Non-uniform dose distributions in whole brain radiotherapy

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Under the supervision of:

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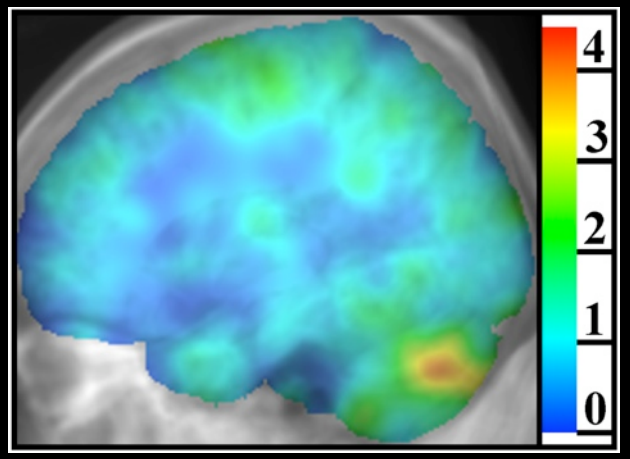

Outline

- Background Information
  - Whole brain radiotherapy and small cell lung cancer
  - Research question
- Atlas of brain metastases
  - Construction technique
  - Description of spatial biases found
- Non-uniform dose prescriptions
  - Modeling
  - Optimal dose distribution
- Conclusion and future work

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Whole Brain Radiotherapy

- Palliative treatment for Multiple Brain Metastases
  - 30 Gy in 10 fractions
  - Possible integrated or serial boost to metastases
- Prophylactic Cranial Irradiation (PCI) for small-cell lung cancer in complete remission
  - 25 Gy in 10 fractions
  - No boost is possible - we don’t know where micro-mets are!

Small Cell Lung Cancer

- For people with SCLC in complete remission, brain metastasis is a significant problem
  - 2 year survival is ~40% with current treatments [1]
  - Incidence of brain metastases at 3 years ~ 59% without PCI [2], ~ 30% with PCI [1]
- A uniform dose is usually prescribed for PCI
  - There is interest in hippocampal sparing WBRT
    - Requires IMRT
    - Hippocampus believed to be a rare site for metastasis

1: Le Péchoux et al. *The Lancet Oncol.* **10**, 467-474 **(**2009)
2: Aupérin et al. *NEJM* **341,** 476**-**484 (1999)

Question

- Are there regional biases in the distribution of brain metastases?
- If so, can we take advantage of the biases when delivering PCI?
  - What is the consequence of sparing the hippocampus?
  - Could we boost high-risk regions?

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Atlas of Brain Metastases

- Distribution has been studied before but no 3D atlas has been created
  - Disease specific atlases will be created by mapping all brain metastases to a standard image set

Ghia et al. Int. J. Radiation Oncology Biol. Phys. **68**, 971-977 (2007)
Delattre et al. Arch. Neurol. **45**, 741-744 (1988)
Tuskada et al. *Cancer* **52**, 2349-2354 (1983)

Atlas Brain Metastases

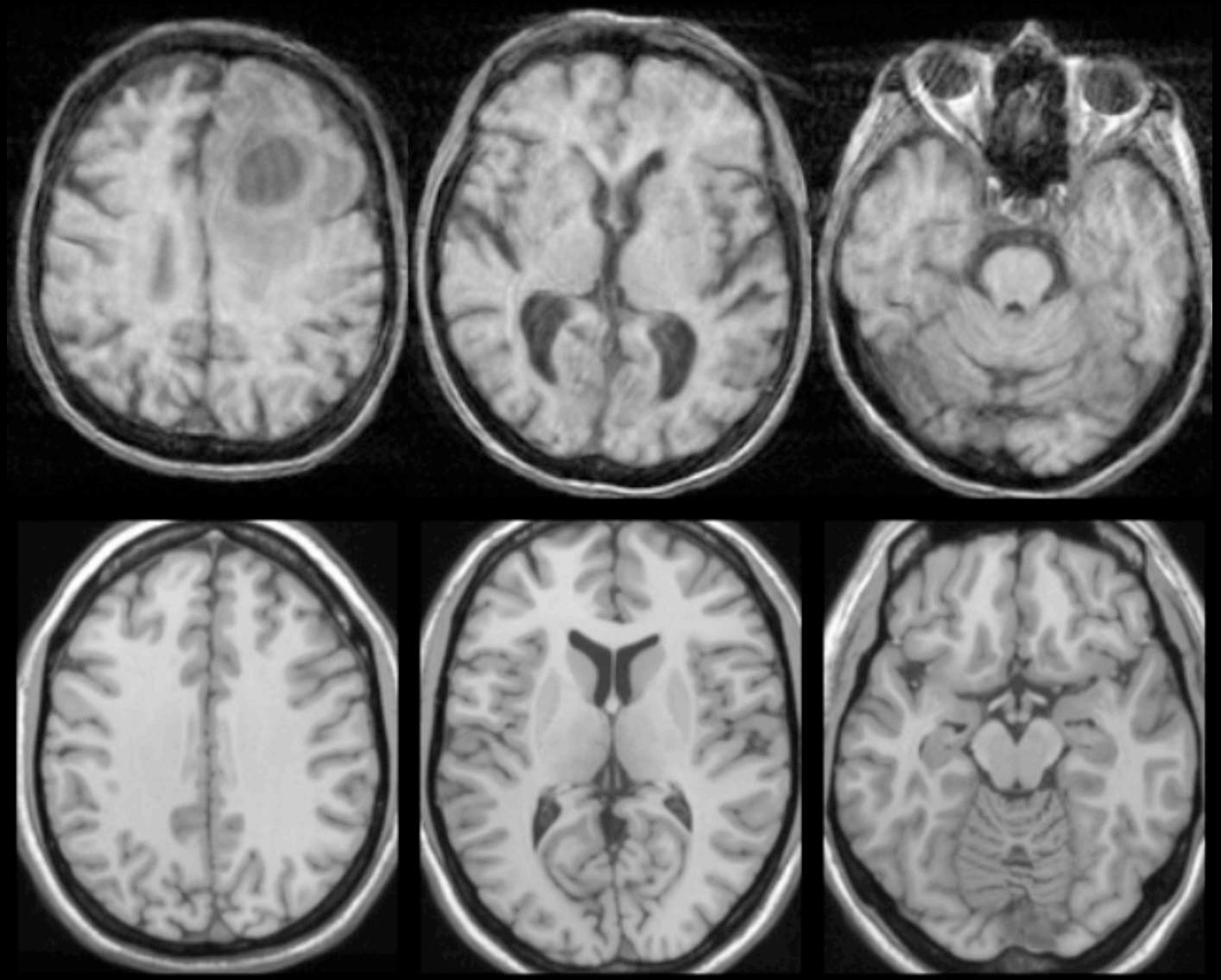
- 499 Brain Metastases from 163 patients were mapped to the ICBM template

Disease type	Number of Patients	Number of Metastases	Patients with a solitary lesion (%)
Breast	30	118	36.7
NSCLC	63	174	38.1
SCLC	22	53	45.5
Renal	11	43	45.5
Gynecologic	8	38	62.5
Melanoma	29	73	48.3
Total	**163**	**499**	**42.3**

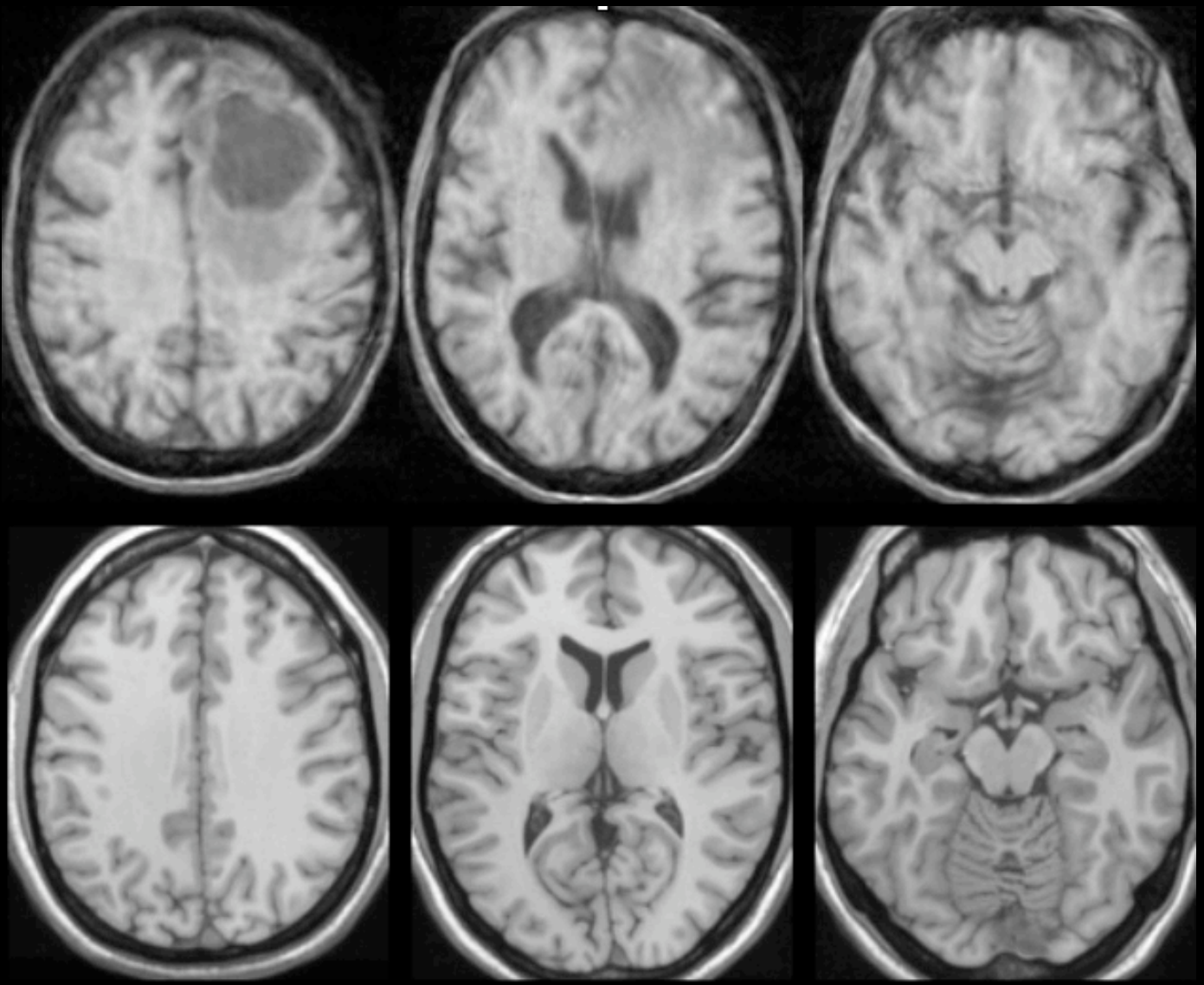
Atlas Construction

- Step 1: Deform patient images to match the ICBM template image

Before deformation

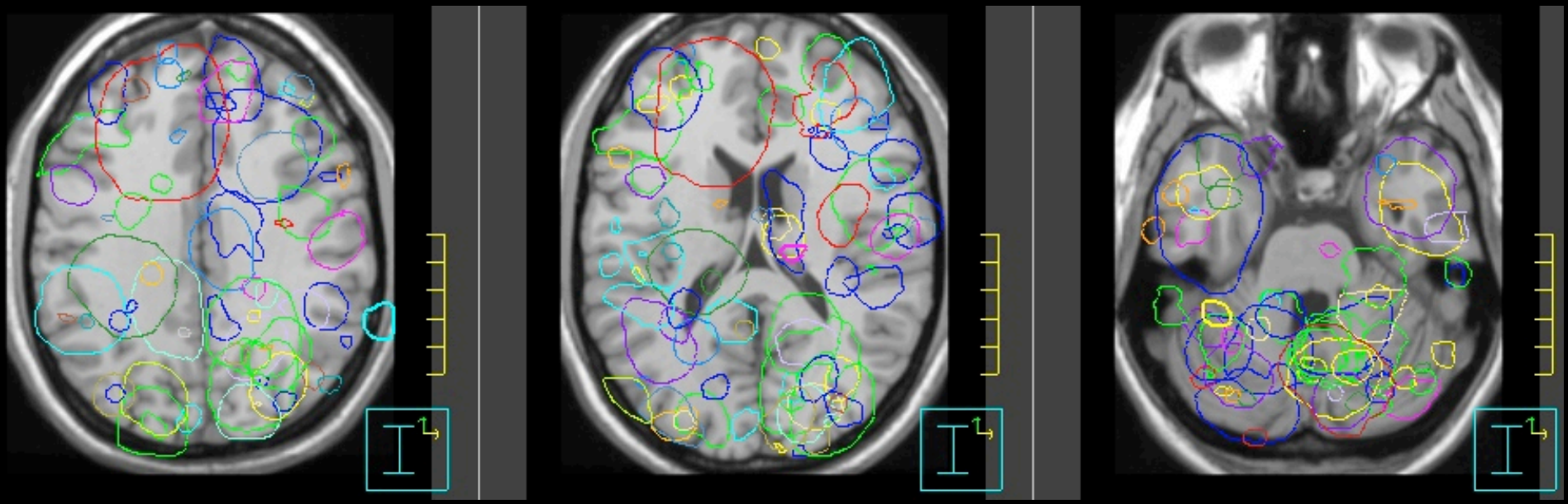


After deformation

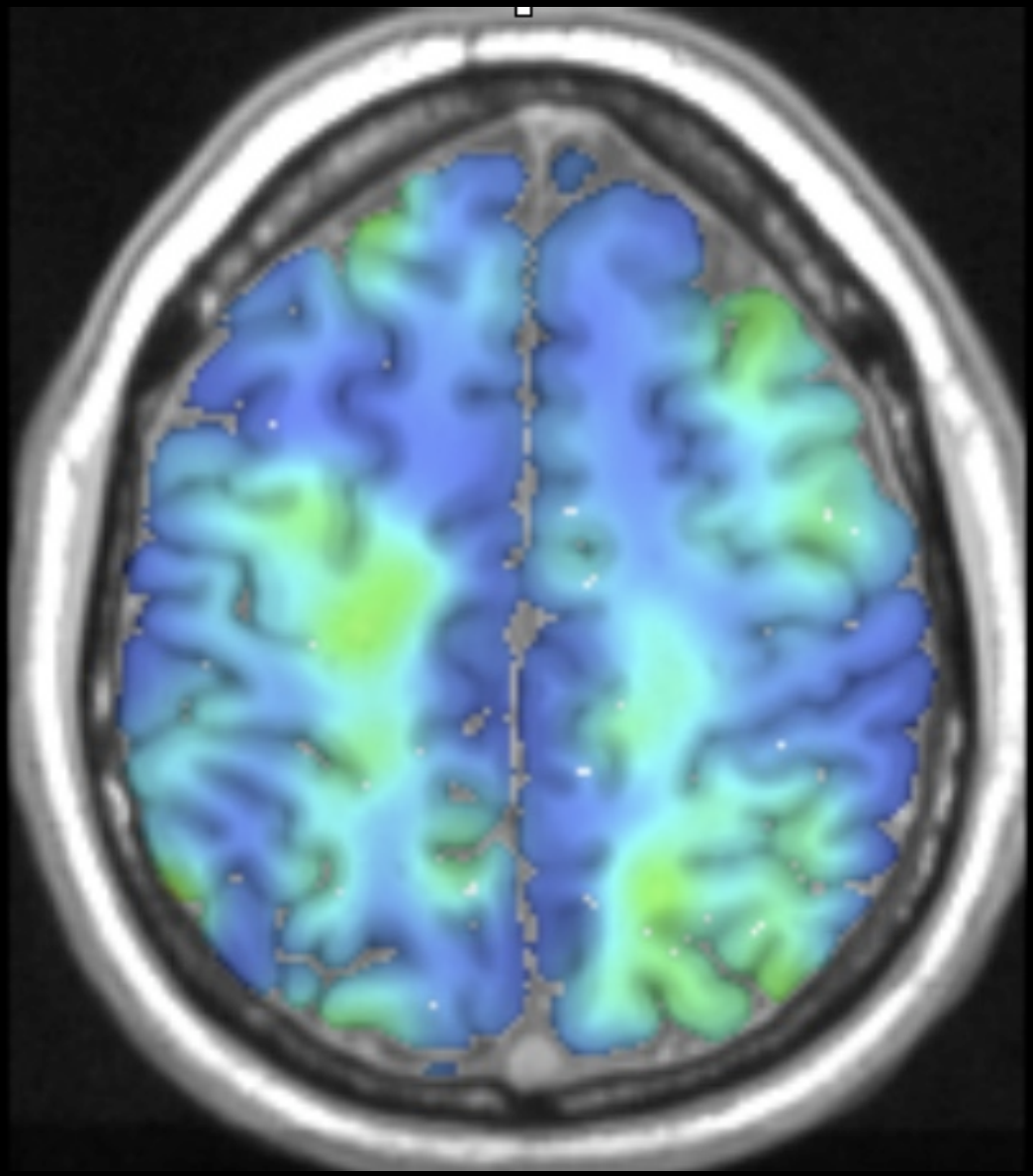


Atlas construction

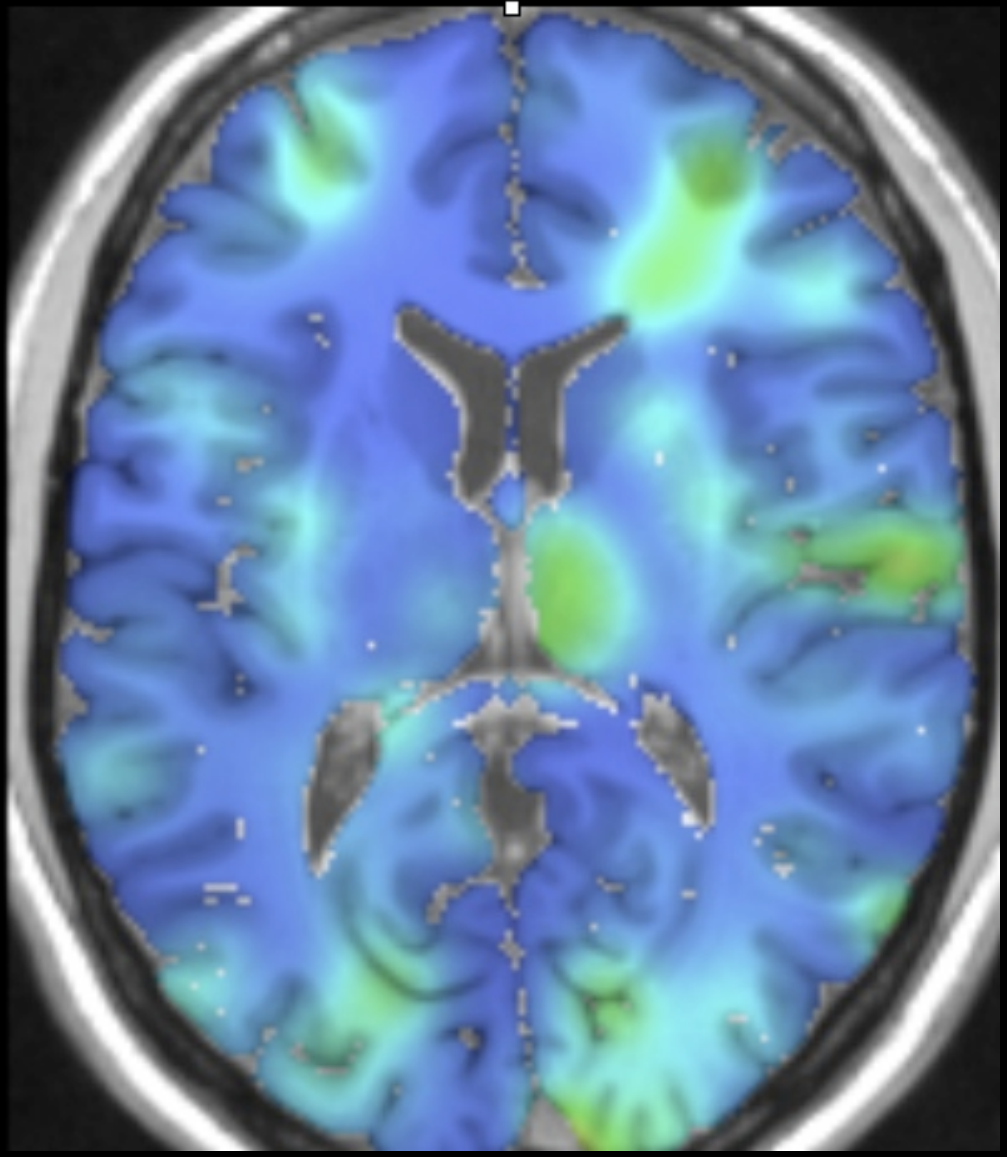
- Step 2: All metastases are collected in the ICBM template image
  - Can create disease specific atlases and one for all diseases combined



All diseases combined - Saturated at 7



All diseases combined - Saturated at 7



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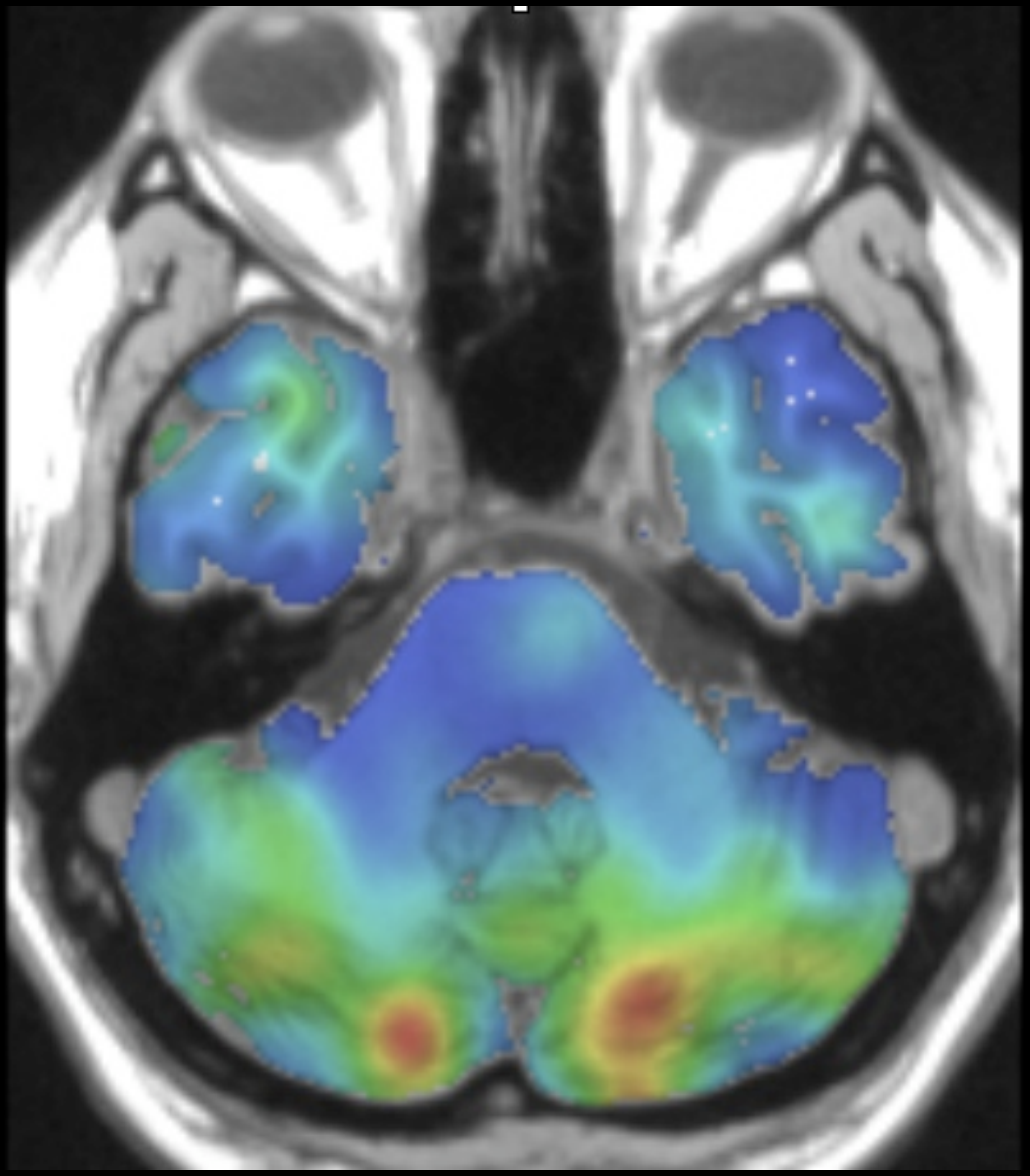
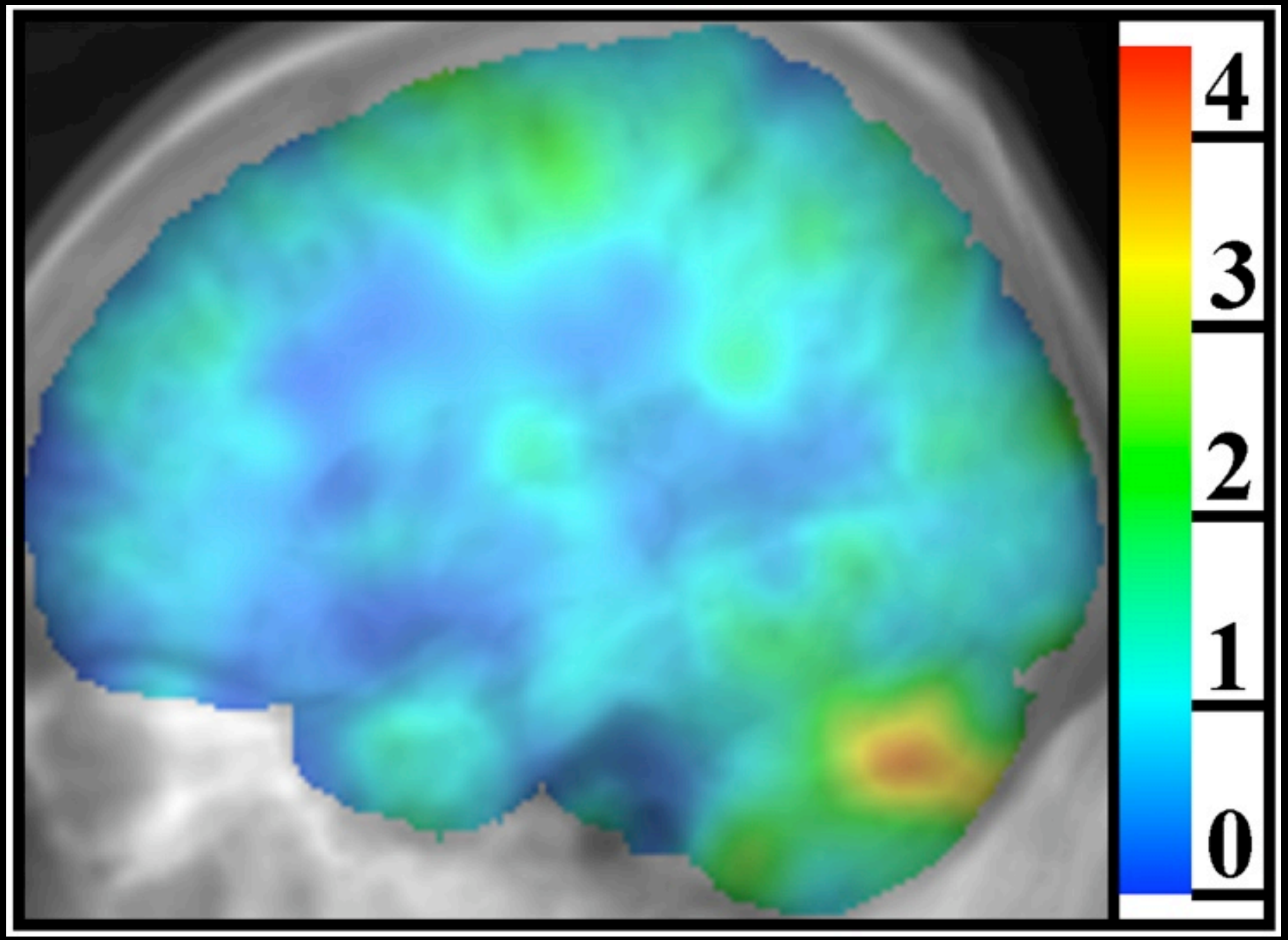
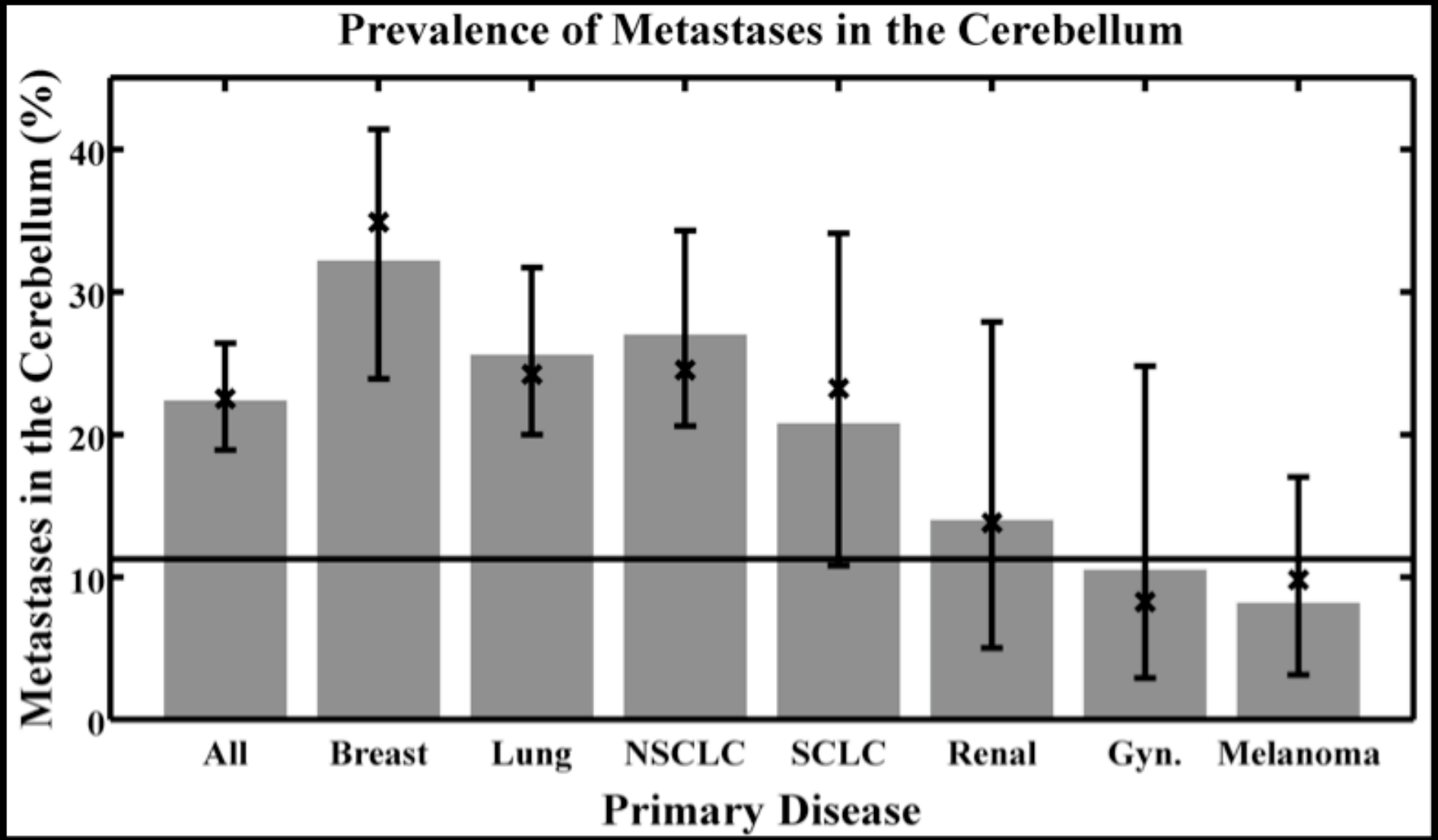
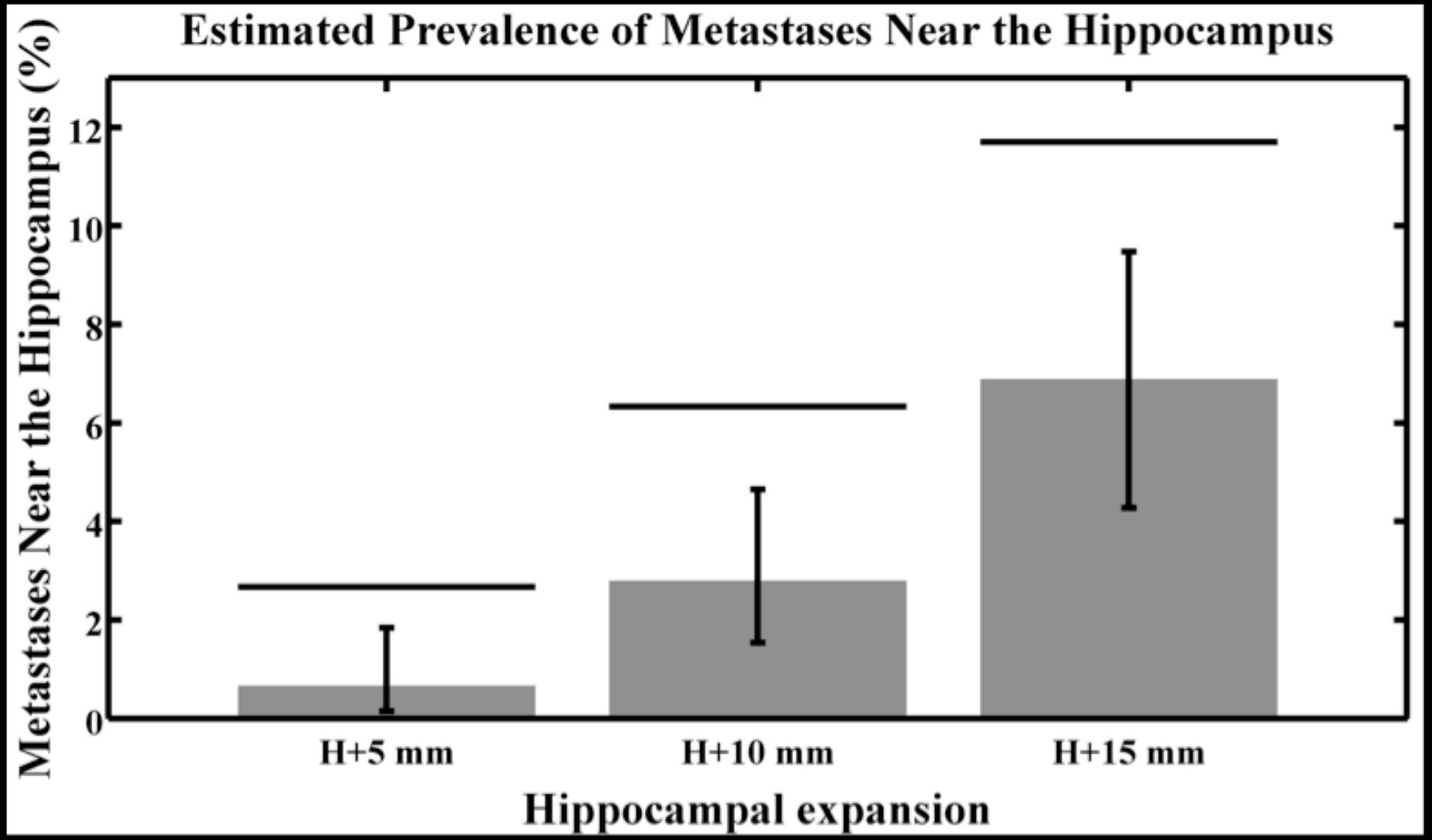



4
3
2
1
0


Prevalence of Metastases in the Cerebellum
Metastases in the Cerebellum (%)
0
10
20
30
40
All
Breast
Lung
NSCLC
SCLC
Renal
Gyn.
Melanoma
Primary Disease


Estimated Prevalence of Metastases Near the Hippocampus
Metastases Near the Hippocampus (%)
0
2
4
6
8
10
12
H+5 mm
H+10 mm
H+15 mm
Hippocampal expansion

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Radiobiological modeling

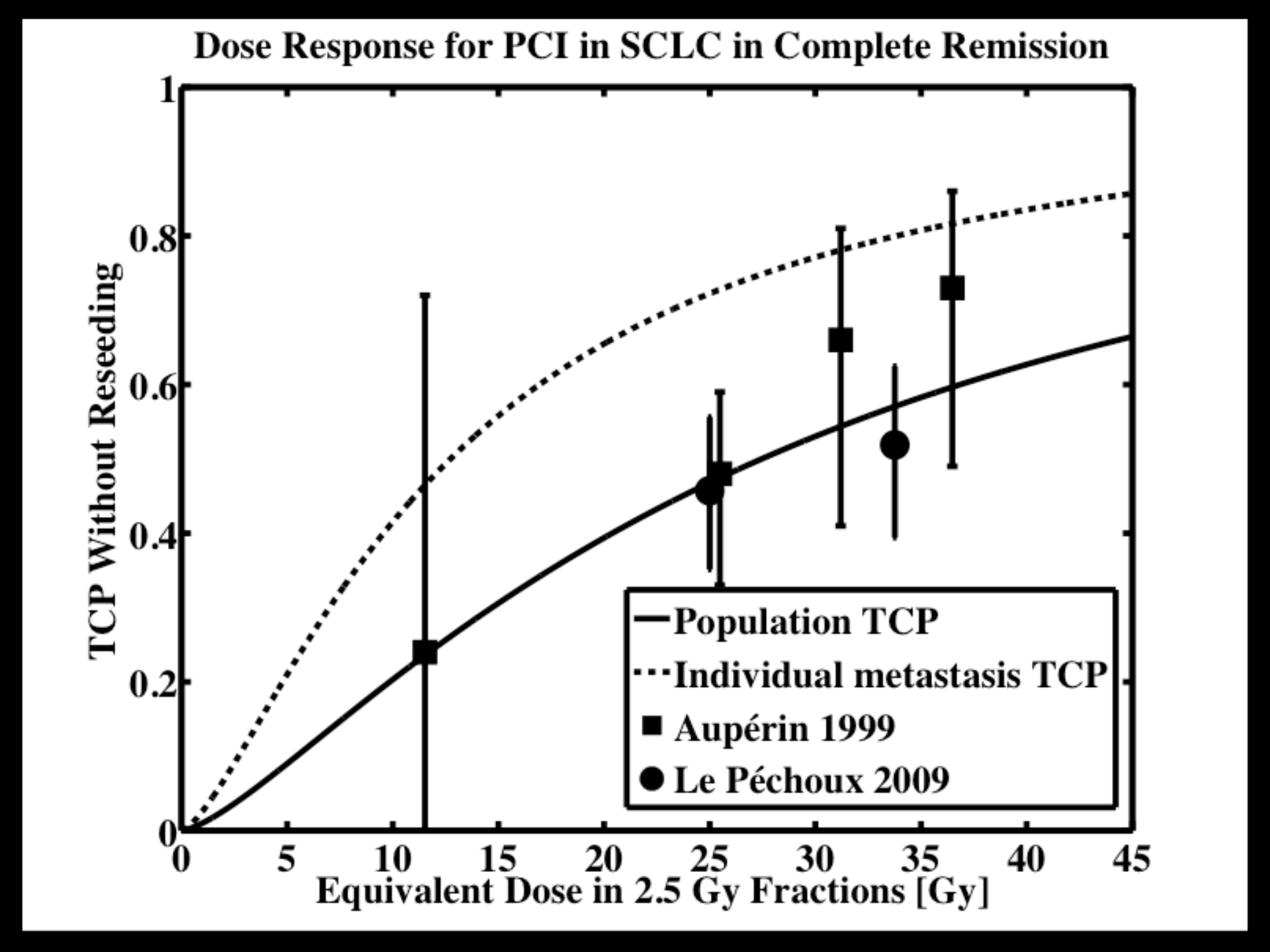
- How would non-uniform dose distributions affect the relative risk for brain metastases?

TCP Model for Non-Uniform Dose

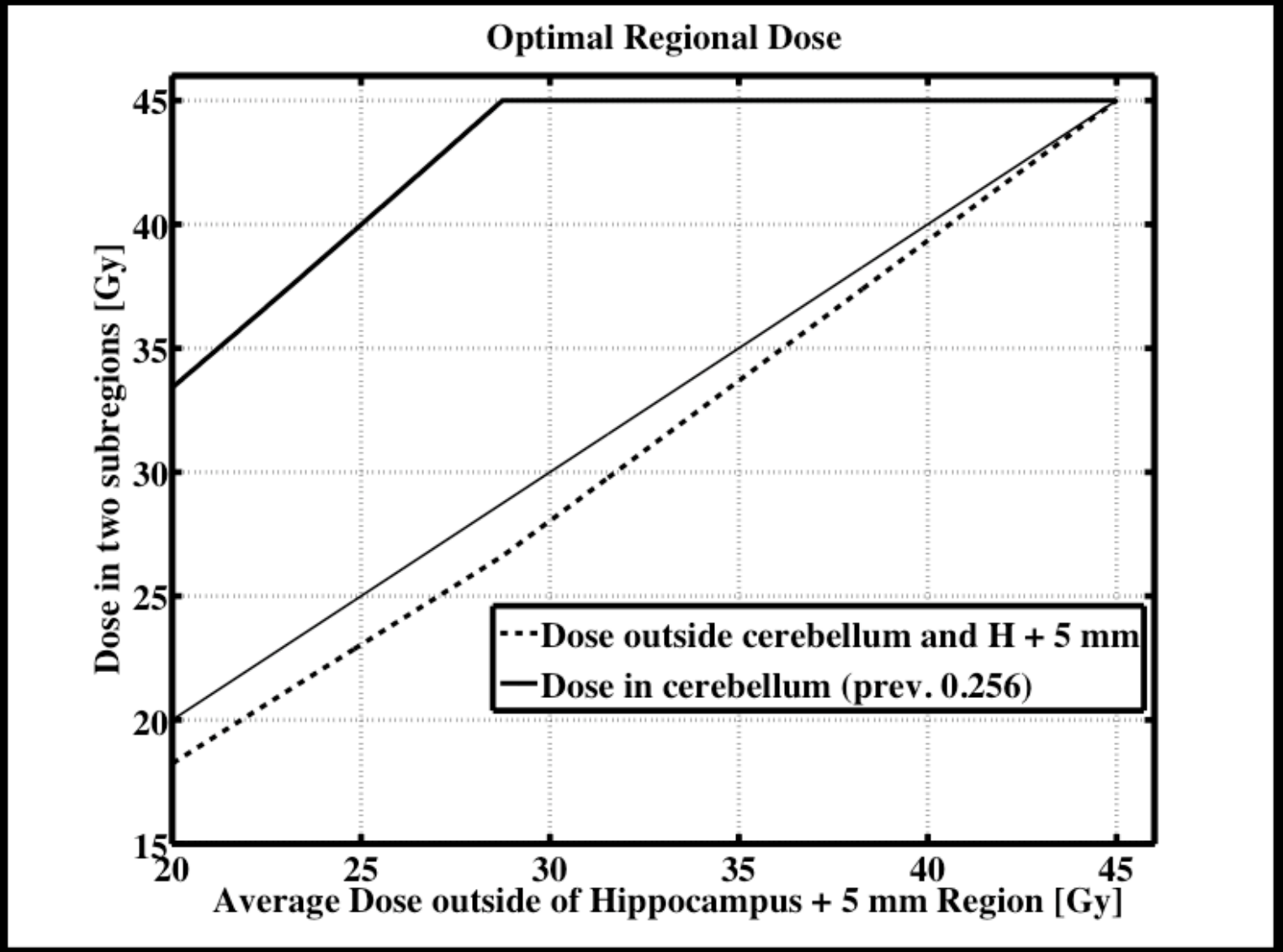
- Model has to account for varying numbers of micro-metastases in the population
- Average dose is constrained

$$TCP_{Pop}(\{d\}) = \sum_{N=1}^{N_{\max}} \left(\Pr(N) \left(\sum_{i=1}^{R} a_i TCP_1(d_i) \right)^N \right)$$

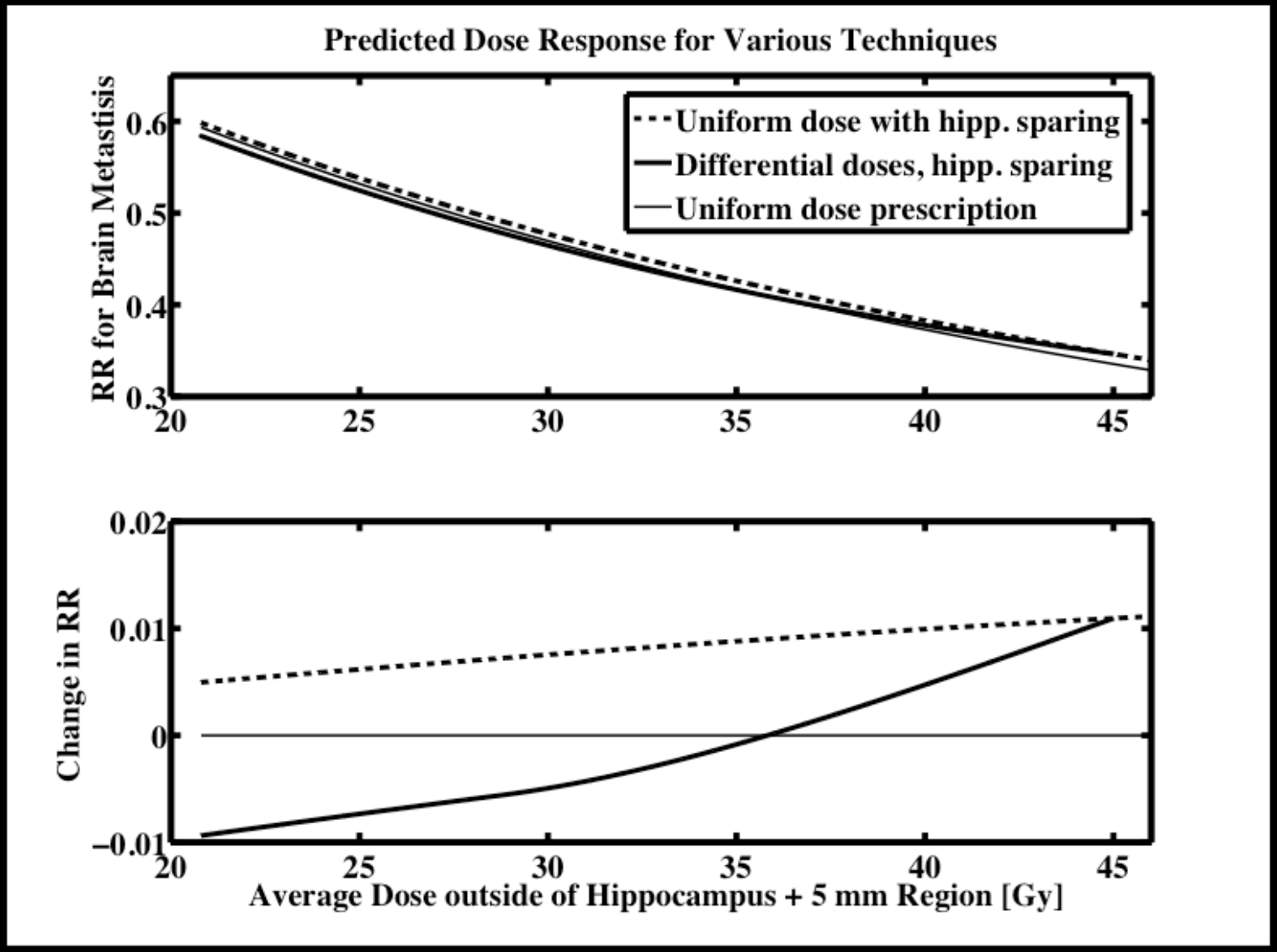
$$\sum_{i=1}^{R} v_i d_i = D \qquad TCP_1(d) = \frac{1}{1 + \left(TCD_{50} / d \right)^{4\gamma_{50}}}$$


Dose Response for PCI in SCLC in Complete Remission
TCP Without Reseeding
Equivalent Dose in 2.5 Gy Fractions [Gy]
0
0.2
0.4
0.6
0.8
1
0
5
10
15
20
25
30
35
40
45
Population TCP
Individual metastasis TCP
Aupérin 1999
Le Péchoux 2009

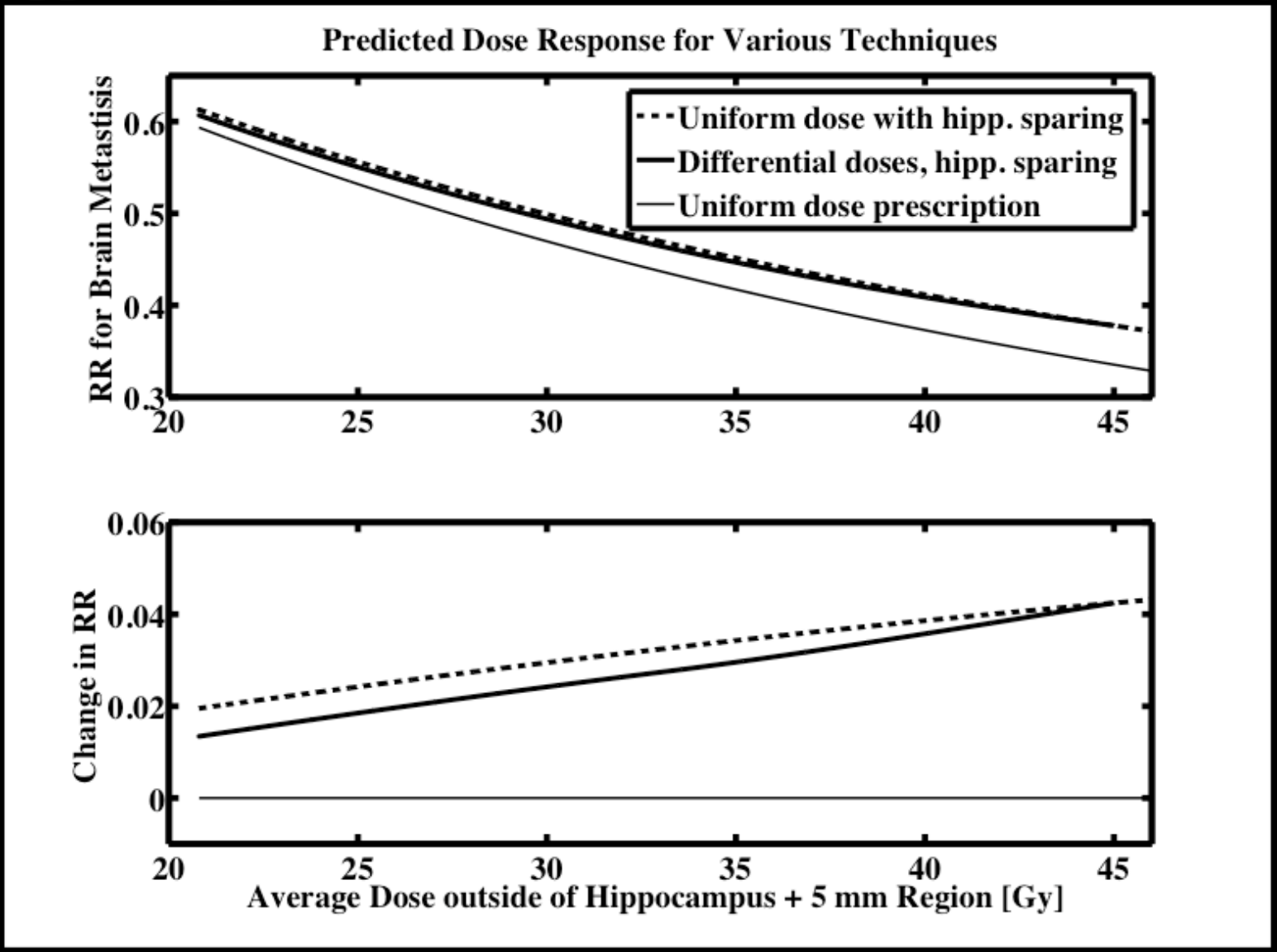
Dose levels for Maximal TCP with most likely estimate for prevalences (no reseeding)



Predicted Change in RR with most likely estimate for prevalences (no reseeding)



Predicted Change in RR - upper 95% for prevalence in hippocampus, lower 95% for cerebelllum (no reseeding)



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Conclusion

- For our database, there is a higher risk for cerebellar metastasis in breast and lung cancer
- The hippocampus region (5, 10, 15 mm expansion) is at lower risk when considering all diseases together
- Hippocampal sparing my increase RR by up to 0.025 for standard fractionation
- Redistribution of dose between cerebellum and elsewhere may lower RR by about 0.01

Future Work

- Is there a cerebellar bias in recurrences after PCI for SCLC?
- Dose painting with multiple structures
  - This is feasible with current technology
  - How high can we push the TCP for constant integral dose?
- Inclusion of NTCP models
- TCP estimates based on physically deliverable dose distributions

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