

# iRECIST

## Modified RECIST for Immunotherapy

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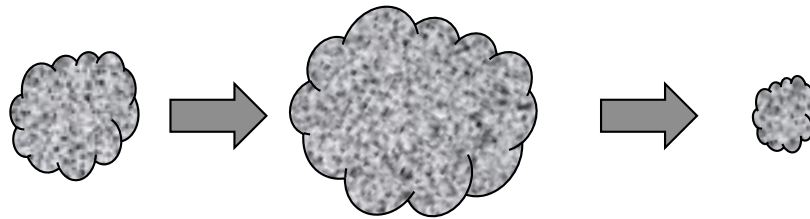


# Outline

- Brief rationale/history
- New concepts and response categories
- Decision-making after RECIST PD
- Examples/exercises

# Rationale And Summary

- Atypical response pattern to immunotherapies
  - Initial growth of tumor followed by response




- At RECIST PD, may continue to treat
  - If clinically stable, at investigator discretion
  - Until “confirmed progression”

# History

- 2009 Wolchok irRC
  - 2D, WHO logic
  - Measure new lesions, PD only quantitative
  - Confirmation of PD required
- Combination of irRC with RECIST: “irRECIST”
  1. Make irRC one dimensional
  2. Preserve logic of RECIST, but add PD confirmation
- Broad collaboration to harmonize → iRECIST
  - Pharma, academia, FDA, EORTC, CCTG, NCI...

# Please Note!

- All criteria papers have “gaps”
  - Applying criteria requires interpretation
  - Judgment calls made in filling gaps
- These slides = MSD interpretation
- Possible minor variations



# **New Concepts and Response Categories**

# It's Just RECIST Until PD

- iRECIST begins at RECIST 1.1 PD
- Until then, iRECIST = RECIST 1.1
  - Definitions of measurable disease
  - Target and non-target selection rules
  - Response categories and thresholds

# Concept: Confirming PD

- At initial appearance of PD
  - Investigator decision to continue
  - Clinical stability
    - Stable performance status
    - No worsening signs or symptoms
    - No urgent intervention needed
  - Re-scan in **4-8 weeks** to confirm
- If not confirmed → pseudoprogression



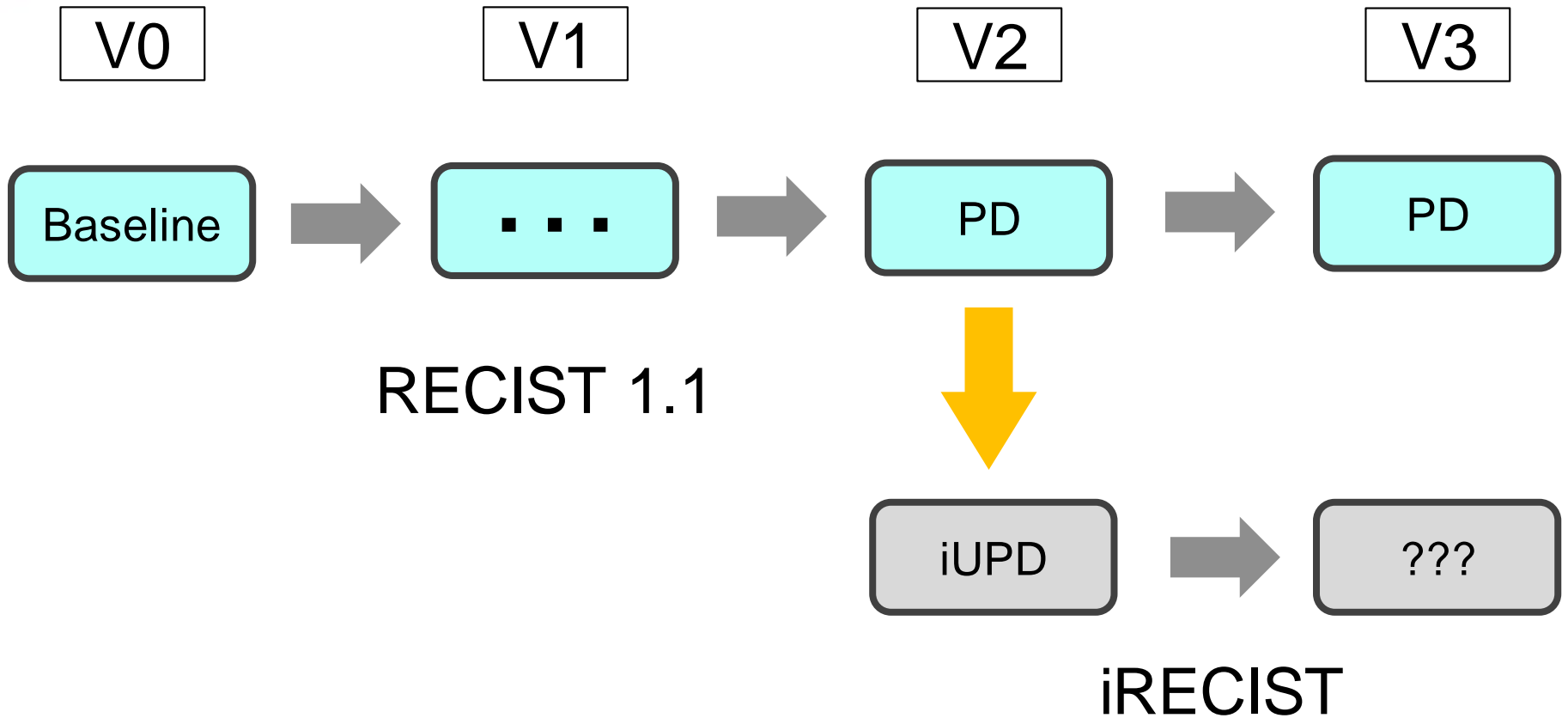
# Concept: New Lesion Assessment

- Measurable vs non-measurable
    - Rules identical to baseline
    - Based on size and reproducibility
  - Up to 5 new lesion targets (NL-T)
    - NL sum of diameters (NL-SOD\*)
    - Distinct from baseline target lesion SOD\*
    - All others → NL-NT
- \* - iRECIST paper uses “SOM” for “sum of measurements”

# New Response Categories

- i\_\_ = responses based on iRECIST
  - At or after RECIST 1.1 PD
  - e.g. iSD = SD after RECIST PD
    - iPR, iCR, non-iCR/non-iUPD
- iUPD = Unconfirmed PD
  - Always the first iRECIST visit response
  - Can occur multiple times, even in a row
- iCPD = Confirmed PD
  - Only possible immediately after iUPD

# iRECIST begins at RECIST PD

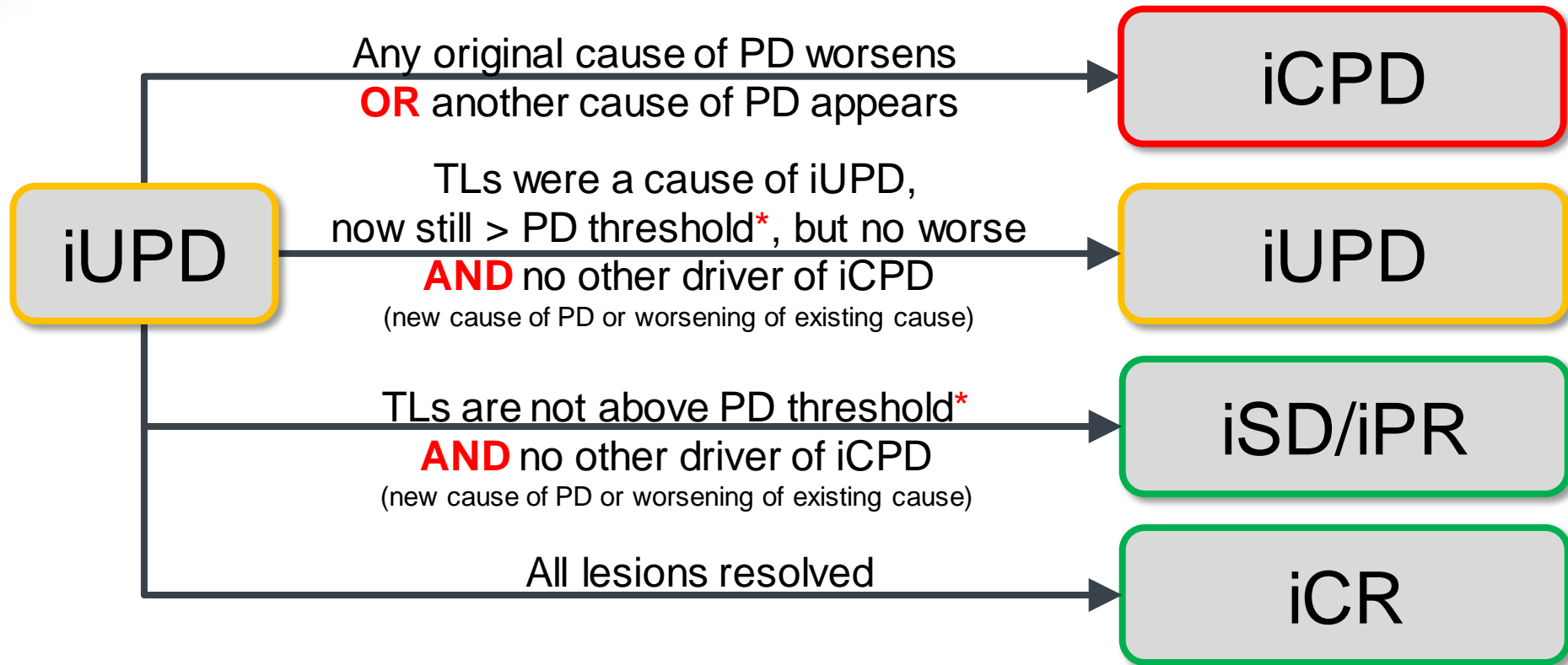


# “Causes” of PD

- Any factor/category showing PD by RECIST 1.1
- Target SOD\*  $\geq 20\%$  and  $\geq 5$  mm  $\uparrow$  from nadir
- Non-target lesions show unequivocal progression
- New lesions have appeared

- \*
  - RECIST 1.1 paper, SOD = “sum of diameters”
  - iRECIST paper, SOM = “sum of measurements”

# Resolving Initial iUPD



Note: Only target lesion PD, if present at iUPD, must resolve to achieve iSD/iPR.  
e.g. PR in TLs + unequivocal PD of NTLs + new lesions → unchanged = iPR

\* PD threshold = 20% & 5 mm ↑ from nadir

# What is “Worsening”

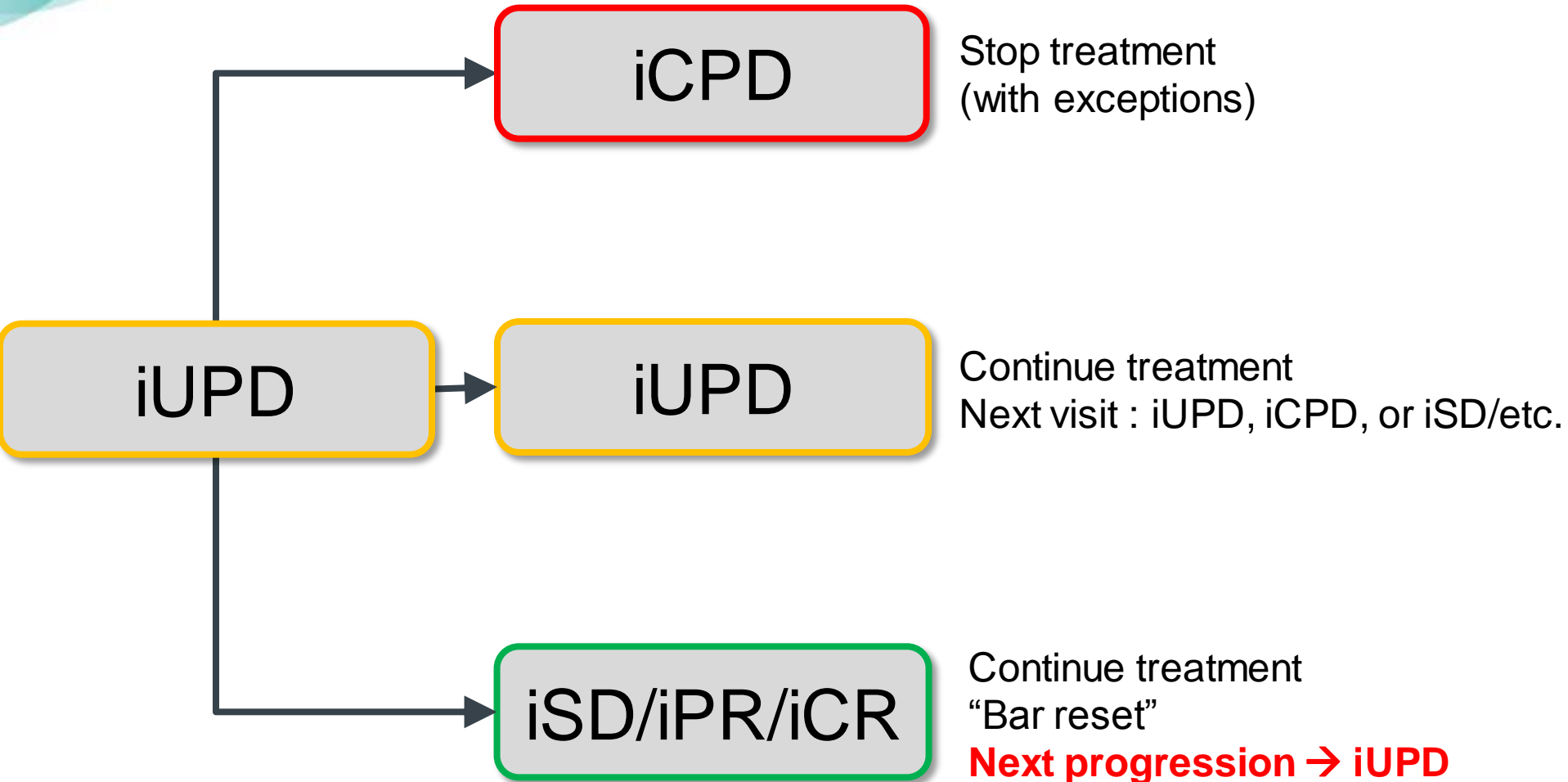
- Bayesian approach
  - Prior + new data → post-test likelihood
  - High prior → less new data for same conclusion
- Prior PD **by a cause** = high prior **for that cause**
  - Suspicious for true PD
- Need little more growth to confirm, **for that cause**
  - “Low bar” to confirm PD

# “Worsening” = low bar for iCPD

(for any existing cause of iUPD)

- Target: SOD increases  $\geq 5$  mm
  - Does not have to increase 20% from iUPD
- Non-target: any further increase
  - Does not have to meet “unequivocal” standard
- New:
  - Number increases: any additional new lesions
  - OR**
  - Size increases
    - Target NL: NL-SOD increases  $\geq 5$  mm
    - Non-target NL: Any significant growth

# What Happens After iUPD





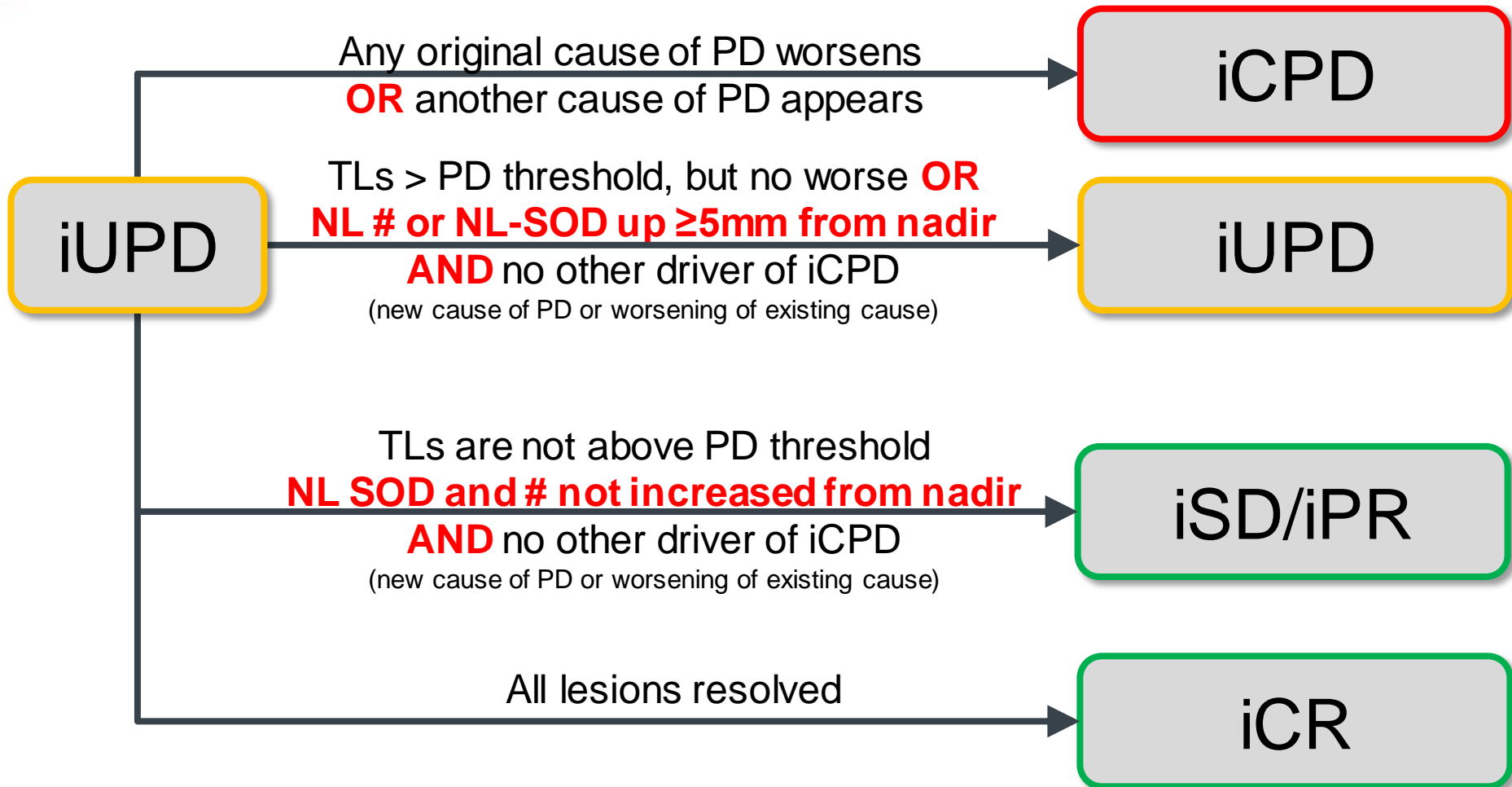
# Progression After iSD/iPR/iCR

- Target lesions
  - SOD crosses PD threshold (1<sup>st</sup> time, or again)
  - Based on the nadir (i.e. smallest value ever)
- Non-target lesions
  - New unequivocal progression OR
  - If already showed PD, and did not regress, ANY growth

# Progression After iSD/iPR/iCR

- New lesions
  - New lesions appear for the first time
  - Additional new lesions appear
  - If lesions appeared, but did not regress, ANY growth
    - 5 mm increase in SOD for NL(T)
    - Visible growth for NL(NT)
  
- Note – track nadir for:
  - New target SOD
  - Total # of new lesions

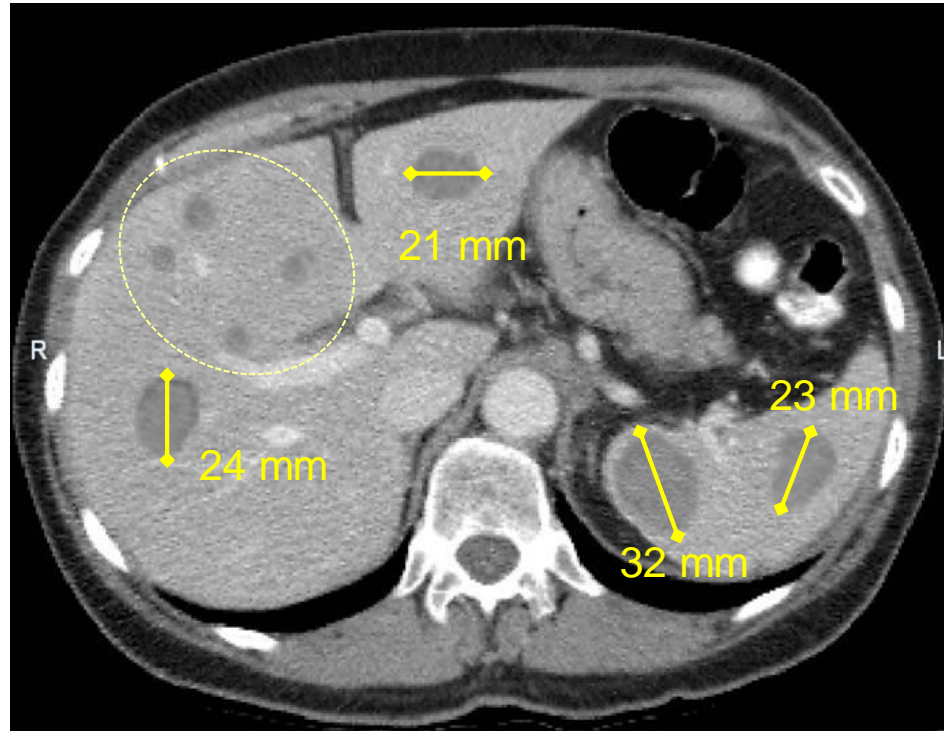
# Resolving second iUPD (almost the same as the first)



Please note: MSD approach to a gap

# Case Examples

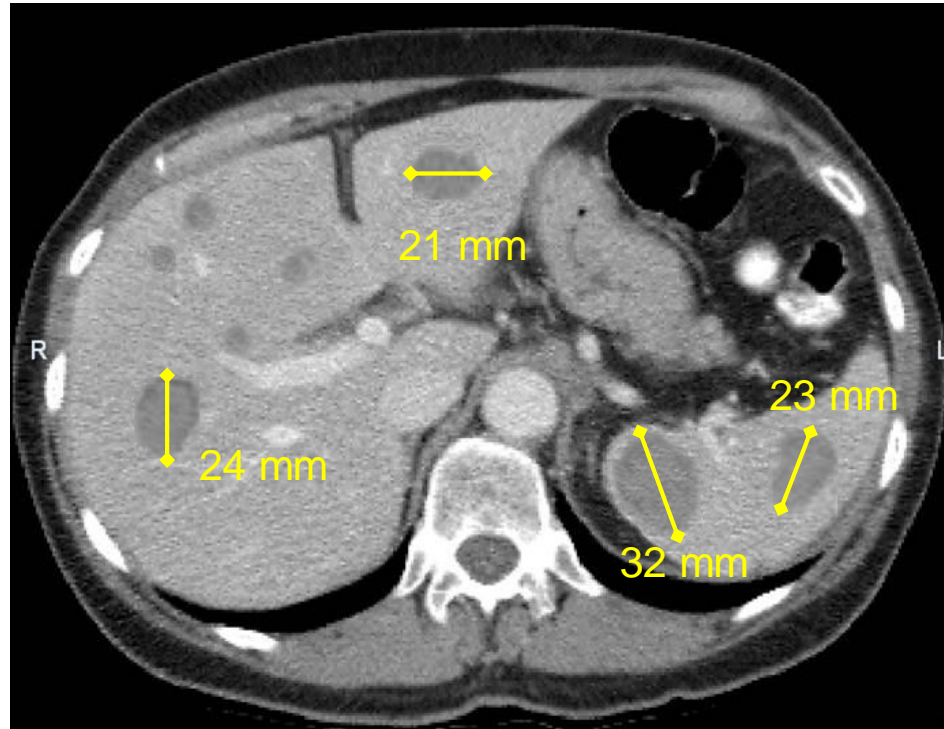
# Baseline For All Examples



These are the only lesions

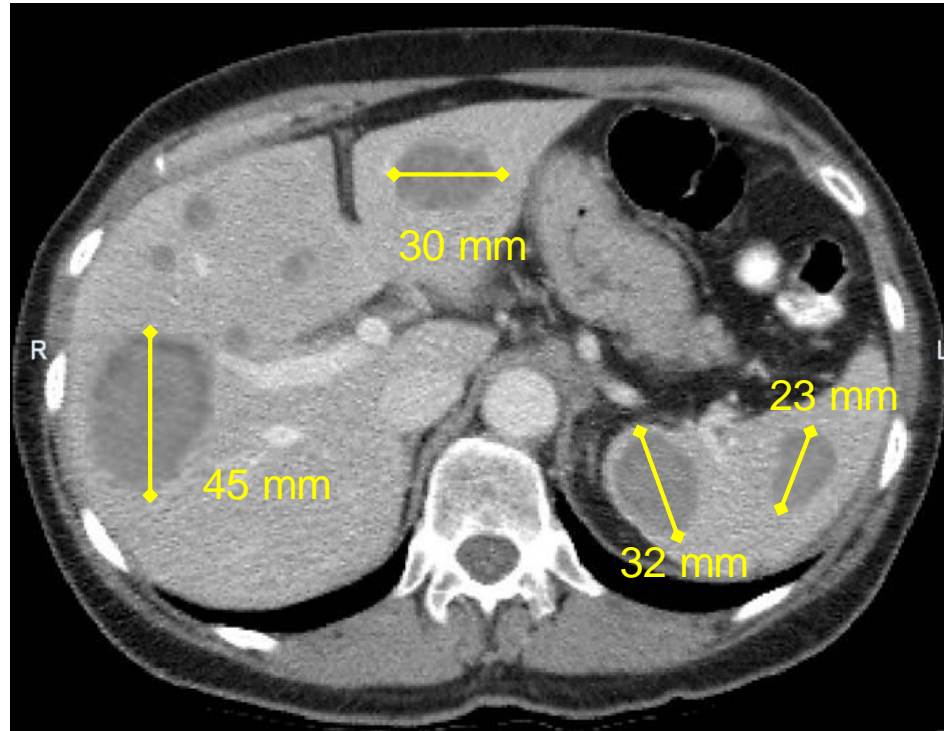
# Case 1

# Case 1 – Baseline



	BL
SOD (mm)	100
TL Resp	N/A

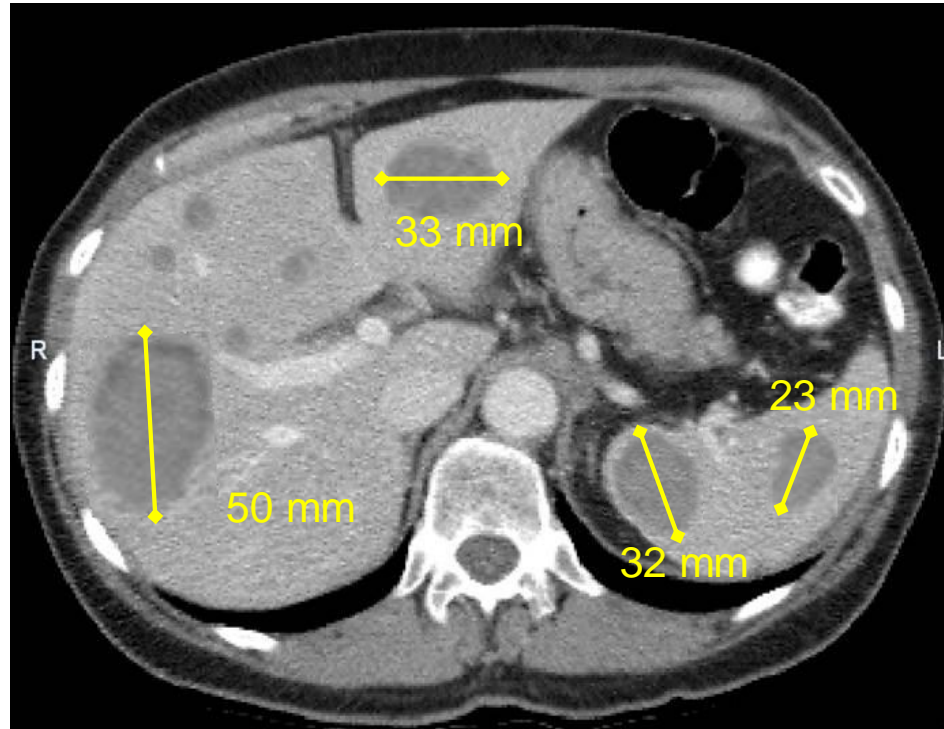
# Case 1 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp	N/A	iUPD



# Case 1 – Visit 2

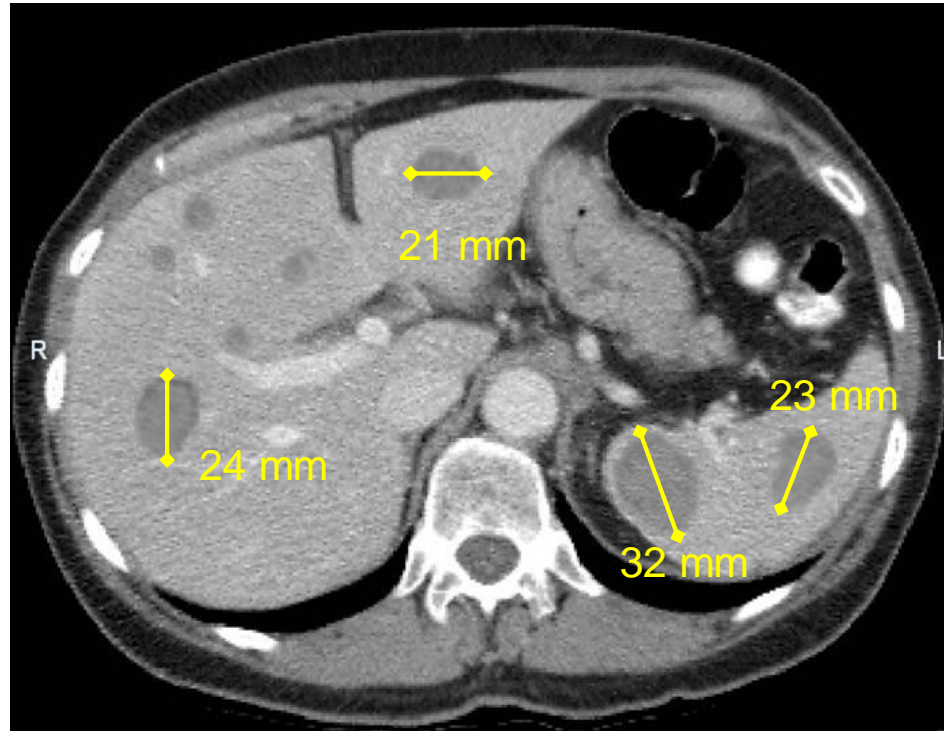


	BL	V1	V2
SOD (mm)	100	130	138
TL Resp	N/A	iUPD	iCPD

≥5 mm increase

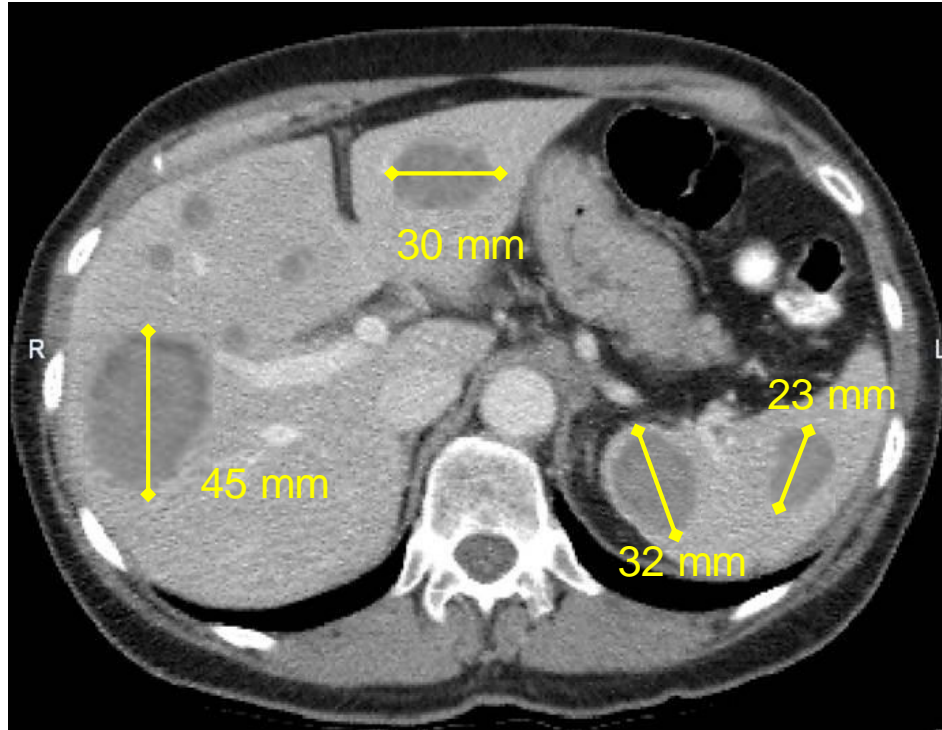
# Case 2

# Case 2 – Baseline



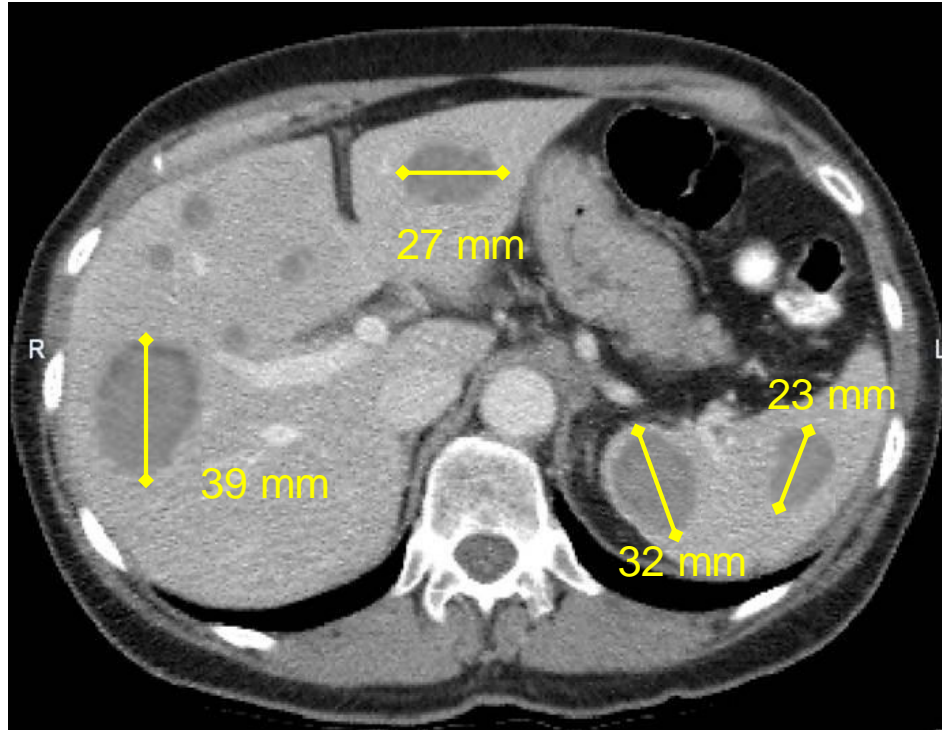
	BL
SOD (mm)	100
TL Resp	N/A

# Case 2 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp	N/A	iUPD

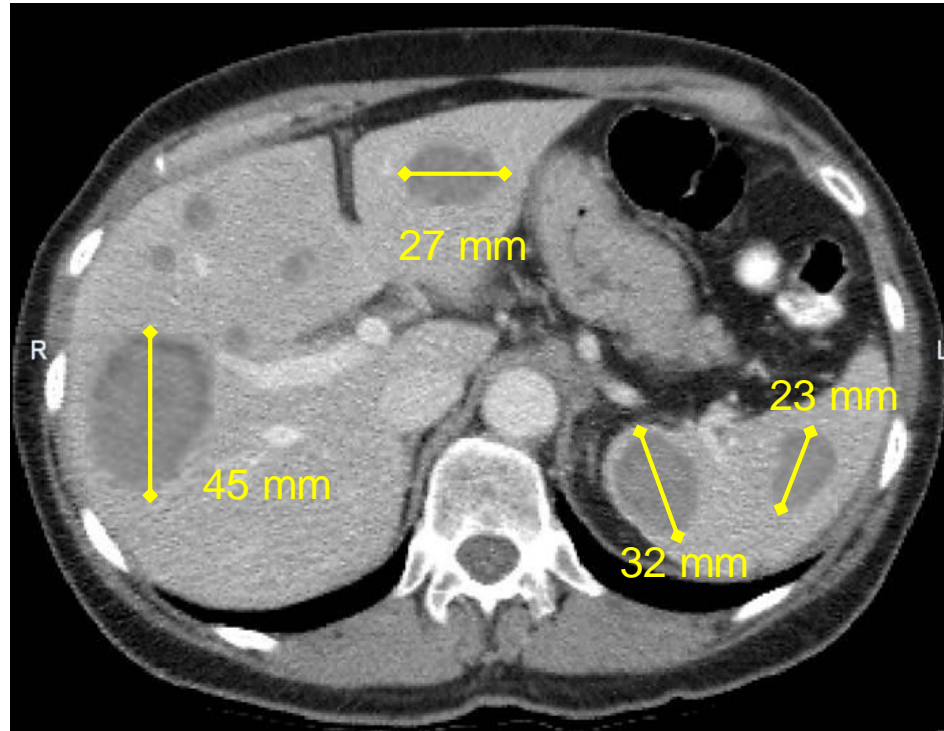
# Case 2 – Visit 2



	BL	V1	V2
SOD (mm)	100	130	121
TL Resp	N/A	iUPD	iUPD

Decreased, still >PD threshold

# Case 2 – Visit 3

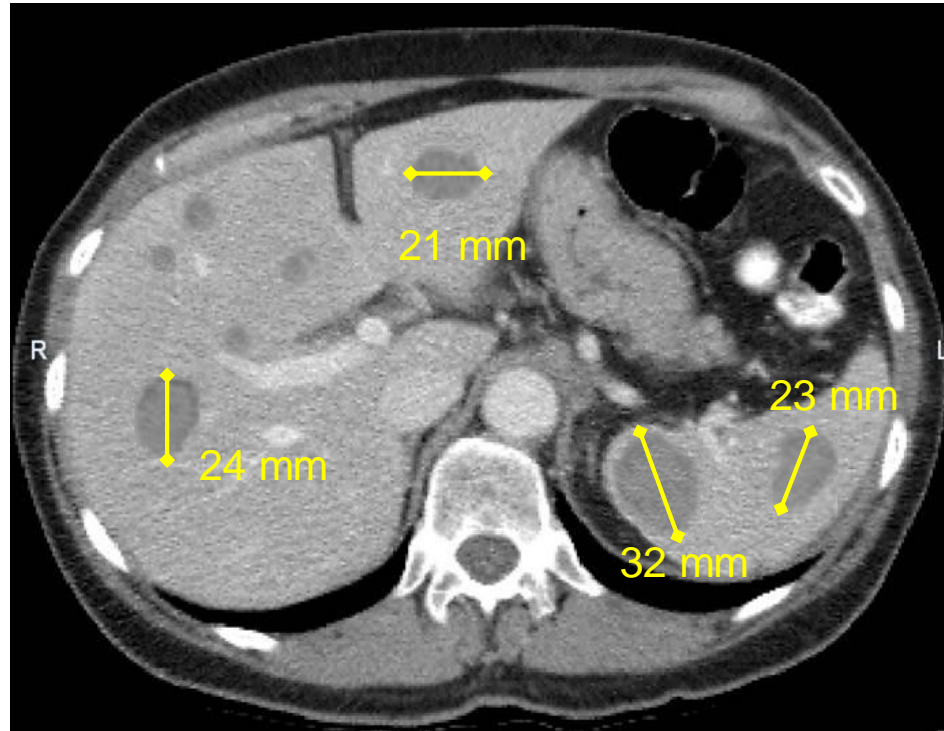


	BL	V1	V2	V3
SOD (mm)	100	130	121	127
TL Resp	N/A	iUPD	iUPD	iCPD

≥5 mm increase

# Case 3

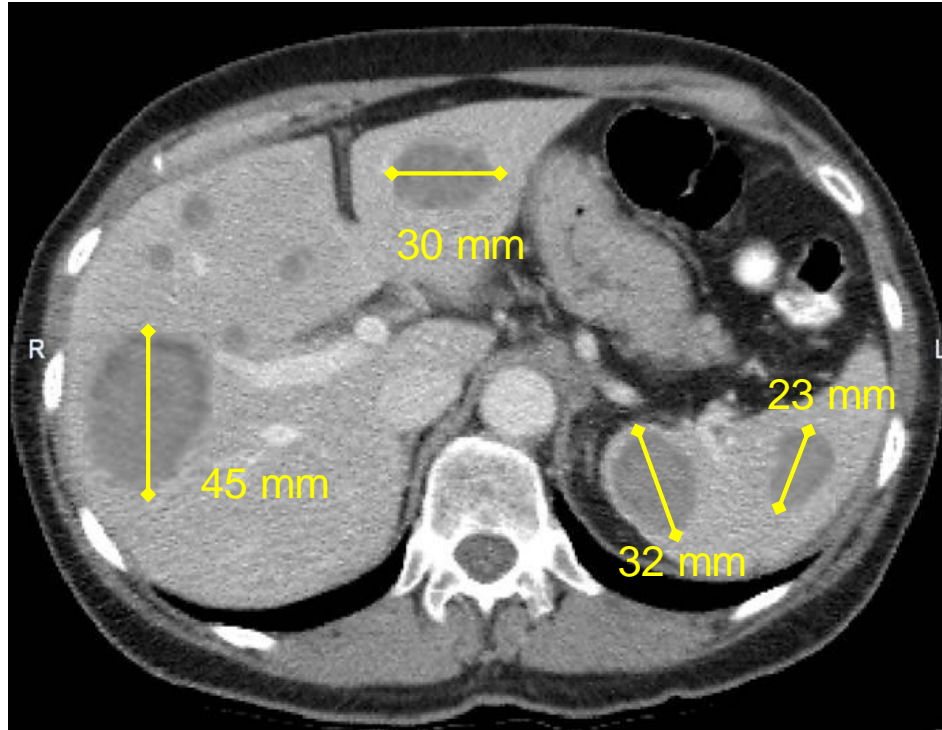
# Case 3 – Baseline



	BL
SOD (mm)	100
TL Resp	N/A

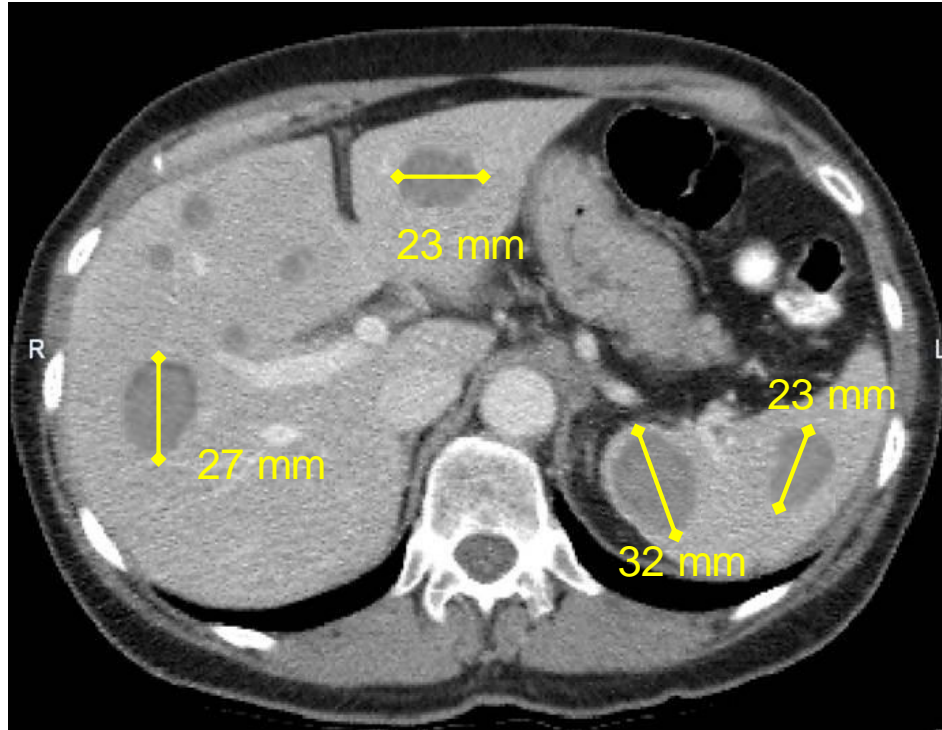


# Case 3 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp	N/A	iUPD

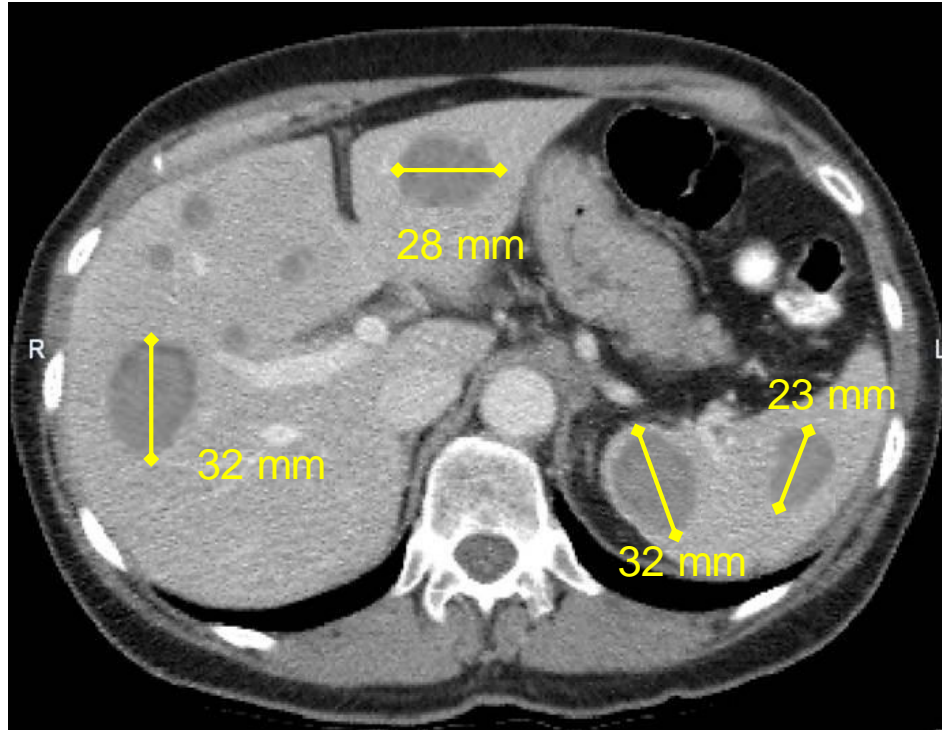
# Case 3 – Visit 2



	BL	V1	V2
SOD (mm)	100	130	105
TL Resp	N/A	iUPD	iSD

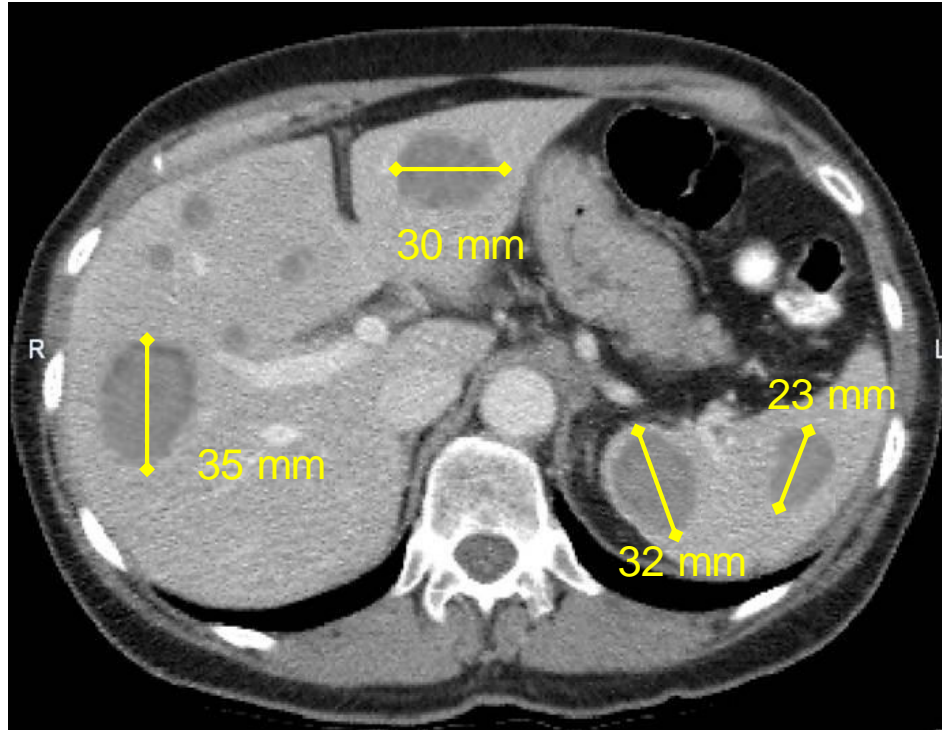
“reset bar”

# Case 3 – Visit 3



	BL	V1	V2	V3
SOD (mm)	100	130	105	115
TL Resp	N/A	iUPD	iSD	iSD

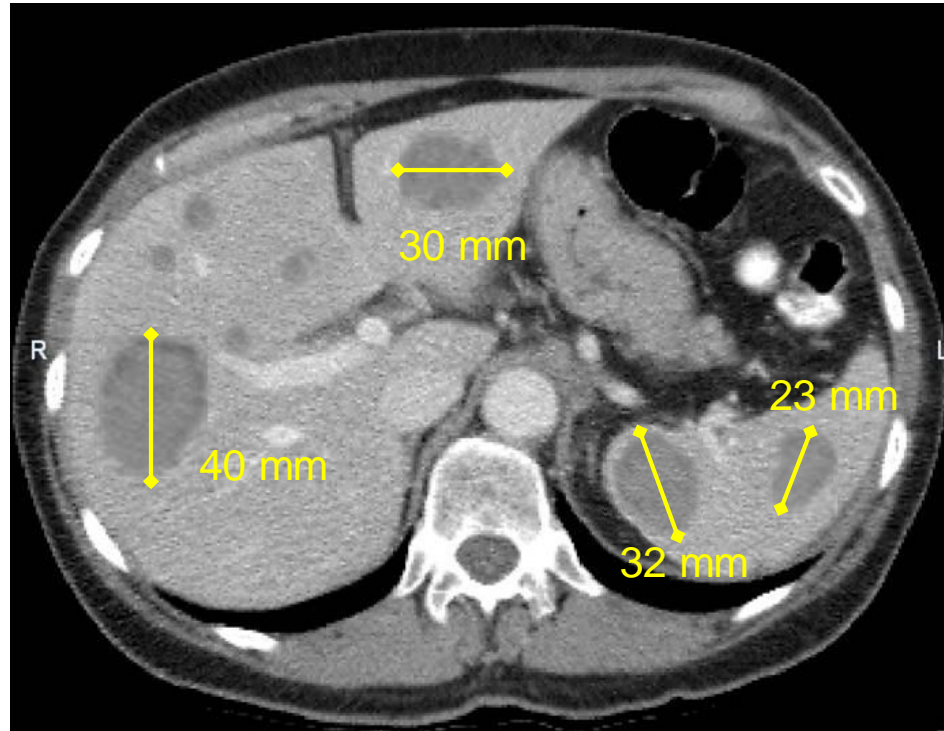
# Case 3 – Visit 4



	BL	V1	V2	V3	V4
SOD (mm)	100	130	105	115	120
TL Resp	N/A	iUPD	iSD	iSD	iUPD

20% above nadir

# Case 3 – Visit 5

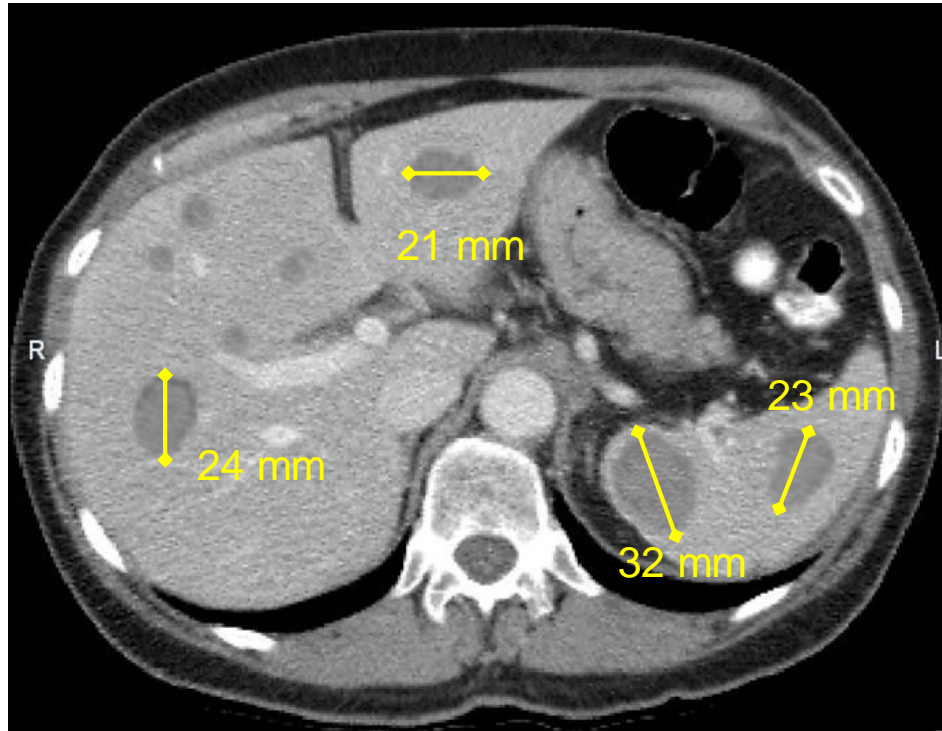


	BL	V1	V2	V3	V4	V5
SOD (mm)	100	130	105	115	120	125
TL Resp	N/A	iUPD	iSD	iSD	iUPD	iCPD

≥5 mm increase

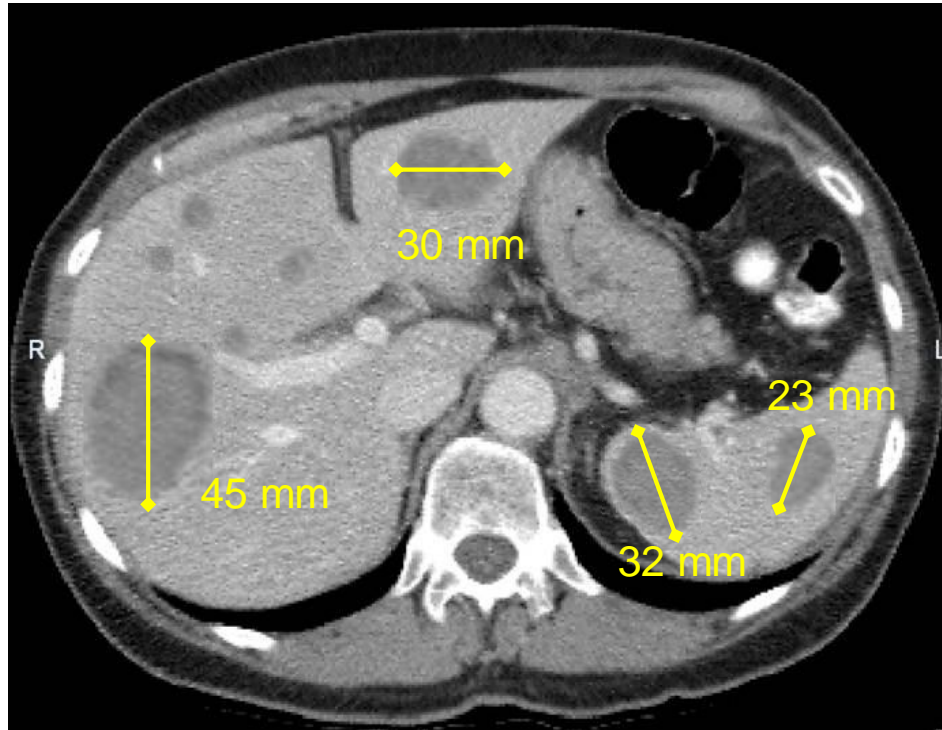
# Case 4

# Case 4 – Baseline



	BL
SOD (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

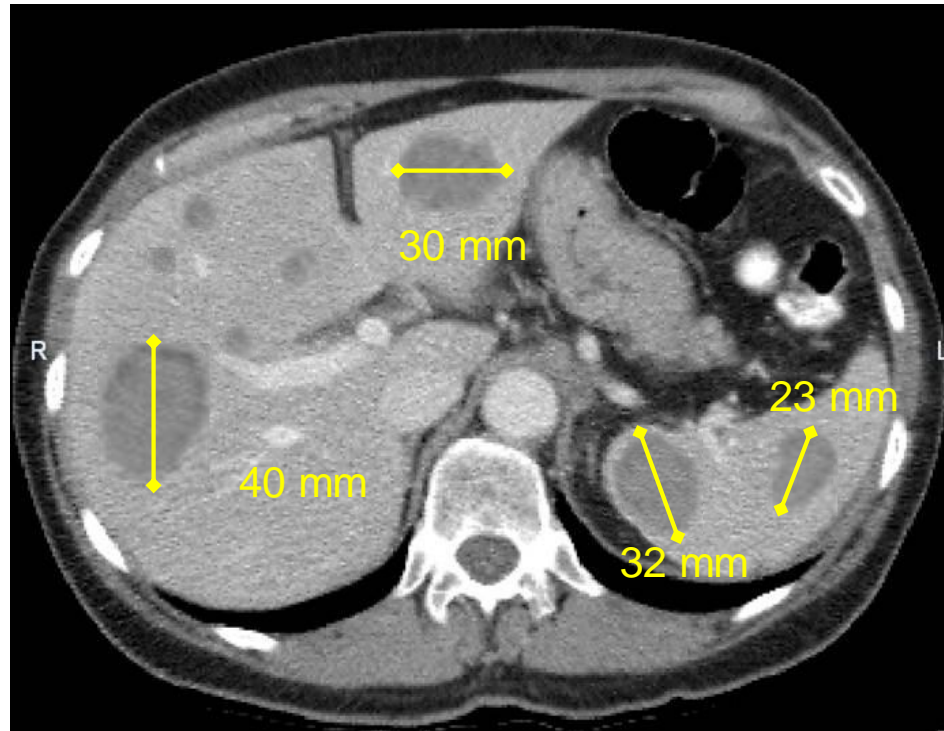
# Case 4 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-iCR/Non-iUPD
New		
Overall Resp		iUPD

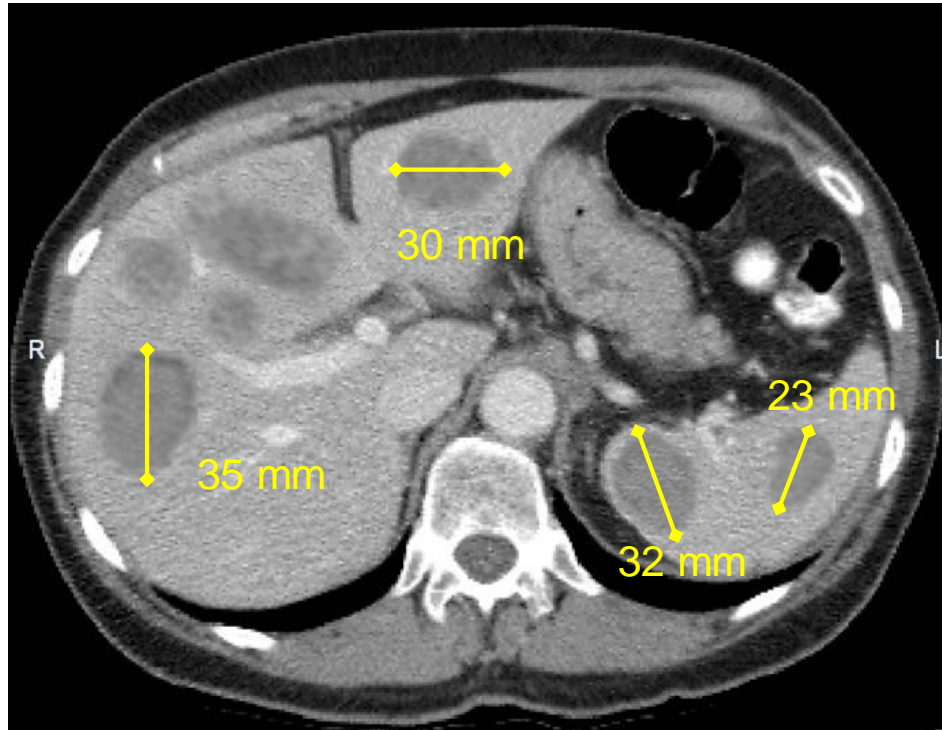


# Case 4 – Visit 2



	BL	V1	V2
SOD (mm)	100	130	125
TL Resp		iUPD	iUPD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New			
Overall Resp		iUPD	iUPD

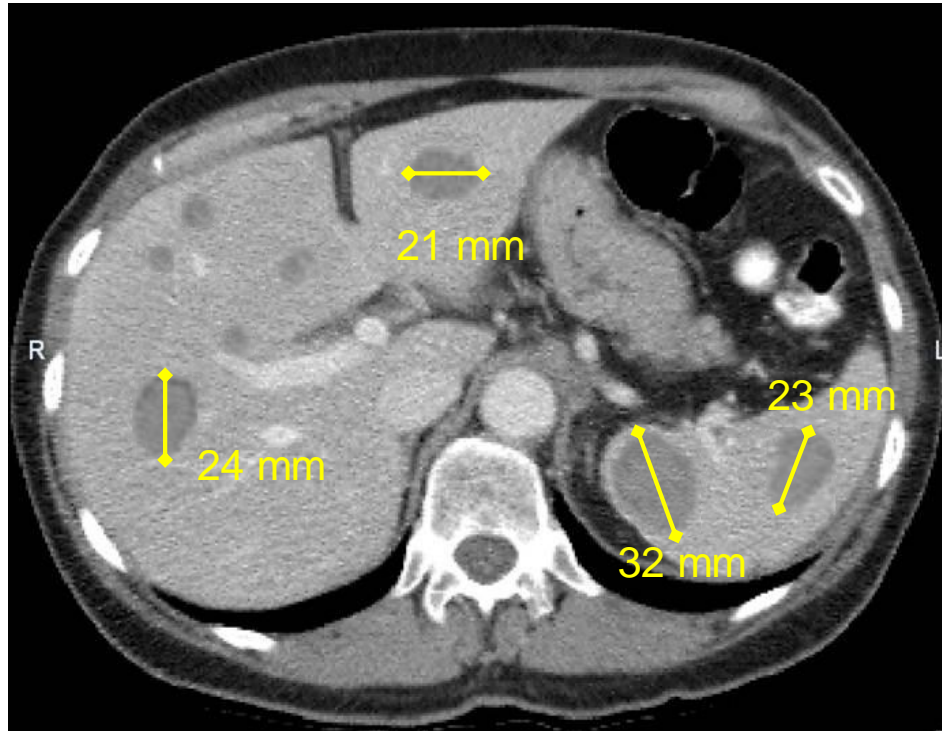
# Case 4 – Visit 3



	BL	V1	V2	V3
SOD (mm)	100	130	125	120
TL Resp		iUPD	iUPD	iUPD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	iUPD
New				
Overall Resp		iUPD	iUPD	iCPD

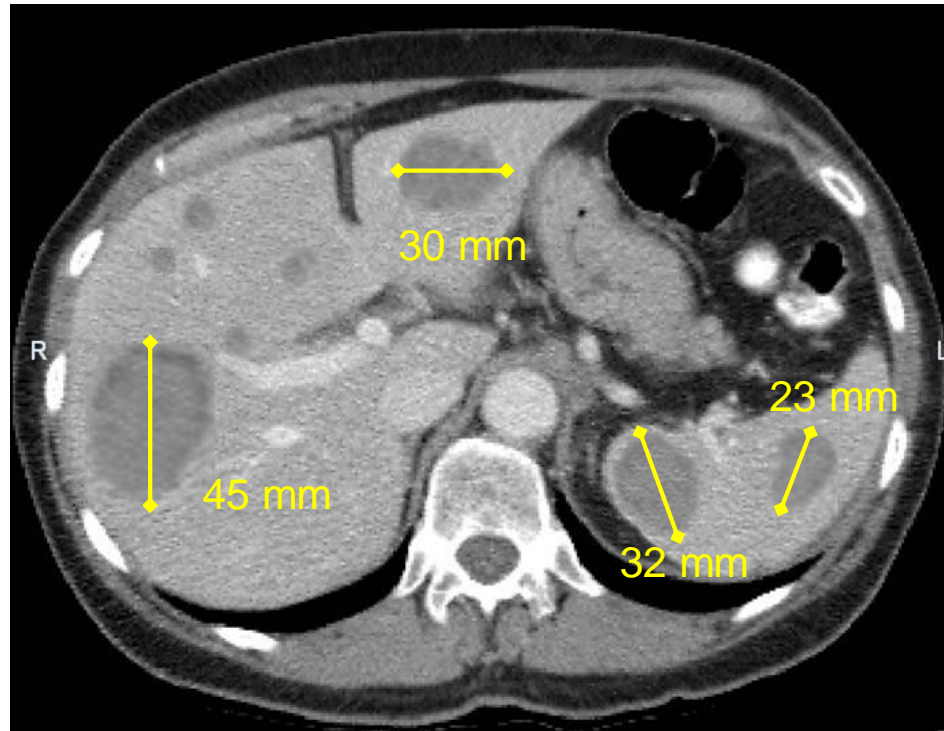
# Case 5

# Case 5 – Baseline



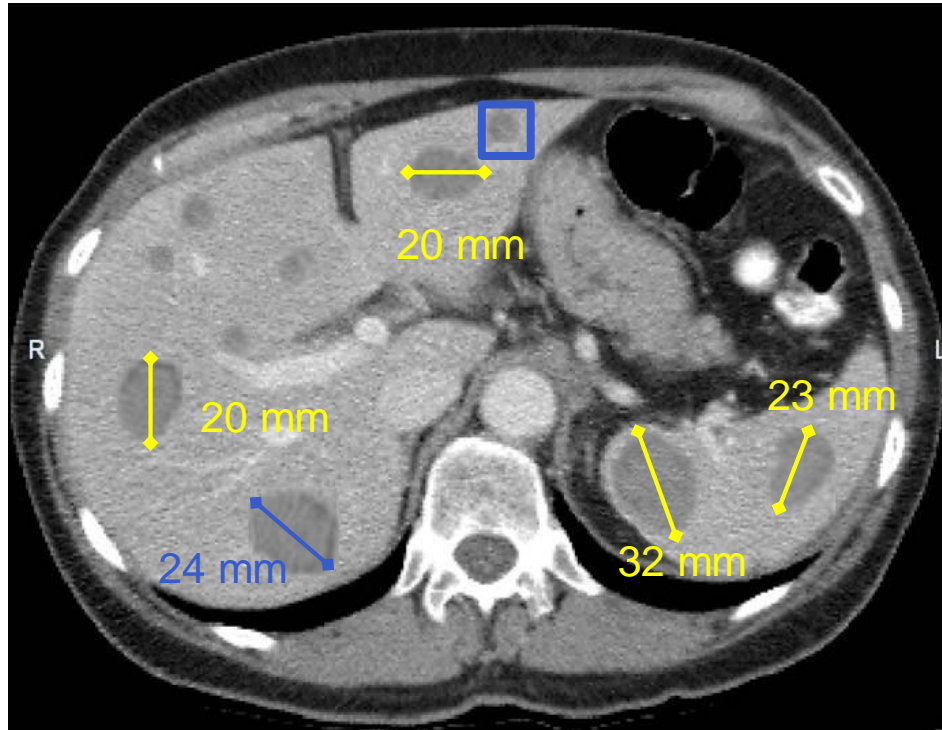
	BL
SOD (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

# Case 5 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-iCR/Non-iUPD
New		
Overall Resp		iUPD

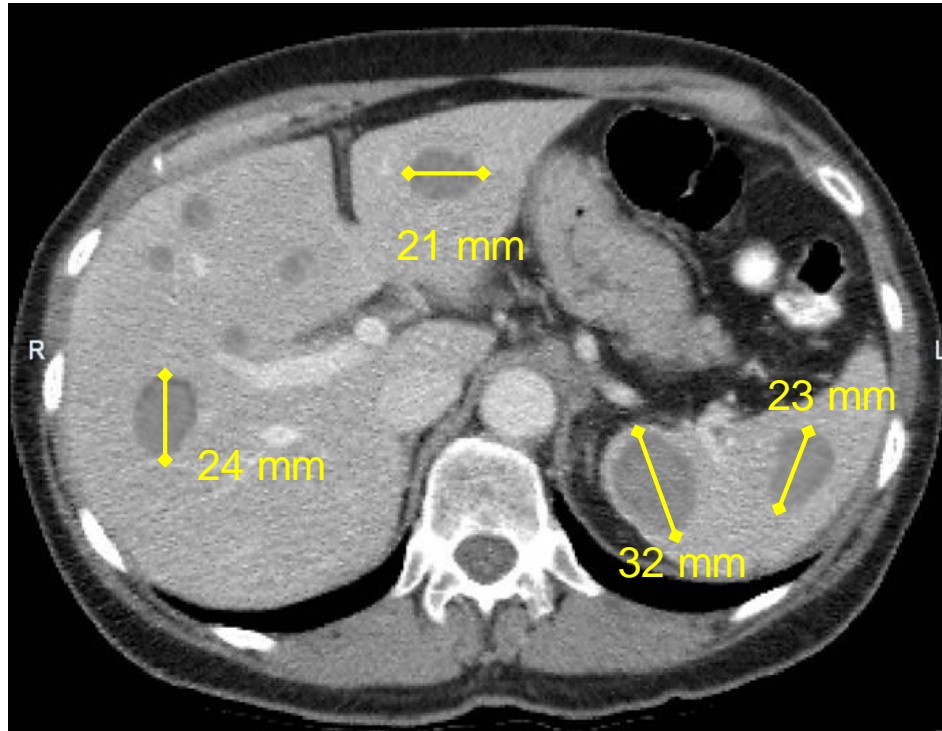
# Case 5 – Visit 2



	BL	V1	V2
SOD (mm)	100	130	95
TL Resp		iUPD	iSD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New			24 mm / NT +
Overall Resp		iUPD	iCPD

# Case 6

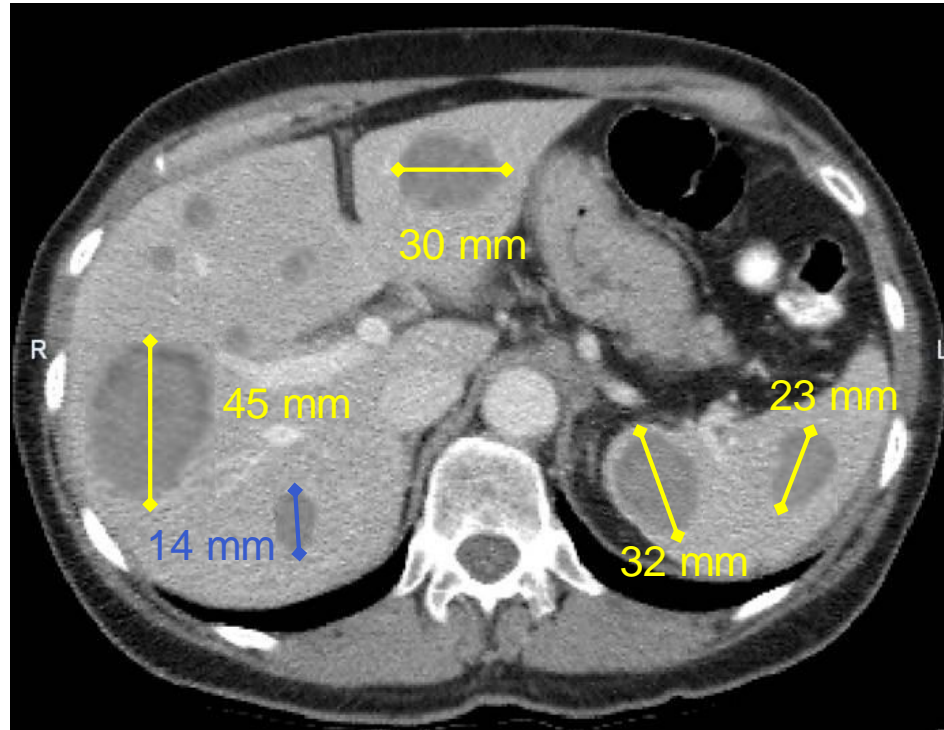
# Case 6 – Baseline



	BL
SOD (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

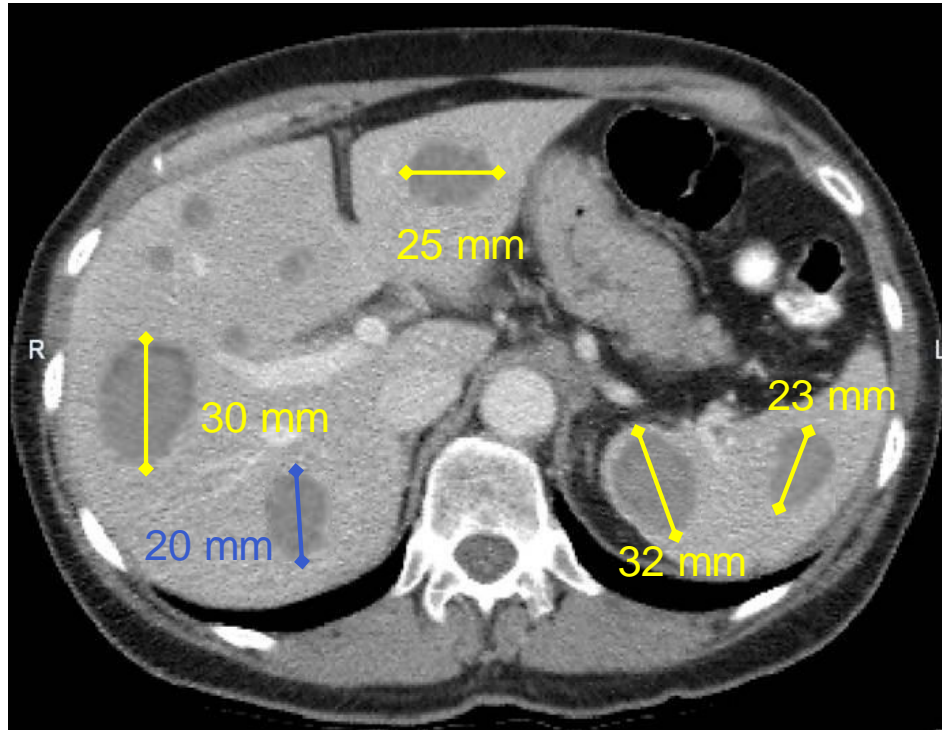


# Case 6 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-iCR/Non-iUPD
New		14 mm
Overall Resp		iUPD

# Case 6 – Visit 2



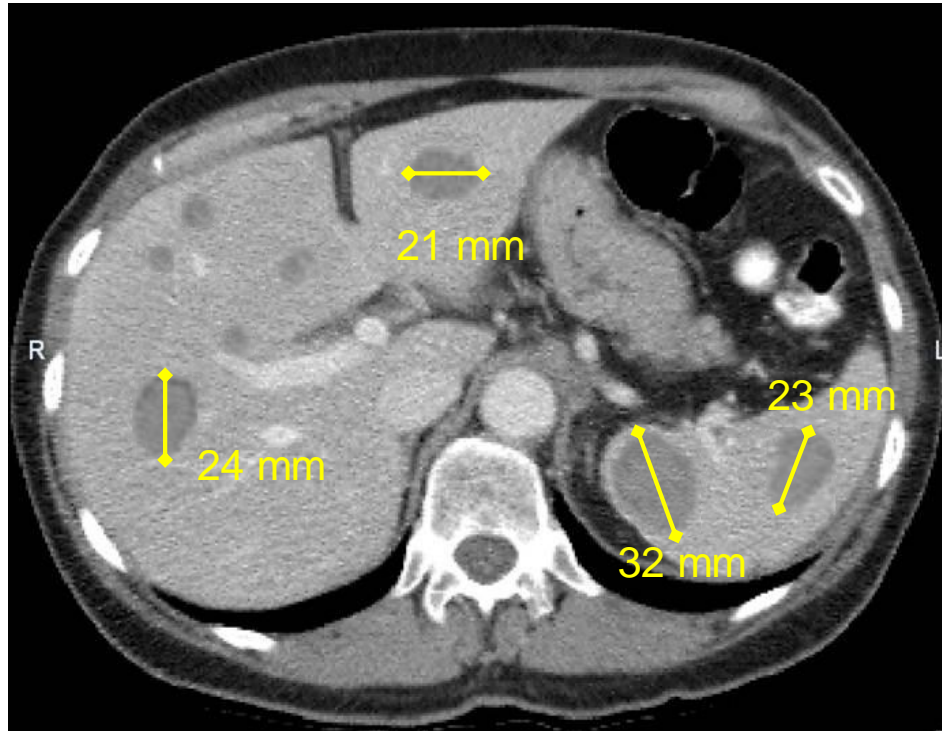
	BL	V1	V2
SOD (mm)	100	130	110
TL Resp		iUPD	iSD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	20 mm
Overall Resp		iUPD	iCPD

≥5 mm increase



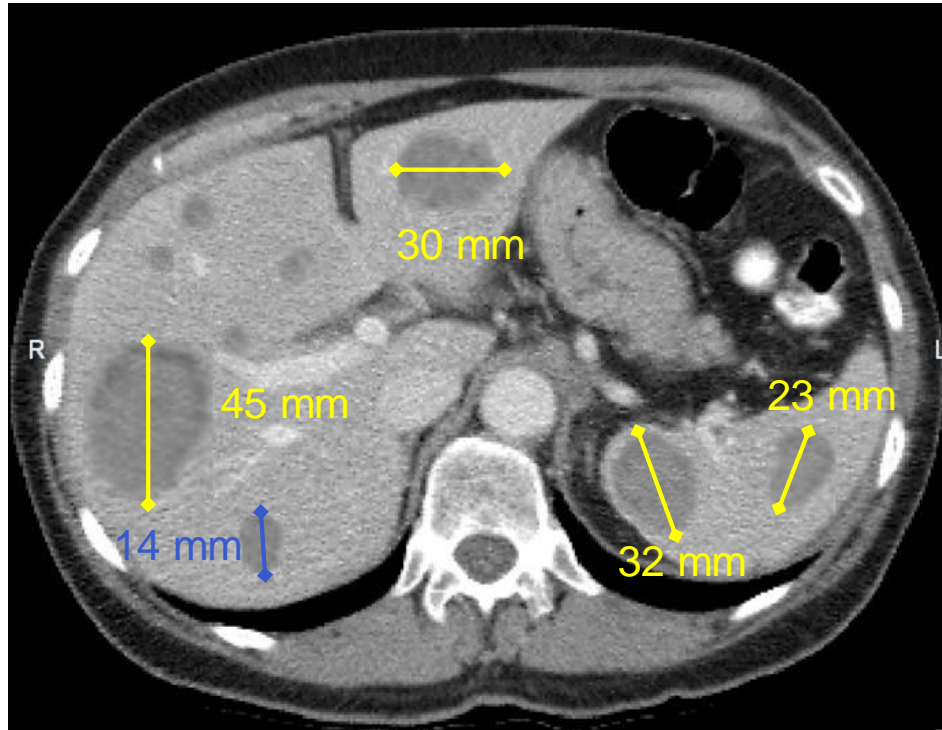
# Case 7

# Case 7 – Baseline



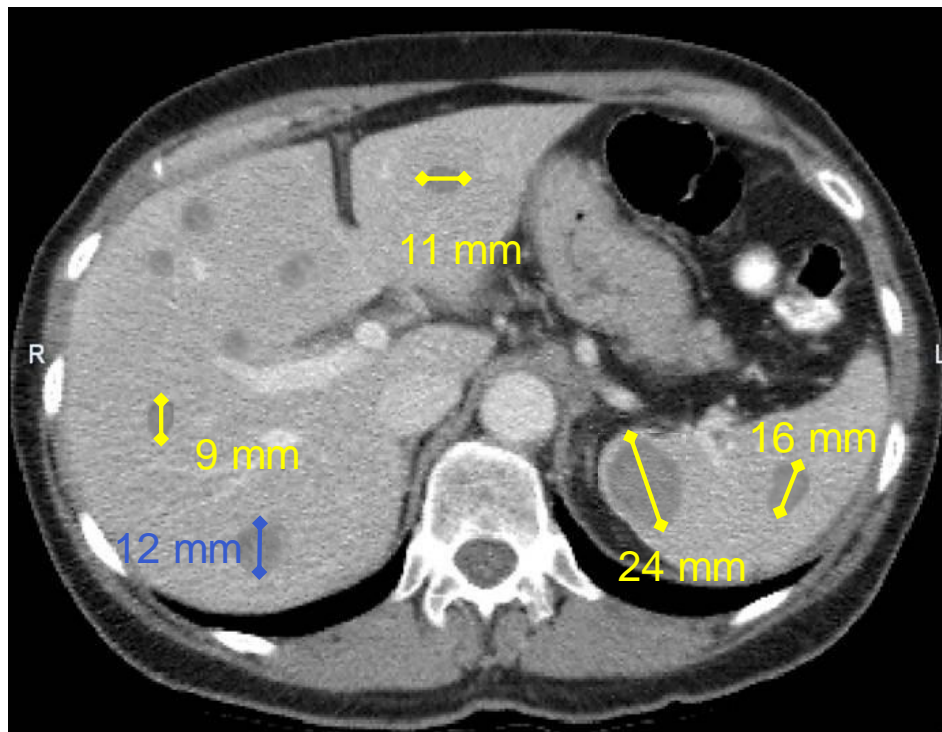
	BL
SOD (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

# Case 7 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-iCR/Non-iUPD
New		14 mm
Overall Resp		iUPD

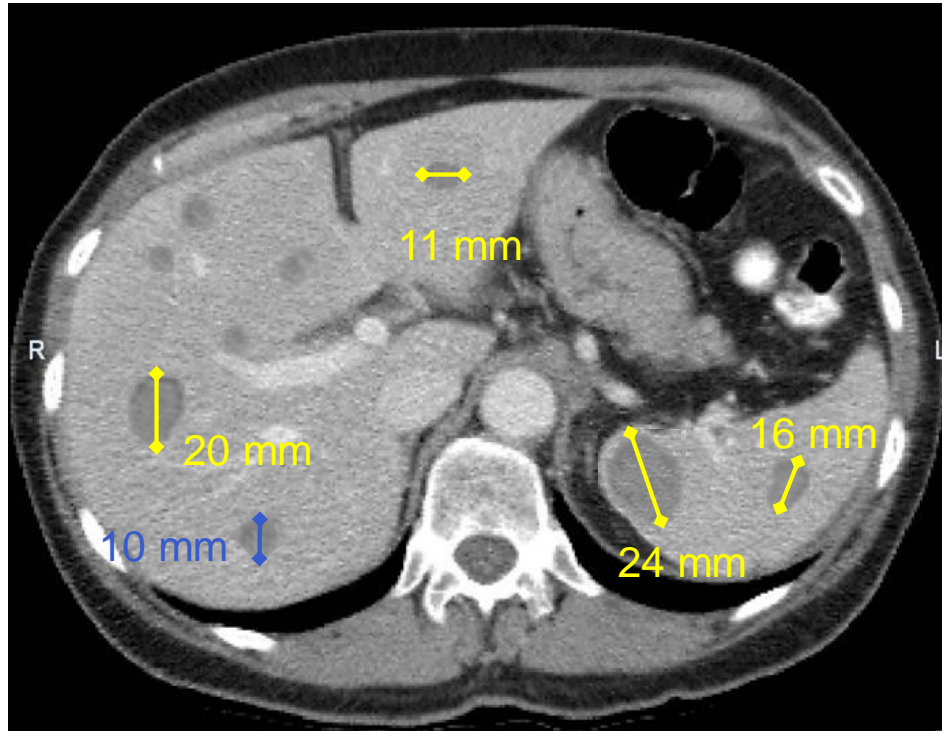
# Case 7 – Visit 2



	BL	V1	V2
SOD (mm)	100	130	60
TL Resp		iUPD	iPR
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm
Overall Resp		iUPD	iPR

“reset bar”

# Case 7 – Visit 3

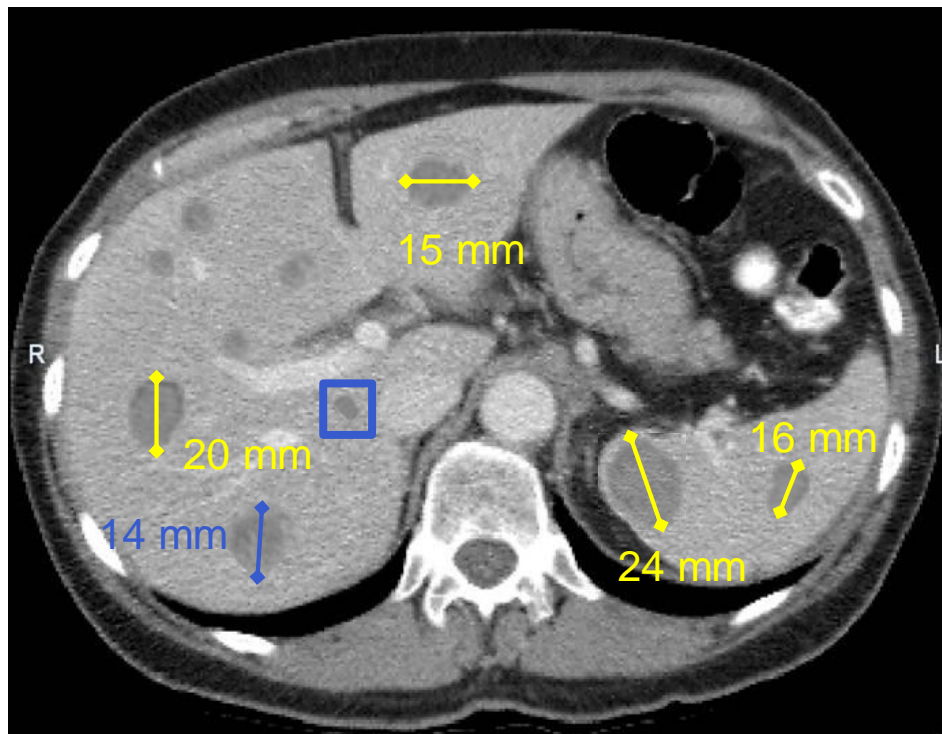


	BL	V1	V2	V3
SOD (mm)	100	130	60	71
TL Resp		iUPD	iPR	iSD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm	10 mm
Overall Resp		iUPD	iPR	iSD

18% increase



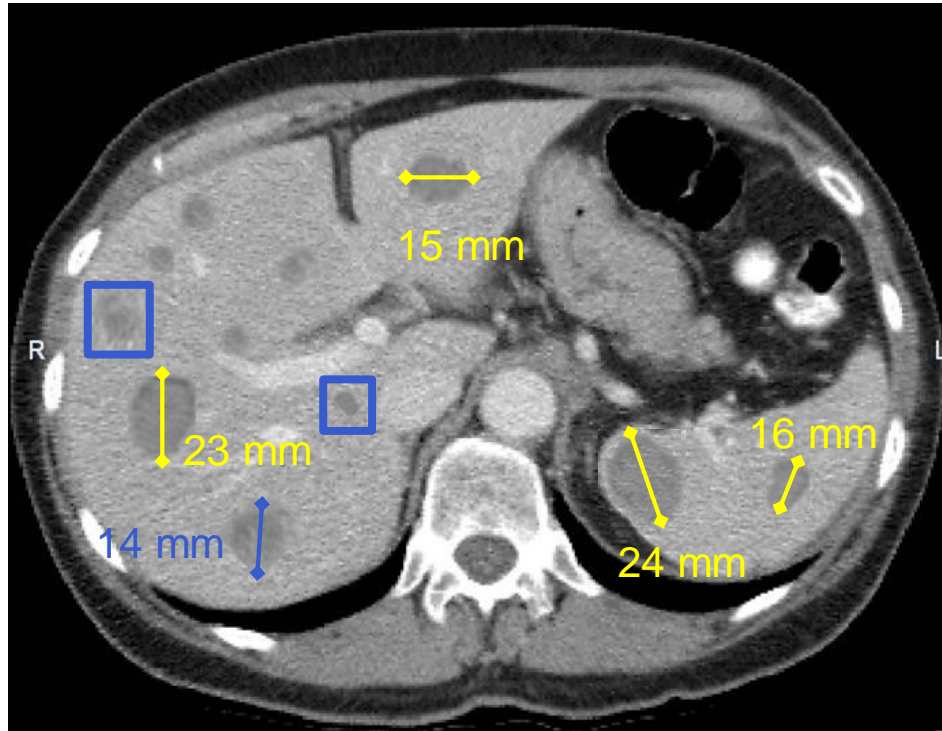
# Case 7 – Visit 4



	BL	V1	V2	V3	V4
SOD (mm)	100	130	60	71	75
TL Resp		iUPD	iPR	iSD	iUPD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm	10 mm	14 mm / NT+
Overall Resp		iUPD	iPR	iSD	iUPD



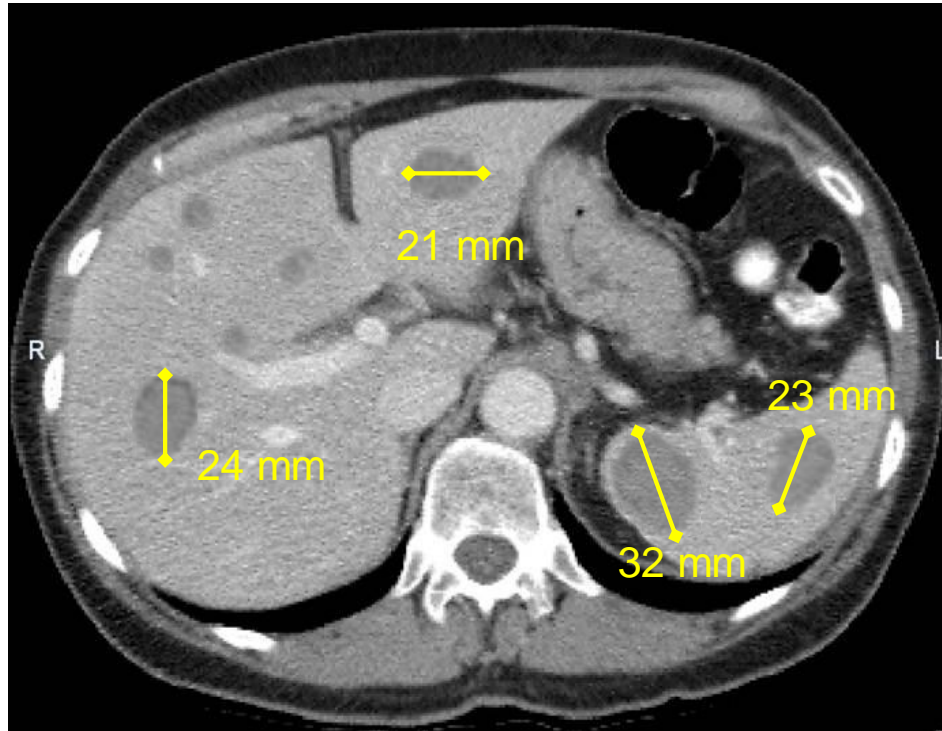
# Case 7 – Visit 5



	BL	V1	V2	V3	V4	V5
SOD (mm)	100	130	60	71	75	78
TL Resp		iUPD	iPR	iSD	iUPD	iUPD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm	10 mm	14 mm / NT+	14 mm / NT++
Overall Resp		iUPD	iPR	iSD	iUPD	iCPD

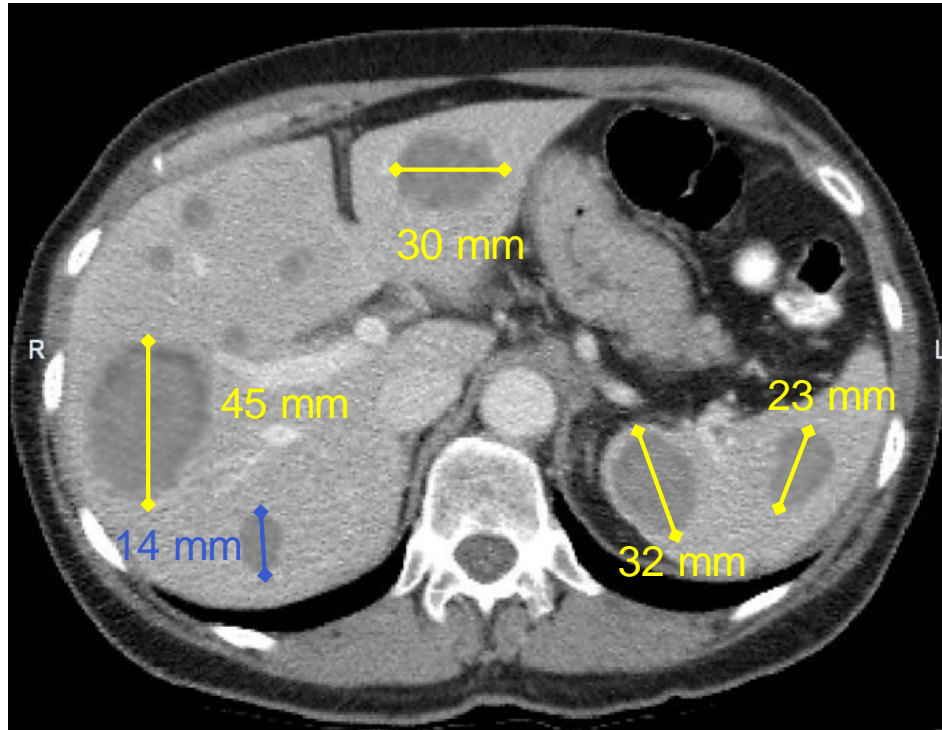
# Case 8

# Case 8 – Baseline



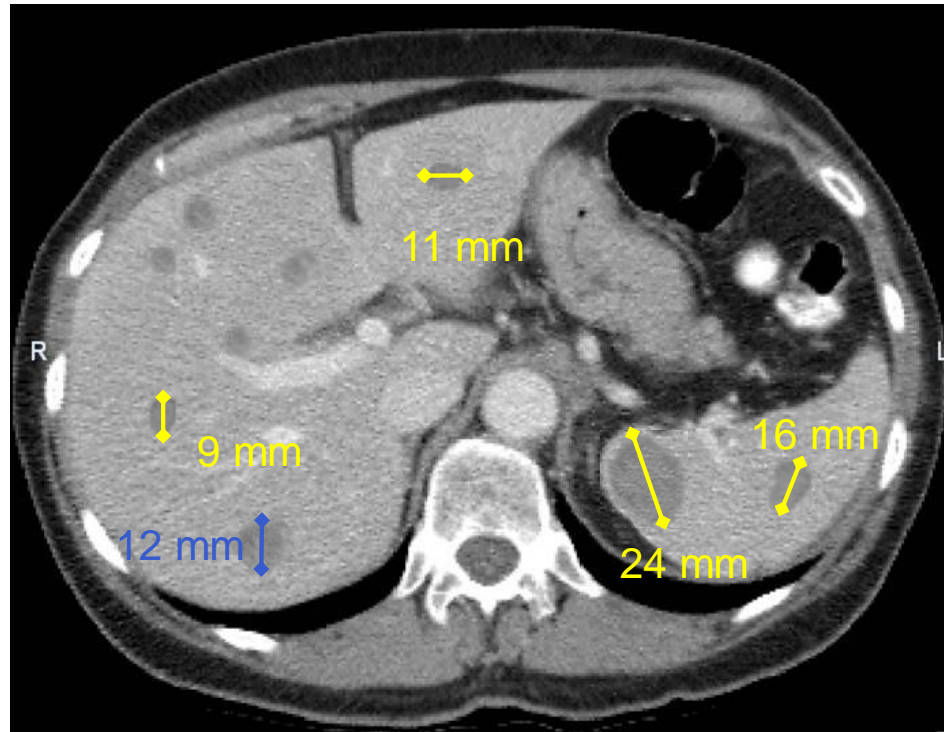
	BL
SOD (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

# Case 8 – Visit 1



	BL	V1
SOD (mm)	100	130
TL Resp		iUPD
NTL Resp		Non-iCR/Non-iUPD
New		14 mm
Overall Resp		iUPD

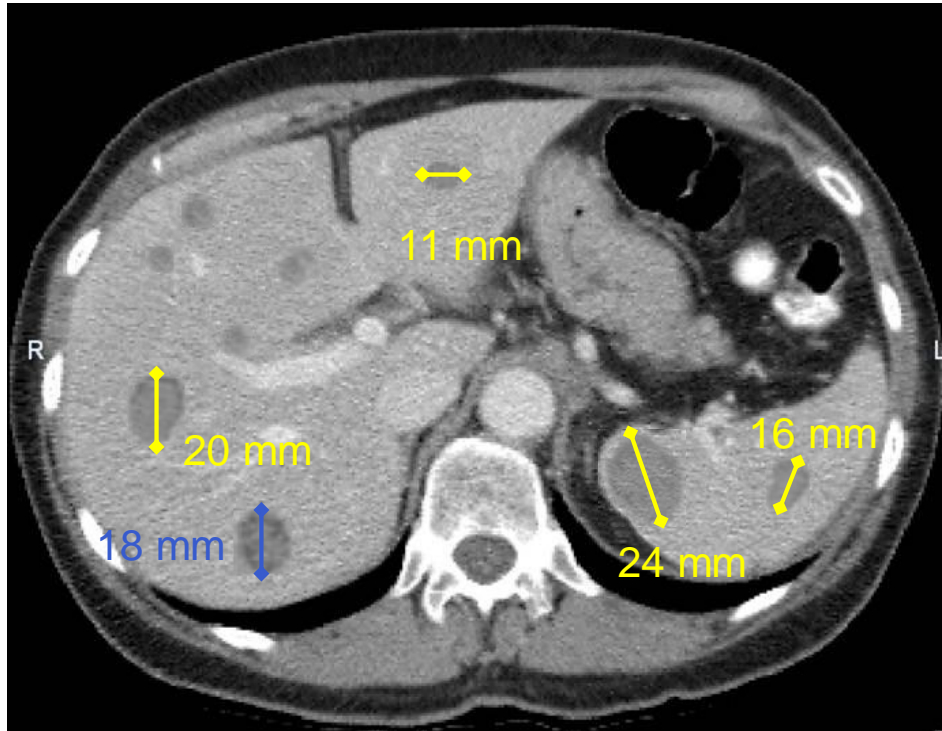
# Case 8 – Visit 2



	BL	V1	V2
SOD (mm)	100	130	60
TL Resp		iUPD	iPR
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm
Overall Resp		iUPD	iPR

“reset bar”

# Case 8 – Visit 3



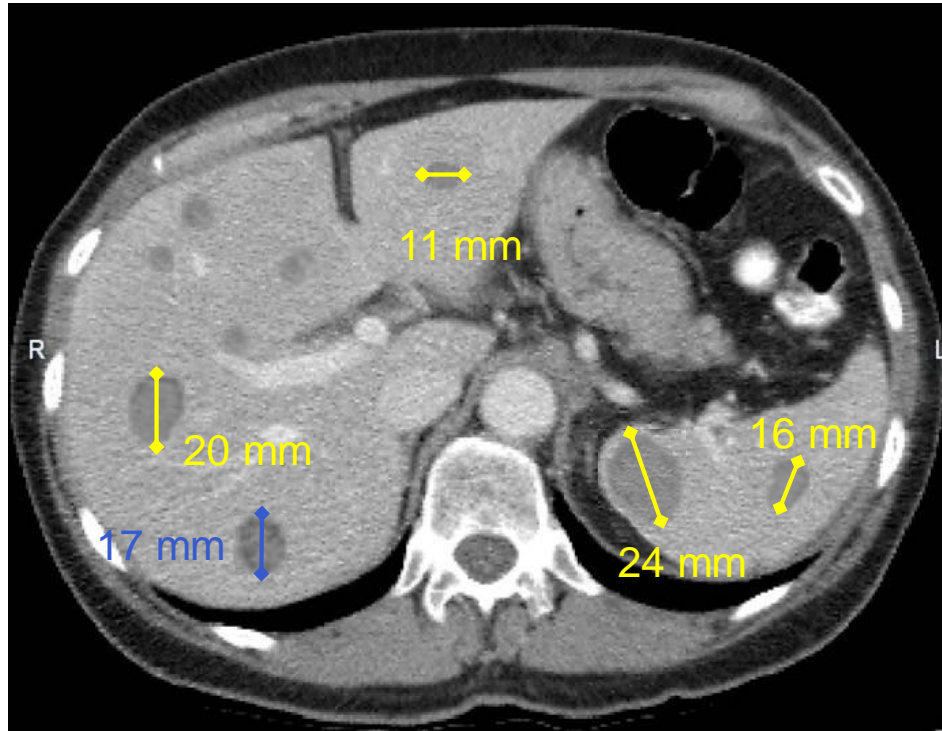
	BL	V1	V2	V3
SOD (mm)	100	130	60	71
TL Resp		iUPD	iPR	iSD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm	18 mm
Overall Resp		iUPD	iPR	iUPD

18% increase

≥5mm increase



# Case 8 – Visit 4

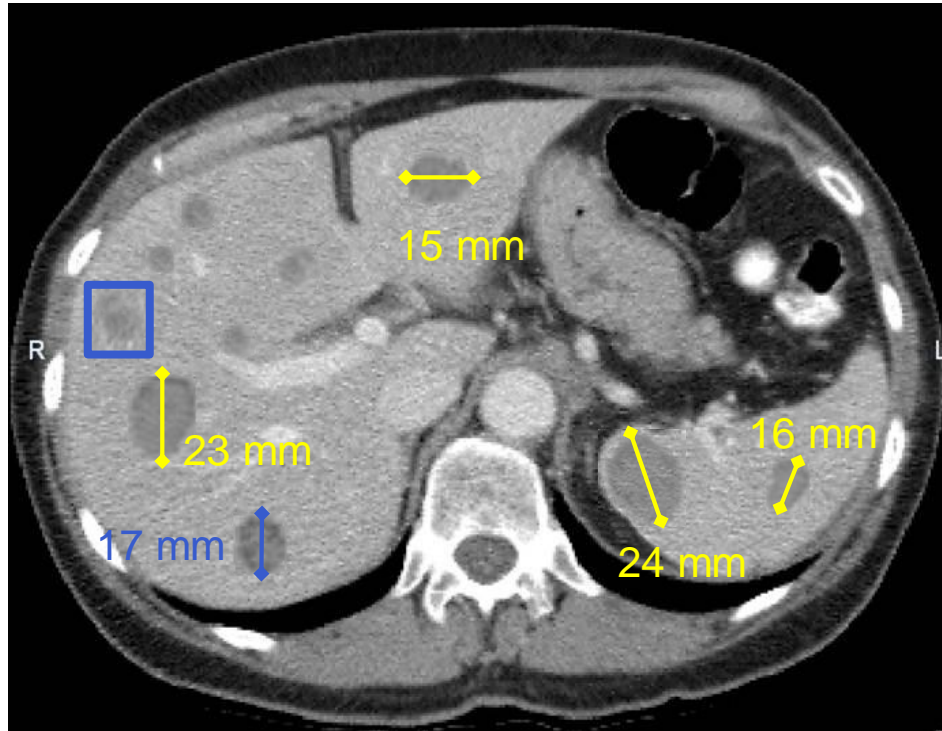


	BL	V1	V2	V3	V4
SOD (mm)	100	130	60	71	71
TL Resp		iUPD	iPR	iSD	iSD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm	18 mm	17 mm
Overall Resp		iUPD	iPR	iUPD	iUPD

Still  $\geq 5\text{mm}$   
above nadir



# Case 8 – Visit 5

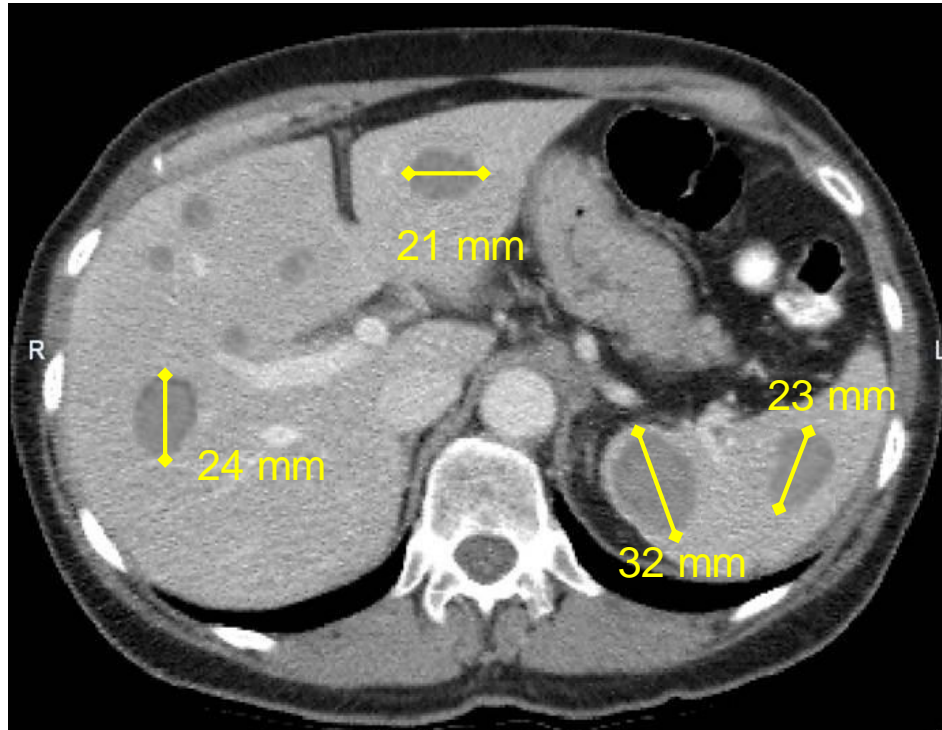


	BL	V1	V2	V3	V4	V5
SOD (mm)	100	130	60	71	71	78
TL Resp		iUPD	iPR	iSD	iSD	iUPD
NTL Resp		Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD	Non-iCR/Non-iUPD
New		14 mm	12 mm	18 mm	17 mm	17 mm / NT+
Overall Resp		iUPD	iPR	iUPD	iUPD	iCPD



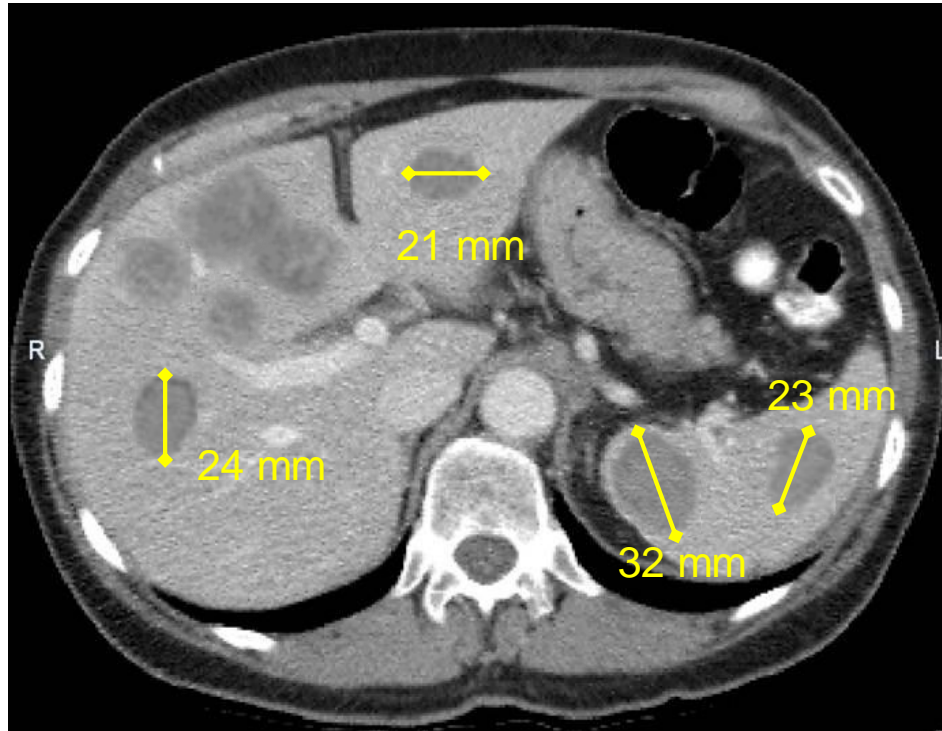
# Case 9

# Case 9 – Baseline



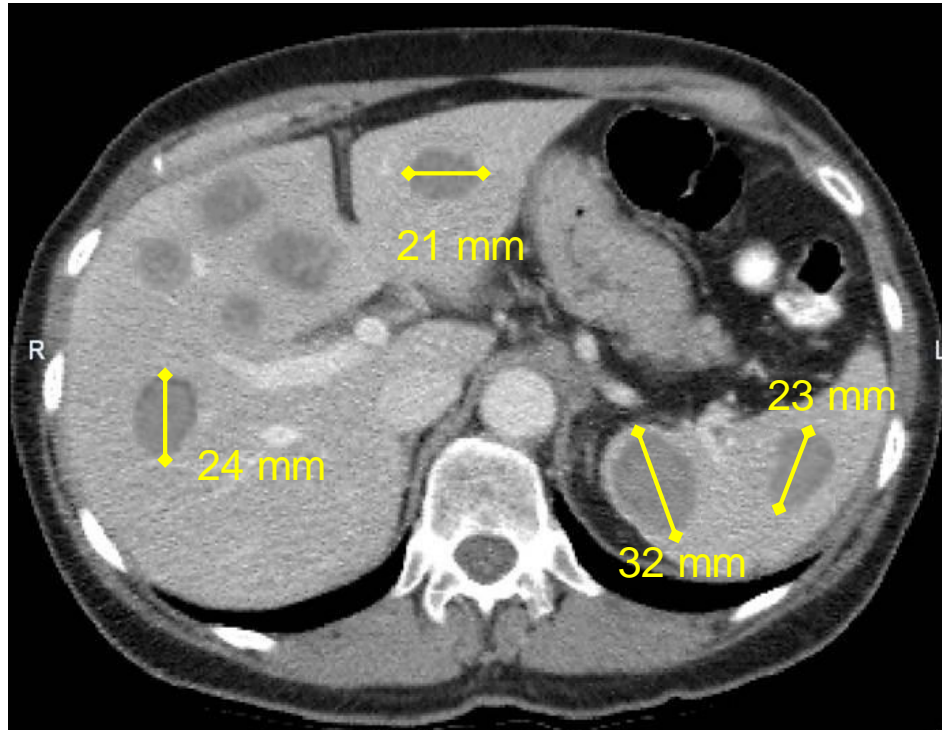
	BL
SOD (mm)	100
TL Resp	
NTL Resp	
New	
Overall Resp	

# Case 9 – Visit 1



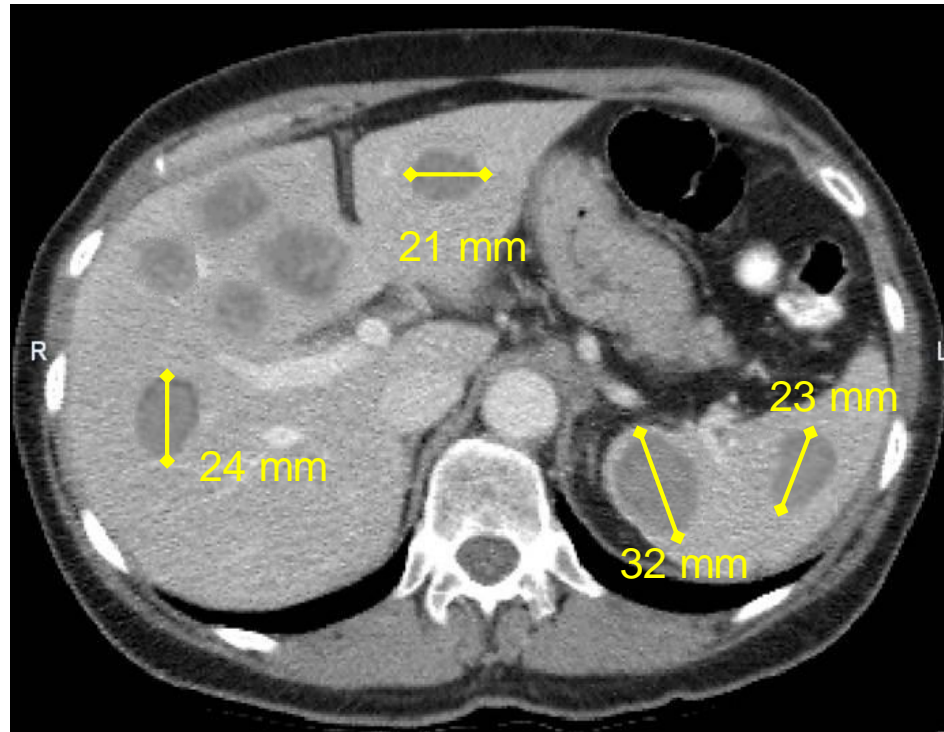
	BL	V1
SOD (mm)	100	100
TL Resp		iSD
NTL Resp		iUPD
New		
Overall Resp		iUPD

# Case 9 – Visit 2



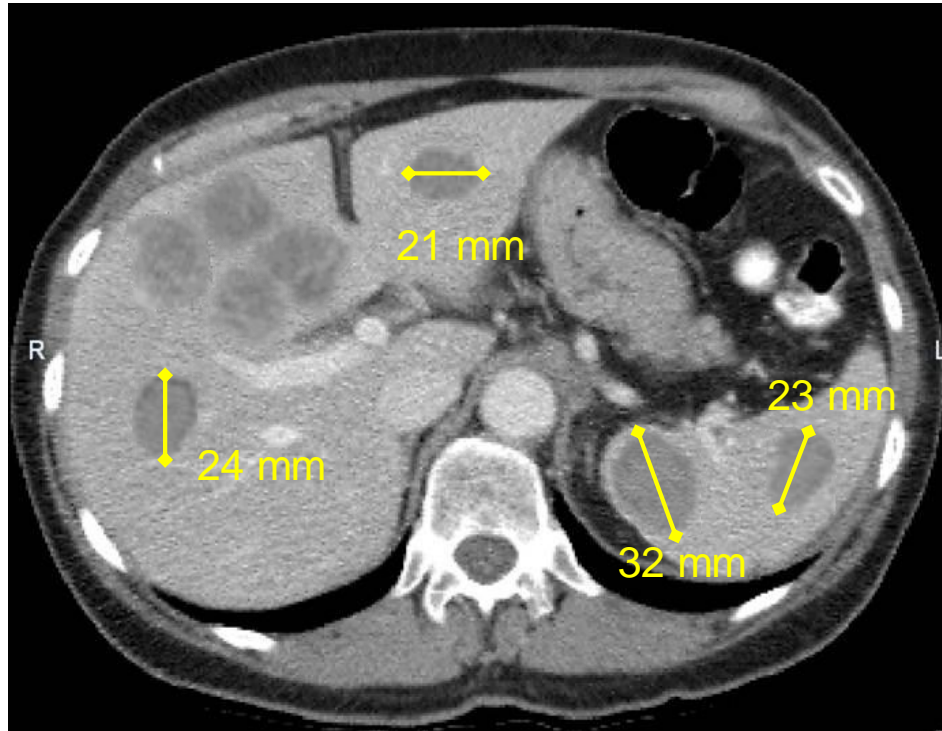
	BL	V1	V2
SOD (mm)	100	100	100
TL Resp		iSD	iSD
NTL Resp		iUPD	Non-iCR/Non-iUPD
New			
Overall Resp		iUPD	iSD

# Case 9 – Visit 3



	BL	V1	V2	V3
SOD (mm)	100	100	100	100
TL Resp		iSD	iSD	iSD
NTL Resp		iUPD	Non-iCR/Non-iUPD	iUPD
New				
Overall Resp		iUPD	iSD	iUPD

# Case 9 – Visit 4



	BL	V1	V2	V3	V4
SOD (mm)	100	100	100	100	100
TL Resp		iSD	iSD	iSD	iSD
NTL Resp		iUPD	Non-iCR/Non-iUPD	iUPD	iCPD
New					
Overall Resp		iUPD	iSD	iUPD	iCPD

# Recap of iUPD

- iUPD → iCPD if
  - Any new cause of PD
  - Existing causes of PD worsen (+5 mm / any growth)
- iUPD → iUPD if
  - TLs  $\geq$  PD threshold, without worsening
  - Nothing else causes iCPD
- iUPD → iSD/iPR if
  - Target lesions below PD threshold
  - NTLs and NLs have not caused iCPD
    - For subsequent iUPD, NLs aren't above nadir

# PD After Flare

- iSD/iPR/iCR: “reset the bar”
  - Need iUPD before iCPD is possible:
    - TLs (re) entering PD range
    - NTLs and NLs showing PD for the first time, or worsening (low bar) if they had shown PD and not regressed
- “Reset the bar” ≠ “rebaselining”
  - PR judged relative to baseline SOD
  - PD judged relative to nadir (smallest SOD ever seen)



# Endpoint Determination

- Progression = first iUPD that turned into iCPD
  - e.g. BL – iUPD – iSD – **iUPD** – iUPD – iCPD
- iBOR = best response seen since iUPD
  - No confirmation or PR/CR required generally
  - Protocol should specify

# Conclusions

- RECIST PD = iUPD → scan again in 4-8 weeks
- iUPD can be confirmed, remain, or regress
- “Bayesian” approach to confirmation
- Target lesions still dominant factor
- Guideline, not yet formal criteria

