

MIRD \overline{y} 90

Microsphere activity calculator

User Manual

Version 1.0

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Disclosure

The MIRDygo software aids a user in performing goY SIRT treatment planning calculations and is intended for educational and research use only. MIRDygo has not been approved by the U.S. Food and Drug Administration (FDA) and is not intended for clinical use or use as a medical device. MIRDygo and any results generated from the use thereof are not substitutes for medical diagnosis, advice, and/or treatment of specific medical conditions. A physician should always be consulted for any health problem or medical condition. This research was funded in part through the NIH/NCI Cancer Center support grant P30 CA008748 and NIH U01 EB028234. No other potential conflict of interest relevant to this article was reported.

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Overview

The MIRDy90 calculation worksheet was built as a tool for evaluating ⁹⁰Y SIRT prescribed activity calculation models. Features of MIRDy90 include:

- Parallel implementation of BSA, MIRD single compartment, MIRD dual compartment, and MIRD multicompartment tumor model dosimetry;
- Simple to use single screen interface & Informative model summaries;
- Instant calculations for interactive user experience, provided with supporting graphics;
- Straightforward and simple comparison of activity calculation models;
- Easy-to-review (open-source) code and calculations.

The MIRDy90 worksheet was built on the Microsoft Excel platform. The platform allows for an organized input/output user interface, and reviewable calculations. The worksheet has been designed to be straightforward and utilizes the formatting and graphical capabilities of Excel. Using appropriate input parameters – region volume, sphere uptake measurements, and relevant dose limits - models will generate administration activity estimates. A screenshot of the MIRDy90 interface is shown in Figure 1.

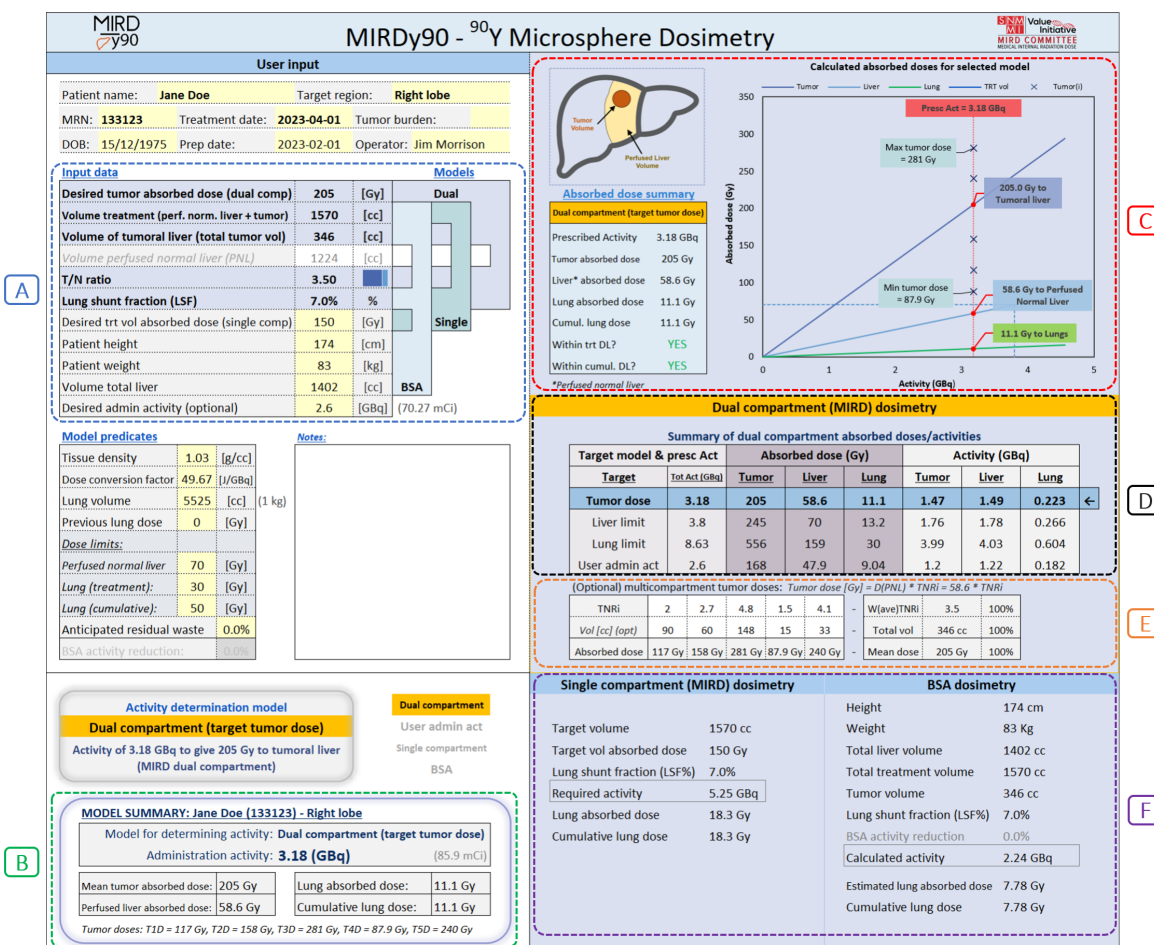


Figure 1: A screenshot of the MIRDy90 software GUI. User input area is on the left, and worksheet calculations are shown on the right. In this case, the MIRD dual compartment model is selected, and the target absorbed dose is prescribed to deliver 205 Gy to the tumor. A) input data fields for each of the models. The input parameters used in the selected model are highlighted. B) model summary box displays the user's selected calculation outputs. C) selected model graphical display and absorbed dose summary table. D) MIRD dual compartment dosimetry model outputs displaying activity and absorbed dose summaries for each of the 4 prescribed activity targets. E) (Optional) MIRD multicompartment input (TNRI) and projected tumor absorbed doses. F) Single compartment (MIRD) and BSA dosimetry model outputs providing conventional model summaries.

Data input

The intended flow of the worksheet is that users may enter data based on simulation or case measurements, review and compare model estimates, select the desired model and save the case and/or print the screen. The requisite parameters to support each model are displayed on the input screen (Fig. 1 panel A). As users enter data into the fields, the available models become activated, and respective calculations will be displayed on the screen. Figure 2 shows the input data required for the BSA, MIRD single compartment, and MIRD dual compartment models:

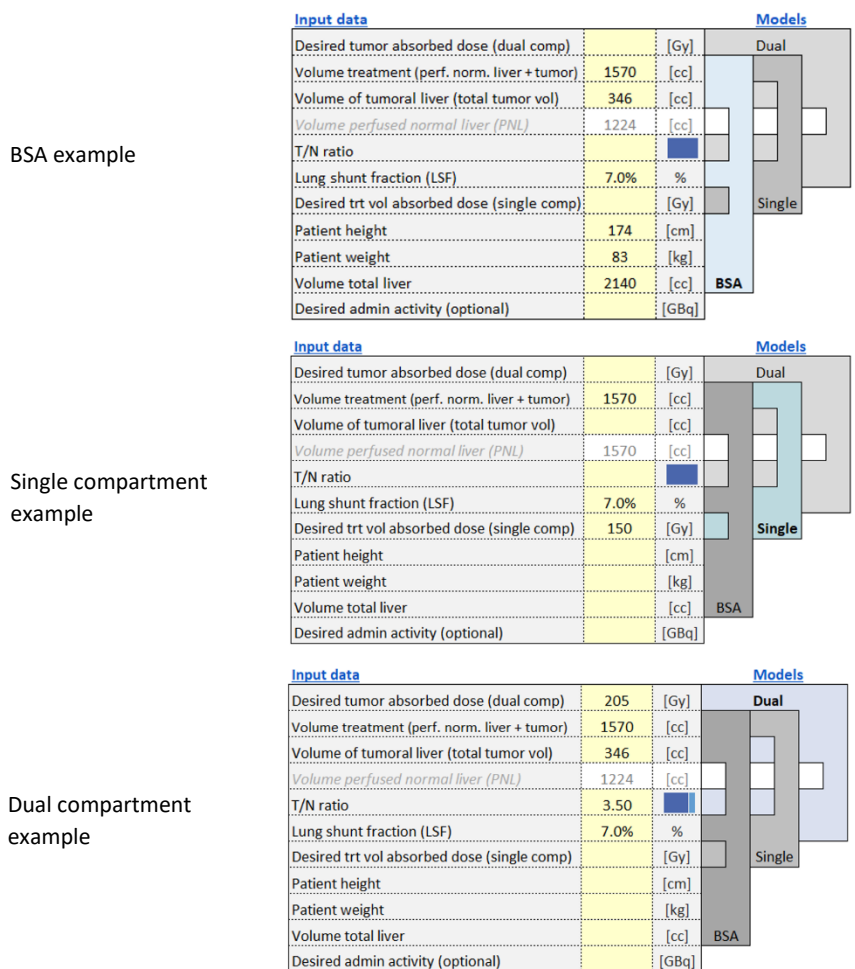


Figure 2. Relevant input data for the BSA (top), MIRD single compartment (middle), and MIRD dual compartment (bottom) models. The model panel to the right of the input data table will highlight once the requisite information is entered, indicating that the model is now available to perform calculations.

Model selection

The user can navigate and select one of the models from the drop-down menu shown in Figure 3. The drop-down menu will only display models that are available based on the input data.

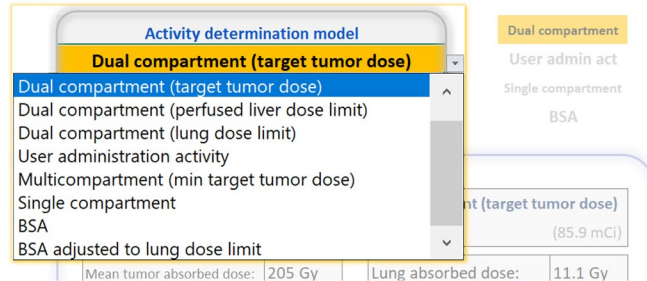


Figure 3: Model selection drop-down menu.

Once a model is selected, the inputs used for the calculations are highlighted, along with the respective output dosimetry module.

Model outputs

The selected model dosimetry module will be highlighted. For example, Figure 3 shows the “dual compartment (target tumor dose)” model selected, and Figure 4 shows the highlighted “Dual compartment (MIRD) dosimetry” panel.

Dual compartment (MIRD) dosimetry							
Summary of dual compartment absorbed doses/activities							
Target model & presc Act		Absorbed dose (Gy)			Activity (GBq)		
Target	Tot Act (GBq)	Tumor	Liver	Lung	Tumor	Liver	Lung
Tumor dose	3.2	205	58.6	11.2	1.48	1.5	0.224 ←
Liver limit	3.83	245	70	13.3	1.77	1.79	0.268
Lung limit	8.61	551	157	30	3.98	4.03	0.603
(Optional) multicompartment tumor doses: $Tumor\ dose\ [Gy] = D[PNL] * TNRI = 58.6 * TNRI$							
TNRI	2	2.7	4.8	1.5	4.1	W(ave)TNRI:	3.5 100%
Vol [cc] [opt]	90	60	148	15	33	Total vol	346 cc 100%
Absorbed dose	117 Gy:	158 Gy:	281 Gy:	87.9 Gy:	240 Gy:	Mean dose:	205 Gy 100%
Single compartment (MIRD) dosimetry				BSA dosimetry			
Target volume	1570 cc			Height	174 cm		
Target vol absorbed dose	150 Gy			Weight	83 Kg		
Lung shunt fraction (LSF%)	7.0%			Total liver volume	1402 cc		
Required activity	5.29 GBq			Total treatment volume	1570 cc		
Lung absorbed dose	18.4 Gy			Tumor volume	346 cc		
Cumulative lung dose	18.4 Gy			Lung shunt fraction (LSF%)	7.0%		
				BSA activity reduction	0.0%		
				Calculated activity	2.24 GBq		
				Estimated lung absorbed dose	7.8 Gy		
				Cumulative lung dose	7.8 Gy		

Figure 4: The “Dual compartment (MIRD) dosimetry” module is highlighted when the “dual compartment (target tumor dose)” model is selected in the “activity determination model” selection panel (Fig. 3).

Selected model display

The dose summary table and graphical display (Fig. 1, panel c) will show the prescribed activity and compartment doses for the selected model, as well as indicators confirming if the treatment exceeds any of the specified dose limits. The plot presents an overview of the prescribed activity (GBq) versus absorbed dose (Gy) as well as relative doses in each of the compartments for the selected model. A close-up view of the model absorbed dose summary and graphical display is shown in Figure 5.

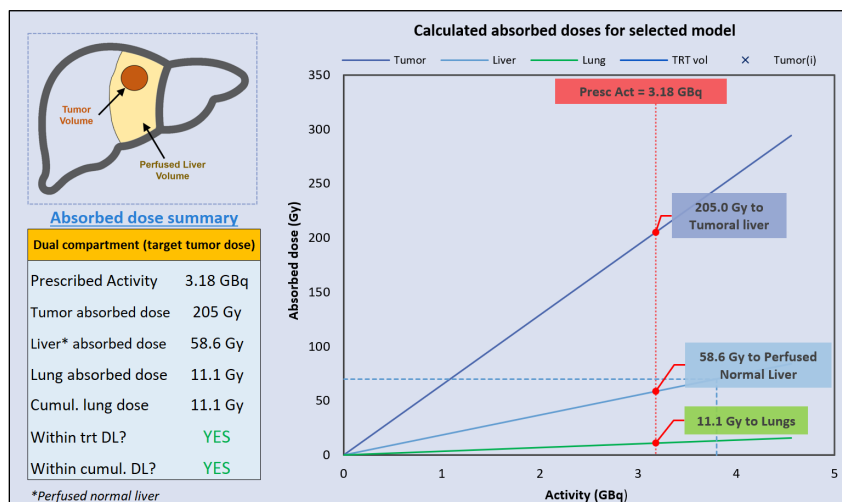


Figure 5: Absorbed dose summary and graphical display for the selected model.

Calculation summary

The model summary (Fig.1 panel B) displays all the important summary information for the current case, including the model used for determining ⁹⁰Y activity, the administration activity, and the relevant absorbed dose calculations. An example is shown in Figure 6.

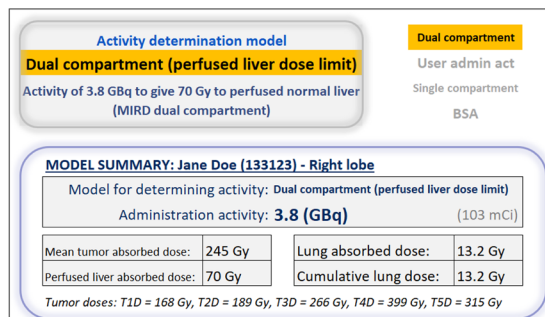


Figure 6. Example showing the model summary when for a case where the “Dual compartment (perfused liver dose limit)” model is selected.

Model descriptions

BSA

The SIR-Spheres **BSA model** requires several input parameters: total treatment volume, tumor volume, lung shunt fraction (LSF), patient height and weight, and the total liver volume. As input for the BSA model, a body surface area (BSA) first needs to be calculated. While there are several published equations for deriving this, the equation used in the SIR-Spheres package insert is presented in Equation (1). The patient BSA is determined from the patient's height and body mass:

$$BSA [m^2] = 0.20247 \times height[m]^{0.725} \times mass[kg]^{0.425} \quad [1]$$

The BSA model prescribed activity $A_{0,BSA} [GBq]$ can be calculated using Equation (2) with treatment, tumor, and total liver volumes obtained from the patient's CT or MRI images.

$$A_{0,BSA} [GBq] = \left[BSA - 0.2 + \frac{V(Tumor)[cc]}{V(PLV)[cc]} \right] \times \left[\frac{V(PLV)[cc]}{V(TotalLiver)[cc]} \right] \quad [2]$$

where $V(Tumor)$ is the volume of the tumor, $V(PLV)$ is the volume of the perfused liver being treated, and $V(TotalLiver)$ is the volume of the whole liver. Along with the prescribed activity, the BSA model requires that the absorbed dose to the lung also be calculated and considered. This is achieved by first determining the zero-time activity within the lung:

$$A(Lung)[GBq] = A_{0,BSA}[GBq] \times LSF \quad [3]$$

where the LSF is the lung shunt fraction (1). The absorbed dose to the lung is calculated as follows:

$$D(Lung)[Gy] = \frac{DCF \times A(Lung)[GBq]}{M(Lung)[kg]} \quad [4]$$

where $M(Lung)$ is the mass of the lungs, typically assumed to be 1 kg, and DCF is the ^{90}Y dose conversion factor. In MIRDy90, the user can change the lung mass based on a volume measurement and an assumed mean lung density of $\rho=0.181$ g/cc; the default volume in MIRDy90 is 5525 cc to give a lung mass of 1.0 kg. The dose conversion factor relates the energy deposited locally in tissue per unit of activity, expressed in units of J/GBq. In the ^{90}Y dosimetry models described herein, the DCF values commonly used reflect an assumption of charged particle equilibrium and complete self-absorption; this assumption results in an overestimate of the absorbed doses to varying degrees depending on the microsphere distribution volume (see Fig. 4 in ref (2)). It can also be noted that various publications provide somewhat different values for the DCF: AAPM report 144 and ICRU report 96 uses 49.38 J/GBq (3,4), SIR-Spheres package insert uses 49.67 J/GBq, TheraSphere treatment calculator uses 50 J/GBq, and the EANM dosimetry committee endorses a value of 49.75 J/GBq (2). Values of 49.67 J/GBq and 49.77 J/GBq can be derived from NNDC (5) and MIRD decay data, respectively. The differences appear to be due to small variations in the source decay data used, specifically the average energy emitted per nuclear transition and precision of the isotope half-life. MIRDy90 is pre-populated with the MIRD decay data derived DCF of 49.77 J/GBq, users may opt to change this.

MIRD single compartment

The **MIRD single compartment model** assumes that the activity of ^{90}Y is distributed uniformly throughout the target treatment site. The absorbed dose and prescribed activity are calculated using the activity of ^{90}Y , its physical half-life, its dose deposition characteristics, and the volume of the liver region being treated. The model requires a minimal number of inputs: the target region (perfused liver/treatment volume) mass (mass = volume*density), the LSF, and the desired absorbed dose to the target region. The desired absorbed dose is defined in Equation (5):

$$D(\text{Target}) = \frac{DCF \times A(\text{Target})[\text{GBq}]}{M(\text{Target})[\text{kg}]} \quad [5]$$

The prescribed activity is then calculated using Equation (6), noting that this equation accounts for shunting of spheres by including a correction for the LSF:

$$A_{0,MIRD}[\text{GBq}] = \frac{D(\text{Target})[\text{Gy}] \times M(\text{Target})[\text{kg}]}{DCF \times (1 - \text{LSF})} \quad [6]$$

The MIRD single compartment model assumes that the activity of ^{90}Y is distributed uniformly throughout the target treatment site. The absorbed dose and prescribed activity are calculated using the activity of ^{90}Y , its physical half-life, its dose deposition characteristics, and the volume of the liver region being treated. The model requires a minimal number of inputs: the target region (perfused liver/treatment volume) mass (mass = volume*density), the LSF, and the desired absorbed dose to the target region. The desired absorbed dose is defined in Equation (5):

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$$A_{0,MIRD}[\text{GBq}] = \frac{D(\text{Target})[\text{Gy}] \times M(\text{Target})[\text{kg}]}{DCF \times (1 - \text{LSF})} \quad [6]$$

If the MIRD single compartment (or BSA) model is selected, the respective dosimetry module is highlighted (Fig. 1, panel F). The dose summary table and graphical display (Fig. 1, panel C) will show the conventional outputs for the single compartment and BSA models. The MIRDy90 BSA model presents outputs akin to the SIR-Spheres SMAC (SIRTeX Microspheres Activity Calculator), a dose prescription calculator developed and provided by SIRTeX (Sirtex Medical Limited) (6). The BSA model has the option for BSA activity reduction (%), or for dosing to the lung limit by selecting the model "BSA dose to lung limit". The single compartment dosimetry module summarizes the conventional single compartment (MIRD) model inputs and outputs akin to the TheraSphere calculator (7). Figure 7 shows the MIRDy90 GUI when the MIRD single compartment model is selected.

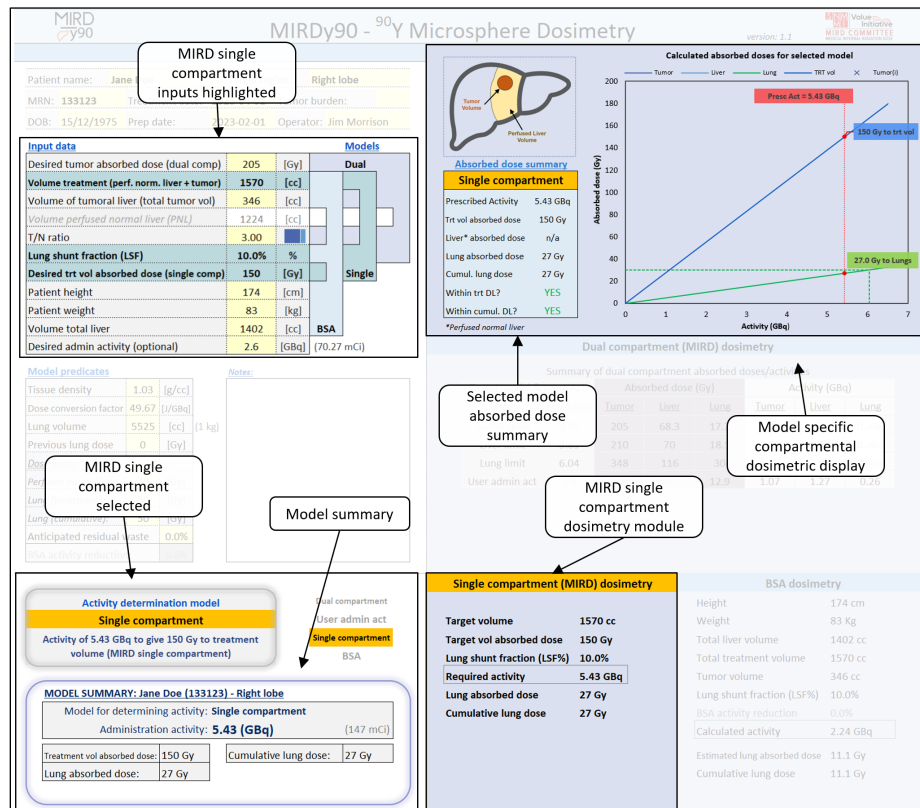


Figure 7. MIRD single compartment model selected.

MIRD dual compartment

The **MIRD dual compartment model**, also known as the **Partition Model**, requires several patient-specific inputs: the desired absorbed dose to the tumoral liver compartment (Gy), target volume (the perfused normal liver volume plus tumor volume), tumor volume, LSF, and TNR. To calculate the ⁹⁰Y prescribed activity, the MIRD dual compartment model requires the volumes of the tumor and normal perfused liver in the lobe being treated and the anticipated uptake in the tumor, perfused normal liver, and lung, typically measured using the pretreatment ^{99m}Tc-MAA SPECT. The TNR is calculated as the ratio of activity concentrations in the tumoral liver to that of the perfused liver tissue (Equation (7)). The TNR ratio is unitless and is represented by Equation (7):

$$TNR = \frac{A(Tumor)[GBq]/M(Tumor)[kg]}{A(PNL)[GBq]/M(PNL)[kg]} \quad [7]$$

where $A(Tumor)$ is the activity in the tumoral liver, $M(Tumor)$ is the mass (kg) tumoral liver, $A(PNL)$ is the activity in the perfused normal liver, and $M(PNL)$ is the mass (kg) of the perfused normal liver. The absorbed dose to the tumor is calculated as follows:

$$D(Tumor)[Gy] = TNR \times D(PNL)[Gy] \quad [8]$$

where $D(PNL)$ is the mean absorbed dose to the perfused normal liver tissue. The prescribed activity of ^{90}Y can then be calculated as follows (accounting for the lung and normal tissue dose limits):

$$A_{0,DC} [GBq] = \frac{D(PNL)[Gy] \times [TNR \times M(Tumor)[kg] + M(PNL)[kg]]}{DCF \times (1 - LSF)} \quad [9]$$

where $A_{0,DC}$ is the prescribed activity of microspheres calculated using the MIRD dual compartment model.

If the MIRD dual compartment model is selected, the MIRD dual compartment dosimetry module (Figure 1, panel D) will be highlighted. The dose summary table (Figure 1, panel C) and MIRD dual compartment dosimetry module will display a summary of the prescribed activities and compartment doses, as well as indicators confirming whether treatment exceeds any of the specified liver, lung and cumulative lung absorbed dose limits. Users can refine calculations by adjusting parameters, aided by graphical display of the output absorbed doses.

Users can select one of four target constraints: (1) **prescribed target absorbed dose to the tumor** (Gy), (2) **absorbed dose limit to the liver**, (3) **absorbed dose limit to the lung**, or 4) **user-defined administered activity** (GBq). In each scenario, the worksheet calculates the required prescribed activity. The displayed plot presents prescribed activity (GBq) versus dose (Gy) as well as the relative doses in each of the compartments. The plot updates automatically, depending on which of the four MIRD dual compartment model targets is selected.

In Figure 1, The dual compartment model (target tumor dose) is selected, and the graphical display shows the prescribed activity of ^{90}Y (dashed-red line), as well as the absorbed doses to the tumor (dark blue line), perfused normal liver tissue (light blue line), and lung (green line). The dual compartment dosimetry module also displays the prescribed activity and the compartment absorbed doses and activities for all target constraints simultaneously, only highlighting the model that is selected.

MIRD multicompartment

The MIRD dual compartment model can be extended to a **multicompartment tumor model** by considering individual tumors that make up the tumoral liver compartment as separate compartments:

$$D_i(Tumor_i)[Gy] = TNR_i \times D(PNL)[Gy] \quad [10]$$

where D_i is the absorbed dose to the individual tumor ($Tumor_i$), which is scaled according to the tumor TNR (TNR_i) relative to the absorbed dose to the perfused normal liver. For the model to be implemented as presented in equation 10, the absorbed dose to the perfused normal liver, $D(PNL)$, needs to be calculated a priori. In MIRDy90 this is achieved through implementation of the dual compartment model, which must be calculated prior to any multicompartment calculations. MIRDy90 facilitates multicompartment dosimetry, i.e., calculation of individual tumor absorbed doses, if users provide individual tumor TNRs (Fig. 1, panel E).

In MIRDy90, individual tumor doses are scaled relative to the perfused normal liver absorbed dose according to equation 10. As the user enters in individual tumor TNRs and their respective volumes MIRDy90 will calculate additional statistics to check if the TNRs and volumes match the mean tumor TNRs and total tumor volume provided in the main input data table (Fig. 1, panel A); these statistics include a volume weighted average TNR ($w(ave)TNR_i$), total vol, and mean absorbed dose and are displayed in Fig. 1 panel E. The volume weighted average of the individual entered TNR_i values ($w(ave)TNR_i$) is calculated as follows:

$$TNR_{ave} = \frac{\sum_i(TNR_i \times Vol_i)}{\sum_i(Vol_i)} \quad [11]$$

Section (5) in the Engine provides additional graphical display of the multicompartment calculation so that users may better understand how the summary statistics are calculated. Figure 8 shows the summary statistics display with an example of the multicompartment model where a single lesion is missing from the multicompartment input table.

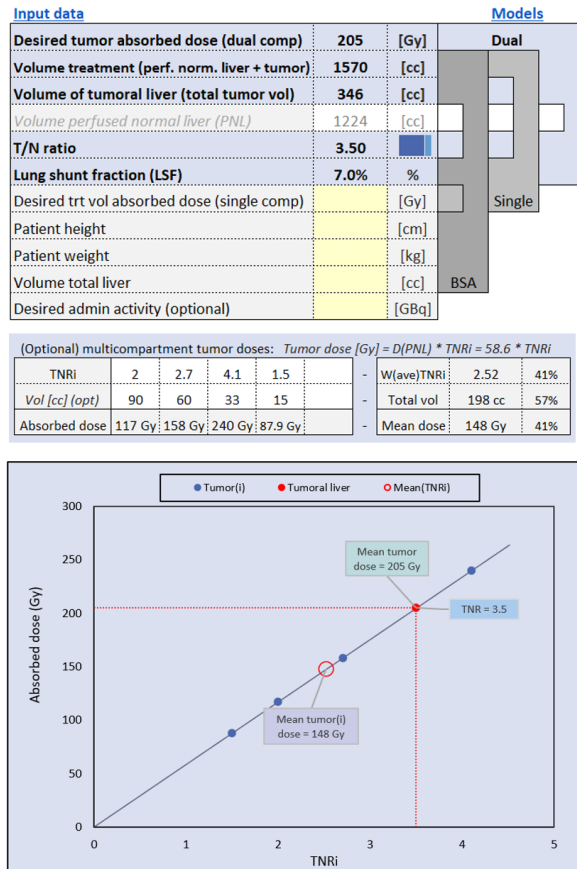


Figure 8. Multicompartment display in the Engine showing mismatch with the dual compartment input data due to a missing lesion.

The main input data table specifies the volume of tumoral liver to be 346 cc with a TNR of 3.5; the multicompartment table has individual lesion TNRs and volumes that accounts for 57% of the total tumoral liver volume, with a w(ave)TNRI of 2.52. The graphical display in the Engine indicates where w(ave)TNRI, total volume, and the mean absorbed dose of the entered individual lesions sits relative to the MIRD dual compartment model. If the individual lesion TNRs and volumes entered in the multicompartment table matches the dual compartment inputs (volume of tumoral liver and TNR) then the red circle will overlay with the dual compartment model as seen in Figure 9.

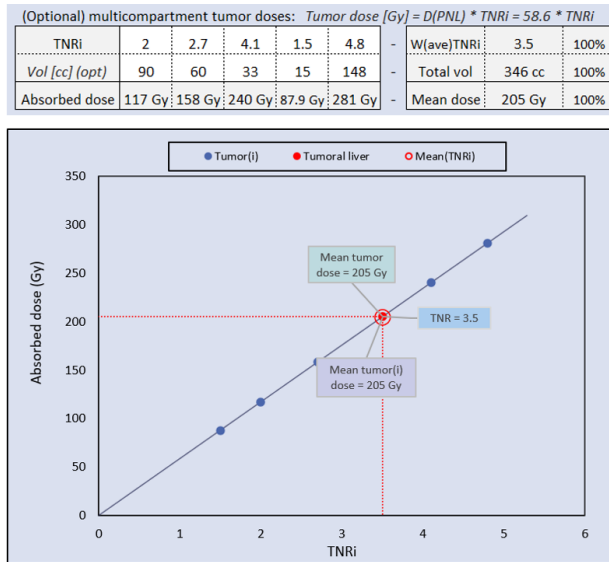


Figure 9. Multicompartment inputs match the MIRD dual compartment model inputs.

If an individual tumor TNRI is entered into the multicompartment table, an additional target constraint will be available in the prescribed activity calculation model drop-down list (Fig. 3). This model, “multicompartment (min target tumor dose)”, calculates the prescribed activity required to deliver a minimum tumor absorbed dose according to the “Desired tumor absorbed dose” input value (Fig.1, panel A). An example of this is shown in Figure 10.

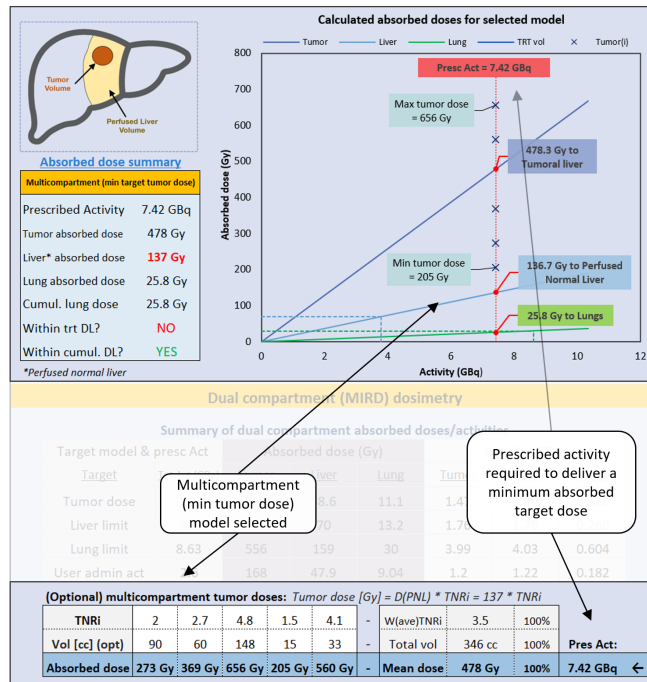


Figure 10. Multicompartment (min target tumor dose) model selected.

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