SUPPLEMENTAL DATA

First Strike personalized predictive radioiodine prescription
for inoperable metastatic differentiated thyroid cancer

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2023

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RATIONALE AND EXAMPLES

Our predictive method is a conceptual simplification of the established method of "maximum tolerated activity" prescription, where resource intensive serial blood sampling and dosimetry is replaced by choices of population kinetics carefully selected by the user. Our method is based on established principles of radionuclide internal dosimetry and average population kinetics extracted from real-world data. This means that the core dosimetric structure of our method is objectively sound, whereas its main uncertainty lies in the user's subjective assessment of metastatic extent. Therefore, the safety of our method (and to a lesser extent, its efficacy) largely depends on the user's gestalt assessment of metastatic burden based on all available clinical information. If the user's clinical gestalt is incorrect (e.g., lung vs marrow as limiting organ), our predictive calculator might derive an inappropriate prescription.

The most common clinical scenario of inoperable metastases is a female patient with oligometastasis in soft tissue and/or bone without diffuse lung metastasis. With the pre-requisite of good urine output, these patients are assumed to exhibit average I-131 kinetics for a patient with metastasis prepared by THW i.e., whole body TIAC 33.5h and percentage of whole body TIAC attributed to blood 16.6% (Tables 1 and 2). Their prescriptions are constrained by marrow dose rate 0.265 Gy/h per fraction, where blood TIAC is normalised to A_0. In these patients, prescription by 2 Gy marrow dose constraint will exceed the maximum safe marrow dose rate and is not recommended (Figure 1).

Using three Standard Man examples (Table 3), a Standard Asian Female (160cm; 51kg) is expected to safely tolerate 7.09 GBq, a Standard Female (163cm; 60kg) 8.03 GBq (Figures 1 and 2) and a Standard Male (176cm; 73kg) 10.46 GBq as the First Strike. Examples of when a First Strike prescription of 11.11 GBq might be safe in oligometastasis include a female of height 174cm and weight 90kg, or a man with the same height weighing 80kg.

However, if the patient's metastases are assessed by clinical gestalt to be extensive, the prescription is constrained by either the lungs or 2 Gy marrow limit, causing the suggested prescription to decrease in accordance with worsening I-131 kinetics (Table 3). In these scenarios, the marrow dose rate constraint of 0.265 Gy/h per fraction is not exceeded and therefore not a safety consideration. If the metastatic burden is suspected to be moderately or highly extensive, the assumed I-131 kinetics become unfavourable for our method of predictive prescription because its dosimetric constraints tend to sacrifice tumour efficacy in the interest of safety. Such patients should undergo formal theranostically guided predictive prescription, unless in the palliative setting.

THYROID HORMONE WITHDRAWAL IS PREFERRED OVER RH-TSH

Our calculator spreadsheet uses I-131 population kinetics derived from THW data, not rhTSH. This is because THW is better than rhTSH in improving the tumour TIAC and therefore more beneficial in metastatic disease [3, 32-35]. Mechanistically, the absorbed dose (Gy) of I-131 avid tissue is directly proportional to its TIAC [3, 6]. This means that for the same tumour mass, geometry and administered activity, a longer tumour TIAC achieved by THW will result in a greater absorbed dose, and therefore a better tumour response [3]. Furthermore, thyroxine contains iodine, making a low iodine diet less effective. Therefore, the better tumour TIAC by THW relative to rhTSH may be explained by the combination of endogenous TSH increase, hypothyroidism and a more effective low iodine diet by the omission of additional iodine in thyroxine [3].

This is in contrast to rhTSH which exogenously increases TSH, leaving tumour tissue in an euthyroid (or even hyperthyroid) state and a relatively less effective low iodine diet due to additional iodine in high dose thyroxine [3]. This is radiobiologic reason why THW is preferred over rhTSH for treatment of metastatic disease, unless in clinical situations where iatrogenic hypothyroidism is medically, psychologically or socially intolerable [3]. In situations where iatrogenic hypothyroidism is contraindicated, our First Strike methodology can also be applied to rhTSH by substituting THW kinetics with the corresponding rhTSH kinetics shown in Tables 1 and 2.

The synergistic possibility of THW boosted by rhTSH offers a theoretical advantage over either method alone by further increasing the tumour TIAC, but the safety of this combination (e.g., marrow or lung toxicity, enclosed tumour oedema) is currently unknown and will require future studies to elucidate.

TABLES: PUBLISHED STUDIES AND I-131 KINETICS

Whole body TIAC by rhTSH			
	n	Mean (h)	SD (h)
Hanscheid et al. 2006 [23]	32	17.3	3.9
Remy et al. 2008 [24]	11	15.2	3.1
Taieb et al. 2010 [25]	39	21.3	3.0
Grenfell et al. 2015 [26]	19	16.6	7.6
Ravichandran et al. 2016 [27]	17	17.2	6.1
Paolo de Barros et al. 2021 [28]	80	16.1	2.9
Kao 2023 [present work]	16	20.7	4.1
Weighted average	214	17.6	3.9

Whole body TIAC by THW			
	n	Mean (h)	SD (h)
Hanscheid et al. 2006 [23]	27	24.1	7.8
Remy et al. 2008 [24]	19	23.0	7.7
Taieb et al. 2010 [25]	40	24.7	4.1
Grenfell et al. 2015 [26]	31	19.2	9.1
Ravichandran et al. 2016 [27]	28	21.5	3.6
Paolo de Barros et al. 2021 [28]	123	19.6	5.2
Klain et al. 2021 [29]	166	23.1	13.0
Kao 2023 [present work]	6	23.8	2.8
Weighted average	440	21.9	8.4

Whole body TIAC by THW with bone metastasis	
Verburg et al. 2010 [30]	$n = 1$
Abuqbeitah et al. 2018 [31]	$n = 8$
Klain et al. 2021 [29]	$n = 26$
Kao 2023 [present work]	$n = 1$
Weighted mean ± SD (h)	33.5 ± 17.0

Whole body TIAC by THW with any metastasis	
Verburg et al. 2010 [30]	$n = 10$
Abuqbeitah et al. 2018 [31]	$n = 12$
Klain et al. 2021 [29]	$n = 33$
Kao 2023 [present work]	$n = 5$
Weighted mean ± SD (h)	28.0 ± 15.1

Whole body TIAC by rhTSH with any metastasis	
Abuqbeitah et al. 2018 [31]	$n = 7$
Kao 2023 [present work]	$n = 7$
Weighted mean ± SD (h)	24.0 ± 13.5

Blood TIAC by rhTSH by Hanscheid et al. 2006 [23]			
	n	Mean	SD
Blood (h)	33	2.34	0.73
Total body (h)	32	17.3	3.9
Percentage of whole body TIAC attributed to blood (%)		13.24	1.24

Blood TIAC by THW by Hanscheid et al. 2006 [23]			
	n	Mean	SD
Blood (h)	30	3.53	1.63
Total body (h)	27	24.1	7.8
Percentage of whole body TIAC attributed to blood (%)		13.92	2.26

Whole body TIAC attributed to blood by THW			
	n	Mean (%)	SD
Thomas et al. 1993 [9]	49	15.35	4.5
Hanscheid et al. 2006 [23]	30	13.92	2.26
Weighted mean	79	14.81	3.65

Whole body TIAC attributed to blood by rhTSH with any metastasis	
Abuqbeitah et al. 2018 [31]	*n* = 6
Mean ± SD (%)	15.2 ± 6.0

Whole body TIAC attributed to blood by THW with any metastasis	
Abuqbeitah et al. 2018 [31]	*n* = 12
Mean ± SD (%)	16.6 ± 7.9

Whole body TIAC attributed to blood by THW with bone metastasis	
Abuqbeitah et al. 2018 [31]	*n* = 8
Mean ± SD (%)	16.1 ± 6.8

FIRST STRIKE PERSONALISED PREDICTIVE RADIOIODINE (I-131) PRESCRIPTION ©Dr YH Kao
FOR INOPERABLE METASTATIC DIFFERENTIATED THYROID CANCER v280322

By Dr Y.H. Kao MBBS MRCP FAMS FRACP FAANMS, Department of Nuclear Medicine Print pg 1&2

Surname	Standard	Date of Birth		
Given name	Asian	Height	160	cm
Gender	Female	Weight	51	kg

The Royal Melbourne Hospital

Consider risks of lung AND marrow toxicity to prescribe according to the dose (Gy) limiting organ.
Preparation: thyroid hormone withdrawal. INVALID in severe chronic kidney disease or paediatrics

5.68	GBq will likely be safe in diffuse lung metastases
4.34	GBq will likely be safe in worst case lung metastases*

If diffuse lung metastases is clinically unlikely (i.e. lung is not the dose limiting organ), **AND**;
If the patient is clinically suspected to have **oligometastasis** with **average I-131 kinetics**:

7.09	GBq constrained by marrow dose rate (Gy/h) is likely to be safe for oligometastasis
11.73	GBq constrained by marrow absorbed dose (Gy) might exceed safe dose rate (Gy/h)

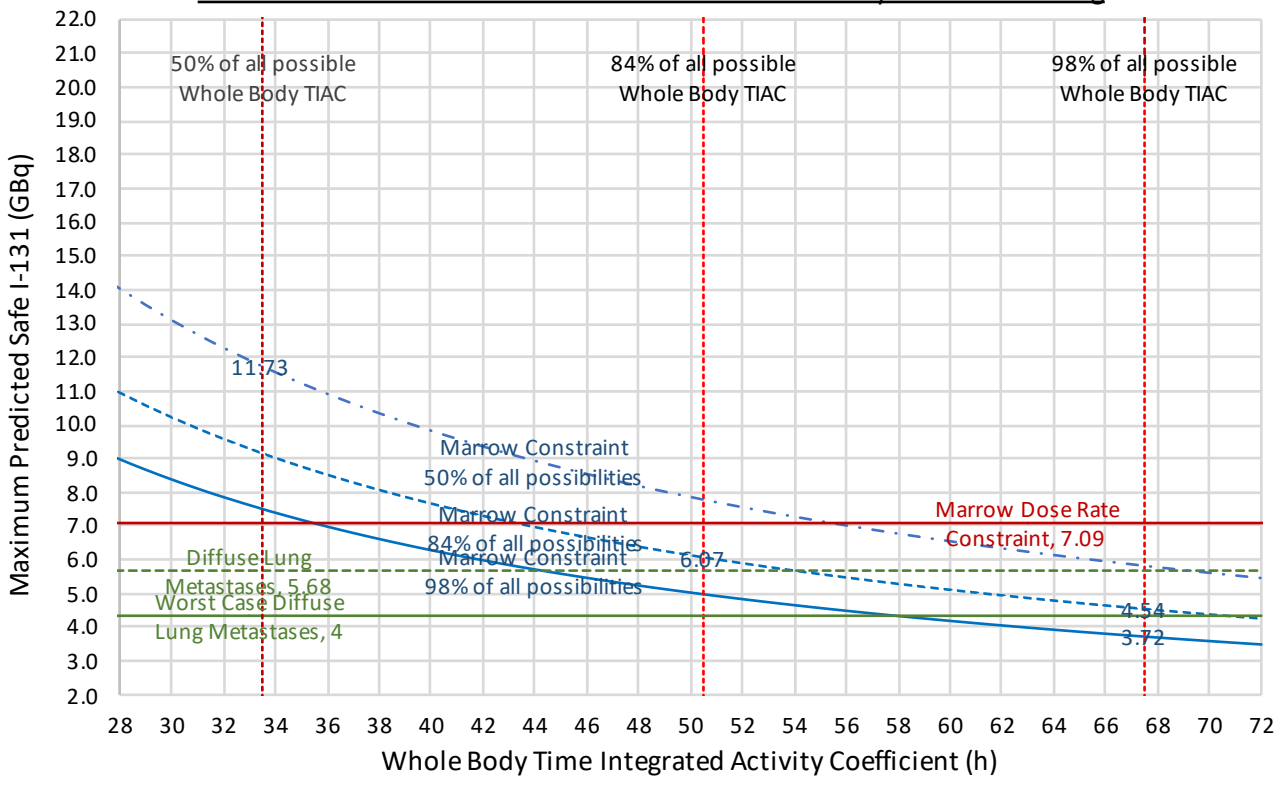
If **EXTENSIVE** soft tissue and/or bone metastases is clinically suspectec

6.07	GBq: 77% probability of marrow safety (likely safe in mildly extensive metastases)
4.54	GBq: 84% probability of marrow safety (likely safe in moderately extensive mets)*
3.72	GBq: 96% probability of marrow safety (likely safe in highly extensive metastases)*

** Likely inadequate for tumour control, unless palliative intent. Theranostic guidance recommended*

Marrow dose constraint	*2.0*	*Gy*	*Where blood is surrogate for marrow*
Marrow dose rate constrain	*0.265*	*Gy/h*	*Where blood TIAC is normalised to* ***A*** *o*
Lung activity constraint	*2.91*	*GBq at 48h*	*Whole body retained activity at 48h*

First Strike Maximum Predicted Safe I-131 Constrained by Marrow and Lung



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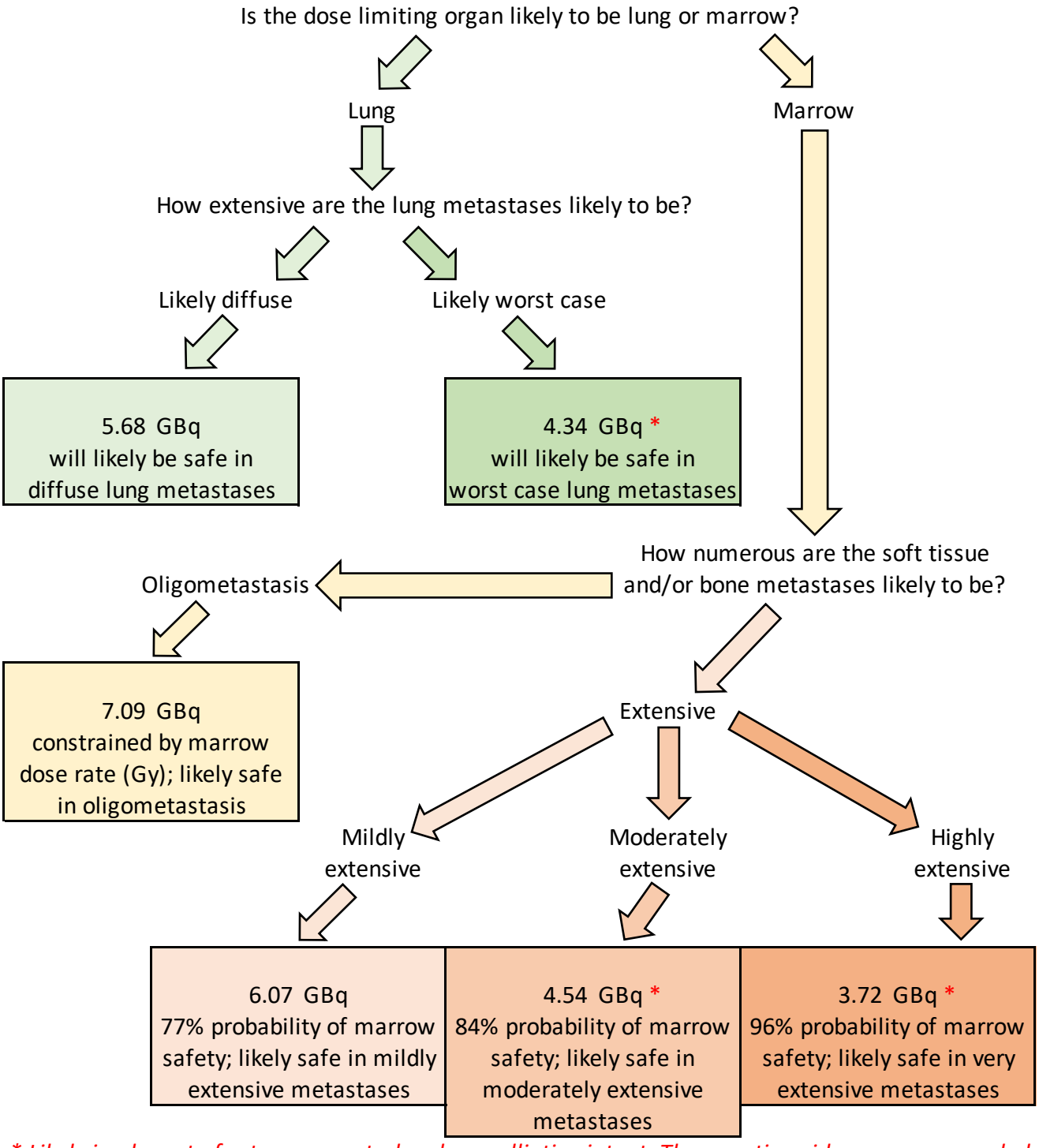
Surname	Standard	Date of Birth	00/01/1900	
Given name	Asian	Height	160	cm
Gender	Female	Weight	51	kg

The Royal Melbourne Hospital

Consider risks of lung AND marrow toxicity to prescribe according to the dose (Gy) limiting organ.
Preparation: thyroid hormone withdrawal. INVALID in severe chronic kidney disease or paediatrics



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Surname	Standard	Date of Birth		
Given name	Female	Height	163	cm
Gender	Female	Weight	60	kg

The Royal Melbourne Hospital

Consider risks of lung AND marrow toxicity to prescribe according to the dose (Gy) limiting organ.
Preparation: thyroid hormone withdrawal. INVALID in severe chronic kidney disease or paediatrics

5.79	GBq will likely be safe in diffuse lung metastases
4.42	GBq will likely be safe in worst case lung metastases*

If diffuse lung metastases is clinically unlikely (i.e. lung is not the dose limiting organ), **AND**;
If the patient is clinically suspected to have **oligometastasis** with **average I-131 kinetics**:

8.03	GBq constrained by marrow dose rate (Gy/h) is likely to be safe for oligometastasis
13.17	GBq constrained by marrow absorbed dose (Gy) might exceed safe dose rate (Gy/h)

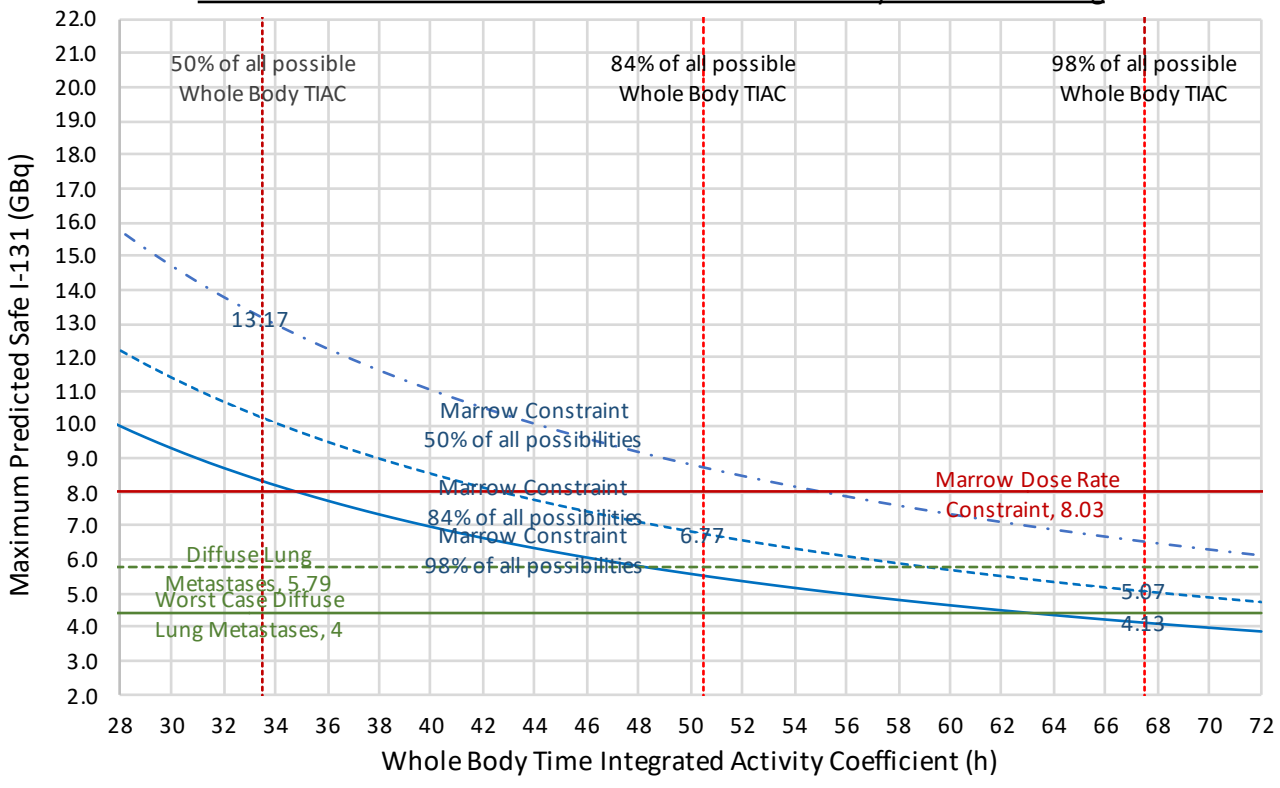
If **EXTENSIVE** soft tissue and/or bone metastases is clinically suspectec

6.77	GBq: 77% probability of marrow safety (likely safe in mildly extensive metastases)
5.07	GBq: 84% probability of marrow safety (likely safe in moderately extensive mets)*
4.13	GBq: 96% probability of marrow safety (likely safe in highly extensive metastases)*

** Likely inadequate for tumour control, unless palliative intent. Theranostic guidance recommended*

Marrow dose constraint	*2.0*	*Gy*	*Where blood is surrogate for marrow*
Marrow dose rate constrain	*0.265*	*Gy/h*	*Where blood TIAC is normalised to* ***A*** *o*
Lung activity constraint	*2.96*	*GBq at 48h*	*Whole body retained activity at 48h*

First Strike Maximum Predicted Safe I-131 Constrained by Marrow and Lung



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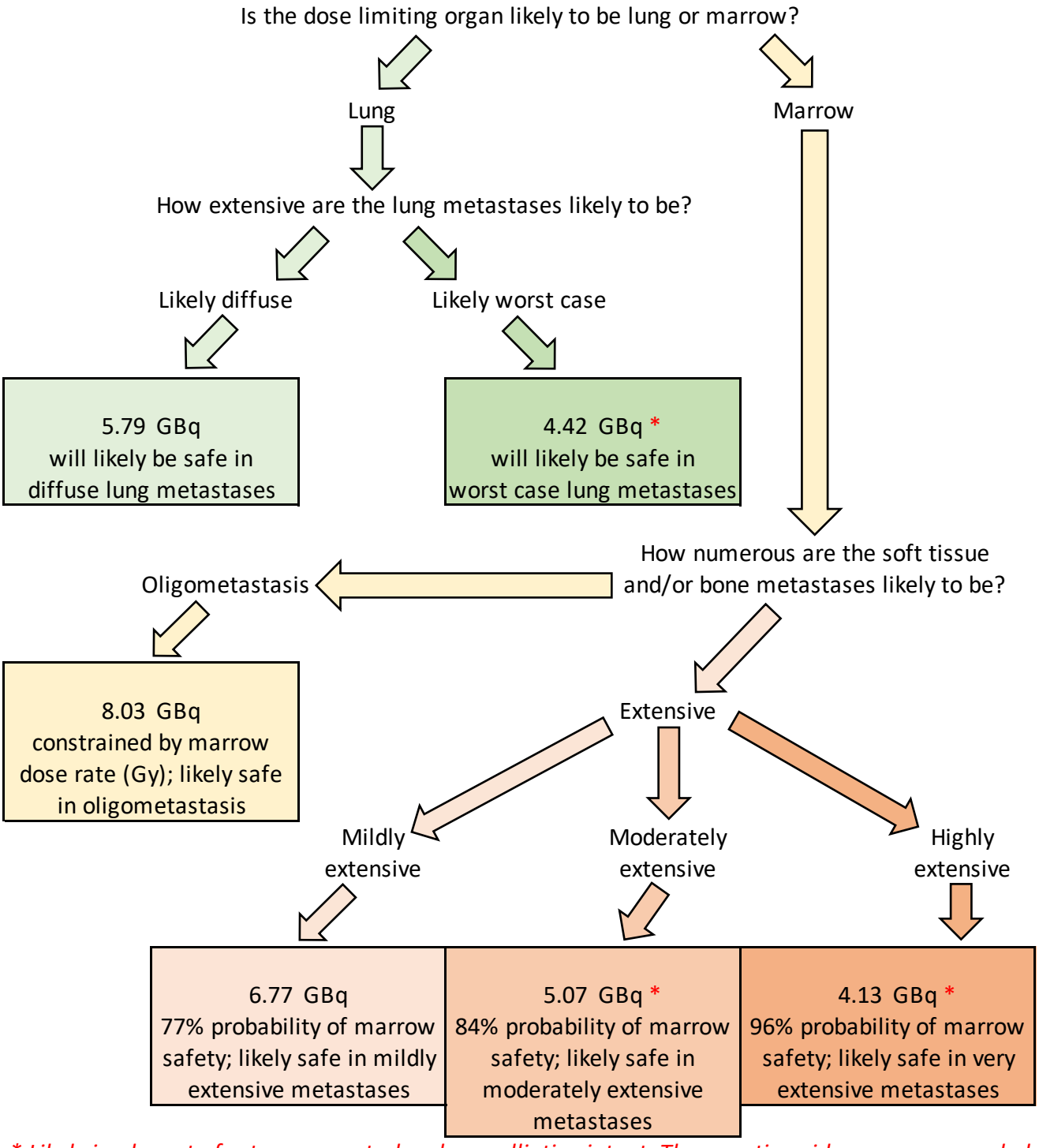
By Dr Y.H. Kao MBBS MRCP FAMS FRACP FAANMS, Department of Nuclear Medicine Print pg 1&2

Surname	Standard	Date of Birth	00/01/1900	
Given name	Female	Height	163	cm
Gender	Female	Weight	60	kg

The Royal Melbourne Hospital

Consider risks of lung AND marrow toxicity to prescribe according to the dose (Gy) limiting organ.
Preparation: thyroid hormone withdrawal. INVALID in severe chronic kidney disease or paediatrics



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Surname	Standard	Date of Birth		
Given name	Male	Height	176	cm
Gender	Male	Weight	73	kg

The Royal Melbourne Hospital

Consider risks of lung AND marrow toxicity to prescribe according to the dose (Gy) limiting organ.
Preparation: thyroid hormone withdrawal. INVALID in severe chronic kidney disease or paediatrics

6.25	GBq will likely be safe in diffuse lung metastases
4.78	GBq will likely be safe in worst case lung metastases*

If diffuse lung metastases is clinically unlikely (i.e. lung is not the dose limiting organ), **AND**;
If the patient is clinically suspected to have **oligometastasis** with **average I-131 kinetics**:

10.46	GBq constrained by marrow dose rate (Gy/h) is likely to be safe for oligometastasis
17.43	GBq constrained by marrow absorbed dose (Gy) might exceed safe dose rate (Gy/h)

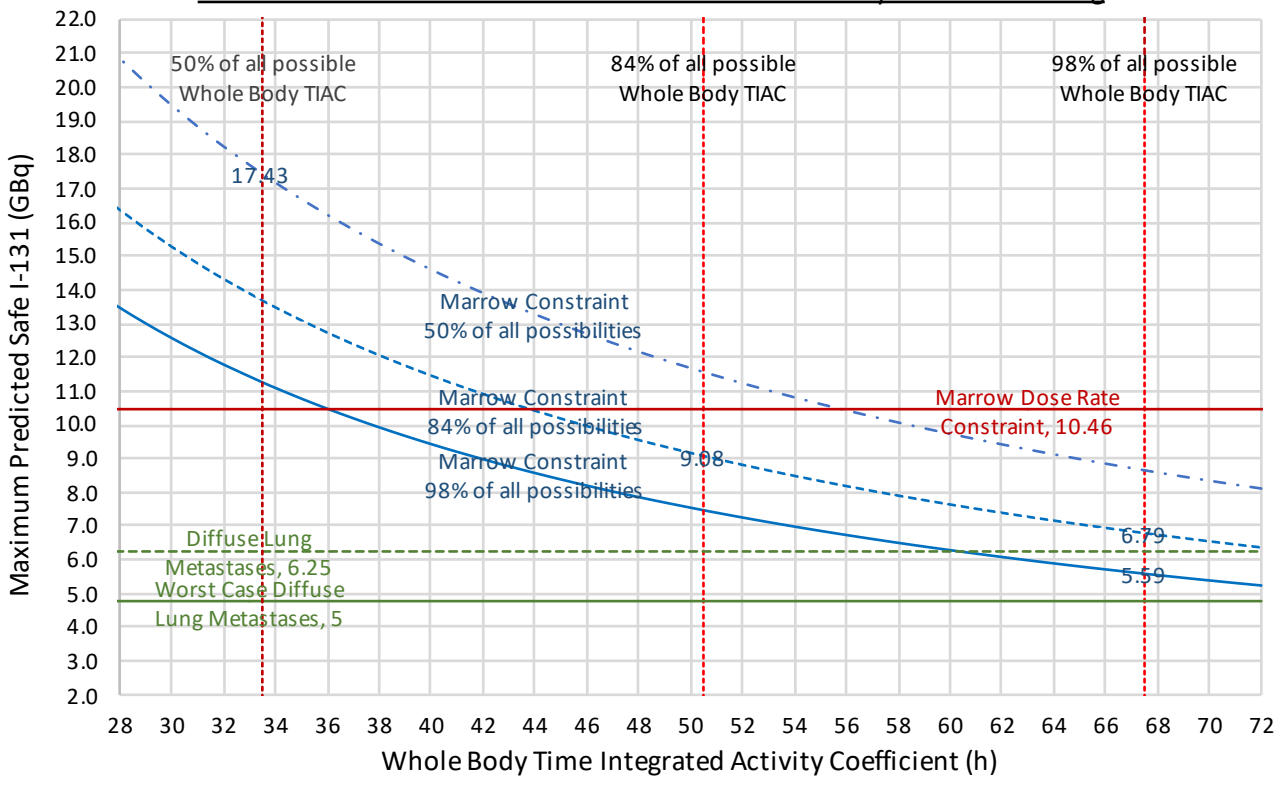
If **EXTENSIVE** soft tissue and/or bone metastases is clinically suspectec

9.08	GBq: 77% probability of marrow safety (likely safe in mildly extensive metastases)
6.79	GBq: 84% probability of marrow safety (likely safe in moderately extensive mets)*
5.59	GBq: 96% probability of marrow safety (likely safe in highly extensive metastases)*

** Likely inadequate for tumour control, unless palliative intent. Theranostic guidance recommended*

Marrow dose constraint	*2.0*	*Gy*	*Where blood is surrogate for marrow*
Marrow dose rate constrain	*0.265*	*Gy/h*	*Where blood TIAC is normalised to* ***A*** *o*
Lung activity constraint	*3.20*	*GBq at 48h*	*Whole body retained activity at 48h*

First Strike Maximum Predicted Safe I-131 Constrained by Marrow and Lung



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Surname	Standard	Date of Birth	00/01/1900	
Given name	Male	Height	176	cm
Gender	Male	Weight	73	kg

The Royal Melbourne Hospital

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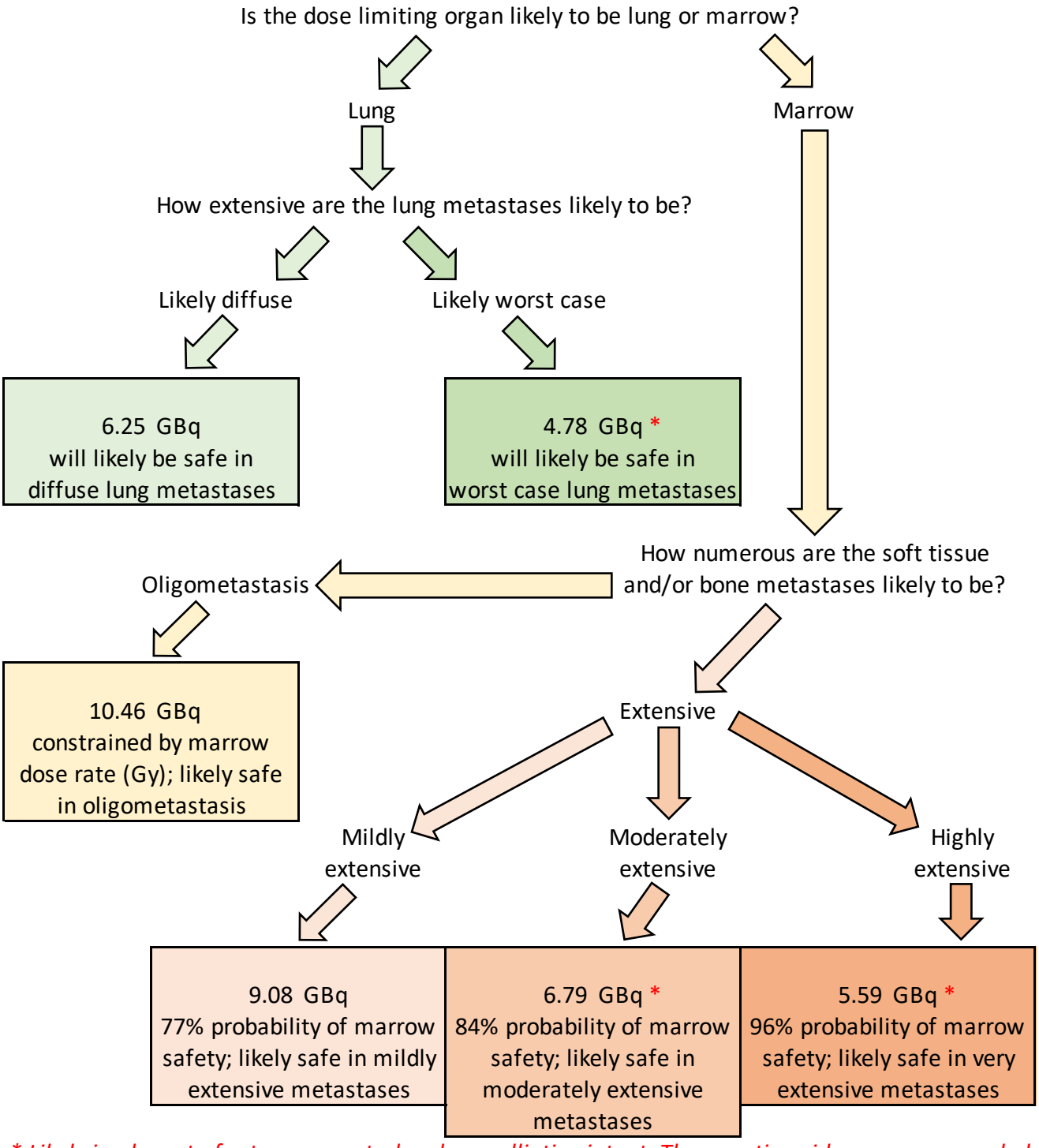

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