catheterization of the hepatic artery.

1.31 Peri-Procedural Precautions

1.31.1 Peri-Procedural Medications

To date, over 1,500 patients with liver cancer have been treated using SIRT since SIR-Spheres microspheres were approved in 2002 by the US Food and Drug Administration and the product was CE Marked for the EU. Over 85% of these patients have been treated as outpatients (defined as stays in hospital of 23 hours or less). Most patients are discharged within eight hours of treatment.

Optimizing peri-procedural care and discharge planning of all patients is very important. This is especially so for patients receiving SIRT, as most of these patients are treated in the palliative setting where quality of life is an important consideration.

The following clinical recommendations have been developed by physicians experienced in treating patients with liver cancer using SIRT.

1.31.1.1 Gastrointestinal prophylaxis to prevent GI inflammation and ulceration

A proton pump inhibitor (e.g. omeprazole or pantoprazole) or H2-blocker (e.g. ranitidine) commencing 1 week prior to treatment with SIRT and continuing for 4 weeks post treatment is recommended. While the Interventional Radiologist must ensure that SIR-Spheres microspheres do not enter the GI tract, radiation from large volume tumors in the left lobe of the liver overlying the stomach may be sufficient to irritate the stomach and cause gastritis and ulceration.

1.31.1.2 Anti-nausea prophylaxis

Anti-emetics (e.g. ondansetron or granisetron) for post-treatment nausea are recommended and should be commenced on the morning of the day of SIRT treatment.

1.31.1.3 Post-embolization syndrome prophylaxis

Fever, malaise and lethargy can occur as a result of the radiation injury and embolic effect of the SIR-Spheres microspheres on the tumor neo-vasculature. Provided the patient is not diabetic – and oral steroids are not otherwise contra-indicated – a tapering dose of oral corticosteroids (e.g. methylprednisolone or dexamethasone) is recommended.

1.31.1.4 Pain control

Oral analgesia (e.g. ketorolac) may be required for 1 week following treatment to relieve pain from radiation injury and the embolic effect of SIR-Spheres microspheres, and liver capsular pain from tumor edema.

1.31.1.5 Antibiotic prophylaxis

The use of empirical antibiotic prophylaxis is not routinely recommended and should be based upon assessment of each patient's individual infection risk.

1.31.2 *SPECT Imaging*

Sirtex recommends a SPECT scan of the upper abdomen be performed immediately after implantation of SIR-Spheres microspheres. The SPECT scan will detect the Bremsstrahlung radiation from the yttrium-90 to confirm placement of the microspheres in the liver. This is an optional test used for confirmation of correct placement only.

1.31.3 *Patient Monitoring*

1.31.3.1 Access Ports

If an access port has been implanted, weekly flushing with heparinized saline is the only maintenance required.

RADIATION

1.32 Radiation Regulation

SIR-Spheres microspheres are radioactive and hence are subject to regulations regarding receipt, storage, handling, use and disposal. SIR-Spheres microspheres can only be provided to facilities complying with the relevant regulations.

The body responsible for regulatory control of radioactive materials varies in each jurisdiction hence it is only possible to provide general guidance on the requirements. The relevant local authorities should be consulted to determine the regulatory requirements for handling SIR-Spheres microspheres. For example, in the USA, the Nuclear Regulatory Commission (NRC) is responsible for radiation controls and the regulations are in Title 10 part 35 of the Code of Federal Regulations. In the European Union, the Euratoms are the series of regulations that pertain to radiation controls required in various settings.

All persons involved in any aspect of handling, storing or disposing of SIR-Spheres microspheres must be familiar with and abide by all Local, State and Federal regulatory requirements governing therapeutic radioactive materials. If any Sirtex general recommendations conflict with local regulations pertaining to handling therapeutic radioactive devices, the local regulation takes precedence and must be observed.

1.33 Facility Requirements

Facilities using SIR-Spheres microspheres are subject to a number of requirements. These relate to the facility itself, the documentation and licensing required and the personnel and equipment that must be on site.

The information provided here is a general guide only and the exact requirements for each jurisdiction must be determined before introducing SIR-Spheres microspheres into the facility to avoid breaches of accreditation standards.

1.34 Physical Requirements

The physical requirements of the facility can be divided into a number of sections, these being:

- an area to receive the product
- an area to prepare the specific patient radiation doses
- an area to implant the device
- an area for storage of microspheres and items used in dose preparation or implantation that may be contaminated and are awaiting disposal or recovery
- an area for disposal of waste materials
- an area to accommodate, observe and nurse the patient after implant until their release.

The minimum requirement for all areas in which isotopes are used is:

- access strictly limited to those staff members with appropriate authorization;
- no opportunity for access by the general public;
- physical barriers, warning signs and alarms if appropriate.

The area receiving or taking delivery of radioisotopes must have restricted access. SIR-Spheres microspheres will normally be delivered to the hospital one day before intended implantation. In all facilities a secure storage area that may be shielded with lead or acrylic is generally required.

In Treatment Centers that receive specific radiation doses pre-measured and packed at a separate nuclear medicine facility or pharmacy, such a restricted area may be all that is required.

Where facilities receive 3GBq devices for the preparation of the specific patient doses, further regulations are likely to apply. These regulations are likely to address, for example:

- the floor and surface specifications – typically these need to be clean, undamaged, smooth and seamless. Floors must generally be watertight and services are therefore generally provided through the wall. Surfaces are designed to reduce dust and be easy to clean;
- work spaces – these should generally be arranged to allow traffic without obstruction. Workflow should be arranged to reduce movement of isotopes and passing traffic. Generally, movements of isotopes during operations should not involve leaving the restricted area;
- a storage area for isotopes and for material decaying until suitable for disposal - this is often shielded and at the back of the area away from passing traffic. If lead bricks are used on a bench to provide a shielded storage area, the bench will need to support the weight;
- sinks and drains – generally any drains designated as waste disposal are separated from other drainage systems in the facility. Sinks and basins should generally be wrist or foot operated to reduce possible contamination. Any sinks into which radioactive waste is poured should have splash-free water flow;
- safety – these generally include appropriate emergency exits, wash and first-aid stations;
- lighting – fluorescent lighting is generally avoided in counting rooms as they increase the background counts in Geiger-Muller tubes or liquid scintillation counters;
- pressure – generally radiation facilities are held under negative pressure to contain contamination.

This list is not exhaustive, and **local regulations must always be consulted**.

***Note:** Although aseptic transfer of the microspheres from the shipping vial to the v-vial is required, this procedure should **not** be performed under a laminar flow hood. Laminar flow hoods protect the product from contamination by the operator by directing air flow onto the operator. This is inappropriate with a radioactive material.*

The rigor of the regulation is generally determined by the types and quantities of isotopes handled by the facility, as well as the kinds of manipulations undertaken on the isotopes. Generally, the

requirements for handling diagnostic isotopes are lower than for therapeutic levels, and gamma emitters require greater infrastructure than most beta emitters.

The area for implanting the microspheres has some basic requirements, these being:

- separation from other procedures due to radioactive nature of the device;
- separation with solid partitioning, rather than curtaining (avoids intrusion and potential accidents);
- sterile access to the hepatic artery (via port or transfemoral catheter);
- an ability to contain and readily decontaminate any radiation spills; and
- adequate floor space for the necessary personnel and equipment.

If the patient is having the microspheres implanted via a transfemoral catheter, the procedure must take place in an appropriate area such as an angiography suite or laboratory.

After the implant, the patient requires observation, general nursing care and accommodation. Most facilities accommodate patients in single rooms, although a multi-bed unit with reasonable spacing between beds is sufficient, provided the patient is confined to the bed-space. This is because the patient's body attenuates the majority of the radiation.

Whether patients are in single or multi-unit rooms, the rooms should be away from high traffic areas (for staff, visitors and other patients). Most facilities group such patients in a single ward with staff experienced in nursing patients treated with radioisotopes. No other special facilities are required for the patient.

1.35 Documentation and Licensing

1.35.1 Licensing

Licensing of the facility in some form is likely to be required. The licensing required to introduce SIR-Spheres microspheres into a facility generally depends on the licensing currently in place, and reflects the type and quantity of isotopes on site and how the facility intends to handle the device.

In addition to licensing the facility, staff responsible for using, or performing various tasks using radioisotopes may require individual licenses. There may be a set application process and licenses to be issued on the basis of qualifications and/or positions held in the facility by the applicant, which are likely to require routine renewal.

1.35.2 Documentation

In addition to facility or personnel licenses, other documentation is generally required to accommodate the use of therapeutic isotopes within the facility. Such documentation generally includes certification or licenses supported by evidence of compliance with a raft of industry

standards for facilities, equipment, installation and maintenance. This documentation would normally be part of the requirements to be met to receive the license for the facility. Routine audit of the facility and supporting documentation may be part of general hospital or radiation safety accreditation systems.

The other documentation that is normally required is procedural, and this would cover standard working procedures and records for all staff handling isotopes. These procedures and records generally address issues such as traceability of all isotopes on the premises, including use, storage, location and movements, training and qualification records for personnel involved in handling isotopes, contamination monitoring procedures and records, personnel monitoring procedures and records, procedures for a safe working environment and compliance to regulations.

Introduction of a new product into a facility will require new procedures or revision of existing procedures. New procedures would be directly related to SIR-Spheres microspheres, but existing procedures may relate to internal training on safety requirements, risk analyses, decontamination procedures, for example. Again, these procedures must generally be in place to receive a license to handle the new device.

Guidance on procedural documentation specifically for SIR-Spheres microspheres can be found in Appendix 6 of this document.

1.36 Equipment

Equipment required falls into two major groups:

- equipment required for measuring radiation and
- equipment required to protect staff (shielding).

The equipment requirements will vary with the activities at the facility.

1.36.1 Radiation Measurement

Two main items of measuring equipment are generally required for SIR-Spheres microspheres; a beta counter or equivalent for determining environmental radiation from beta sources and an ion chamber or dose calibrator, such as a Capintec, for determining the activity of the device. All facilities will generally require a beta counter. These items of equipment should be kept in good working order and routinely calibrated for their purpose.

These items of equipment are generally held in the Nuclear Medicine Department (or equivalent) however, a beta counter is also required in the implant suite as part of routine monitoring for room clearance and if necessary, decontamination procedures. Measuring and monitoring equipment is not routinely required in post-implant room or ward.

The dose calibrator may not have been previously calibrated for yttrium-90, and this will need to be done before routine use for preparing specific patient doses. Yttrium-90 is a short penetration beta emitter, and the geometry of the source in the vial can affect measurement determination due to self-shielding effects. It is therefore imperative that:

- the microsphere slurry is as well dispersed and uniform as possible when taking measurements. This requires measurements to be taken quickly after dispersion, before the microspheres settle to any appreciable extent, and
- all measurements of a device be made in a container of the same dimensions and shape.

This means that confirmation of the radiation dose drawn from the shipping vial and placed into the v-vial, as described in Module 4, should be confirmed by difference by re-measuring the activity left in the shipping vial. Again, the microspheres must be as homogeneously suspended as possible to reduce inaccuracies due to changes in source geometry.

1.37 Shielding

Shielding of staff from radiation requires:

- distance between staff and the radiation source;
 - use of remote handling equipment;
- deliberate barriers when working with isotopes;
- appropriate protective clothing and
- working areas that will contain or restrict any contamination.

Radiation protection for other hospital occupants and the general public is generally achieved through restriction of access to nuclear medicine departments (or equivalents) and through strict controls on disposal of radioactive waste.

Distance between staff and the radiation source is achieved in most areas by physical distance between working areas and storage areas. Only staff involved in a procedure should be in attendance. Furthermore, staff should stand well clear at stages not directly involving them. The general rule is doubling the distance from any radiation source reduces the radiation exposure to 25%. Distance therefore provides significant shielding, particularly with the short penetration radiation produced by yttrium-90. Beta emissions from yttrium-90 are absorbed well by the air, hence the double distance rule overstates the radiation received at any given distance. These principles should be applied in the area preparing the specific patient dose, the implant suite and the ward.

The shipping vial, the v-vial containing the patient radiation dose, all instruments and disposable items used for preparing the dose and implanting the device should be handled with forceps to reduce finger doses.

Appropriate barriers to provide shielding will be a mandatory requirement. As SIR-Spheres microspheres are a beta emitter with a short penetration distance, shielding requirements are less than those for gamma emitters.

The device itself requires the greatest level of shielding. The product is therefore shipped and delivered in a package known as a Type A package. Transfer of the patient dose from the shipping vial to the v-vial should be a shielded procedure. This can be done while both vials are in lead pots but it is essential that this procedure be undertaken behind an acrylic or lead shield. This may be of any configuration, but an acrylic shield with a cover angled open away from the operator works well. The shield should allow easy access, generally from the side of the operator's hands. Acrylic provides good shielding for beta emitters and being optically clear, provides an unobstructed field of vision.

As an added precaution, the work area for dose preparation must be on a tray with a disposable absorbent lining to contain any contamination from accidental spillage.

The specific patient dose is encased in an acrylic shield for transport to the implant suite and during the implant procedure.

All staff must wear regulation protective clothing. This includes at least a protective coat or gown, preferably with full-length sleeves, but must also include a lead apron during the implant procedure if it occurs in an angiography suite. Disposable booties may be necessary in the nuclear medicine department. The microspheres form a slurry so there is always a potential risk of contamination as doses are drawn and delivered between vials, and when connecting and disconnecting tubes during the implant procedure. Double gloves are recommended to allow removal of a contaminated outer glove with a gloved hand. As the product is fluid, all persons present during the procedure are strongly advised to wear protective shoe covers.

1.38 Personnel

Personnel involved in any aspect of handling SIR-Spheres microspheres must be suitably qualified and be appropriately trained to deal specifically with this device. This includes nuclear medicine staff, staff involved in the implantation procedure and in post-implant care of the patient. Such staff require the support of a radiation safety officer or expert in radiation physics, and licenses for the facility will normally require that such expertise is available to ensure safe use of isotopes within the facility.

1.39 Checklist

A checklist of the general requirements is included in Appendix 7 of this document.

1.40 Radiation Safety with SIR-Spheres Microspheres

1.40.1 General Principles

As the device is radioactive, it must be regarded as being a serious radiation hazard to the hands of the staff preparing the specific patient dose and the staff involved in the implant procedure. This includes the staff responsible for room clearance after the procedure, typically the radiation safety officer, but possibly also nurses. Furthermore, the operations of preparing a specific patient's dose, implanting the SIR-Spheres microspheres and clearing the delivery apparatus after the procedure, must be regarded as having the potential to be a serious contamination hazard.

The procedure must be regarded as being:

- potentially a serious radiation hazard to the hands of staff preparing the individual patient dose and to the radiologist, surgeon or other doctor implanting the microspheres and
- potentially a serious contamination hazard.

Devices should be stored and handled in accordance with all local regulations pertaining to radioactive implantable device.

Once the device has been implanted, the patient becomes the radiation source. The hazard posed to others by the patient is significantly less than that of the device alone due to tissue absorption of the emissions.

There are three general radiation safety principles, which are:

- operations should be performed as quickly as possible;
- staff should maintain as great a distance as possible from the isotope and
- appropriate shielding should be used wherever possible.

As the emission from yttrium-90 is high-energy beta, shielding is best provided with a low atomic number material such as acrylic. This reduces the amount of Bremsstrahlung radiation produced. In addition, acrylic is optically clear and permits the physician to continually observe the product and procedure.

Dedicated accessories have been designed to meet the general principles of radiation safety and to assist with the handling of SIR-Spheres microspheres. The individual patient dose vial is in its own acrylic v-vial holder designed to be seated in the provided acrylic box. A shielded syringe must be used when preparing the dose. A syringe shield is provided. Yttrium-90 has two features that provide inherent safety for staff and patients. These are:

- the minimal penetration depth of emissions through tissue and air and
- the relatively short half life.

Further description of the safety accessories is provided later in 8.9.8 of this document.

1.40.2 *Monitoring for Radiation*

Monitoring of radiation exposure should occur at two levels. The first should include routine monitoring of the environment using an appropriate beta counter. Acceptable working limits for radiation are defined for most applications. Levels beyond these limits represent contamination and require action, as described in Section 8.9.18 Contamination.

Individual monitoring of staff is generally a requirement in accredited facilities and is highly recommended for all staff handling SIR-Spheres microspheres.

All staff generally wear film badges or some form of personal dosimeters. Badges should be worn to provide representative doses. For example, if a lead apron is standard protective clothing for the trunk, badges should be worn under the apron. In the case of SIR-Spheres microspheres, where finger doses are potentially high, monitoring rings may be used. As most detectors do not differentiate between gamma and beta doses, it is important to wear the rings facing away from the fluoroscopic X-ray source during transfemoral implants.

1.40.3 *Exposure Levels*

The following exposure levels are representative for the technician or pharmacist preparing a typical patient dose, and for the physician implanting that prepared dose.

		Trunk mSv (mrem)	Lens of Eye mSv (mrem)	Hands mSv (mrem)
Pharmacist	Shallow Dose (0.07mm)	0.027 (2.7)	0.026 (2.6)	0.35 (35)
	Deep dose (10mm)	0.003 (0.3)	0.004 (0.4)	
Physician	Shallow Dose (0.07mm)	0.038 (3.8)	0.12 (12)	0.32 (32)
	Deep dose (10mm)	0.004 (0.4)	0.054 (5.4)	
Radiation Safety Officer	Shallow Dose (0.07mm)	<0.02 (<2)	0.04 (4)	0.2 (20)
	Deep dose (10mm)	0.01 (1)	0.017 (1.7)	

Various regulatory bodies may determine acceptable occupational radiation exposure limits.

International Commission on Radiological Protection (ICRP) Occupational Radiation Dose Limits are as follows:

Whole Body Effective Dose Limit

20mSv per year (averaged over 5 years) and no more than 50mSv in any one year

Lens Equivalent Dose Limit

150mSv per year

Extremity (eg Finger) Equivalent Dose Limit
500mSv per year over any 1cm²

These representative exposure levels are additive to other sources of exposure for workers.

The following dose rates may be expected from patients with implants of approximately 2GBq when taken approximately 5-6 hours after implant.

0.25m	18.8 μSv/hr (microSieverts/hour)
0.5m	9.2 μSv/hr
1m	1.5 μSv/hr
2m	0.4 μSv/hr
4m	<0.1 μSv/hr

In the adjoining room at the wall immediately behind patient's bed-head the measurement was <0.1 μSv/hr

Typical measurements within limits are 20μSv in any hour and 250μSv in any seven days.

1.40.4 Handling the Device

1.40.4.1 Receipt

When receiving the device, or the pre-measured specific patient dose, the product should only be handled to the extent required to verify the correct device has been delivered. Unpacking from the Type A package will generally be required, and if hospital regulations require or allow it, the lead pot may be opened to visualize the product for any obvious irregularities. It may be helpful to visually inspect the device on arrival, so that any fault that may preclude use can be identified at the earliest possible time.

After fulfilling incoming inspection requirements, the device should be stored appropriately inside the Type A package until the patient radiation dose is to be drawn. If the microspheres are delivered pre-measured, confirm the product is as ordered and in good order and return it to its shielded container for storage until implant time.

To visually inspect the microspheres, the shipping vial, or v-vial (as applicable) must be removed from the lead pot. This should be done using long forceps or tongs to reduce radiation doses to fingers. Furthermore, if acrylic shielding is available, the inspection should be through such shielding.

1.40.4.2 Storage

The duration of storage will vary depending on when the facility receives the SIR-Spheres microspheres. Devices are generally delivered the day before intended implant to allow time for dose preparation.

During storage, the SIR-Spheres microspheres should remain in the shielding in which they were shipped whenever possible. At the least, this should be the lead pot, if not the Type A package. Pre-measured doses are also likely to be delivered in a lead pot. If the nuclear medicine department prepares a patient dose in advance, the v-vial should be placed into the acrylic v-vial holder for storage until required.

The lead pots or acrylic shields are effective in absorbing the beta emission from yttrium-90. Bremsstrahlung radiation is produced as the emissions hit the shielding, and lead will cause more Bremsstrahlung radiation than acrylic. Where possible, storage of microspheres should be in a separate shielded area away from the general work area. Shielding is best provided by acrylic. However, if a general lead shielded area is available, this is usually sufficient.

In facilities preparing the specific patient doses, excess SIR-Spheres microspheres need storage until decayed sufficiently for disposal. These excess microspheres are generally left in the shipping vial, which should remain in the lead pot until disposal.

Other items requiring storage may include recoverable and disposable equipment or materials from the dose preparation, implant or immediate after-care procedures. Items that become contaminated during these procedures may require storage before meeting limits that allow disposal or routine cleaning by the standard hospital systems. Depending on the storage area set-up, items may be separated into areas for recoverables and disposables, which may be further separated into those with biological contamination and those without.

1.40.4.3 Disposal

There are three general principles for managing disposal of radioactive waste; these are:

- Delay and Decay;
- Concentrate and Contain and
- Dilute and Disperse.

Generally, the principle of delay and decay applies to SIR-Spheres microspheres and any items that may be contaminated with yttrium-90. This principle works well because yttrium-90 has a short half life, thus decay time to safe disposal levels is not extensive. Furthermore, the penetration of emissions in air reduces the relative risks of storing the isotope; this is further enhanced by appropriate shielded storage.

The delivery set, v-vial, catheters and other single-use disposables will contain small residual quantities of microspheres and require monitoring for radioactivity. These items are to be disposed of according to local procedures. This may involve storage to decay prior to disposal through the usual facility waste system. All gowns and surgical gear must be monitored at the end of each procedure.

Contaminated items should be bagged, labeled and returned to the medical physics department or other designated area for decay until safe for laundering or other disposal. Where possible surgical instruments may be decontaminated in the procedure room.

The shipping vial will contain residual microspheres not required for the patient dose. These vials are to be stored to decay if necessary in accordance with local regulation and disposed of appropriately through the general waste system.

The dilute and disperse principle may be used for any body fluids from the patient that may require disposal through the general sewage system in the first 24 hours after implant. Trace amounts of radioactivity have been detected in urine in the past in the order of 25-50 KBq per liter of urine per GBq of dose, which can generally be dispersed to acceptable levels by the double flushing of a standard cistern.

Limits on activity for disposal of various isotopes using the various methods of waste management apply in most jurisdictions. Knowledge of and compliance with applicable radioactive material disposal regulations is mandatory. Facilities generally have strict policies to ensure compliance to this important issue.

1.40.5 Radiation and Dose Preparation

Of all personnel handling the device, staff preparing specific patient doses handle and manipulate the highest activity. This is particularly so if the dose is prepared the day before the implant. Dose preparation is therefore undertaken in an approved facility, which may be a registered or certified nuclear medicine pharmacy or dispensary or a nuclear medicine department within a hospital or other facility.

1.40.5.1 Procedures Related to Radiation Safety

SIR-Spheres microspheres product has been designed and packed to reduce the radiation hazards associated with all stages of handling, including dose preparation. Although the device consists of solid microspheres, these are suspended in slurry to allow the specific patient dose to be withdrawn as a volume in an essentially sealed system, that is, a needle and syringe. This provides two important safety features, these being the ability to conveniently add shielding to the handling process and a low risk of spilling the microspheres.

The shipping vial is delivered in a lead pot; this provides shielding. The shipping vial should remain in the lead pot at all times except when being transferred to and from the dose calibrator. The vial should always be handled with tongs.

The v-vial into which the patient dose is dispensed should be placed into a lead pot in advance of the transfer of microspheres, and placed in close proximity to the shipping vial pot to reduce the distance of transfer and maximize the shielding. The crimp of the shipping vial may be partially removed so that only sufficient septum to allow piercing with the needle need be exposed, and the aluminum crimp provides additional shielding.

A venting needle (25 gauge) should be inserted into the side of the dispensing vial to ensure that there is no pressure in the system.

Once the microspheres have been drawn into the syringe and the needle is clear of the slurry, a slight pull-back on the plunger to remove slurry from the needle will reduce the chance of a drop of fluid dripping during transfer. The transfer should be undertaken as fast as possible commensurate with accuracy and safety.

A venting needle (25 gauge) should be inserted into the side of the dispensing vial to equilibrate pressure.

Once the microspheres have been transferred into the v-vial, the needle should be raised above the fluid line to allow the pressure in the vial to equilibrate. This reduces the chance of a small drop spurting from the needle due to pressure, as it is withdrawn from the v-vial.

Lead pot lids should be kept on unless the vial is being directly accessed. Once the dose in the v-vial has been confirmed, the v-vial should be transferred quickly (using tongs) to the acrylic v-vial holder.

The residual microspheres should remain in the shipping vial, in the lead pot in the designated storage area. The patient dose in the acrylic holder should be similarly stored until required.

1.40.5.2 Equipment Related to Radiation Safety

The syringe used to draw the specific patient dose should be shielded, preferably in a acrylic shield. To reduce the risk of spillage from a very full syringe a 5 ml syringe is recommended, even if volumes less than this are required. Various brands of syringes may fit well into particular shields. The syringe shields routinely used by Sirtex fit 5ml Terumo syringes very well.

Additional shielding is recommended for dose preparation. This could be lead or acrylic. A convenient configuration is shielding with an acrylic 'windshield' with easy side access for performing the tasks.

Performing the dose preparation on a tray with a low lip lined with an absorbent disposable material will assist in containing any drips that may occur.

Standard protective clothing and eyewear are recommended.

The procedure generates a number of disposable items, these being:

- needles and syringes;
- absorbent pads and wipes;
- operator's gloves and
- swabs for the shipping vial septum.

These should be considered contaminated and handled according to the facility procedures.

The syringe shield and pots are recyclable and should be decayed and washed. Forceps may also require decay before cleaning. Protective clothing should be routinely monitored for contamination and handled appropriately.

1.40.6 *Radiation and the Implantation Procedure*

1.40.6.1 Procedures Related to Radiation Safety during Implantation

Equipment used to perform the implant should be positioned close to the patient. Additional instrument and procedure requirements such as swabs and closures should be as close as necessary. Receptacles for contaminated disposable or recoverable items should also be conveniently placed to reduce the risk of spreading contamination. Such receptacles should be clearly labeled as radioactive and either recoverable or disposable.

Standard nursing procedures require reconciliation of all materials used during the procedure, and collection of contaminated items must accommodate the reconciliation without unnecessary exposure, particularly to the hands of staff.

Handling of all actual or potentially contaminated materials should be with forceps. This includes the transfemoral catheter that is removed after the procedure. Double gloving is recommended.

1.40.6.2 Equipment Related to Radiation Safety during Implantation

The acrylic Delivery Box and Delivery Set is provided by Sirtex and the use of these accessories is recommended to provide distance, shielding and containment of any spillage. The Delivery Box contains a removable v-vial holder, as described in Chapter 6. The v-vial containing the patient radiation dose can be delivered from the nuclear medicine department to the implant suite in this holder. The Delivery Box can be placed onto a tray with an absorbent, plastic backed liner and placed on a surgical trolley close to the patient near the point of implantation. This will be the groin area for those being treated transfemorally, and the upper abdomen or lower chest for those with an implanted catheter with port.

General Equipment

Local regulations should be followed regarding the equipment generally required for radioactive treatment and the methods for collecting waste. The following provides some guidance to equipment that may be useful. In general, any waste containers should be placed onto absorbent plastic backed pads as a measure to contain any spillage.

Equipment falls into two groups:

- the items routinely required for the procedure and
- additional items that may be required in the case of contamination, ie a spill pack.

The spill pack includes similar items to those required generally; however, a dedicated pack is recommended to ensure there are adequate supplies to effectively control any contamination. For convenience, the general items and the spill pack may be prepared as two standard boxes of materials for the implant procedure.

General Box (Box 1)

Item	Purpose
Radiation Monitor	Check surfaces, equipment and personnel for possible contamination
Single-use Materials	
<ul style="list-style-type: none"> • Plastic bags 	Receive waste
<ul style="list-style-type: none"> • Absorbent Plastic Backed Pads 	Place under all equipment or containers to contain any spills
<ul style="list-style-type: none"> • Paper hand towels 	General use
<ul style="list-style-type: none"> • Disposable cups with lids 	Received used materials during the procedure; transfer to appropriate containers after stock-take
<ul style="list-style-type: none"> • Gauze swabs 	General use
<ul style="list-style-type: none"> • Sterile disposable gloves 	General use
Trefoil Tape and Pens	Labeling containers with contaminated materials (tape) and for labeling disposables and recoverables containers.
Containers to Collect Waste	
<ul style="list-style-type: none"> • Baskets 	Lined with plastic bags for collection of all used items except instruments and sharps. Generally have two, one for disposables, one for recoverables
<ul style="list-style-type: none"> • Rigid containers 	For collection of sharps and instruments. Generally have a dedicated sharps container and another for recoverable instruments
Disposable Plastic Sheet	Place on the floor under the trolley with the delivery apparatus on it. Allows rapid and safe removal of any spill on the floor during the procedure
Decon 1:10 Dilution	General cleaner for wiping surfaces during room clearance and cleaning surgical instruments during the procedure

Spill Pack (Box 2)

Item	Purpose
<i>Single-Use Materials</i>	
<ul style="list-style-type: none"> • Plastic bags 	Receive waste
<ul style="list-style-type: none"> • Absorbent plastic backed pads 	Place over spills for rapid containment and assistance in removal
<ul style="list-style-type: none"> • Paper hand towels 	General use
<ul style="list-style-type: none"> • Plastic overshoes 	Reduce spread of contamination and protection for staff dealing with the spill
<ul style="list-style-type: none"> • Plastic apron 	Reduce spread of contamination and protection for staff dealing with the spill
<ul style="list-style-type: none"> • Single-use gloves 	General use
<i>Trefoil Tape and Pens</i>	Labeling containers with contaminated materials
<i>Surgical Gown</i>	Staff protection
<i>Decon Concentrate (10%)</i>	Remove all spilled material from surfaces.

1.40.6.3 Room Clearance

Room clearance is generally the responsibility of the radiation safety officer or medical physicist. All contaminated materials (disposable or recoverable) must be available to stock-take throughout the procedure, and particularly for final reconciliation at the end. Once stock-take is complete, containers can be sealed for removal to the storage or disposal area as appropriate.

All gowns and other surgical equipment should be monitored using the radiation monitoring equipment for contamination at the conclusion of the procedure, and if contaminated, bagged and sent to the storage area to await laundering. Surgical instruments should be cleaned in Decon to decontaminate them. Once decontaminated, they can be handled in the normal manner.

Once all materials and staff are removed from the room, a final check with the radiation monitor should verify that the room is not contaminated and is ready for re-use. All staff should be checked, including soles of shoes, hands and body before leaving the area.

1.41 Radiation Safety with the Patient

1.41.1 General

Once the patient has received the implant, they effectively become the radiation source. The minimal penetration distance of the beta emissions in tissue means that patients pose a very small radiation risk to staff and other contacts. Some general precautions should be observed, and local regulations may over-ride these general guidelines.

Pregnant staff should not be involved in treating or nursing these patients at any stage.

1.41.2 Immediate Post-Implant Care

The patient may be moved from the treatment room into a recovery room. This is particularly the case for a transfemoral implant, as angiography suites are heavily utilized. If the implant is via an implanted catheter, and takes place in a routine treatment room, the patient can remain in the room.

It is worthwhile having a qualified staff member in attendance for about an hour after the implant to observe the patient, answer any questions the patient may have and monitor for any unusual circumstances.

If any dressings, such as those over the port or the transfemoral wound need attendance, staff should wear gloves as a matter of routine. It may be advantageous to wear double gloves. Any dressings removed should be placed into a plastic bag, labeled as a radiation hazard and sent to the radiation facility for storage and subsequent disposal.

1.41.3 Accommodation

The facilities required to accommodate patients after implant have been previously described at the start of this module. Additional measures that may be implemented include the following. Local regulations may mandate these or stricter measures.

To indicate that the patient is radioactive, a sign should be placed at the head of the bed and an identity band with the trefoil (or similar warning of radiation hazard) should be worn by the patient. In many facilities, a written ward instruction is issued for radioactive patients. Examples of both these are in Appendix 6 of this document.

The patient should generally be confined to the bedspace or private facilities until discharged or otherwise advised by the Radiation Safety Officer.

1.41.4 General Nursing Care

See also Appendix 10 of this document.

Patients may be nursed in general ward with routine observations of pulse, BP, respiration etc. as for any equivalent small operative procedure. For transfemoral patients, the groin incision should be observed for 24 hours for hematoma formation. The patient may continue these observations at home if admitted as a day patient. The patient should be kept supine for 6 hours, with full mobilization after 24 hours. If a femoral closure device is used, the manufacturer's instructions should be followed.

The patient can receive normal nutrition and fluids as tolerated immediately after the procedure.

With regard to contamination, all body fluids and secretions have been monitored in the past for activity. To date only light contamination (typically 25-50 KBq per liter of urine per GBq of dose), in urine, has been detected in the first 24 hours post-implant. Therefore:

- there is no need to collect bed linen, rubbish or items of clothing;
- if staff need to change catheter bags, drainage bags etc., then gloves are to be worn and the bags are to be discharged into the sluice and flushed twice; and
- the patient may use the toilet in private facilities, using a double flush of the cistern.

See also 8.9.16 for advice upon discharge.

1.41.5 Medical Testing and Other Interventions

During the first few days after implant, it may be necessary for medical tests to be performed. These may include imaging, clinical examinations or taking of tissue or fluid samples. In some cases, a surgical procedure may be necessary. These need not be related to their treatment with SIR-Spheres microspheres. As general guidance, a procedure can be safely undertaken when the person

performing it receives less than 1 mSievert (100mrem). In such cases, additional precautions are not normally required. This should be determined by measurement at one meter from the patient (or tissue sample) before such procedures are conducted as the exposure rate may differ on an individual basis depending on patient anatomy, disease condition, shunting and others.

1.41.6 *Visitors and Contacts*

Visitors may generally be allowed for periods of 30-40 minutes. Pregnant visitors or children under 15 should be asked not to visit in the first two days and should be wary of spending too much time in close proximity to the patient the first week after implant (see also 8.9.16.1).

1.41.7 *Patient Release*

1.41.7.1 Discharge Procedures

Generally, the ward is formally notified in writing of the discharge date or the date to suspend precautions. Sample instructions are given in Appendix 6 of this document.

Generally the patients are physically well after the implant. Many centers may choose to admit the patient for overnight observation, but normally there is no medical reason to hospitalize them. However, in most jurisdictions there are legal limits for patient release and these may be a fixed limit of activity, or determined by the radiation dose received by others in contact with the patient.

For example in the USA, 10CFR 35.75 states that patients may be released from hospital if the total effective dose equivalent to any other individual from exposure to the released individual is unlikely to exceed 5 mSv. Written instructions as to how to minimize exposure to other individuals are to be issued if their exposure rate is likely to exceed 1 mSv. In Australia (see “Recommendations for the Discharge of Patients Undergoing Treatment with Radioactive Substances”, ARPANSA 2002) the effective dose to the general public should not exceed 1 mSv per year but for an appropriately informed carer providing support for the patient the constraint is relaxed to 5 mSv.

When patient specific dose estimates to family members and members of the general public are not available, it is recommended that patients only be released when the ambient dose equivalent rate at 1m from the patient does not exceed 25 μ Sv/hr. Measurements around patients who have received SIRT (see section 8.9.3) show that this dose rate is unlikely to be exceeded even on the day of treatment.

The patient should observe the following recommended precautions after receiving treatment with SIR-Spheres microspheres:

- a) no travel on public transport, including air travel, lasting more than 2 hours for 1 week;
- b) avoid crowded public places for 1 week;
- c) do not sleep in the same bed as your partner for 1 week;
- d) no contact with children or pregnant women for 1 week and
- e) adult visitors may approach the patient for periods of a few minutes at a time, but for prolonged periods they should stay more than 2 metres (6 feet) away for 1 week.

1.41.7.2 Documentation

Ward documentation may consist of, for example:

- ward instruction regarding a radioactive patient;
- a wrist band identifying the patient as radioactive, or
- notification of discharge or to suspend precautions.

Additional documentation that may be required if the patient is released under special approval:

- a letter explaining the treatment that has been given and relevant information for radiation protection, or
- a wristband that will identify them as being under treatment from a radioactive source. (This may be the same as the in-patient wrist band).

Examples of these documents are included in Appendix 6 of this document.

The letter should be such that it may be given to a doctor or any relevant authority to explain the radioactive nature of the patient. The content of the letter should be explained to the patient in appropriate terms.

As a general estimate, the patient should wear the wristband until the implanted activity is of the order of 300MBq. The wristband may include a contact number in case medical attention is required.

1.41.7.3 Travel

The patient should proceed directly home. When the patient must travel by public transport, the traveling time should not exceed that time in which an adjacent passenger would incur a dose of 1/10 MPD, i.e. 100 μ Sv. In practical terms, 5 hours after implantation, the dose rate at 0.5m from a patient is about 9.2 μ Sv per hour, so travel for 11 hours will transmit a dose of 100 μ Sv to a person sitting 0.5m from the patient. The allowable travel time increases as the activity decays. The recommendation is no longer than 2 hours for the first week.

1.41.8 *Patient Death*

In the event of a patient dying while in the hospital, the body may be move to the mortuary in the usual manner. The hospital radiation safety officer should be consulted before any procedures are performed on the body. The maximum level of activity below which disposal of deceased persons can proceed without special precautions depends on the mode of disposal (e.g. embalming, burial, cremation) and will vary in different jurisdictions. Typical examples include:

Necropsy	150MBq
Cremation/Burial	1.00GBq
Embalming	150MBq

1.42 Dealing with Contamination

All contamination with SIR-Spheres microspheres should be treated seriously. Being a solid suspended in liquid, contamination for SIR-Spheres microspheres is likely to be on surfaces or people, rather than airborne. In the absence of an obvious event, routine cleaning and monitoring of surfaces, work areas, floors and equipment should be conducted. Decontamination procedures are the same, regardless of resulting from an occult or obvious event.

Contamination may be transferred from one surface to another, such as bench to hand to bench or surface to person via direct contact. Contamination from SIR-Spheres microspheres is removable contamination, and is therefore easily spread. It is, however, also removable with normal cleaning procedures.

In general the radiation safety officer takes charge of decontamination. The standard procedures in facilities may vary, but are likely to be similar to the example described here.

1. The first task is to prevent access to the contaminated area. This protects staff and limits spread of contamination.
2. The radiation officer dons appropriate protective wear. As SIR-Spheres microspheres contamination consists of a liquid spill of non-volatile materials, respiration equipment is generally unnecessary. Full length surgical clothing is generally standard for a facility, and a gown should be placed over this. Plastic disposable overshoes and a plastic disposable apron should be considered in light of a liquid spill. Double gloves are recommended. Generally the hair is covered in a cap and protective eyewear is worn as radiation protection and splash protection.
3. A radiation monitor is required and should be placed in a fixed position on a non-contaminated surface. All measurements should be taken by holding the item in front of the monitor. This provides stable background readings and allows interpretation of the measurements. In the absence of a non-contaminated surface, a second person, also in protective clothing should hold the monitor in a fixed position. The officer performing the decontamination should avoid holding or touching the monitor after decontamination begins.
4. All personnel in the area of the contamination should be monitored and if non-contaminated should leave the area.
5. Contaminated personnel should be decontaminated before addressing contamination in the facility.
 - 5.1 Remove all contaminated clothing and place it directly into an appropriate receptacle without placing it on any surface, contaminated or not.
 - 5.2 If there is contamination on the skin, the officer should wipe the area using a disposable paper towel moistened with water or soapy water. Wiping should be from the periphery of the contamination towards the centre to avoid spreading the isotope.
 - 5.3 Care needs to be taken not to spread or drip water into the eyes, nose, mouth or ears.
 - 5.4 After each wipe is used, it should be monitored and then placed directly into the appropriate waste receptacle.
 - 5.5 Wiping should continue until monitored wipes demonstrate that the contamination has been removed.

- 5.6 Due to the normal dress standards in an isotope measuring or implant facility, the only skin likely to be exposed to the risk of contamination is the face and neck. As such, washing with water and soap is best avoided due to the risk of rinsing spheres into the eyes or nose etc, and the risk of spreading contamination via splashing.
 - 5.7 Soap is not generally required to remove contamination, as the microspheres and the water in which they are suspended are not sticky or tenacious on skin or other surfaces.
 - 5.8 The radiation officer should always perform the personnel decontamination in a controlled manner. Self-removal of contamination generally increases the risk of spreading contamination.
6. Once all staff have been decontaminated and removed from the area, the facility can be decontaminated.
 7. The radiation officer uses reports from the staff involved, direct observation and objective measurements to determine the extent of contamination.
 - 7.1 The first step is to mark out the area of contamination. At no stage, should anyone cross through this area, as it will spread contamination.
 - 7.2 As a beta emitter, shielding of the area is not generally required, however this should be at the discretion of the radiation officer.
 - 7.3 Decontamination should begin from the periphery and work towards the centre. Forward progress should only occur after objective measurements on the materials used to wipe surfaces or instruments demonstrate that the immediate area is clean.
 - 7.4 An initial step can begin with covering the area of spill with disposable plastic backed absorbent pads. These offer a number of advantages. They will absorb the liquid and microspheres, and the plastic backing prevents the contamination coming through to the top of the cover. This allows these to be picked up without direct contact with the contamination. It is also possible to walk on these if necessary in areas where large spills have occurred.
 - 7.5 Decontamination is by wiping the area with disposable paper towels moistened with water or a suitable cleaner such as Decon. These towels should be monitored before being placed directly into the appropriate receptacle for disposal.
 8. At completion of the decontamination process, the radiation officer should be monitored for contamination and all disposables and protective clothing should be bagged appropriately.
 9. All bags should be sealed and tagged before removal to the disposal area.

The derived working limits (DWL) above which a surface is deemed to be contaminated, are based on external radiation as the limiting hazard for beta radiation. For hand contamination, the limiting hazard is skin irritation for beta radiation.

The ICRP DWL for beta radiation in an active area is 10 Bq per cm². One microsphere has an activity of approximately 30-40 Bq, so spillage of a single microsphere constitutes a hazard requiring decontamination.

End of Program

APPENDIX 1: NUCLEAR MEDICINE BREAK-THROUGH SCAN

Guideline for Performing a Nuclear Medicine Break-Through Scan

The purpose of performing a Nuclear Medicine Break-Through Scan is to assess arterial perfusion of the liver and the fraction of radiopharmaceutical tracer that will pass through the liver and lodge in the lungs.

The Agent used is Technetium-99 labeled MAA (Macro-Aggregated Albumin), at a dose of 150MBq. Any large field of view gamma camera can be used.

In preparation for the scan, the patient needs to have a surgically implanted port or trans-femoral catheter placed in the hepatic artery.

After a qualified medical practitioner injects the Technetium-99 labeled MAA into the port or catheter the patient is positioned supine under the gamma camera and the images recorded.

Analogue: * Anterior and posterior images of planar abdomen and thorax.

Measure 700K –1000 K-cts for abdomen and same time for thorax.

Right lateral Abdomen - same time acquisition as for Anterior.

Digital: * 4 frames; 300"/ frame 64 x 64 matrix Word mode.

Image anterior and posterior abdomen

Image anterior and posterior thorax

To analyze the data draw Region Of Interest around whole of liver and whole of lung fields. Calculate G mean for liver region and lung region. Then calculate Lung/Liver ratio

If percentage lung shunting is >10% then there is need for dose reduction of SIR-Spheres microspheres.

APPENDIX 2: TABLE OF TOXICITY FROM PHASE 3 HAC TRIAL

	Grade 1 and 2¹		Grade 3 and 4²	
Events	FUDR	FUDR + SIR-Spheres microspheres	FUDR	FUDR+ SIR-Spheres microspheres
<i>Haemoglobin</i>	4	5	1	0
<i>Bilirubin</i>	7	2	0	1
<i>AST (SGOT)</i>	110	109	14	7
<i>Alk. Phos.</i>	90	188	5	14
<i>Nausea/vomiting</i>	5	13	2	1
<i>Diarrhoea</i>	6	3	1	0
Total	222	320	23	23

¹ Unpublished source data on file at Sirtex.

² Gray B, Van Hazel G, Hope M, Burton M, Moroz P, Anderson J, GebSKI V. Randomised trial of SIR-Spheres microspheres® plus chemotherapy vs chemotherapy alone for treating patients with liver metastases from primary large bowel cancer. *Annals of Oncology* 2001; 12: 1711-1720.

APPENDIX 3: TABLE OF TOXICITY FOR PHASE 2 IV TRIAL

Grade 3 and 4		
Events	5-Fluorouracil + Leucovorin	5-Fluorouracil + Leucovorin + SIR-Spheres microspheres
<i>Liver Abscess</i>	0	1
<i>Cirrhosis</i>	0	1
<i>Anorexia</i>	1	0
<i>Nausea/vomiting</i>	1	1
<i>Diarrhoea</i>	1	2
<i>Granulocytopenia</i>	0	3
<i>Mucositis</i>	1	4
<i>Gastritis</i>	1	1
Total	5	13

Source: ASCO Presentation by Sirtex 2002

APPENDIX 4: RADIATION DOSIMETRY AND EFFECTS

App 4:1 Point Source Beta Radiation

Radiation dosimetry from implanted point source beta radiation is complex because it requires precise knowledge of the distribution of the radiation sources, the overall activity implanted and the penetration depth of beta radiation in the various implanted and adjacent tissues.

The beta radiation dose to a point in tissue at a given distance from a point source of yttrium-90 may be arrived at, for example, by the application of empirically derived equations proposed by R. Loevinger *et al* in Radiation Dosimetry by Hine and Brownell (1956) pps 693-716.

These equations have been applied to calculate the beta dose rate to tissue at increasing distances from a 1 MBq point source of yttrium-90. The results are shown in Table 1 below. Also shown are the calculated doses as a percentage depth dose of the peak dose.

Table 1: Dosimetry from a point source of Y90

Dist from P (cm)	Dose Rate (c Gy/sec)	% Depth Dose
0.165	0.0883	100.00
0.2	0.0589	66.73
0.3	0.0214	24.37
0.4	0.0088	9.93
0.5	0.0038	4.33
0.6	0.0017	1.97
0.7	0.0008	0.92
0.8	0.0004	0.44
0.9	0.0002	0.21
1.0	0.0001	0.10

$$\text{Dose in Gy} = \text{cGy/s} \times 3600 \times 92.5 \times 1/100$$

This theoretical example demonstrates that the dose is largely confined to 2-3mm from the point source. This means that dosimetry is determined largely by the distribution of the microspheres and clusters thereof in the tumor and the liver. The same applies for any microspheres shunted to the lung or inadvertently placed into other organs.

SIR-Spheres microspheres result in a heterogeneous point source radiation distribution in the liver. This has been demonstrated by microscopic examination of implanted tissues (*Campbell AM, Bailey IH, Burton MA, Tumor dosimetry in human liver following hepatic yttrium-90 microsphere therapy. Phys Med Biol 2001; 46: 487-498*). The dose at any point in any tissue sample can be calculated by computing the distance from that point to each microsphere in the neighbourhood of that point. Microspheres greater than 8mm from any point will not contribute to the radiation dose to that point. The depth dose relationship can be used to determine the dose contribution of each microsphere and

the total dose is the sum of all doses from contributing microspheres. The dose received by any tissue point is thus given by;

$$D = \sum_i 989Q_i(1 - r_i/L)/r_i^2 \quad \text{Gray} \quad \text{for } 0 < r_i < L$$

where Q_i is the activity of i th microsphere in MBq and r_i is the distance to the i th microsphere in mm. The effective range of electrons, L , is taken to be 8mm. Microspheres can be assumed to represent point sources of activity so that there is no lower limit on r_i , but $r_i \neq 0$. In any case the value of r_i is most unlikely to be precisely 0.

A plot of dose, D , normalised by the dose that would have been received if the activity was uniformly distributed throughout the liver, D_u , against the percentage of tissue receiving more than D would show that the vast majority of the liver receives less than D_u . D_u is calculated using the formula;

$$D_u \text{ (Gy)} = 4.97 \times 10^{-2} A/W$$

where A is the total activity in MBq contained in a mass of liver of W kg (see Fox RA, Klemp PFB *et al.*, *Dose distribution following selective internal radiation therapy. Int J Radiation Oncology Biol Phys* 1991;21(2): 463-467).

These mathematical manipulations can be performed in a research setting on tissue samples, but are not applicable to a clinical situation in which it is not possible to predict the absolute ratio of microspheres that will distribute to the tumor and normal liver compartments just by estimating the size of the liver. The tumor to normal arterial blood flow ratio, and hence the radiation dose, is highly variable between patients, and between different metastases within the same patient. The assumption that yttrium-90 microspheres provide a homogeneous radiation source is inaccurate. This is the result of the considerable variation in arterial blood flow between segments of the liver and the microspheres being delivered, as a series of heterogeneously distributed point sources of radiation. This provides highly variable radiation doses to individual cells. Reports of radiation doses to normal liver tissue from yttrium-90 microspheres that exceed known lethal doses from external radiation sources are thus only 'inferred' as not all cells receive doses at this level.

App 4:2 MIRD Theory and the Partition Model

Standard MIRD theory has several limitations when applied to calculations of dosimetry from implanted SIR-Spheres microspheres. Firstly it assumes uniform distribution of activity throughout the source organ, in this case the liver. We know this is not the case, as the microspheres partition between the tumor and the healthy parenchyma in relative concentrations given by the T/N ratio. Heterogeneity of distribution is likely to be significant for sources on the scale 10 – 100 micron. Furthermore, it is known that SIR-Spheres microspheres do not distribute uniformly within each of the tumor and parenchymal compartments.

Secondly, MIRD theory assumes that for beta radiation no dose is received in organs adjacent to the source organ because of their geometric separation, i.e. the absorbed fraction, ϕ , is zero for adjacent organs. Therefore, if the liver is considered the source, no other organs will receive any radiation. This is an inaccurate representation as a large serosal tumor lying adjacent to the stomach will deliver a radiation dose to that organ due to the penetration of beta radiation in tissue. However, there is no easy way to calculate what this dose might be. This applies to adjacent organs such as the stomach,

pancreas and gastrointestinal tract. However, based on penetration depth of beta emissions, the lungs will receive no radiation in the absence of lung shunting.

The partition model was developed from basic MIRD methodology to provide an estimate of the radiation dose separately to tumor and normal liver. The partition model considers the liver and tumor to be effectively separate organs from the point of view of MIRD. The partition model relies on accurate information relating to the degree of lung shunting, liver mass, tumor mass and T/N ratio.

Pathogenesis of Radiation Damage

Research data demonstrate that almost 90% of the liver tissue receives less than the dose predicted by assuming uniform distribution, and a third of the tissue receives less than one third of the predicted dose. This means that for 'inferred' doses to the liver of 70-80 Gray, one third of the liver receives approximately 20-25 Gray. This contributes to the lack of clinical radiation hepatitis at these doses.

Doses to tumor are normally 4-6 times those in the liver, thus radiation doses of 70-80 Gray in the normal liver relate to 280-480 Gray in tumors. Depending on the dose distribution in the tumor, this may still result in some tumor tissue receiving less than a tumoricidal dose.

The other factor contributing to the radiation dose pattern within the liver is the position of the microspheres within the parenchyma. The pathogenesis of radiation damage to the liver is dominated by vascular injury in the central vein region. External beam radiation causes alterations to the centrilobular areas such as eccentric wall thickening and indistinct central veins and this is part of the pattern of radiation hepatitis.

SIR-Spheres microspheres also cause tissue damage, but the pattern is different. Macroscopically there is infarction necrosis and fibrosis with nodularity and firmness. Microscopically there are occasional microinfarcts in portal areas, including chronic inflammation. Radiation from microspheres is deposited primarily in the region of the portal triad and away from the central vein, thus minimising the damage pattern seen in radiation hepatitis from external beam sources.

Therefore, radiation doses to healthy liver parenchyma are determined by:

- the distance from microspheres
- the number of microspheres present
- the activity of the microspheres implanted

The tissue receiving the highest dose is that immediately surrounding the tumor. Microspheres lodge preferentially in the growing rim of the tumor, as the centre may become necrotic and avascular as the tumor size increases. The damage to this area of parenchyma is unavoidable, and probably contributes to destruction of micro-infiltrates in this region.

The remainder of the liver receives less radiation than would be predicted from assuming a homogeneous distribution of radiation dose throughout the parenchyma as discussed previously. Hence the radiation dose to the normal liver can be as high as 80 Gray without a significant risk of radiation hepatitis when distributed as point sources.

Other organs may receive radiation doses if microspheres are inadvertently implanted into them. The primary organ of concern is the lung, as a small percentage of microspheres will always shunt through the liver and into the lung. It is important to ensure that the radiation dose to the lung is kept to a tolerable limit and this can be calculated from the MAA nuclear scan as described in Chapter 7 Implant Procedure in this document.

Organs adjacent to the liver may also receive radiation doses if microspheres are lodged on the periphery of the liver. This may occur from microspheres scattered throughout the healthy liver, or from a surface tumor, in which case, the radiation dose from the surface of the liver may be substantial. The organ most likely affected by radiation from the liver is the GI tract, and some radiation gastritis will occur in these patients. Refer to the use of H₂-blocking drugs under the 'Precautions' section in this module.

The main cause of inappropriate radiation of the stomach or duodenum is as a result of inadvertent reflux of SIR-Spheres microspheres into arteries supplying these tissues at the time of delivering the SIR-Spheres microspheres into the hepatic artery. This may occur for two reasons. Firstly, slowing of blood flow in the hepatic artery may result in embolisation of the capillary bed from the SIR-Spheres microspheres and this may cause reflux of SIR-Spheres microspheres into the gastroduodenal artery, left gastric artery or splenic artery. The second reason is because there are frequently small arteries coming from the left or right hepatic arteries that flow from the liver to the stomach and duodenum. It is essential that SIR-Spheres microspheres not be injected into any of these anomalous vessels, as severe inflammation of the GI tract may result.

More distant organs do not receive radiation doses. Radiation doses to the gonads are unlikely given the proximity to the liver and vascular anatomy. Similarly, radiation doses to the bone marrow are unlikely, and data have not demonstrated myelosuppression with SIR-Spheres microspheres.

APPENDIX 5: ESTIMATED EFFECTIVE DOSE

The table estimates the effective dose for yttrium-90 for various percentages of lung shunting from 0-30%.

Liver Activity	Lung Activity	Liver Dose mGy/MBq	Lung Dose mGy/MBq	Effective Dose mSv/MBq
100%	0%	26.1	4.5×10^{-7}	1.39
95%	5%	24.8	2.48	1.63
90%	10%	23.4	5.00	1.88
80%	20%	20.8	9.95	2.38
70%	30%	18.2	14.90	2.88

The table estimates the effective dose for technetium-99m for various percentages of lung shunting from 0-30%.

Liver Activity	Lung Activity	Liver Dose mGy/MBq	Lung Dose mGy/MBq	Effective Dose mSv/MBq
100%	0%	0.101	0.006	0.0079
95%	5%	0.096	0.012	0.0083
90%	10%	0.091	0.017	0.0088
80%	20%	0.082	0.028	0.0097
70%	30%	0.072	0.039	0.0106

APPENDIX 6: PATIENT DOCUMENTATION

Sample Ward Instruction

NUCLEAR MEDICINE	
Ward Doctor in Charge Doctor Requesting	
TREATMENT WITH RADIOACTIVE SUBSTANCE	
To Nurse in Charge of Ward From Medical Physicist	Isotope: Yttrium-90 Microspheres: SIR-Spheres Intrahepatic Implantation Date: Time: Activity:
NATURE OF HAZARD	
MINOR RADIATION CONTAMINATION HAZARD	RED AND YELLOW SIGN
INSTRUCTION	
IDENTIFICATION <input type="checkbox"/> Wrist Band to be worn NURSING <input type="checkbox"/> For special nursing instructions consult Dr. MOVEMENT <input type="checkbox"/> Restrict to bed space	HYGIENE <input type="checkbox"/> Patient is permitted to use ensuite shower and toilet. <input type="checkbox"/> The sluice room may be used - flush sluice twice. <input type="checkbox"/> Inspect dressing as required. If seepage is evident inform Doctor in Charge and Medical Physics
CONTAMINATION	INSTRUCTIONS
LINEN <input type="checkbox"/> Patient must be dressed in Hospital clothes. <input type="checkbox"/> The dressing may be radioactive. <input type="checkbox"/> Wear gloves when attending the patient and store for monitoring by the Physicist in Charge. <input type="checkbox"/> Keep only patently soiled linen. BODY FLUIDS <input type="checkbox"/> Body fluids are likely to be only slightly radioactive. Wear gloves and dispose of as under linen.	VISITORS <input type="checkbox"/> For psychological reasons it is suggested that children and pregnant females do not visit. <input type="checkbox"/> Other visitors may be allowed at the discretion of the Nurse in Charge of the ward. EMERGENCY <input type="checkbox"/> If further intervention becomes necessary the Medical Physicist must be informed immediately at all hours. Telephone after hours
RELAXATION OF PRECAUTIONS	
Earliest Date for relaxing precautions: When notified by the Physicist in Charge Earliest date for discharge: After this date at the discretion of the Doctor in Charge	

Sample Patient Wrist Band

PATIENT UNDER TREATMENT WITH RADIOISOTOPE	Procedure:	For information call
	Isotope:

Sample Notification of Discharge or to Suspend Precautions

Ward Notification of Discharge Nuclear Medicine		
⁹⁰Yttrium (SIR-Spheres microspheres)		
Ward/Clinic	Family Name	Patient Number
Dr. in Charge	Forenames	DOB
Dr Requesting	Patient Address	
PATIENT DISCHARGE / CEASE PRECAUTIONS		
		DATE:
Activity Implanted:		
Date of Implant:		

Sample of Discharge Letter

THE HOSPITAL

Address:

Isotope:	Yttrium-90 / SIR-Spheres microspheres
Activity:	
Form:	Microspheres
Site:	Liver
Time & Date Implanted:	

You are being discharged from this hospital after having received treatment with radioactive material. For the safety of yourself and others, would you please carry out the following instructions:

1. Proceed straight home and, as far as possible, remain at home for the next days (i.e. until).
2. Avoid or limit close contact with young children and pregnant women until
3. Please carry this form with you and show it to your doctor if you require medical attention of any kind within the next days, i.e. until

To Whom It May Concern

This patient has received a radiotherapeutic treatment for liver cancer with yttrium-90 microspheres. If major medical attention is required or if you require further information, would you please contact:

The Physicist in Charge
The Hospital
Telephone:

.....
(Physicist in Charge)

APPENDIX 7: RADIATION AND TRAINING REQUIREMENTS CHECKLIST

Checklist for _____ Site set-up
 (Name of Institution) Routine check

Checklist by _____ Date (dd/mm/yy)
 (Name of Sirtex Representative)

Number of Treatments Performed since Last Checklist

PART 1 REGULATORY

Facility License(s)

Name of License	Issued By	Expiry Date of License (mm/dd/yy)	Currency of License (Y/N)

Limitations on License _____

Personnel Licenses

Name of License Required	Issued By	Name of License Holder	Expiry Date of License (mm/dd/yy)	Currency of License (Y/N)

PART 2 EQUIPMENT

Radiation Monitor	On Site (Y/N) <input type="checkbox"/>	Make and Model:	
		Last Calibration Date:	
		Calibration Current <input type="checkbox"/> Y/N	(mm/dd/yy)
Dose Calibrator	On Site (Y/N) <input type="checkbox"/>	Make and Model:	
		Last Yttrium-90 Calibration Date:	
		Calibration Current <input type="checkbox"/> Y/N	(mm/dd/yy)
General SIR-Spheres Equipment			
Item	Number On Site	Number Requiring Replacement	Number of Extra Required
Syringe Shields			
Delivery Box			
V-vial Holders			

PART 3 TRAINING

Position	Name	Training Date (mm/dd/yy)	Refresher Required	Refresher Requested
RSO				
NMT				
NMP				
Radiologist				
Surgeon				
Medical Oncology				
Rad. Oncology				

Abbreviations:

- NMT - Nuclear Medicine Technician or Pharmacist
- RSO - Radiation Safety Officer
- NMP - Nuclear Medicine Physician
- Med Onc - Medical Oncologist
- Rad Onc - Radiation Oncologist

Actions Required from this Checklist:

(eg. Training dates, Licence renewals, Calibrations, Equipment)

Actions	Person Responsible	Date Completed

End of Checklist

APPENDIX 8: RADIATION EXPOSURE FOR STAFF DURING DOSE PREPARATION

An example of data obtained from thermoluminescent detectors (TLD) worn by an operator preparing individual patient doses is presented below. TLDs were worn on the trunk, collar and fingers. Note that in this case, the operator's trunk was shielded by a lead wall while carrying out the dispensing operation. The collar detector approximates the dose received by the lens of the eye. Detectors were worn for 3-month periods and then analysed.

The TLDs were used to calculate the dose at 0.07mm depth, representing a surface dose, as well as the dose at 10mm depth representing a deep dose. Surface doses only were calculated for fingers. The data represent the dose per patient treated. In cases where the cumulative dose over several patients failed to reach detection levels (0.02mSv), the data are stated as such. Data below this number represent detection above the limit and divided by the number of patients over which it was collected. This gives some doses below 0.02mSv.

Two lots of data are available; these are sequential 3-month results.

	Trunk		Lens		Finger	
	mSv	mSv/GBq ¹	mSv	mSv/GBq ¹	mSv	mSv/GBq ¹
First 3 month period						
Shallow dose (0.07mm)	0.17	0.054	0.08	0.025	0.67	0.3
Deep dose (10mm)	<0.02	<0.02	0.006	0.002		
Second 3 month period						
Shallow dose (0.07mm)	<0.02	<0.02	<0.02	<0.02	<0.02	<0.02
Deep dose (10mm)	<0.02	<0.02	<0.02	<0.02		

1. Data can also be presented as doses received per GBq handled

APPENDIX 9: RADIATION EXPOSURE FOR STAFF IMPLANTING THE DEVICE

Here exposure data is presented for staff involved in the implantation procedure. The data are presented for the radiologist implanting the microspheres and the radiation safety officer. Data were collected over two sequential 3-month periods. In the second 3 month period, the radiologist placed the catheter whilst a separate physician performed the actual implant. Data are presented here as average exposure per patient treated and again as average exposure per GBq administered.

	Trunk		Lens		Finger	
	mSv	mSv/GBq ¹	mSv	mSv/GBq ¹	mSv	mSv/GBq ¹
<i>Radiologist (catheter placement & implantation)</i> First 3 month period						
Shallow dose (0.07mm)	0.008	0.0035	0.296	0.13	0.11	0.045
Deep dose (10mm)	<0.02	<0.02	0.324	0.14		
<i>Radiologist (catheter placement only)</i> Second 3 month period						
Shallow dose (0.07mm)	0.11	0.063	0.08	0.046	<0.02	<0.02
Deep dose (10mm)	0.04	0.022	0.03	0.018		
<i>Physician (implantation only)</i> Second 3 month period						
Shallow dose (0.07mm)	<0.02	<0.02	<0.02	<0.02	0.84	0.425
Deep dose (10mm)	<0.02	<0.02	0.035	0.018		
<i>Radiation Safety Officer</i> First 3 month period						
Shallow dose (0.07mm)	0.01	0.0045	0.05	0.022	0.33	0.15
Deep dose (10mm)	0.0038	0.0017	0.021	0.0095		
<i>Radiation Safety Officer</i> Second 3 month period						
Shallow dose (0.07mm)	0.019	0.009	0.006	0.003	0.103	0.05
Deep dose (10mm)	0.014	0.007	0.005	0.003		

1. Data can also be presented as doses received per GBq administered

APPENDIX 10: PATIENT NURSING CARE

General

The patient may be removed to the recovery room following the implantation procedure. Patients should receive general nursing care and hospital accommodation in line with local regulations pertaining to patients with therapeutic radioactive implants. The patient can receive normal nutrition and fluids as tolerated immediately after the procedure.

If any further patient care is required in the immediate post-procedural period; it can be safely conducted in the recovery room. The recovery room is ideally a single bed unit. The following precautions should be observed while the patient is in the recovery room:

- the medical physicist or radiation safety officer should remain in attendance to monitor for any unusual conditions and answer any questions regarding radiation issues that the patient may have. This is generally for a period of an hour;
- pregnant staff should not attend the patient;
- if dressings to the implant site/wound need to be changed, staff should wear gloves. The used dressings and gloves are to be placed in the DISPOSABLE black bag, which is returned to the medical physics department for storage and disposal and
- if further intervention is required, the senior physicist must be informed.

Nursing the Patient

Patients can be moved to their room after a short time in the recovery room. Ideally, rooms should be single bed units, although this is not essential. Measurements about a patient with an implant of more than 1.11GBq revealed Bremsstrahlung radiation of the order of 15 microsieverts per hour ($\mu\text{Sv/hr}$) at a distance of 15cm from the liver. Data from patients implanted with an average of 2.1GBq emitted the following Bremsstrahlung radiation at approximately 5-6 hours post implantation at the following distances from the patient's abdomen:

0.25m	18.8 $\mu\text{Sv/hr}$
0.5m	9.2 $\mu\text{Sv/hr}$
1.0m	1.5 $\mu\text{Sv/hr}$
2.0m	0.4 $\mu\text{Sv/hr}$
4.0m	<0.1 $\mu\text{Sv/hr}$

Measurements taken in the room next door to the patient at the wall immediately behind the patient's bed-head <0.1 $\mu\text{Sv/hr}$

The radiation hazard presented by the patient to staff is minor, as the penetration ability of the implanted radiation confines it largely within the patient. The following precautions should still be observed:

- staff do not require monitoring, but film badges may be placed at the head of the bed and at the bedside;

- to indicate that the patient is radioactive, a sign should be placed at the head of the bed and an identity band with the trefoil (or similar) symbol to indicate radiation should be worn by the patient;
- pregnant staff should not nurse the patient;
- visitors may be allowed for 30-40 minutes. Visitors under 15 years of age and pregnant visitors should be cautioned regarding spending the full time in close proximity to the patient;
- the patient should be confined to single bed facilities or the bed-space until advised by the medical physicist or radiation safety officer.

Previous monitoring of all body fluids has revealed only light contamination detected in urine (25-50kBq per liter per GBq of dose in the first 24 hours after implant), and no contamination of other fluids. Therefore;

- there is no need to collect bed linen, rubbish or items of clothing;
- should the patient need catheter bags, drainage bags etc. and these require changing, then staff should wear gloves and discharge the bags into the sluice and flush twice and
- the patient may use the toilet in single bed facilities.

In the case of a patient requiring an abdominal drain, the medical physicist or radiation safety officer should monitor the fluid. If the fluid is radioactive the doctor should be informed as high activity may indicate the need for medical intervention.

If any intervention is required while the implant is still radioactive, the patient is to be managed in accordance with local regulations pertaining to radioactive devices. The relevant radiation authority should advise medical or surgical staff of standard procedures to be observed and the radiation risk posed by the intervention. Medical/surgical staff should proceed (or not) according to these procedures taking into account the radiation risks relative to patient benefit.

The discharge of patients following treatment by radioactive substances is permitted subject to local regulations. For example in the USA, 10CFR 35.75 states that patients may be released from hospital if the total effective dose equivalent to any other individual from exposure to the released individual is unlikely to exceed 5 mSv. Written instructions as to how to minimize exposure to other individuals are to be issued if their exposure rate is likely to exceed 1 mSv. In Australia (see “Recommendations for the Discharge of Patients Undergoing Treatment with Radioactive Substances”, ARPANSA 2002) the effective dose to the general public should not exceed 1 mSv per year but for an appropriately informed carer providing support for the patient the constraint is relaxed to 5 mSv.

When patient specific dose estimates to family members and members of the general public are not available, it is recommended that patients only be released when the ambient dose equivalent rate at 1m from the patient does not exceed 25 μ Sv/hr. Measurements around patients who have received SIRT (see the table above) show that this dose rate is unlikely to be exceeded even on the day of treatment.

We recommend the following precautions are followed when the patient is discharged;

- the patient must proceed directly home and remain there until the usual limit of release is reached. If the patient must travel by public transport, the traveling time must not exceed 2 hours;

- he/she must be given a letter explaining the treatment they have received, including information on the amount of activity administered, when administered and simple precautions for minimizing the dose to others;
- he/she should also be given a letter that can be given to a medical doctor if they need general medical care during the period they are radioactive;
- he/she should wear a wristband until the activity has reached an approved level as set by regulators. This wrist band should identify that the patient has received a radioactive implant and have a contact number in case medical attention is required;
- he/she should avoid any prolonged close contact with other people, especially children and pregnant women, until the implanted activity has decayed.

In the event of a patient dying while in the hospital, the body may be move to the mortuary in the usual manner. The hospital radiation safety officer should be consulted before any procedures are performed on the body. The maximum level of activity below which disposal of deceased persons can proceed without special precautions depends on the mode of disposal (e.g. embalming, burial, cremation) and will vary in different jurisdictions.

APPENDIX 11: IMPLANTATION ROOM SET-UP

The room where the SIR-Spheres microspheres are implanted, such as Catheter Suite or Operating Room should be set up with appropriate equipment. The important concepts are to separate contaminated and non-contaminated materials and recoverable and non-recoverable items.

A typical set-up may be as follows:

- Two wire baskets each lined with a black plastic bag. Label one basket DISPOSABLE and the other RECOVERABLE. Use trefoil tape to indicate radiation hazard to prepare the labels
- A surgical trolley with the following items on the top shelf, which is lined with an absorbent plastic-backed pad
 - Sharps container for RECOVERABLE instruments and syringes
 - Sharps container for DISPOSABLE instruments and syringes
 - Container for Decon to decontaminate surgical instruments
- A contamination monitor on the bottom shelf

A medical physicist or radiation safety officer must be available for all implants and is responsible for control of contamination. All disposable and recoverable items that are contaminated must be available for stock take or counting as per standard nursing procedures.

All gowns and surgical gear must be monitored at the end of each procedure. Contaminated items should be bagged, labeled and returned to the medical physics department or other designated area for decay until safe for laundering or other disposal. Where possible surgical instruments should be decontaminated in the procedure room.

APPENDIX 12: RESECTABILITY AND EXTENT OF LIVER DISEASE

Patients should be deemed non-resectable if they meet any one of the following criteria:

- multiple liver tumors together with involvement of both lobes
- tumor invasion of the hepatic confluence where the three hepatic veins enter the IVC such that none of the hepatic veins could be preserved if the tumors were resected
- tumor invasion of the porta hepatis such that neither the origin of the right or left portal veins could be preserved if resection were undertaken
- widespread tumors such that resection would require removal of more liver than required to sustain life.

Diagnosis of resectability should be undertaken via imaging with triple phase contrast angio-portal CT scanning or MRI.

The extent of tumor can be assessed using tumor markers such as CEA (carcinoembryonic antigen) or AFP (alpha fetoprotein). These are non-specific tumor markers which are frequently elevated in hepatic cancer. The extent of active tumor is generally reflected in the blood level of patients who secrete these markers.

Abnormalities in liver function tests provide additional clinical information regarding the extent of disease. Markedly abnormal synthetic and excretory liver function tests preclude treatment with SIR-Spheres microspheres.

Patients who have disease considered resectable for cure should not receive treatment with SIR-Spheres microspheres. For those patients who are not resectable for cure, the extent of the liver disease is a determinant of the radiation dose required.

APPENDIX 13: EXTRAHEPATIC DISEASE

An assessment of the presence and extent of extra-hepatic disease is required to determine the potential benefit of regional radiation treatment for the individual patient. SIR-Spheres microspheres provide regional treatment only, and use of SIR-Spheres microspheres in patients with disseminated disease, and in whom the liver disease is not the life-threatening event, is questionable. Furthermore, decisions regarding concurrent use of chemotherapy may rest with diagnosis of extra-hepatic disease.

The most common sites of extra-hepatic disease include the abdominal cavity, abdominal and clavical lymph nodes, the lung and bones. Patients should generally undergo a CT scan of the chest, abdomen and pelvis, a CT scan of the liver and abdomen supplemented with a chest X-ray and abdominal/pelvic ultrasound. A bone scan will detect skeletal metastases. Further investigations should be conducted on the basis of the clinical index of suspicion.

Tumor markers such as CEA and AFP can be used to detect the presence of extrahepatic disease in patients demonstrating diminished or stable disease in liver imaging studies.

APPENDIX 14: CLINICAL DATA

SIR-Spheres microspheres have been used to treat over 2,000 patients in a variety of clinical settings in US, Australia, New Zealand, Europe and Asia. These include trial patients in Phase 1, 2 and 3 trials in major teaching hospitals and non-trial patients. Approximately 170 patients have been treated in Perth, Australia since 1987, and approximately 200 in Hong Kong since 1991 and over 40 in New Zealand since 1997. Of those treated in Australia, approximately 130 have been treated in phase 1 and 2 clinical trials and a randomized phase III clinical trial of 70 patients closed in June 1997.

In the randomized trial using SIR-Spheres microspheres together with regional hepatic perfusion chemotherapy and regional hepatic perfusion chemotherapy as the comparator, significant tumor regression was observed in the vast majority (75%) of patients treated with SIR-Spheres microspheres. This translates into a clinically, but not statistically significant increase in survival time of 26% between those patient treated with SIR-Spheres microspheres plus chemotherapy and those treated with chemotherapy alone. There are currently no reliable predictive factors to indicate which patients will benefit most from SIR-Spheres microspheres.

Determining the required radiation dose based on the percentage of liver replaced by tumor is empirical however this method was used in the phase III randomized trial of SIR-Spheres microspheres in metastatic liver cancer from large bowel. This method achieved a 52% response rate when used with regional hepatic perfusion chemotherapy with FUDR compared with 25% response in patients treated only with regional hepatic chemotherapy. Progressive Disease was delayed for approximately 20 months in patients treated with SIR-Spheres microspheres compared with 10 months for those who received only FUDR.

Although SIRT is generally considered a palliative treatment, there has been experience of histological cure of patients who were considered to have advanced non-resectable tumors. In a phase III randomized clinical trial of patients with metastatic disease from large bowel, some patients had their tumors down-staged to allow resection for cure. There are additional reports in the scientific literature of patients with primary hepatocellular carcinoma being treated with SIR-Spheres microspheres and subsequently being resected for cure. See Appendix 11, Reference 7.

A response rate of nearly 90% has been demonstrated in both the New Zealand and Hong Kong patients. In New Zealand, as in Australia, nearly all patients had metastatic disease, while in Hong Kong the majority had primary cancer. Many patients treated in Hong Kong were treated with concurrent systemic chemotherapy, while in New Zealand and Australia, the majority of patients received regional chemotherapy.

Currently the best evidence for the use of SIR-Spheres microspheres is in metastatic disease, arising largely from primary disease in the large bowel as the phase 3 randomized clinical trial was conducted with these patients, although there is considerable experience in using SIR-Spheres microspheres in hepatocellular carcinoma. Other liver cancers have been treated with SIR-Spheres microspheres but the numbers are small. As the randomized phase III trial provides the strongest evidence for response with SIR-Spheres microspheres, this is the current indication for use.

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APPENDIX 16: Use Of Sir-Spheres In Patients With Impaired Liver Function

Note to U.S. Physicians: The use of SIR-Spheres discussed herein has not been approved by the Food and Drug Administration and is provided to U.S. physicians for educational purposes only. Your attention is directed to the U.S. prescribing information for SIR-Spheres which may be obtained from the Sirtex Medical office, any member of staff or from the website at www.sirtex.com.

Many patients who develop primary hepatocellular carcinoma (HCC) have pre-existing cirrhosis and impaired liver function. As treatment of HCC with Selective Internal Radiation Therapy (SIRT) has been shown to be an effective treatment for non-resectable HCC, many of these patients are candidates for treatment with SIRT, however there are precautions which should be used when using SIR-Spheres microspheres in patients with cirrhosis and other forms of impaired liver function.

SIRT involves administering SIR-Spheres microspheres into the hepatic arterial circulation following which the SIR-Spheres microspheres preferentially target tumor within the liver. This results in the tumor receiving a high dose of radiation. However, some spheres always reach the normal hepatic parenchyma and therefore the normal liver receives a small radiation dose. Generally SIRT is well tolerated as the radiation dose to the normal liver is small and any damage is not clinically significant and is soon repaired.

However, patients with pre-existing liver damage, as in cirrhosis, have impaired ability to tolerate any insult to the normal liver. For this reason patients with HCC can frequently not have their tumor resected, as removal of only a small portion of the remaining normal liver leads to progressive liver failure.

Patients with pre-existing cirrhosis also have an impaired ability to tolerate SIRT. Radiation doses that are tolerated by healthy hepatic parenchyma may cause irreversible damage to cirrhotic liver.

Therefore the radiation dose delivered to the normal liver compartment must be reduced in these patients. There are two ways to reduce the chance of seriously damaging the normal liver in cirrhotic patients, viz; selectively targeted delivery of SIR-Spheres microspheres or dose reduction

1. Selectively targeted delivery of SIR-Spheres

When HCC develops as a single or small number of tumor masses, it is frequently possible to selectively catheterize the arteries supplying only tumor and deliver the SIR-Spheres microspheres directly to the tumor with preservation of the remaining non-tumorous liver. This has two benefits. Firstly the dose received by the tumor is far greater than when the

whole SIR-Spheres microspheres dose is delivered into the general hepatic circulation and secondly, as the normal liver is not being irradiated it provides a great margin of safety. This is by far the preferred method of treating these patients.

2. Dose reduction

If the tumor masses are numerous and it is not possible to selectively target only tumor with selective catheterization, then the dose should be reduced by approximately 25% below that which would be delivered if the background liver function was not impaired. It is not possible to provide accurate levels of dose reduction and the physician should use discretion when calculating the dose. However a dose reduction of 25% for patients with moderately impaired liver function should be tolerated. In patients with severely impaired liver function, when the serum bilirubin level is greater than twice normal or when the serum albumin level is reduced by more than 15%, then SIRT should not be administered at all.

There are several potential methods for calculating the SIR-Spheres microspheres dose to be administered to patients. Physicians are advised to use the BSA formula method found in this manual in Section 7, 7.1.1.2 of this manual.

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