Supplementary Material for:

Early pseudoprogression and progression lesions in glioblastoma patients are both metabolically heterogeneous

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1 Abbreviations list

SCER: suspicious contrast-enhancing voxel, PP: pseudoprogression, R: response, S: stable, TP: true progression

2 Patients

Summary of patients and voxels used per patient.

Supplementary table 1. NEV: no enhancing voxels; EXCL: excluded due to lack of SCER in the P1M exploration; NoExp: Patient was not explored.

Patient	IDH status	MGMT metylation	WHO classification	Date P1M	Fulfils criteria 3 months post RX	Label	Number of voxels in grid	Number of SCER voxels at P1M	Number of SCER voxels included in the analysis	Number of SCER voxels > SNR 20	Number of artifactual SCER voxels (excluded)	% of SCER artifactual voxels excluded from analysis
10	Unavailable	YES	2007	14/07/2016	YES	TP	256	2	2	2	0	0
11	Negative	YES	2016	28/07/2016	YES	TP	256	1	1	1	0	0
12	Unavailable	YES	2007	09/09/2016	YES	TP	256	7	7	5	0	0
13	Negative	YES	2016	06/10/2016	YES	PP	256	13	13	12	0	0
14	Negative	YES	2016	18/10/2016	YES	PP	256	2	2	0	0	0
15	Negative	YES	2016	25/10/2016	YES	R	256	4	4	4	0	0
16	Negative	NO	2016	18/11/2016	YES	TP	256	12	12	12	0	0
17	Negative	YES	2016	10/01/2017	YES	S	256	9	8	7	1	11,11
18	Negative	YES	2016	02/02/2017	NEV	R	256					
19	Negative	YES	2016	21/02/2017	YES	PP	256	1	0	0	1	100
20	Negative	NO	2016	24/02/2017	YES	R	256	4	0	0	4	100
21	Negative	YES	2016	10/03/2017	YES	PP	256	11	9	0	2	18,18
22	Negative	YES	2016	10/03/2017	YES	TP	256	4	0	0	4	100
23	Negative	NO	2016	16/03/2017	YES	PP	256	6	0	0	6	100
24	Negative	NO	2016	13/04/2017	YES	PP	256	16	12	10	4	25
25	Negative	NO	2016	13/04/2017	YES	R	256	4	2	2	2	50
26	Negative	YES	2016	26/04/2017	YES	PP	256	5	5	5	0	0
27	Negative	YES	2016	12/05/2017	YES	PP	256	10	1	1	9	90
28	Negative	NO	2016	30/05/2017	YES	TP	256	42	0	0	42	100
29	Negative	Unknown	2016	15/06/2017	NO	EXCL	256					
30	Negative	NO	2016	11/07/2017	YES	TP	256	8	8	7	0	0
31	Negative	NO	2016	21/07/2017	YES	PP	256	22	17	12	5	22,73

Patient	IDH status	MGMT metylation	WHO classification	Date P1M	Fulfils criteria 3 months post RX	Label	Number of voxels in grid	Number of SCER voxels at P1M	Number of SCER voxels included in the analysis	Number of SCER voxels > SNR 20	Number of artifactual SCER voxels (excluded)	% of SCER artifactual voxels excluded from analysis
32	Negative	YES	2016	10/08/2017	YES	TP	256	7	7	7	0	0
33	Negative	NO	2016	10/08/2017	NEV	S	256					
34	Negative	NO	2016	23/08/2017	YES	TP	256	12	7	5	5	41,67
35	Negative	YES	2016	30/08/2017	YES	PP	256	7	5	4	2	28,57
36	Negative	NO	2016	05/09/2017	NEV	S	256					
37	Negative	NO	2016	26/09/2017	YES	PP	256	3	3	3	0	0
38	Negative	YES	2016	28/09/2017	NoExp	EXCL	256					
39	Positive	YES	2016	11/10/2017	YES	TP	256	13	13	13	0	0
40	Negative	NO	2016	14/11/2017	NEV	R	256					
41	Negative	NO	2016	21/11/2017	YES	R	256	8	6	6	2	25
42	Negative	YES	2016	30/11/2017	YES	PP	256	6	6	3	0	0
43	Negative	NO	2016	03/01/2018	NEV	S	256					
44	Negative	NO	2016	03/01/2018	YES	TP	256	11	11	10	0	0
45	Negative	YES	2016	23/01/2018	NEV	S	256					
46	Negative	NO	2016	08/03/2018	YES	PP	256	10	3	2	7	70
47	Negative	NO	2016	22/03/2018	YES	PP	256	11	11	3	0	0
48	Negative	YES	2016	22/03/2018	NEV	S	256					
49	Negative	NO	2016	27/03/2018	YES	TP	256	3	2	1	1	33,33
50	Negative	YES	2016	12/04/2018	Exitus	EXCL	256					
51	Negative	NO	2016	12/04/2018	YES	TP	256	21	17	9	4	19,05
52	Negative	NO	2016	12/04/2018	YES	PP	256	17	0	0	17	100
53	Negative	YES	2016	15/05/2018	YES	S	256	16	3	0	13	81,25
54	Negative	YES	2016	25/06/2018	YES	S	256	7	7	1	0	0
55	Negative	NO	2016	02/07/2018	YES	TP	256	4	0	0	4	100
56	Negative	NO	2016	21/09/2018	YES	PP	256	70	11	11	59	84,29
57	Negative	NO	2016	28/11/2018	NEV	S	256					
58	Negative	NO	2016	28/11/2018	YES	PP	256	7	4	1	3	42,86
59	Negative	YES	2016	11/01/2019	YES	PP	256	28	14	9	14	50
60	Negative	NO	2016	21/01/2019	YES	PP	256	3	3	0	0	0
61	Negative	NO	2016	21/01/2019	YES	PP	256	3	3	3	0	0
62	Negative	NO	2016	25/01/2019	YES	PP	256	5	5	1	0	0
Total							13568	455	244			
							10752					

3 Classifier parameters *

- TP vs PP
    - LDA

{'n_components': 0, 'solver': 'svd'}
Number of components (< n_classes - 1) for dimensionality reduction.
Solver: solver to use.

    - LR

{'C': 0.1, 'penalty': 'l2'}
C: Inverse of regularization strength
Penalty: Specify the norm of the penalty

    - RF

{'max_features': 'sqrt', 'n_estimators': 50}
Max_features: The number of features to consider when looking for the best split
N_estimators: The number of trees in the forest

    - SVM

{'C': 100, 'gamma': 0.01}
C: Inverse of regularization strength
Gamma: Kernel coefficient

- TP vs PP+R+S
    a. LDA

{'n_components': 0, 'solver': 'svd'}
Description: ‘n_components’: Number of components (< n_classes - 1) for dimensionality reduction.
'solver': Solver: solver to use.

    b. LR

{'C': 1.0, 'penalty': 'l2'}
‘C’: Inverse of regularization strength
’penalty’: Specification of the norm of the penalty

    c. RF

{'max_features': 'sqrt', 'n_estimators': 50}
´max_features’: The number of features to consider when looking for the best split
’n_estimators’: The number of trees in the forest

    d. SVM

{'C': 1, 'gamma': 1}
‘C’: Inverse of regularization strength
’gamma’: Kernel coefficient

* Software used for the classifiers, available from: https://scikit-learn.org/stable/index.html

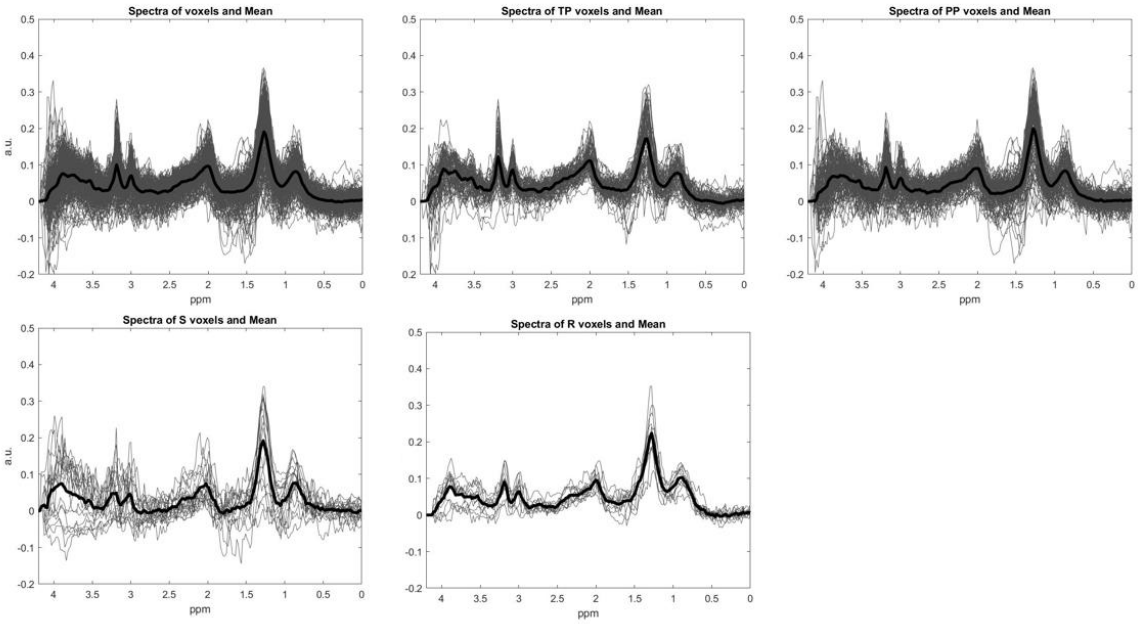
4 Classification results for two classes (TP vs {PP, R and S})

Supplementary table 2.

Classifier	Train/Test	Classification task	Balanced Accuracy	Accuracy	Sensitivity	Specificity	AUC
LDA	Train	Patient	70.1	71.2 ± 3.3	65.7 ± 3.3	75.3+/-3.2	70.1 ± 6.4
LDA	Test	Patient	66.3	66.4 ± 3.3	66.4 ± 3.3	75.3 ± 3.5	66.4 ± 3.3
LR	Train	Patient	70.4	75.2 ± 2.2	65.1 ± 2.8	92.2 ± 2.7	70.3 ± 3.0
LR	Test	Patient	68.3	63.4 ± 2.2	59.7 ± 2.8	79.8 ± 2.1	70.1 ± 2.2
RF	Train	Patient	68.7	75.2 ± 3.5	33.1± 3.5	79.9 ± 3.2	68.1 ± 3.1
RF	Test	Patient	55.4	56.8 ± 5.6	33.3 ± 6.4	74.7 ± 4.3	54.4 ± 3.7
SVM	Train	Patient	72.4	75.2± 3.5	75.2± 2.1	65.6 ± 4.7	67.9 ± 3.2
SVM	Test	Patient	70.1	71.4 ± 3.5	75.3± 3.5	66.2 ± 3.3	70.4 ± 3.2
LDA	Train	Voxel	69.2	67.3 ± 2.3	77.8 ± 2.2	53.5 ± 2.2	65.7± 2.2
LDA	Test	Voxel	68.3	65.6 ± 2.2	78.1 ± 2.4	54.1 ± 2.4	65.3 ± 2.2
LR	Train	Voxel	68.7	70.1± 2.7	60.2± 3.7	92.1± 2.1	70.1 ± 2.7
LR	Test	Voxel	65.2	58.3 ± 3.3	62.1± 2.7	90.1 ± 1.1	64 ± 3.5
RF	Train	Voxel	65.1	71.2 ± 2.2	50.1 ± 2.5	80.1± 1.8	65.4 ± 2.2
RF	Test	Voxel	63.3	68.2 ± 2.2	45.4± 2.4	78.2 ± 1.8	62.3 ± 2.1
SVM	Train	Voxel	67.2	69.1± 2.8	78.2 ± 2.3	48.2 ± 2.5	66.4 ± 2.1
SVM	Test	Voxel	69.3	67.1± 2.1	78.4 ± 2.1	54.2 ± 2.1	66.2 ± 1.9

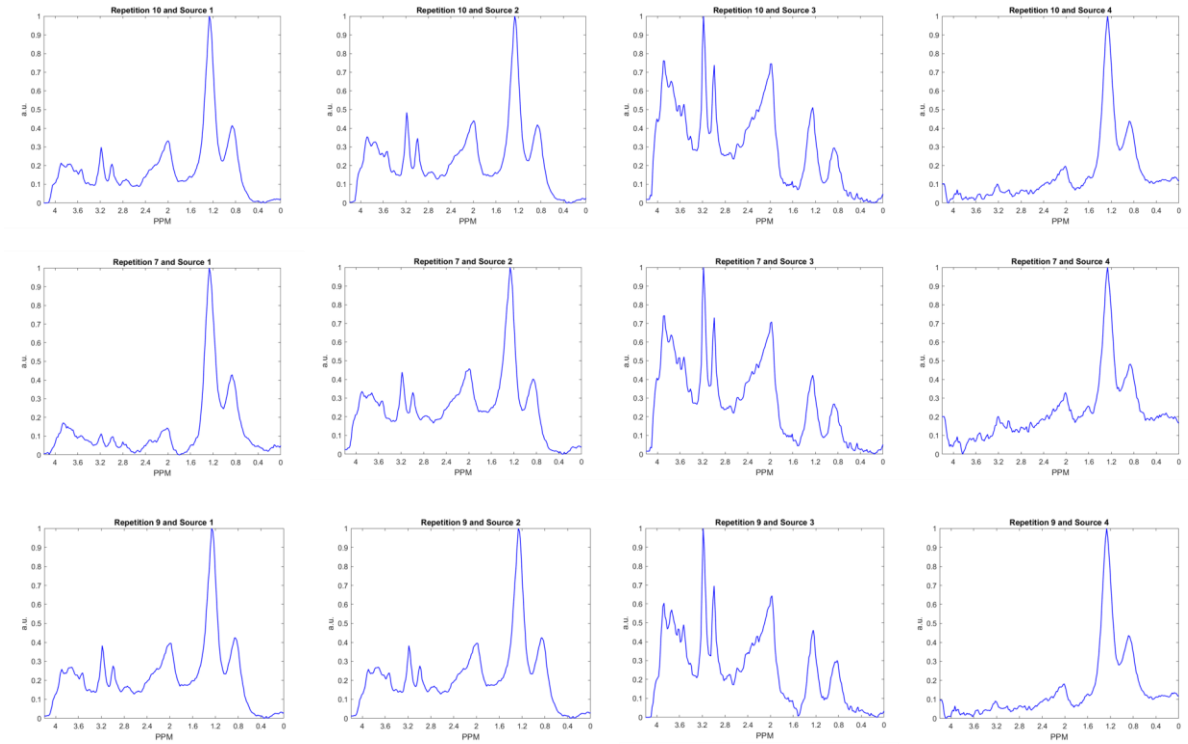
Train/Test Split: 80/20. Balanced accuracy, accuracy, sensitivity, specificity and AUC in % ± 95% CI.

5 Superimposed spectra of voxels, not taking into account any SNR Threshold

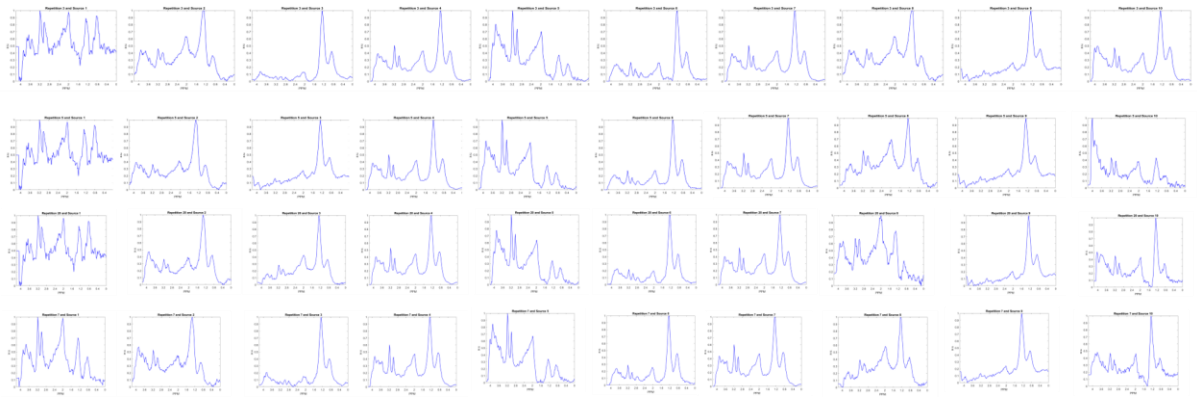


Supplementary figure 1. Overlay of individual spectra of each class and mean (thick line).

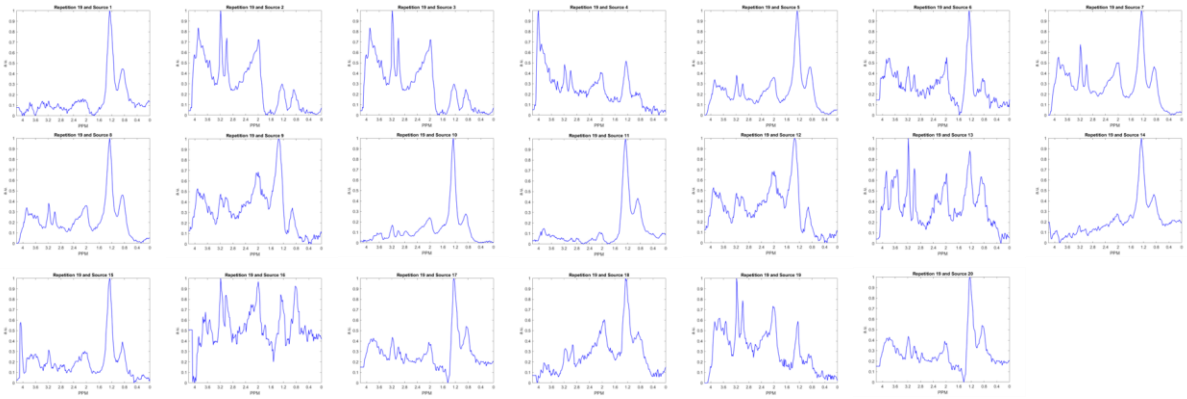
6 Source extraction results



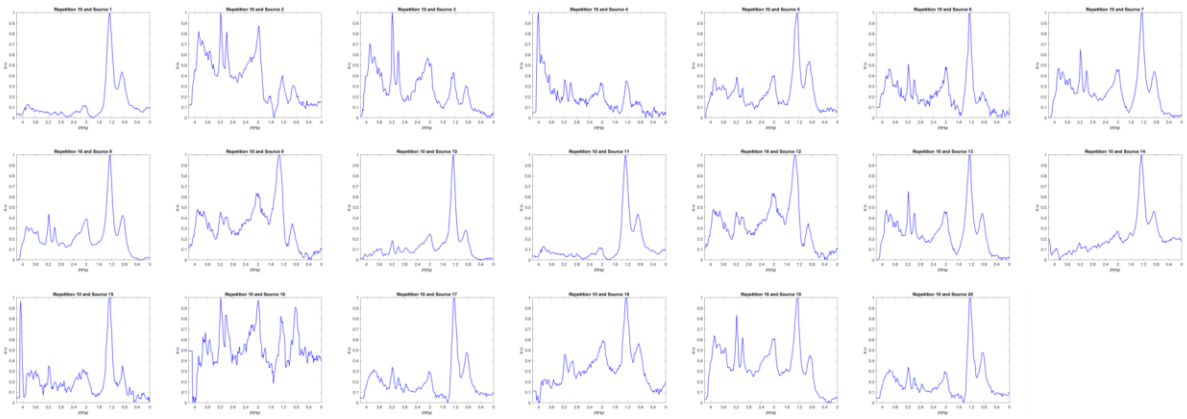
Supplementary figure 2. The three different solutions obtained when extracting four sources.



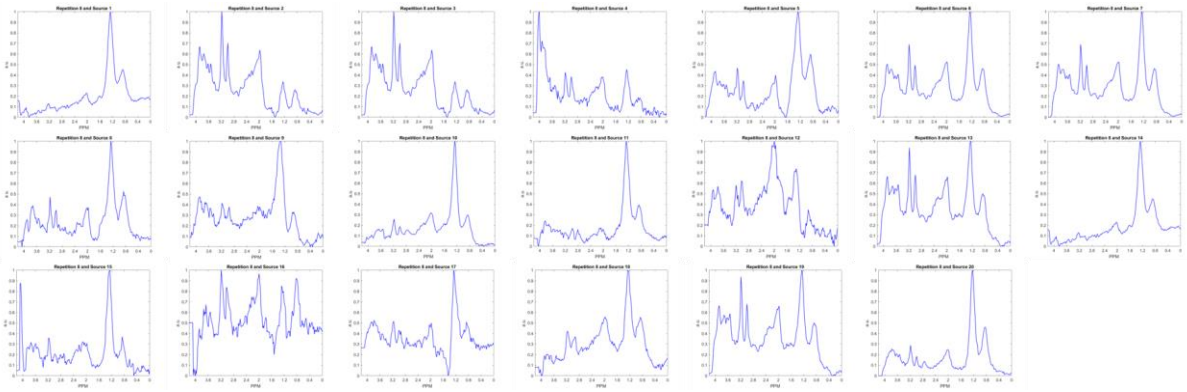
Supplementary figure 3. Four different solutions obtained when extracting ten sources.



Supplementary figure 4. One solution obtained when extracting twenty sources.



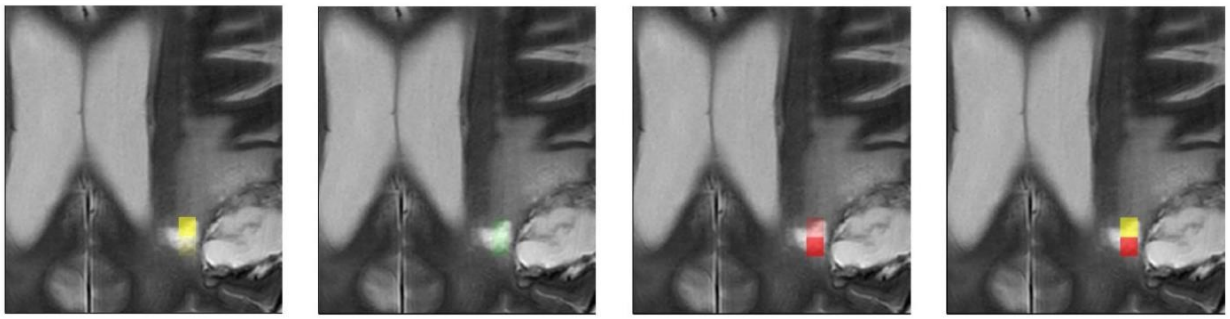
Supplementary figure 5. Another solution when extracting twenty sources.



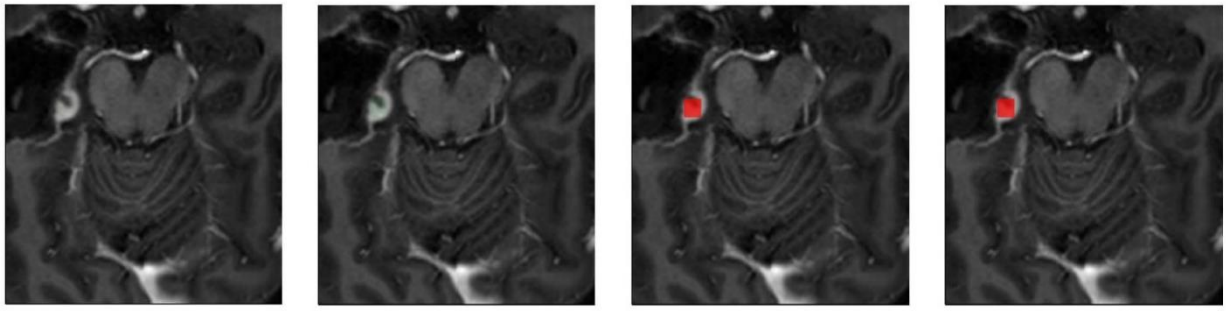
Supplementary figure 6. Another different solution obtained when extracting twenty sources.

7 Color maps for all patients included in the analysis

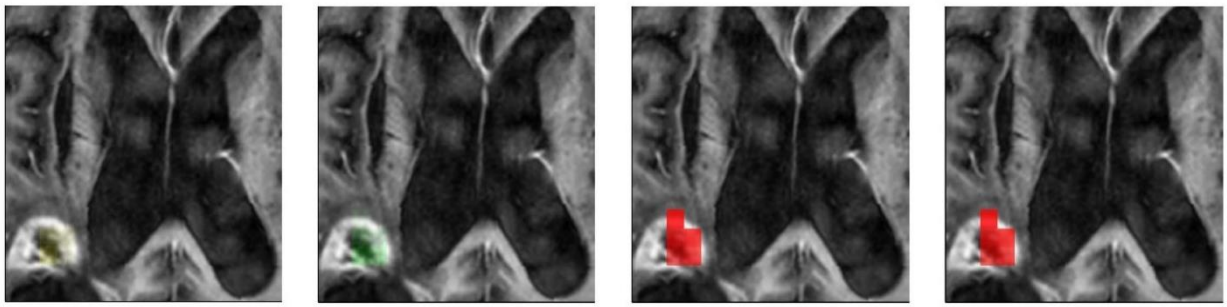
For all figures from 7 to 37, the legend is the same. From left to right: source 1 contribution map (yellow), source 2 contribution map (green), source 3 contribution map (red) and winning source map, from the SCER voxels, overlaid onto the reference image.



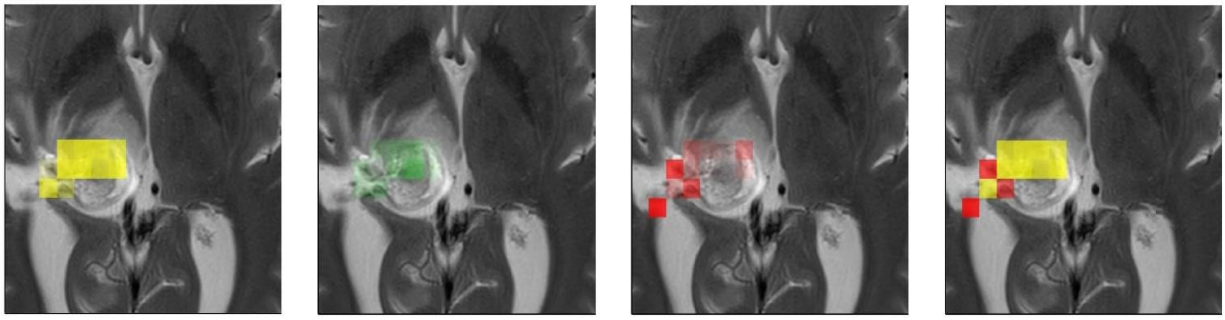
Supplementary figure 7. Case 10: TP.



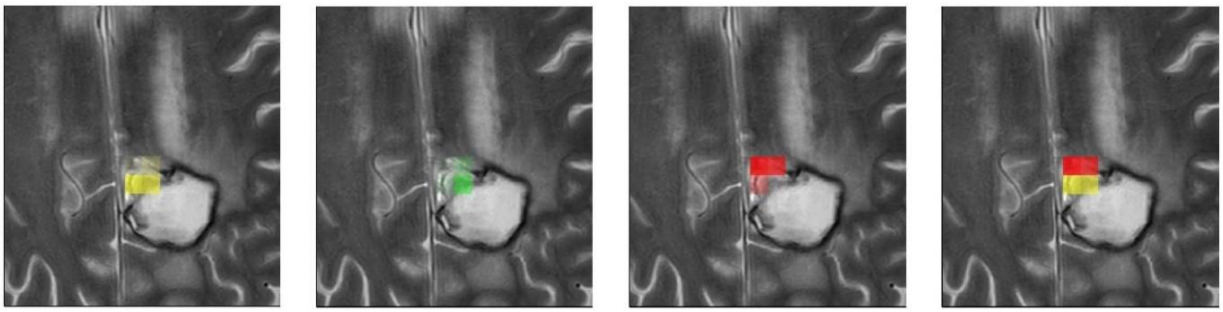
Supplementary figure 8. Case 11: TP.



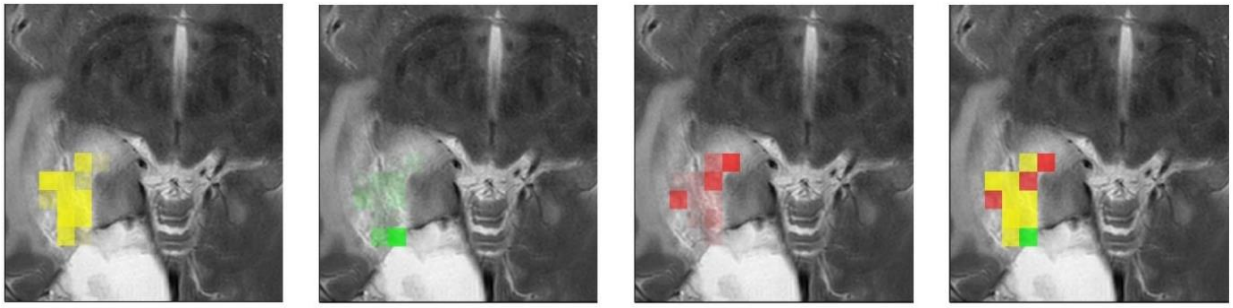
Supplementary figure 9. Case 12: TP.



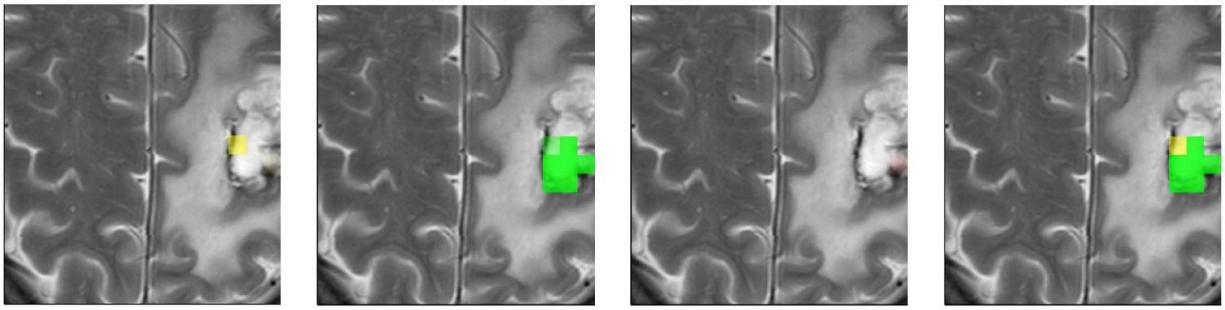
Supplementary figure 10. Case 13: PP.



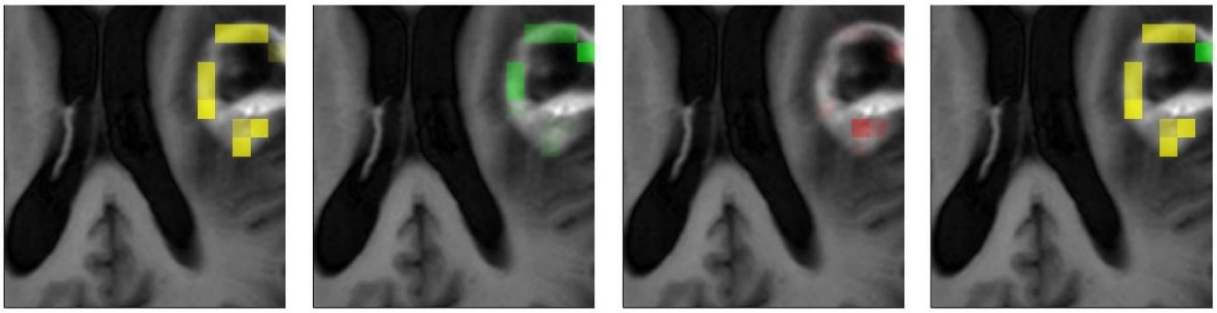
Supplementary figure 11. Case 15: R.



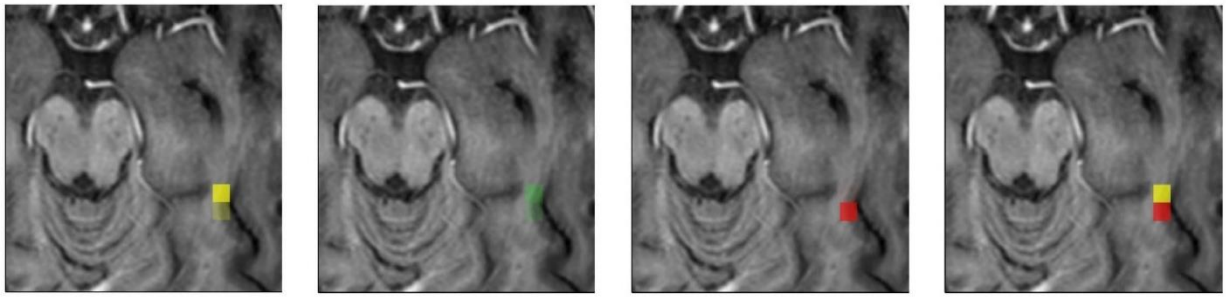
Supplementary figure 12. Case 16: TP.



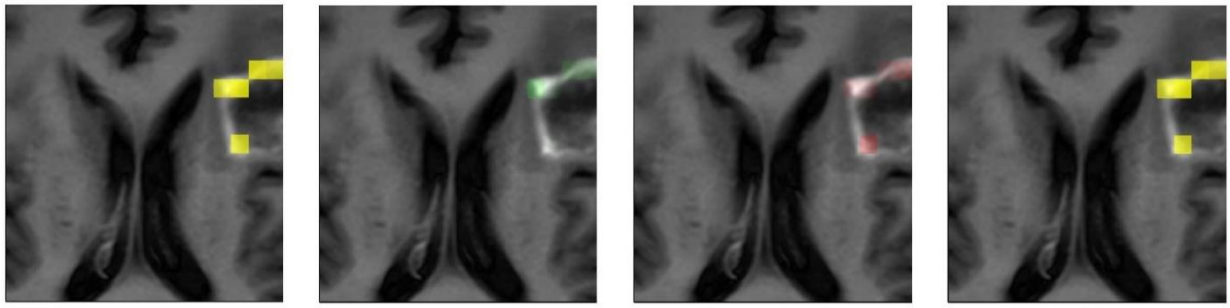
Supplementary figure 13. Case 17: S.



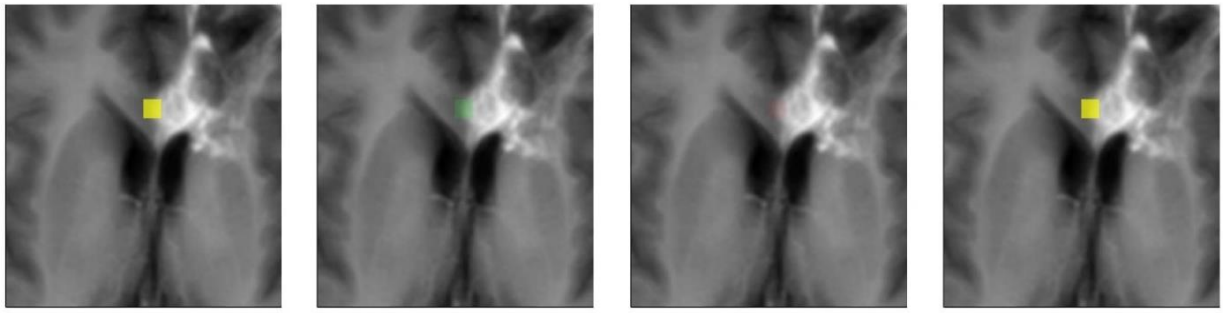
Supplementary figure 14. Case 24: PP.



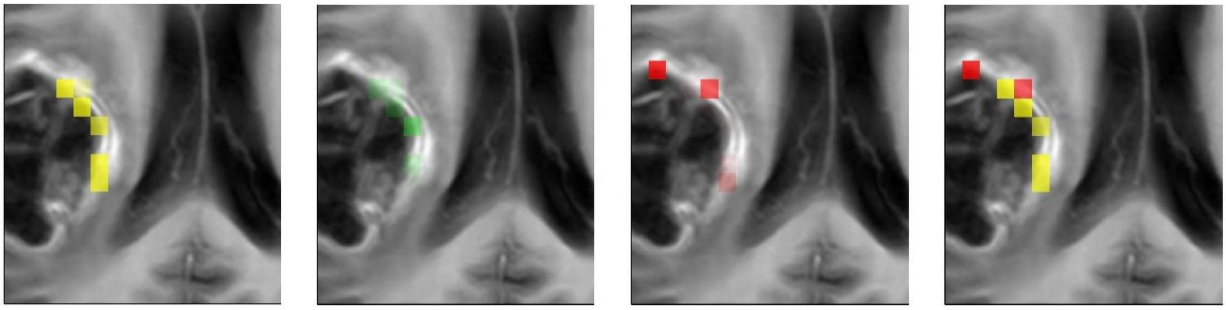
Supplementary figure 15. Case 25: R.



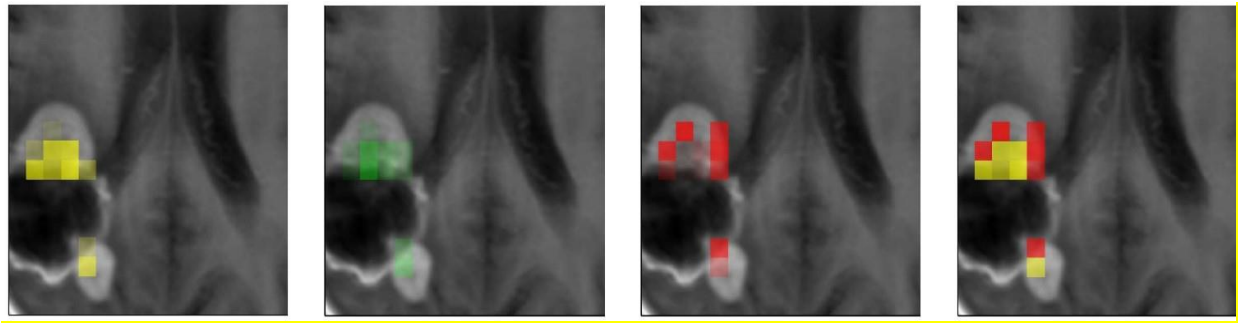
Supplementary figure 16. Case 26: PP.



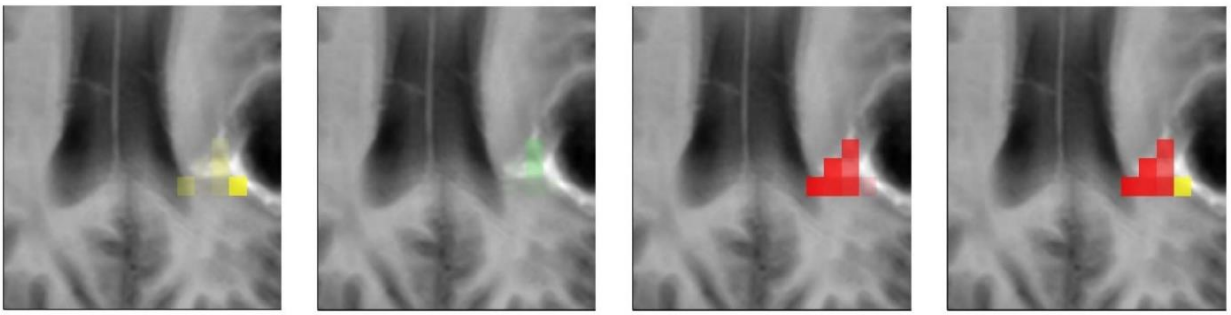
Supplementary figure 17. Case 27: PP.



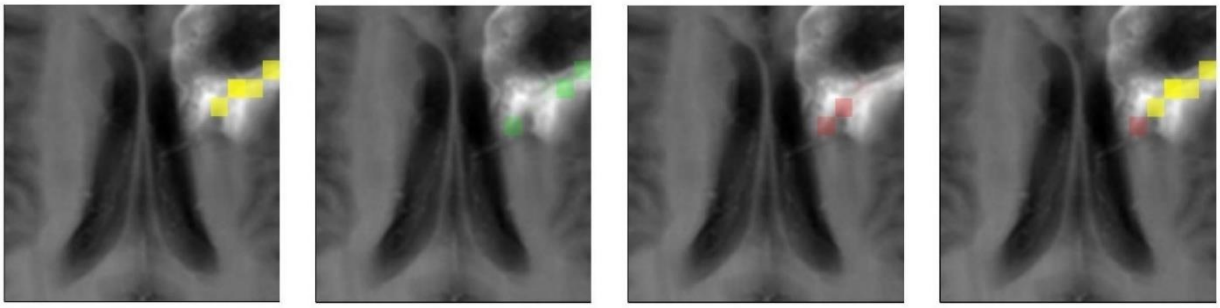
Supplementary figure 18. Case 30: TP.



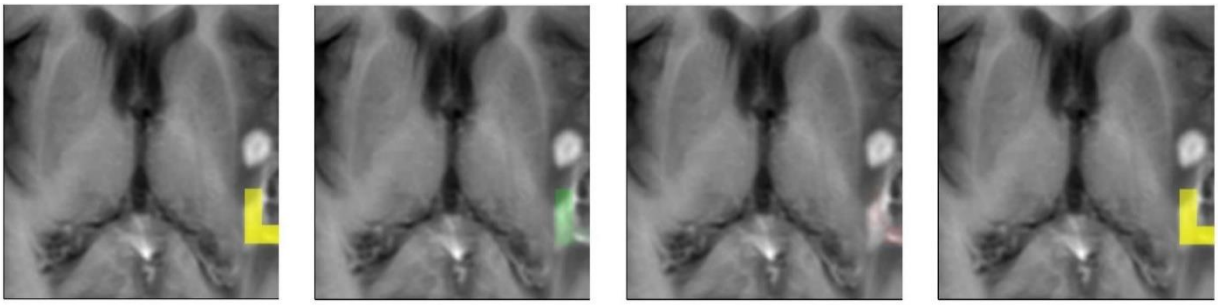
Supplementary figure 19. Case 31: PP.



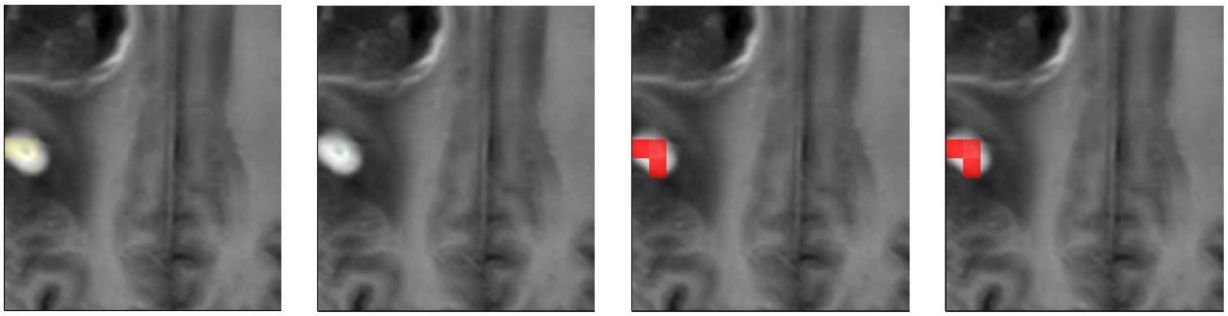
Supplementary figure 20. Case 32: TP.



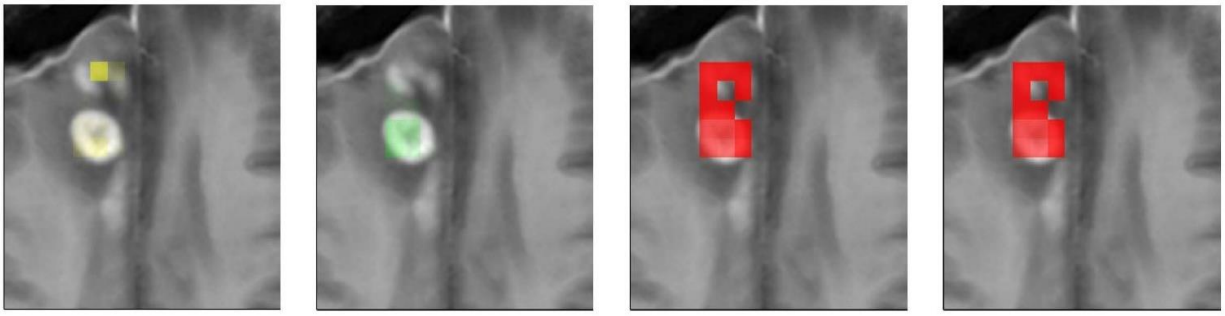
Supplementary figure 21. Case 34: TP.



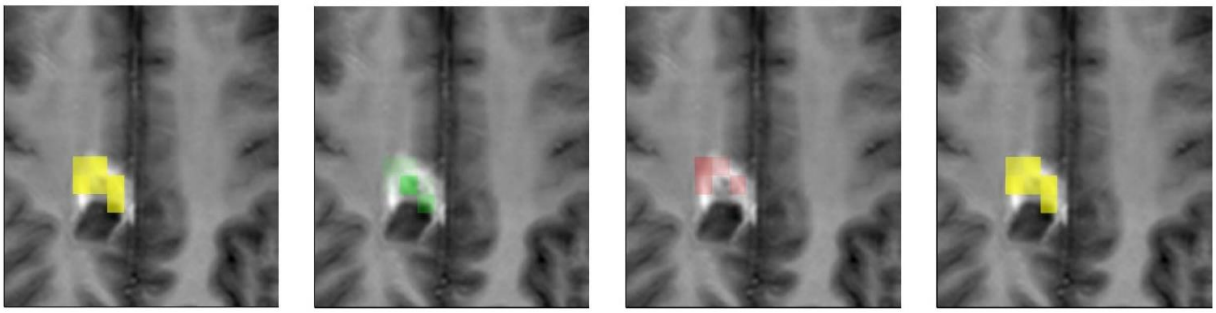
Supplementary figure 22. Case 35: PP.



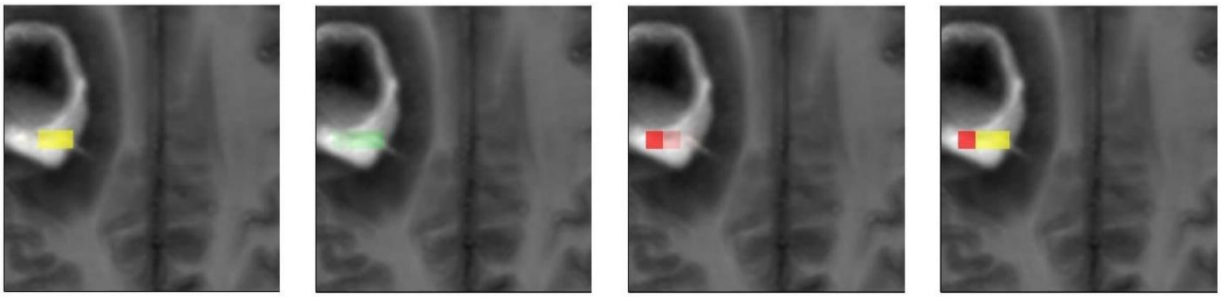
Supplementary figure 23. Case 37: PP.



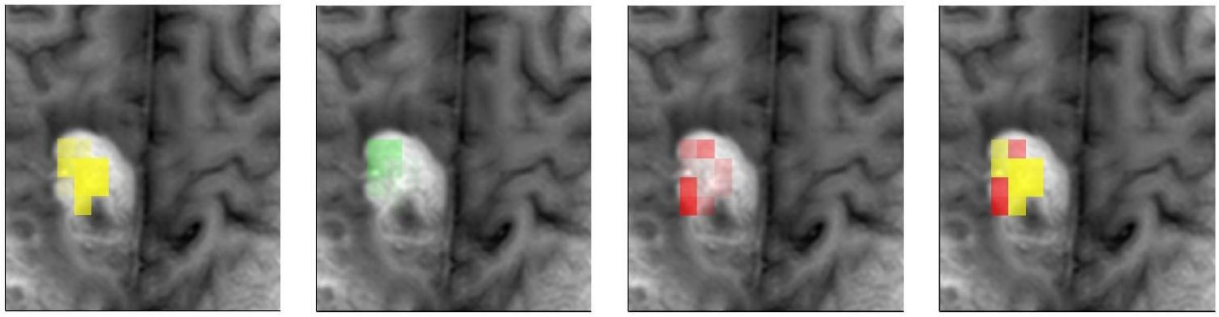
Supplementary figure 24. Case 39: TP.



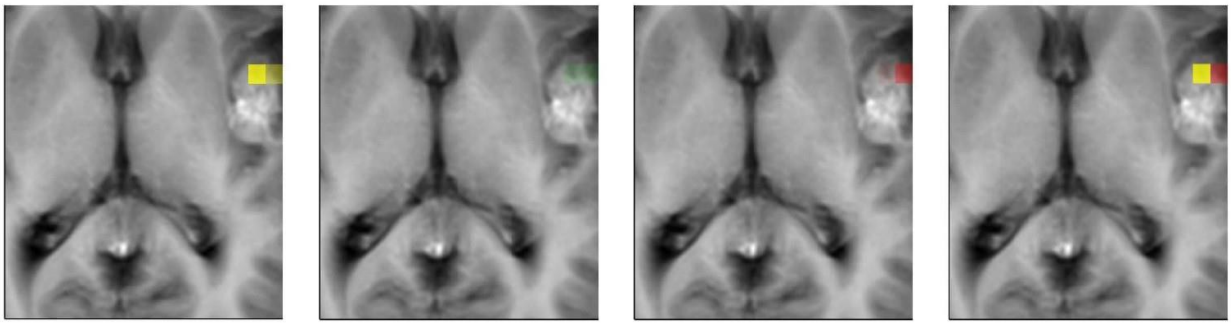
Supplementary figure 25. Case 41: R.



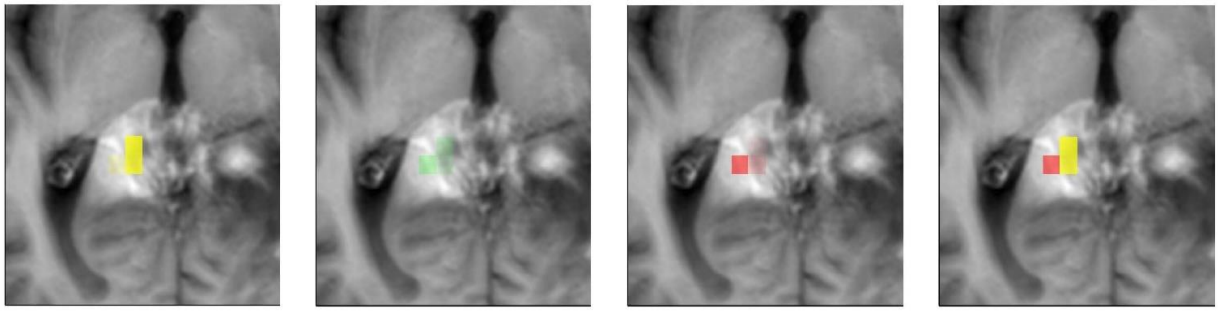
Supplementary figure 26. Case 42: PP.



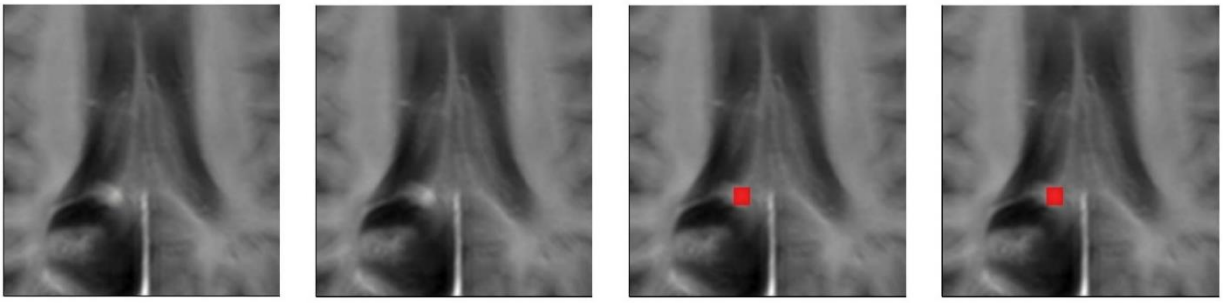
Supplementary figure 27. Case 44: TP.



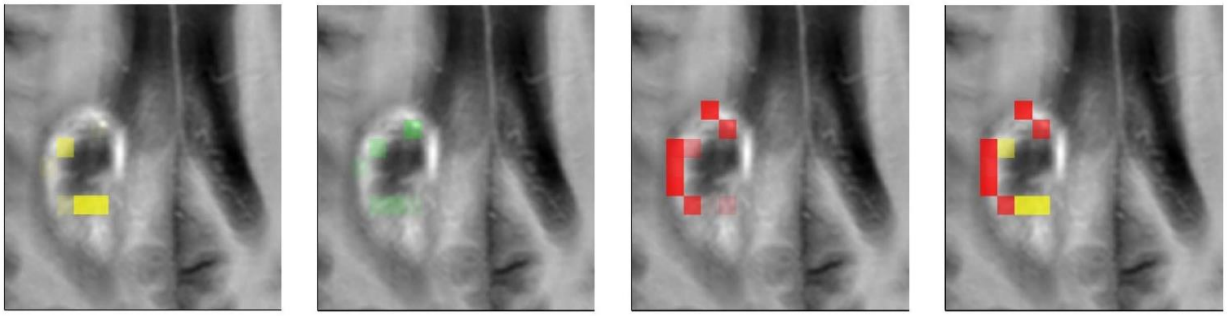
Supplementary figure 28. Case 46: PP.



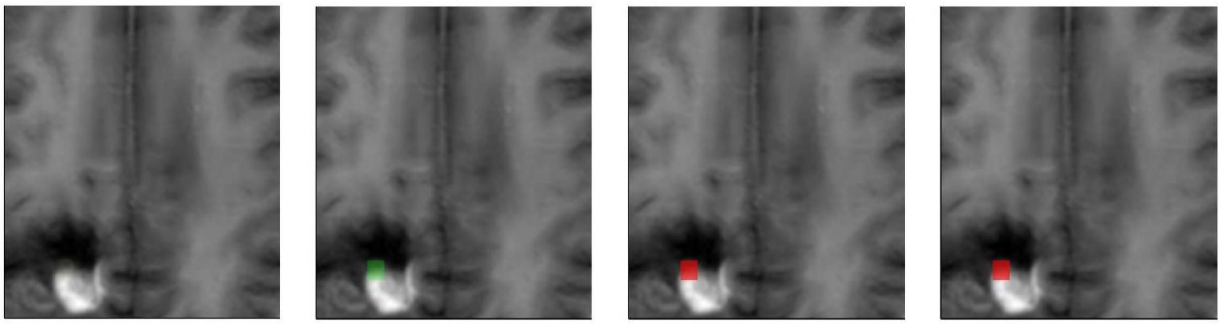
Supplementary figure 29. Case 47: PP.



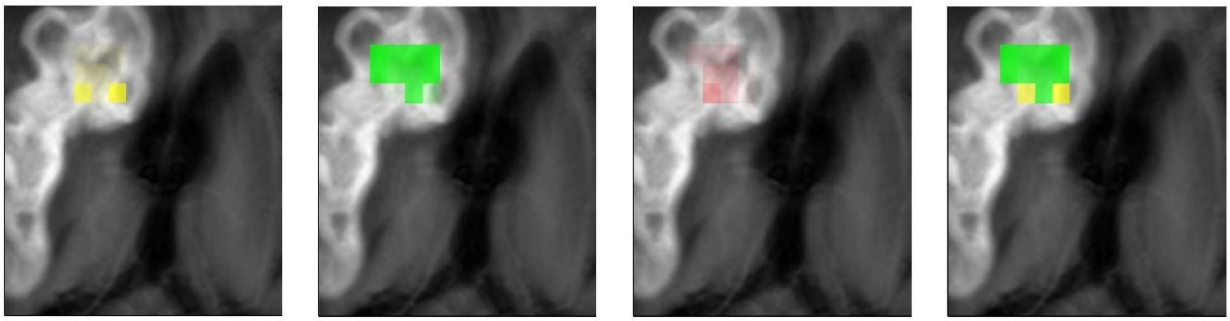
Supplementary figure 30. Case 49: TP.



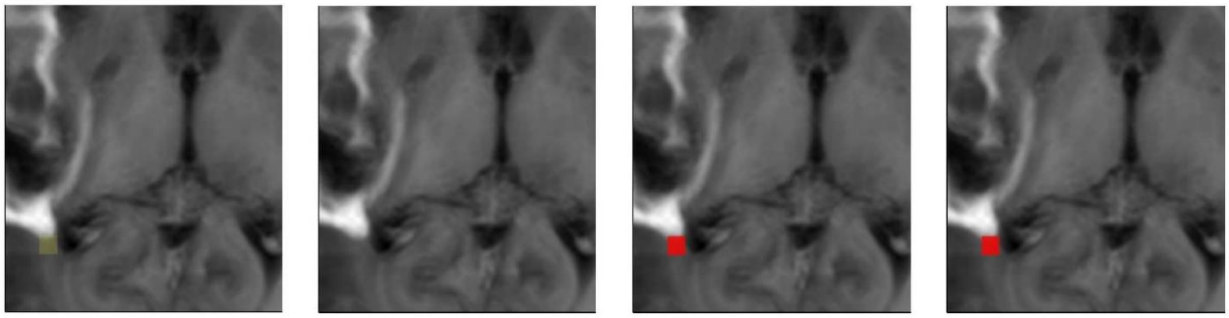
Supplementary figure 31. Case 51: TP.



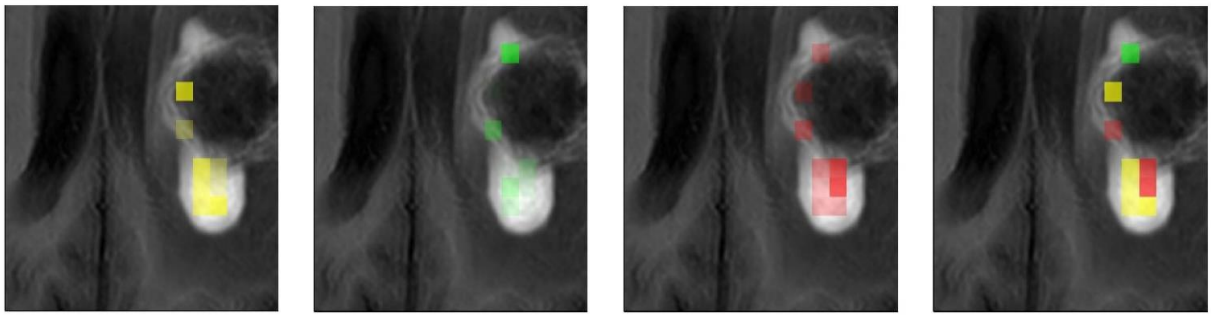
Supplementary figure 32. Case 54: S.



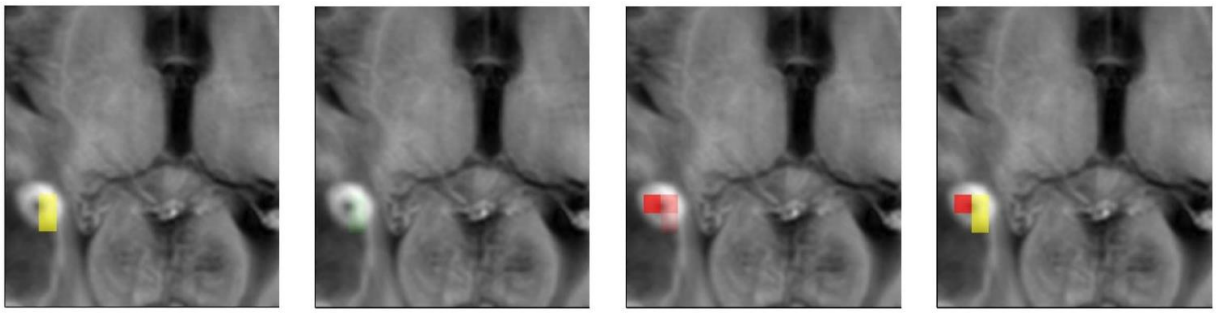
Supplementary figure 33. Case 56: PP.



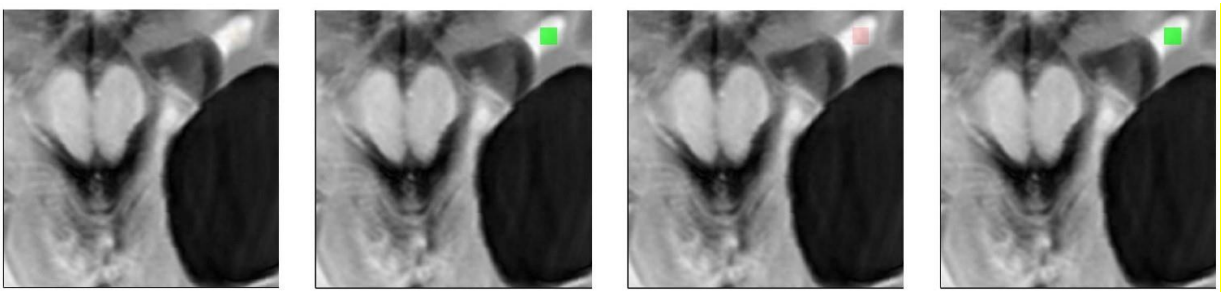
Supplementary figure 34. Case 58: PP.



Supplementary figure 35. Case 59: PP.



Supplementary figure 36. Case 61: PP.



Supplementary figure 37. Case 62: PP.