Dosimetry and Dose Calculation

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6.1 Introduction

Two components relate to the topic of dosimetry in microsphere therapy. Dose (Gy) that is desired to be delivered to tumor tissue in the liver; and the activity (GBq) of yttrium-90 (^{90}Y) delivered to the target organ. Classically, dosimetry is a Radiation Oncology term for the estimation of the absorbed dose expressed in units of Gy of radiation in tissue that will be or has been delivered. For microsphere treatment, it is more appropriate to describe an activity of radiation that will be implanted into the liver tumors, as there is not yet a proven way of preplan or post-plan confirmation of the absorbed dose in the target tissue. In other brachytherapy sites, seeds measuring several millimeters in size can be readily identified on CT scan or plain film and the resultant absorbed dose in the tissue calculated by hand or software solution. Microsphere implantation is a hybrid of interstitial brachytherapy and radioactive liquid therapy which at the present time is more accurately characterized by Nuclear Medicine conventions (Medical Internal Radiation Dose, MIRD) Committee of the Society of Nuclear Medicine [1] MIRD [2–5] and Partition Model [6, 7] than current or historical brachytherapy dose calculation methods (Patterson Parker, Point Source, and Volume Implant Rules).

The selection of an activity of ^{90}Y to deliver into the liver is a critical but imperfect task that requires experience and knowledge of many factors. Paramount among these factors is an understanding of liver health and reserve. This is difficult to know and is often unknown as the long-term effects of newer chemotherapy agents (Oxaliplatin, Irinotecan, Gemcitabine, etc.) on the liver parenchyma are not yet documented and in the short term have caused liver fibrosis and cirrhosis. Unfortunately no single laboratory test is a valid measure of liver health. Surrogates include non-specific liver enzymes, transaminases and bilirubin levels. The liver's complex and varied functions are a challenge for treatment teams as they attempt to assess the risk of acute and permanent liver injury and determine the suitability of an individual patient for microsphere therapy. Clinical experience in non-radioactive arterial-based parti-

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cle therapy has established patient selection criteria that protect against treatment of livers where serious and sometimes fatal liver dysfunction is likely to result. Although these guidelines are a helpful starting point for radioembolization, they represent in some ways a more stringent standard based on the particle size, flow pattern, deposition properties and effect on hepatic neovascularization compared to what we now know is the case for the much smaller radioactive microspheres. In short, many patients that are not candidates for transarterial chemoembolization (TACE) or bland embolization are able to safely receive radioembolization with excellent outcomes. Moreover, it is essential that radioembolization research teams continue the development of clinically proven guidelines for radiation activity and patient selection. This section will discuss the selection of ^{90}Y activity and what is known about microsphere dosimetry at the level of the hepatic lobule where microspheres become permanently embedded.

6.2 Liver Tolerance to Ionizing Radiation

Nearly all the experimental and clinical data to date has been using external beam radiation. Furthermore, animal models are not good surrogates for human hepatic radiation response. Whole liver radiation by external beam causes radiation induced liver disease (RILD) in 5%–10% of patients [8–10]. RILD is a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes (especially alkaline phosphatase) which occurs usually from 2 weeks up to 90 days post radiation delivery and can lead to permanent, progressive and/or fatal liver dysfunction [11, 12].

Studies of liver effects from external beam radiotherapy date back to the 1920s [13–16]. Brachytherapy in the lung and liver also has a significant history of investigation [17]. Preclinical studies utilized a variety of animal models, and various infusion methods (vein, heart, aorta, hepatic artery, and portal vein) with and without liver tumors to study microsphere deposition in normal and tumors tissues. Common observations in animals and humans confirmed arterial delivery of microspheres causes them to embed in the periphery of the tumor in highly nonuniform (but not random) patterns with nearly all located within a few millimeters of tumor nodules. Groups or clusters of a few microspheres up to several dozen spheres were identified per cluster [18]. Attempts were made to quantify the radiation dose delivered in the early 1960s with dog and rabbit systems which crudely measured the location and intensity of microspheres from sectioning of the liver for autoradiography [19–21]. Geiger-Mueller survey meters or scintillation crystal probes recorded the location of Bremsstrahlung gamma ray production in the liver [22], or tiny Teflon coated lithium fluoride phosphor discs [23]. Human subjects receiving resin microspheres during laparotomy provided an opportunity to measure portions of the liver and tumors directly from small biopsies with a specialized three-channel liquid scintillation β-radiation detection probe, which also responded to gamma rays. After infusion of 49–118 million microspheres (diameter 17 or 32 μm) [24–26], Burton estimated that normal liver received 9–75 Gy, and tumor from 34–1474 Gy, via T:N ratios of 0.4:1 to 45:1 [26]. Gray later reported on a review of liver biopsies from microsphere-treated patients after 7–9 months post treatment with similar activities of ^{90}Y. Gray reported on a review of liver tissues from resin microsphere-treated patients via biopsies taken 7–9 months post treatment. Serum biochemical data and microscopic review of core biopsies from normal liver tissue confirmed minimal detectable effects from microsphere therapy [27].

6.3 Human Microsphere Dose Studies

Human liver tissue analyses to calculate absorbed dose in Gy have been done. Fox [28] patients that received resin microspheres during laparotomy provided an opportunity to measure portions of the liver and tumors directly from small biopsies with a specialized three-channel liquid scintillation β-radiation detection probe, which also detected gamma rays. After infusion of 49–118 million microspheres (diameter 17 or 32 μm) [24–26], Burton estimated that the normal liver received 9.0–75 Gy, and tumor 34–1474 Gy, as calculated by tumor: normal ratios of 0.4:1 to 45:1 [26]. Fox et al. [28] studied the left lobe of a patient with metastatic colon cancer which was resected after having previously received resin microspheres. Predicted isodose curves by microspheres which could be seen

on pathologic sectioning were produced similar to standard brachytherapy reports. Tumor received 75 Gy, and the normal liver received an estimated dose of 30 Gy. It was also shown that for analysis of pathology sections for dosimetry calculations, sampling of tissues at 500 μm intervals was as accurate as smaller intervals [28]. Campbell et al. [29, 30] also used tissues from a lobe of liver containing colon cancer metastases, in a single patient previously treated with resin microspheres to study the distribution of embedded microspheres and the resulting radiation absorbed. Samples of four regions were taken: normal liver, the interface of tumor with normal liver, the surface of the tumor and the center of the tumor. The patient studied had previously received 3.2 GBq (60×10^6 microspheres) delivered with systemic Angiotensin II which constricts normal hepatic arteries but not tumor arteries. A residual 8-cm tumor nodule was resected and analyzed. Cluster analysis showed most sphere groupings were <1200 μm apart, and contained fewer than 15 individual spheres/grouping. The tumor center and normal liver contained a similar number of spheres, but the periphery of the tumor contained a 50–70 times higher concentration of spheres than the other areas [29, 30]. This area was about 6 mm wide around tumors. The average doses found in portions of the tumor periphery were 200–600 Gy, with minimums of 70–190 Gy. Only 1% of the normal liver absorbed a dose of 30 Gy or higher [30]. Kennedy et al. studied four whole livers from patients previously treated with microspheres. Two patients with hepatocellular carcinoma that had previously received glass microspheres prior to lifesaving cadaveric transplantation; and two patients with metastatic colon cancer that had received resin microspheres were examined [17]. The distribution of microspheres was almost exclusively in the periphery of tumor nodules, and was similar for both microsphere types. Microscopic three dimensional radiation dose calculations using Monte Carlo method were performed on a tumor nodule implanted with glass microspheres. The 100-Gy isodose volume encompassed a 2-cm^3 tumor volume, with significant areas receiving 1000–3000 Gy [31].

A retrospective review of radiation parameters [32] reported details of activity selection method used, actual delivered radiation activity, prior liver treatments, liver lobe or whole liver treated (treated volume), acute and late radiation toxicity and development of RILD, and tumor response in solid tumors affecting the liver. All demographic, tumor, radiation and outcome data was analyzed for significance and dependencies to develop a predictive model for RILD. Toxicity was scored via the CTCae 3.0 scale. A total of 515 patients (287 m; 228 f) from 14 US and two EU centers received 680 separate treatments with resin ^{90}Y-microspheres between 2003 and 2006. The most common tumor types were: colorectal 310 patients (46%); carcinoid 84 patients (12%); HCC 79 patients (12%); breast 50 patients (7%); and unknown primary 33 patients (5%). Multivariate analyses identified multiple factors related to toxicity including: dose (GBq) delivered (<0.0001), prescribed (GBq) dose (<0.0001), empiric method (GBq) delivered (<0.0001), lobe treated (<0.0001), number of prior liver treatments (<0.0008), center treating (<0.0001), and percent of body surface area (BSA) dose (GBq) delivered (0.0046). RILD was diagnosed in 28/680 treatments (4%), with 21/28 cases (75%) were planned by empiric method from one center, four from other centers using the BSA method and three via the physician's alternate prescription. There was a dose response curve in colorectal metastases separate from the dose causing RILD. Toxicity was Grade 0=69%, 1=23%, 2=6%, 3=2%. The authors concluded that important factors leading to RILD included: empiric method and actual delivered GBq activity independent of calculation method. Surprisingly, tumor origin (HCC vs. metastases) was not a factor, but a dose response curve below the threshold of RILD was found for colorectal tumors. Toxicity was low overall with 92% Grade 0–2. RILD occurrence is very low, but further gains in safety may be obtained using the BSA method. A predictive model for RILD was not yet possible given the large variance in these data. Further attempts are ongoing to develop a more complete dataset to complete this goal.

6.4 Selection of ^{90}Y Activity

6.4.1 Therapeutic Isotope

^{90}Y is a pure-beta emitter that decays to stable zirconium-90 with an average energy of 0.9337 MeV via a half-life of 2.67 days (64.1 h). It is produced by neutron bombardment of ^{89}Y in a commercial nuclear reactor, which yields ^{90}Y beta radiation hav-

ing a tissue penetration of 2.5 mm and a maximum range of 1.1 cm. One GBq (27 mCi) of ^{90}Y delivers a total dose of 50 Gy/kg in tissue. Commercially available radioactive microspheres include a glass (TheraSphere, MDS Nordion, Inc., Ontario, Canada) and resin (SIR-Spheres, SIRTex Medical Limited, Sydney, Australia), a microsphere in which ^{90}Y is permanently embedded within its structure. No significant amount of ^{90}Y leaks from the microsphere within the patient.

6.4.2 Glass Microspheres

The recommended approach to selecting an activity for these high-activity microspheres (2500 Bq/sphere) is to use the MIRD convention and adjust downward according to the calculated shunt of particles to the lung. Microspheres are delivered in preset activities based on the day of calibration, ranging from 3–20 GBq, depending upon user request. The target dose of glass microspheres is 100–150 Gy predicted absorbed dose per the MIRD formulation which assumes uniform distribution of microspheres in the treatment volume. The appropriate volume and mass (whole liver or single lobe) are determined using the CT or MR images, assuming a conversion factor of 1.03 g/cm^3.

The amount of radioactivity required to deliver the dose to the selected liver target (whole liver or single lobe) is calculated using the following formula:

$$\text{(1) Activity Required (GBq)} = \frac{[\text{Desired Dose (Gy)}][\text{ Mass of Selected Liver Target (kg)}]}{50\ [1-F]}$$

Calculation of the liver absorbed dose is in Gy delivered after injection:

$$\text{(2) Liver Dose (Gy)} = \frac{50\ [\text{Injected Activity (GBq)}][1-F]}{\text{Mass of Selected Liver Target (kg)}}$$

Where **F** is the fraction of injected activity deposited into the lungs as measured by Tc-99 MAA. In these equations for glass microspheres **F = 0.61** when GBq is used, (representing the upper limit of activity that can safely be delivered to the lungs in a single glass microsphere administration) to estimate the fraction of dose that could be deposited into the lungs.

Many factors are taken into consideration when determining the activity to use for an individual patient. The formulae above have been clinically verified in more than 1000 patients over the past 10 years. However, there are limitations to using the MIRD convention. It is not the case that microspheres are uniformly deposited in the treatment volume, in fact from the preclinical and human clinical data it is very much the opposite. However, the MIRD formulae do enable microspheres to develop confidence in the range of activity that is suggested by these conventions, and must use their experience, skill and collaborative medical expertise to choose the most appropriate activity for a particular patient.

6.4.3 Resin Microspheres

Because resin microspheres carry less activity (50 Bq/sphere) compared to glass microspheres, many more are used to deliver an adequate dose tumor. With upwards of 40 million–60 million delivered for a typical 2-GBq activity distributed in both lobes of the liver, many patients can experience temporary embolic side effects (pain, fever, nausea) which are similar but far less intense than is seen in TACE post-embolic symptoms. However, not all hepatic vascular beds can accept the number of microspheres desired from the pre-treatment planning formulae, and thus the delivery of microspheres discontinued prior to completely emptying the volume of microspheres planned. It is not the desire or plan to perform an embolic treatment, rather it is a brachytherapy procedure and therefore it is recommended that the delivery of microspheres not cause stasis and/or reflux. Optimal implantation of microspheres is for the tumor only to have spheres, and the normal adjacent liver to be free of radiation. Once stasis has occurred, however, the normal liver arteries have also been filled with microspheres and the selectivity and therapeutic benefit to brachytherapy is lost. If the whole lobe or segment is receiving the same dose of radiation (tumor and normal liver) then external beam radiation could have been used instead. Also, many patients are selected for microsphere therapy specifically because an embolic treatment was not felt to be safe or in their best interests.

The manufacturer's User's Manual (Sirtex User's Manual issued March 2002, pp 38–42) suggests three methods of estimating the activity to use for resin microsphere treatment: (6.4.3.1) BSA method,

(6.4.3.2) empiric method, and (6.4.3.3) partition method [33, 34], which appears in the manual as equation #3. The manufacturer's recommendation for the use of Equation 3 did not appear to be intended for diffuse tumors; however, the guidelines regarding the appropriateness of this equation are unclear. Therefore, we tested its application for all tumor types.

To better understand the following activity calculations (1–4), a brief review is shown of the schema developed by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine [1].

In this formalism the dose rate, $\dot{D}$ can be written as

$$1)\ \dot{D} = k\frac{A}{m}\langle E\rangle$$

Where k is a constant to yield the dose rate in desired units, A is the source activity, m is the mass of tissue that the radiation is absorbed within, and $\langle E\rangle$ is the average energy emitted per nuclear transition. Since we are dealing with a source undergoing nuclear decay, the activity of the source is not constant in time. Also the source is permanently implanted in the patient with no biologic excretion. Thus the activity as a function of time is described by the radioactive decay equation

$$2)\ A(t) = A_0 e^{-\ln(2)\,t/T}$$

Where A_0 is the calibrated activity, t is the time from calibration, and T is the half-life of the radioactive source. The absorbed dose, calculated by integrating over all time, is then given by the following

$$3)\ D = \frac{k\langle E\rangle A_0}{m}\int_0^{\infty} e^{-\ln(2)t/T}dt = k\frac{A_0}{m}\langle E\rangle\frac{T}{\ln(2)}$$

From the published decay data in MIRD format (http://www.nndc.bnl.gov/useroutput/90y_mird.html), the average energy released in the β^- decay of ^{90}Y is 0.9337 MeV (Bq s)$^{-1}$ or 0.5385 Gy kg (GBq h)$^{-1}$, assuming that all of the energy of the β^- decay is absorbed in tissue. Using the half-life T = 64.2 h, the total radiation absorbed dose after the complete β^- decay of ^{90}Y is given by

$$4)\ D = [Gy] = 49.9\frac{A_0[GBq]}{m[kg]}$$

The difference between the 49.9 constant given here and the 49670 constant given below is explained by taking the mass in kilograms instead of grams and current values for the average energy released in the decay process.

6.4.3.1
Body Surface Area Method Calculation (1–5)

$$1)\ BSA\,[m^2] = 0.20247 \times (height[m])^{0.725} \times (weight[kg])^{0.425}$$

$$2)\ A[GBq] = (BSA - 0.2) + \frac{V_T}{V_T + V_L}$$

$$3)\ A[GBq]_{resin} = \frac{D_{Liver}\left[(T:N \times M_{Tumor}) + M_{Liver}\right]}{49670\,(1 - L/100)}$$

D_{liver} = Nominal dose (Gy) to the liver
T:N = Tumor to normal ratio was calculated (see below)
L = Shunt fraction (%) of microspheres from liver to lung based on macro-agglutinated albumin (MAA) nuclear medicine scan
M_{liver} = Total mass of liver (g) from CT volume
M_{tumor} = Total mass of tumor (g) from CT volume
49670 = Absorbed dose conversion constant from infinite decay
V_T = cc from CT scan
V_L = cc from CT scan

$$4)\ T:N = (A_{tumor}/M_{tumor})/(A_{liver}/M_{liver})$$

A_{tumor} = Activity in tumor from MAA scan
A_{liver} = Activity in liver from MAA scan
M_{liver} = Mass in g of normal liver (excluding tumor) from CT scan
M_{tumor} = Mass in g of tumor in liver (excluding normal liver tissue) from CT scan

$$5)\ L\,[\text{Lung Shunt }\%] = \frac{\text{ROI Lung Counts} \times 100}{\text{ROI Lung Counts} + \text{ROI Liver Counts}}$$

6.4.3.2
Empiric Method Calculation

Tumor $\leq$ 25% of the total mass of the liver by CT scan
= use 2 GBq whole liver delivery
Tumor > 25% but < 50% of liver mass by CT scan
= use 2.5 GBq whole liver delivery
Tumor > 50% of liver mass by CT scan
= 3 GBq for whole liver delivery

6.4.3.3
Partition Method Calculation – "Equation 3"

$$\text{Tissue Radiation Dose}\,[\text{Gy}]\ \text{Liver} = \frac{49670 \times \text{Total}\ ^{90}\text{Y activity in liver}\,[\text{GBq}]}{\text{Mass of liver}\,[\text{g}]}$$

6.4.4
Body Surface Area Method

Van Hazel first instituted this modification during clinical trials where radiation hepatitis appeared in patients with smaller liver volumes [35]. Unfortunately there has not been a subsequent publication showing the rationale, validity or correlation between BSA, liver volume, tumor volume and radiation hepatitis. It represents a sometimes significant decrease in activity (small patient, small liver) compared to the empiric approach, and at other times, it calls for a modest increase in activity (small patient, large liver) compared to the empiric. It has been demonstrated that the empiric and BSA methods usually overestimate the activity that can be delivered to a patient [36, 37] (Fig. 6.1).

6.4.5
Empiric Method

The first method developed for resin microspheres was clinically derived with the added data of intraoperative activity calculations [24–26, 38]. There are important details regarding the differences in these patients and those now treated worldwide with resin microspheres. First, patients were previously untreated by chemotherapy or early in a course of standard 5-fluorouracil and Leucovorin. Typical patients with breast, colorectal and primary cancers of the liver have often received multiagent chemotherapy reducing overall and liver-specific tolerance to additional anticancer therapies. Second, the volume treated included both lobes at the same time. This is not much different to current treatment approaches which try to treat all of the tumors in each lobe with placement of microcatheters in more than one position or at the bifurcation of the right and left hepatic arteries. However, if less than the whole liver is intended for treatment, this must be accounted for with a proportional reduction in the calculated activity planned for delivery. Third, concurrent infusion of the vasoactive agent angiotensin II shifted

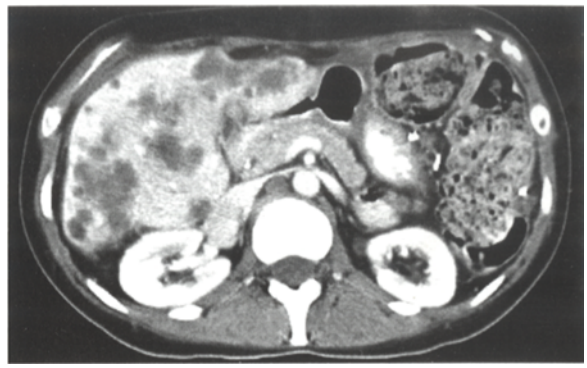

Fig. 6.1. Typical tumor volume and distribution in metastatic cancer to the liver. Resin microsphere radiation activity planning can be performed via two of the three methods recommended by the manufacturer. The distribution of disease is such that the third method – the partition method – is not valid in this case

microsphere deposition away from normal liver and toward irregular tumor-related neovascular arteries [24, 26, 27, 35, 38–41]. Although this is potentially a useful pharmacologic strategy for broad adoption, this agent is currently only available in limited circumstances in Japan [42–48]. Fourth, older resin microspheres held less activity per sphere, and therefore up to 120 million spheres were used per treatment.

It is a now common finding that if the empiric is used, up to 50% of treatments will be incomplete, i.e. not all of the microspheres can be implanted due to vascular stasis [36, 37, 49]. This issue is important not only from a radiation safety and clean up standpoint, but also warrants careful attention in the procedure not to try and deliver all the microspheres. This is not to suggest that the empiric method is not useful, as it does delineate the upper limit of safety in the conditions listed above in which it was developed; however, in most modern-day patients, a more consistent and accurate calculation approach is the BSA method. The majority of patients will have aggregate tumor volumes of between 5%–23%. Obviously in this wide range, individual patients cannot be optimally treated with a single activity recommendation, i.e. 2 GBq.

6.4.6
Partition Method

There are special situations in which a discrete lesion in the liver can be identified and the total

volume of the three compartments, liver, tumor and lung, are accurately known. Using the partition method, absorbed dose can be very accurately determined. This approach has been validated by Ho et al. [33, 34, 50] in a series of important papers based on human patients treated with resin microspheres. Sarfaraz et al. [51] concluded that using state of the art computerized radiation dose planning compared favorably to the partition method in selected patients receiving glass microspheres [6, 7, 51]. However, when the partition method is misapplied and used in patients with diffuse disease it will recommend activities that would be life-threatening if delivered as shown by Kennedy et al. [36, 37] (Fig. 6.2).

6.5 Conclusions

Selection of the optimal activity of microspheres for an individual patient is a complex and challenging endeavor. There is not yet a software solution or data from a prospective clinical trial that will accurately predict the activity to deliver to a patient that will provide the highest dose possible to the tumor while not damaging adjacent normal liver. Like much of medicine in general, and oncology in particular, clinical experience provides the "art" of dose selection, while a strong understanding of radiation, liver tolerance and vascular anatomy is the science that makes for effective use of microsphere brachytherapy.

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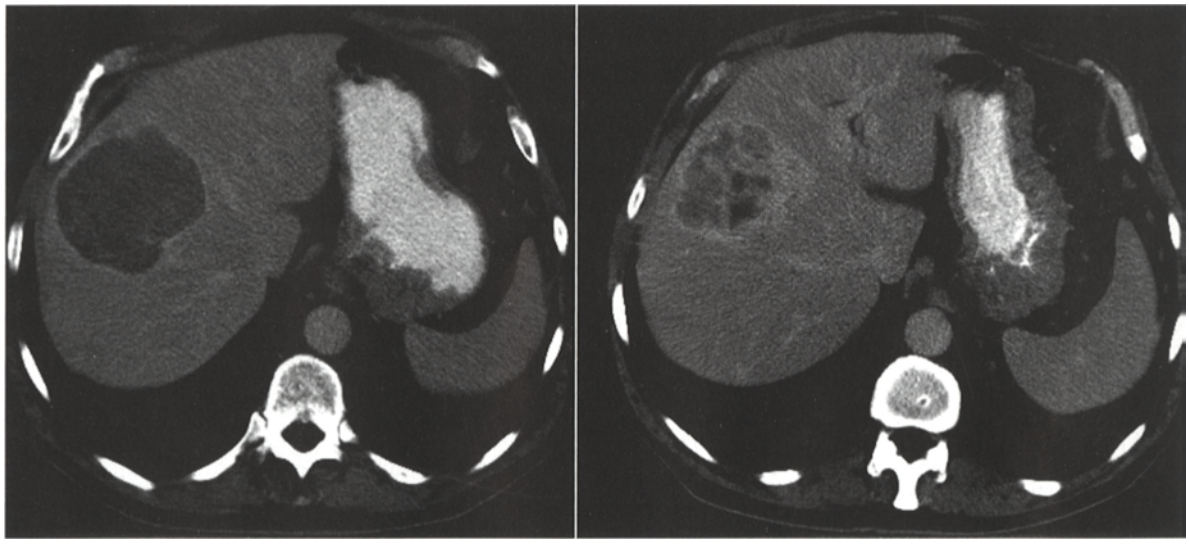

Fig. 6.2. This patient is able to undergo the partition method activity calculation as the tumor volume can be clearly identified and measured in relation to lung and normal liver. Pre- and post-microsphere treatment CT scans show a significant response at 3 months. The partition model calculated a minimum dose to the tumor mass of 300 Gy. Ultimately the patient achieved a complete response by tumor marker and CT scan

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