

Quantification of ventricle and tumor volume change in treatment of glioblastoma

Ivar Thokle Hovden

I would like that we take the discussion and questions after I have done the presentation

I'm appreciating to not be interrupted too much, because it makes it more difficult for me to present

And please remember that I have not a clear medical background. I'm perhaps closer to physics, computer science and mathematics

Goal of the presentation: Present motivation and results of comparing tumor and ventricle volume changes in conventional glioblastoma treatment, and have discussion for useful input for leading up to a publication about this topic.

Questions: remember it or write it down for asking it after I have finished speaking.

Treatment of glioblastoma

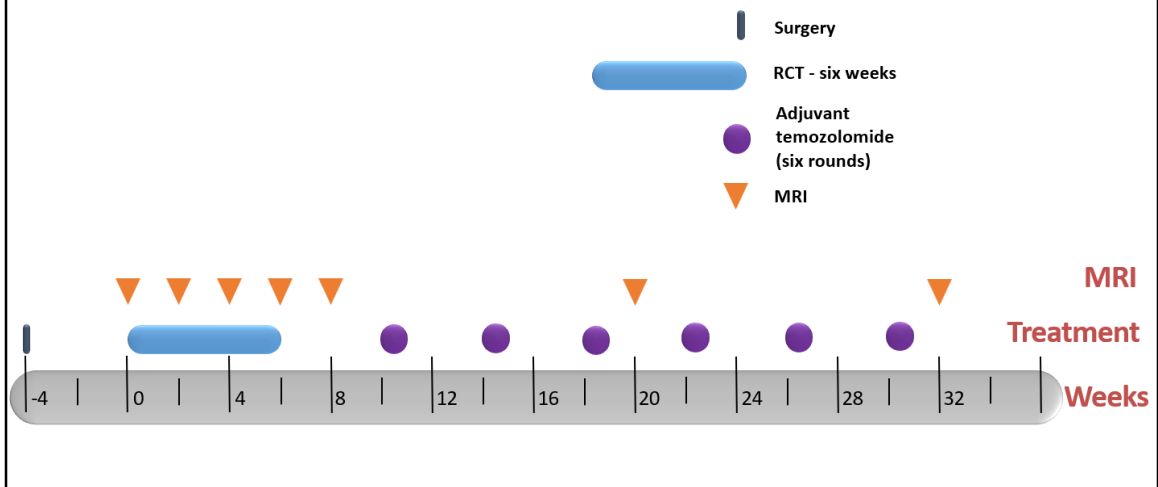
- Grade 4 glioma (most aggressive type of the primary glioma brain tumor)
- [Conventional treatment](#) involving surgery, followed by regularly radiation -and chemotherapy
- [12-15 months overall survival](#) (15 months ~450 days, ~62 weeks)
 - Most glioblastomas recur despite conventional treatment
- Typical observation: 'shrinkage' of the tumor volume or volume of surgical resection if successful radiochemotherapy (RCT), then recurrence of new tumor tissue at various places in the brain at later time points ('expansion')

Radiotherapy plus Concomitant and Adjuvant Temozolomide

'concomitant': accompanying, associated, connected -> clinicians' word for concurrent, parallel (?)

'adjuvant': drug or collection of drugs that is used to increase the efficacy or potency of certain drugs (ad-hoc treatment, 'tilleggsbehandling' (til kirurgien og strålingen (til kreftbehandlingen))) -> the temozolomide

Conventional treatment at OUS (SAILOR)



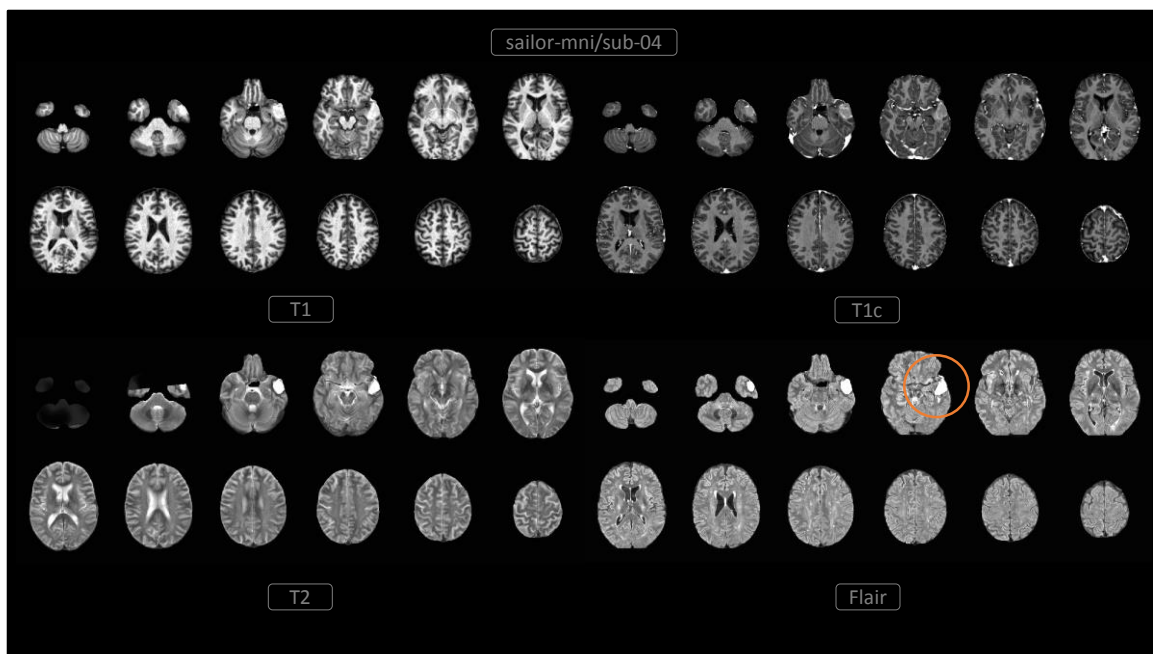
From the SAILOR study.

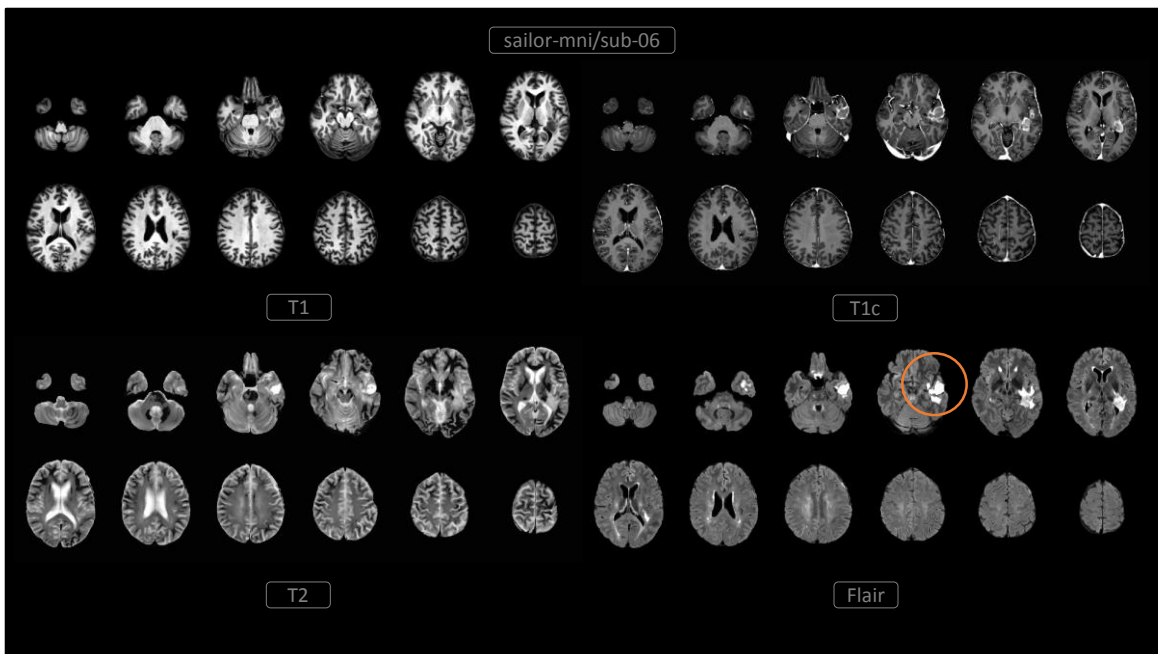
Treatment scheme during ~half of the documented maximum overall survival

Stupp.

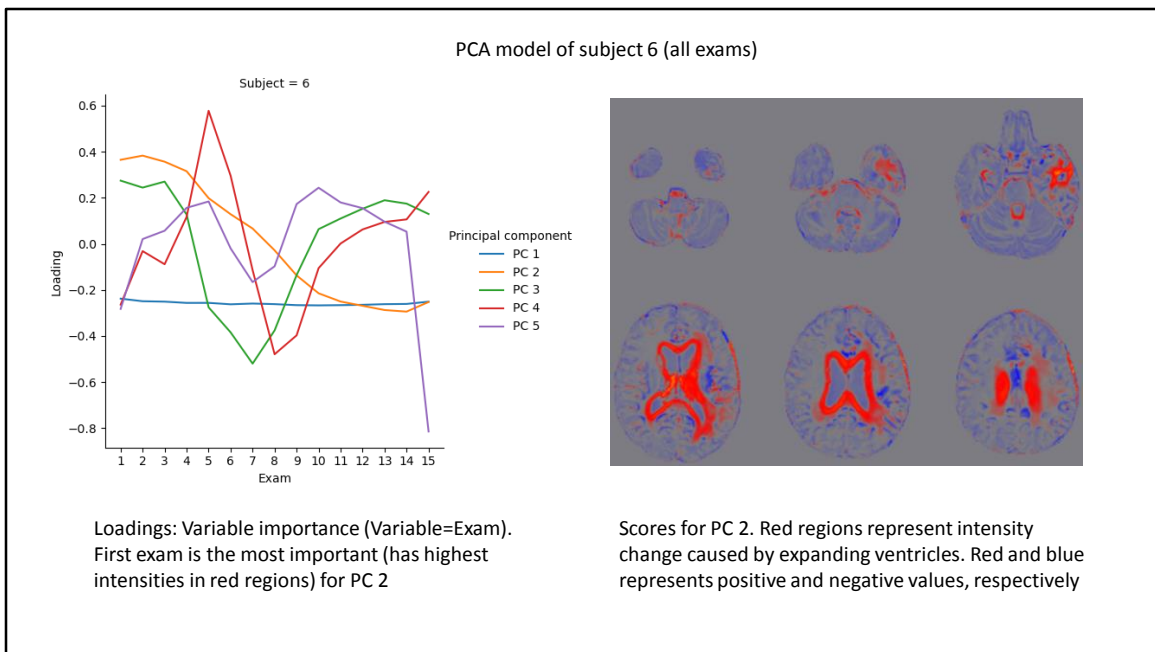
The first MRI is the 'baseline' (baseline is post-surgery in the data that I have used)

36 weeks=252 days





- I would like to perform some analysis that can quantify common responses to the treatment
- The main point is that perhaps such an analysis could lead up to some new knowledge about the conventional treatment
- For instance: ventricle expansion is clearly more recognizable than tumor expansion in this treatment



- Better to be approximately right than precisely wrong
- Quantification without segmentation: traditional clustering directly in the image intensities
- In PCA, possible to reconstruct an image for a given deconstructed component (from a longitudinal series of T1c MRI for a patient)
- Typically, component 2 describes structural changes related to the ventricles
- PCA is related to Autoencoder, see link to a previous presentation in the hypothesis slide

Subject (t1c) (SAILOR)	Component describing ventricle change
1	2,3,4
4	2,3
6	2
14	2,3
23	2,3
24	2,3
26	2,3

What is component 2?

- High intensity change caused by expanding ventricles

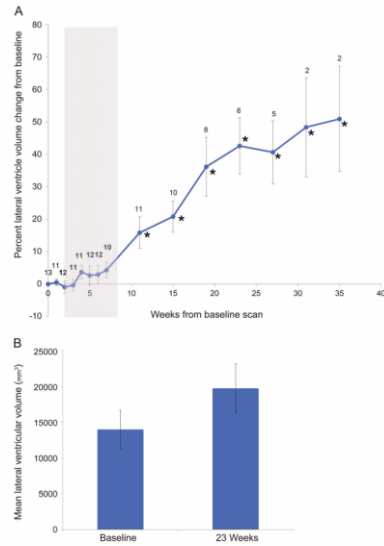
Component 2 seems to describe/capture ventricle abnormality in glioblastoma

Ventricle change: relevant literature

- [Evidence of ventricle expansion as part of brain atrophy \(shrinkage\) as an effect of radiation therapy on glioblastoma \(2015\)](#)
- [Atrophy of various brain regions and of the whole brain is associated with radiation therapy \(2021 review\)](#)
- Ventricle dilation as a well-known marker of brain disease and damage
 - Dementia, Alzheimer's
 - Hydrocephalus ('water head')
 - Ageing
 - Electroshock therapy

Suggestions for references to ventricle change associated with brain disease and damage?

Figure 4 Longitudinal progression of anterior lateral ventricular volume



(A) Lateral ventricular volumes across the treatment period. Data points represent the sample mean of percent volume change from baseline at each time point. Error bars represent the SEM. Sample sizes are indicated at each time point. Gray shading indicates combined chemotherapy and radiation. One participant was excluded because of extensive ventricular tumor involvement. *Time points at which volumetric changes are statistically significant ($p < 0.05$). (B) Lateral ventricular volumes at baseline and 23 weeks in participants remaining on the protocol to this point ($n = 6$). Bars represent sample means at baseline and 23 weeks; error bars represent the SEM.

2015 reference

Tomas Sakinis

- 40 weeks=280 days
- I would like to perform a similar analysis

Main hypothesis

- [Ventricle expansion is a stable quantifiable imaging pattern across many glioblastoma patients](#) (my previous presentation)
 - More stable than tumor volume measurements?
 - Insights into glymphatic aspects of glioblastoma/treatment?
- H_0 : In standard treatment of glioblastoma, the change of tumor volume is not associated with change of ventricle volume (ventricles 1 and 2)

Ventricle change: increase or decrease

Future additions

- Stratification between early (RCT) and late (TMZ) treatment
- Associating with overall survival

Datagrunnlag

Navn	Sykdom	N	Antall undersøkelser	Valgt anatomisk MR-bilde	Offentlig (j/n)	Kreftsegmentering	Referanse
SAILOR	Gliom (3 grad III, 24 grad IV)	27	3-14	T1	n	Ødem, nekrotisk, kontrastforsterkende	1
BOSTON-NHX	Gliom IV (glioblastom)	14	6-15	T2 (5), ADC (8), FLAIR (1)	n	kontrastforsterkende	1

Sorry about Norwegian

Data for eksperimenter

- sailor-mni + boston-nhx (41 pas $\cdot$ ~ 9 intervaller = 369 N)

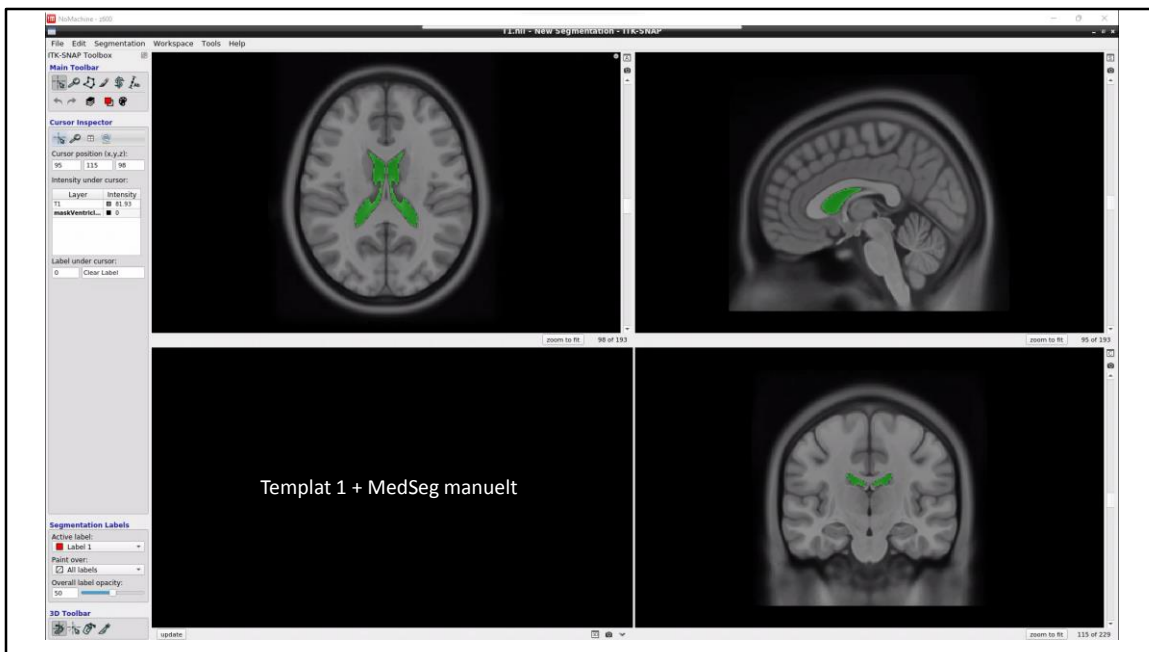
Eksperiment 0, informasjon

- Mål: Segmentering av 1. og 2. ventrikk
- Templat 1: T1 og T2 Montreal Neurological Institute (MNI) 152 International Consortium for Brain Mapping (ICBM) [2009c nonlinear symmetric](#)
- Templat 2 fra Statistical Parametric Mapping (SPM) 12
 - Sannsynlighetstetthetskart for ulike vevstyper (Tissue Probability Map, TPM) :
 1. Grå materie
 2. Hvit materie
 3. Cerebrospinal veske (CSF)
 4. Skalle
 5. Utenfor skalle
 6. Utenfor hode
 - 136 koregistrerte manuelt segmenterte områder fra [Neuromorphometrics, Inc.](#)

Eksperiment 0, metode B

- Manuell segmentering av 1. og 2. ventrikkel basert på T1-bilde fra templat 1
- [MedSeg.ai](#)
- Segmenteringen er utført av meg, og de valgte områdene er basert på områdene fra Neuromorphometrics, Inc.
- Sammenligning med T1-bilde fra templat 1

Alternatives: Using
FastSurfer
MNI152 CSF template



Eksperiment 0, metode B

- Manuell segmentering av 1. og 2. ventrikkel basert på T1-bilde fra templat 1
- [MedSeg.ai](#)
- Segmenteringen er utført av meg, og de valgte områdene er basert på (lært av) områdene fra Neuromorphometrics, Inc.
- Sammenligning med T1-bilde fra templat 1
- Konklusjon: Matchende segmentering

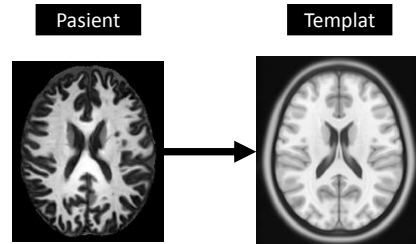
Eksperiment 1, informasjon

- Mål: ANTs Symmetric diffeomorphic image registration (SyN) for å segmentere 1. og 2. ventrikk i pasient med glioblastom
- Templat 1: T1 Montreal Neurological Institute (MNI) 152 International Consortium for Brain Mapping (ICBM) [2009c nonlinear symmetric](#)
- Segmenterte 1. og 2. ventrikk for templat 1 med MedSeg
- T1-bilde fra SAILOR, pasient 1, første scan postkirurgisk

Eksperiment 1, metode

1. Pasient T1 koregistreres til templat T1

- Fixed: templat T1
- Moving: pasient T1
- `command="antsRegistration \`
 - `--dimensionality 3 \`
 - `--float 0 \`
 - `--output $out_prefix \`
 - `--interpolation Linear \`
 - `--winsorize-image-intensities [0.001,0.999] \`
 - `--use-histogram-matching 1 \`
 - `--transform SyN[0.1,3,0] \`
 - `--metric CC[$fixedimg,$movingimg,1,4] \`
 - `--convergence [100x70x50x20,1e-6,10] \`
 - `--shrink-factors 8x4x2x1 \`
 - `--smoothing-sigmas 3x2x1x0vox \`
 - `--verbose 0"`
- Gir forflytningfelt for forover og bakover deformasjon av voksler



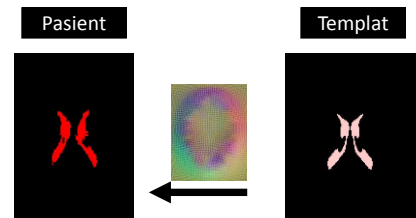
ANTs: Advanced Normalization Tools

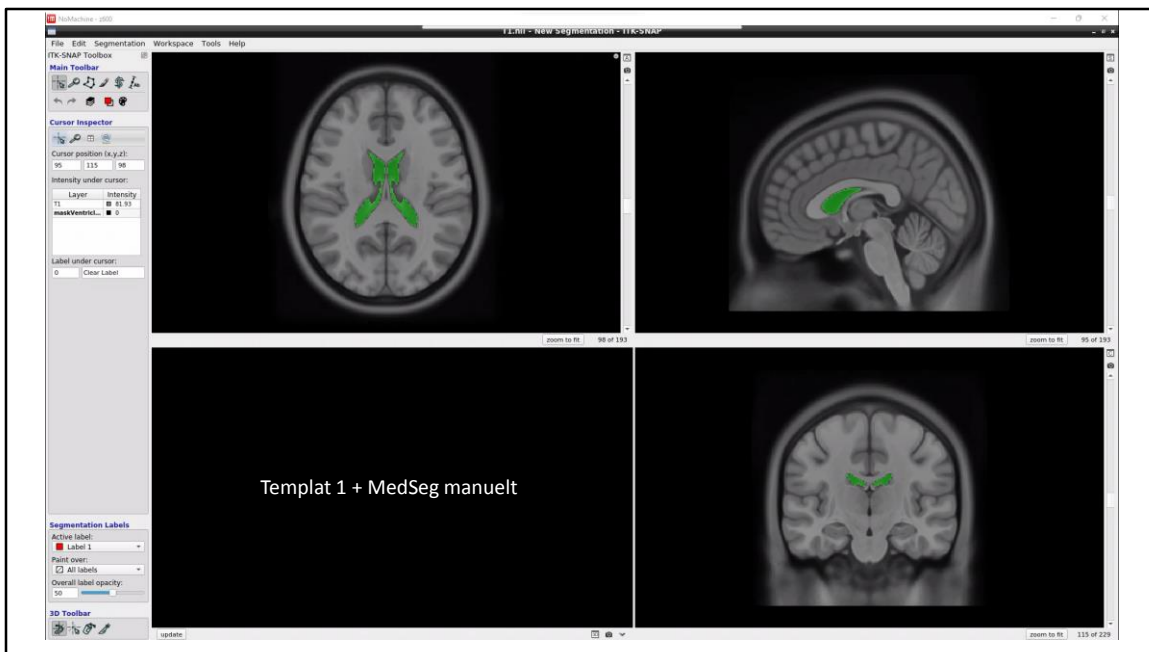
Nonrigid (nonlinear, deformable coregistration)

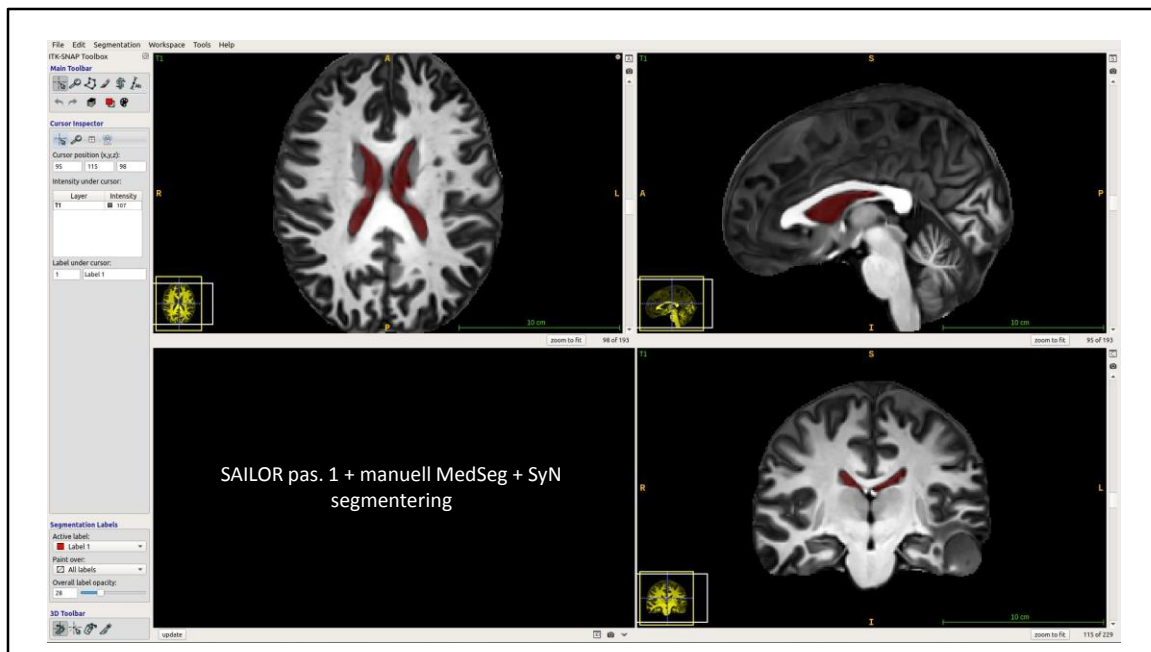
Eksperiment 1, metode

2. Ventrikkemaske deformeres til pasient

- Basert på bakover deformasjonsfelt
- k-nærmeste nabo interpolasjon
- `antsApplyTransforms --dimensionality 3 \`
 - `--input $file \`
 - `--reference-image $ref \`
 - `--output $ofile \`
 - `--interpolation NearestNeighbor \`
 - `--transform $transform \`
 - `--verbose 0`







Eksperiment 1, konklusjon

- ANTs SyN kan brukes til å segmentere ventrikler
- Basert på:
 - T1 MNI templat 1
 - Manuelt segmenterte ventrikler
- ~4 min kjøretid (64-kjerner AMD Threadripper CPU, miniserver 2)

Fra 14 T1-bilder fra SAILOR, pasient 26



The behaviour of the volume of the tumor throughout the treatment, is a lot more complex than the behaviour of first and second lateral ventricles.

Eksperiment 5, informasjon

- Mål: Plått endring av ventrikkelvolum i forhold til baseline scan over tid (to datasett, 41 pasienter, 387 intervaller)
- Computation of ventricle volume [mm³] from ventricle masks: `compute-vent-vols.sh`
- Collection of interval measures relative to baseline: `print-from-baseline-interval-measures.sh`

Oslo and Boston dataset

Dataset versions in Experiment 5

Dataseett	Git commit	Beskjed
SAILOR	d4c59083a4075191deb6e1e28b77a693501ee3a	modify treatment.txt to re-label a few late time steps where the six cycles of temozolomide were completed, by labeling the treatment to 'unknown'
BOSTON	b2baf585aa80c95ec2c4d7a07b9dbb1371d244e0	modify treatment.txt to re-label a few late time steps where the six cycles of temozolomide were completed, by labeling the treatment to 'unknown'

<https://github.com/CRAI-QUS/bidsdir>

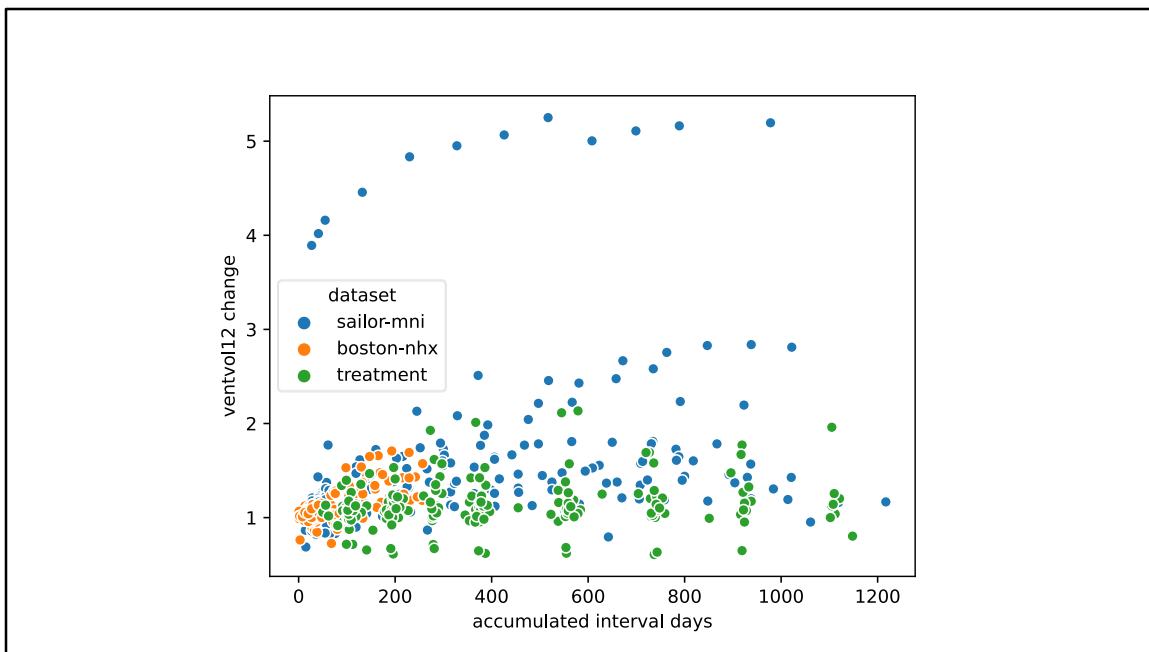
This is how I envision a more reproducible way of organizing your data for research.

Research community approved Brain Imaging Data Structure (BIDS) file organization + Data science community approved Data Version Control (DVC) + Git + Local (hospital) hosting of the imaging data for full control and security.

Like with Git, possible to 'checkout' a specific version of a dataset based on the git commit hash.

Eksperiment 5, metode

- A bunch of python and bash scripts on a messy server



1200 days= $\sim$ 171 weeks

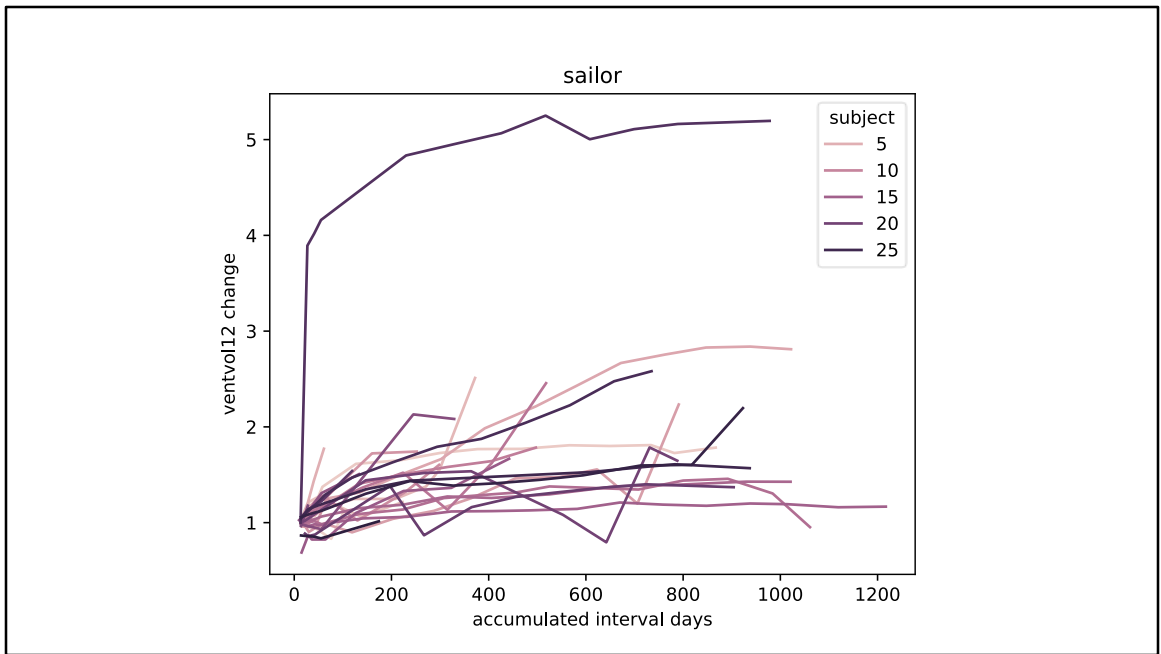
Time changed: 1=unchanged, < 1 , shrinkage

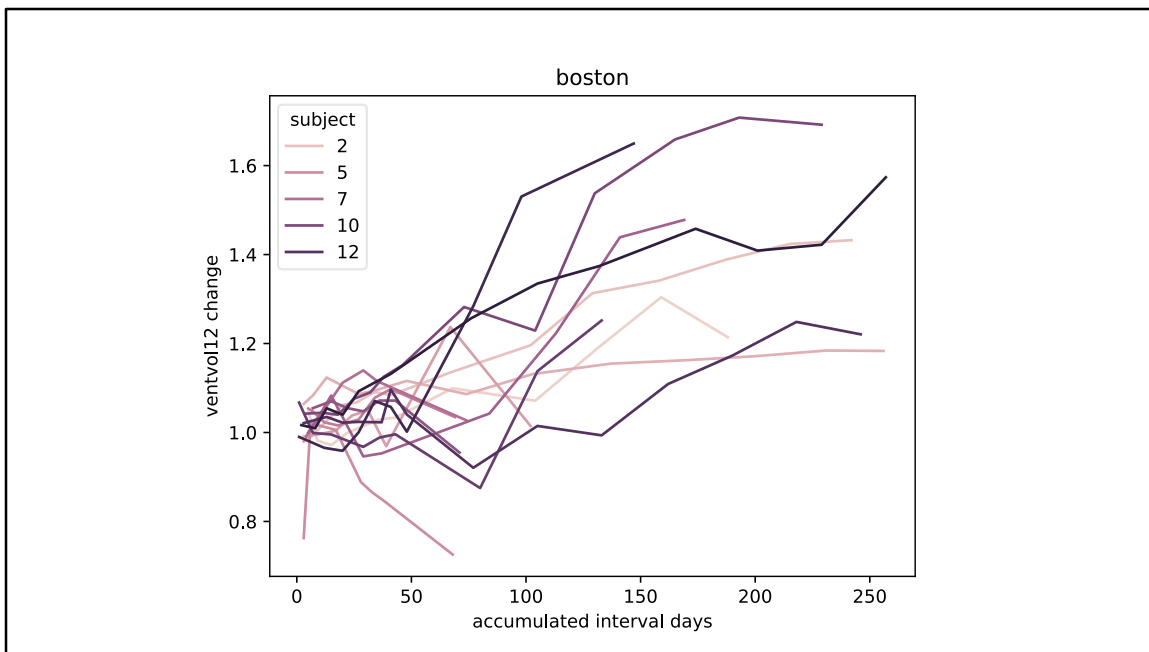
Most samples describe volume increase

Most data is in the 0-250 (35 weeks) days range

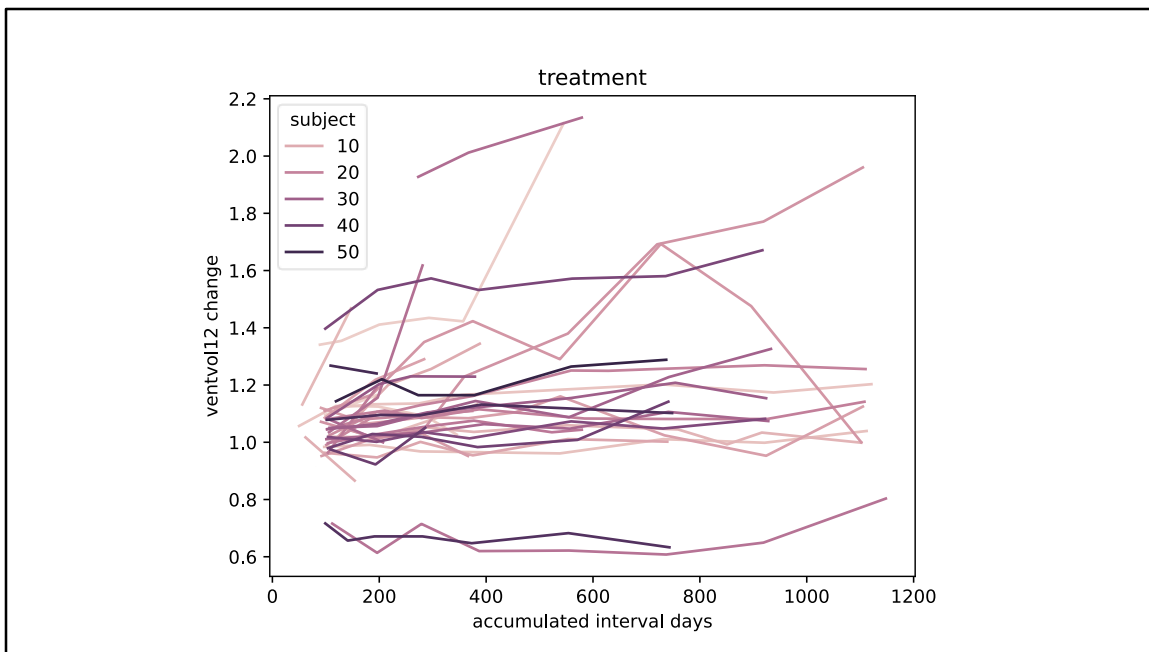
Sailor pas. 23 er en outlier: Veldig rask ekspansjon

A third dataset of brain metastases from lung and skin cancer is also included for comparison, but it is not included in the analysis any further.

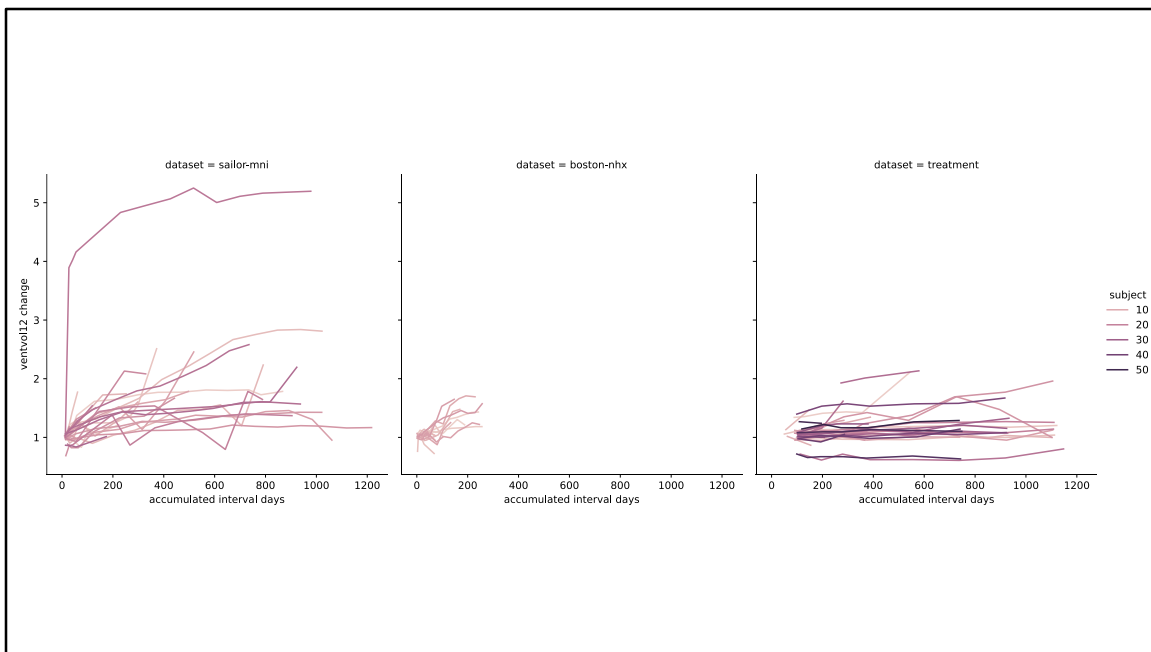


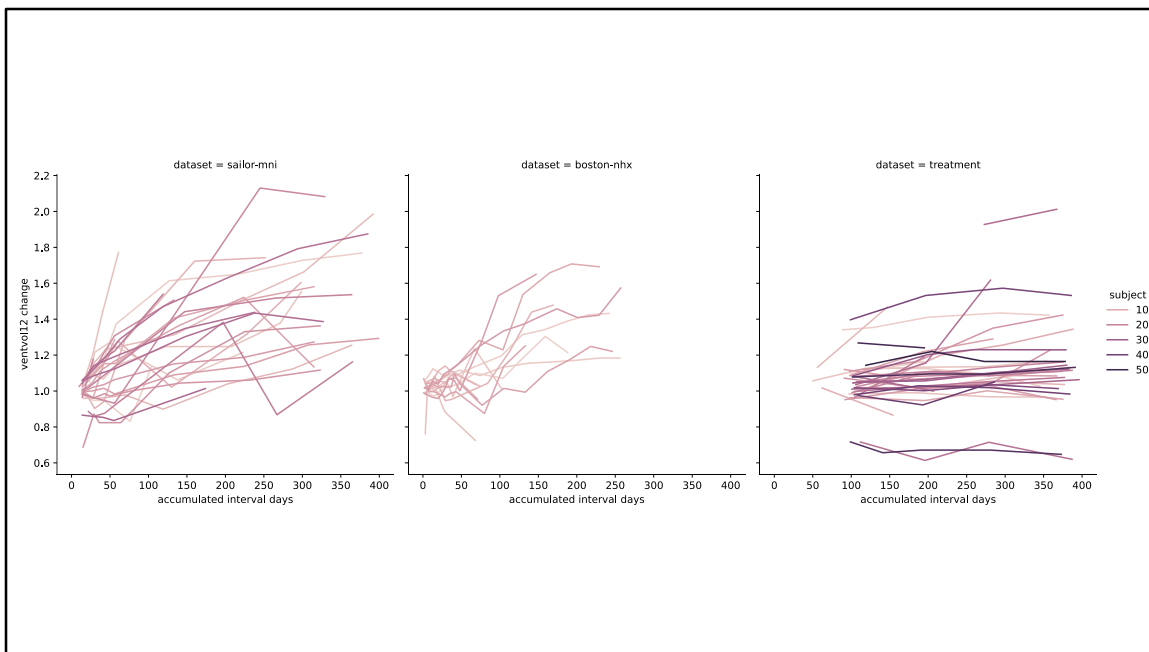


A lot longer timespan of patients in the Oslo (sailor) dataset than in the Boston dataset

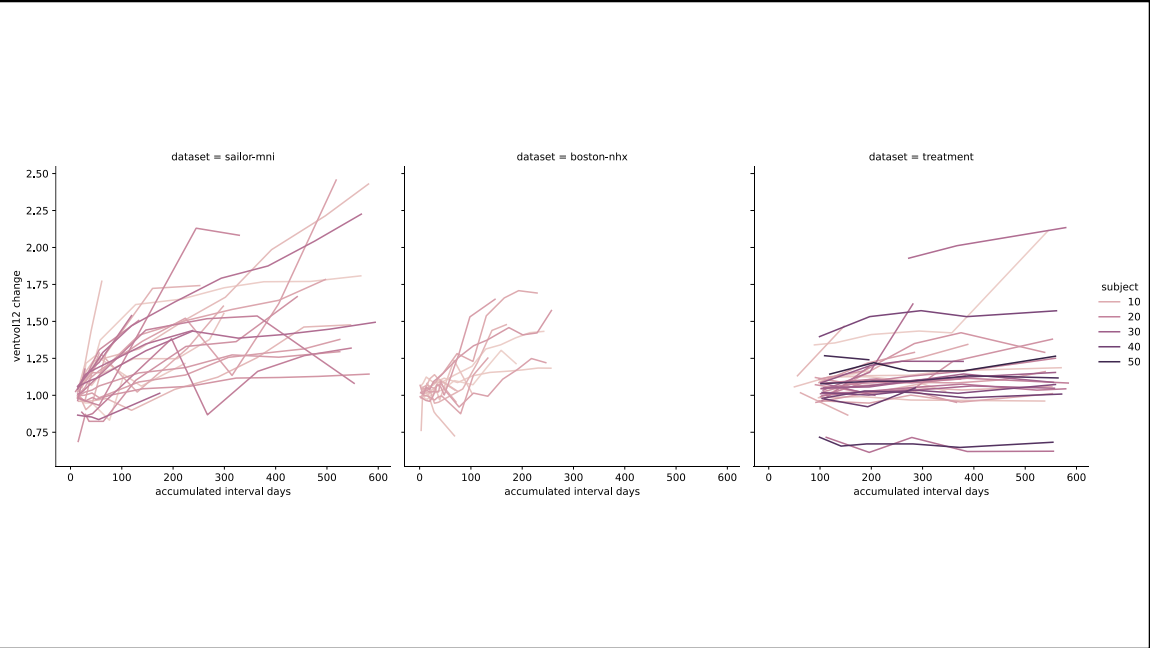


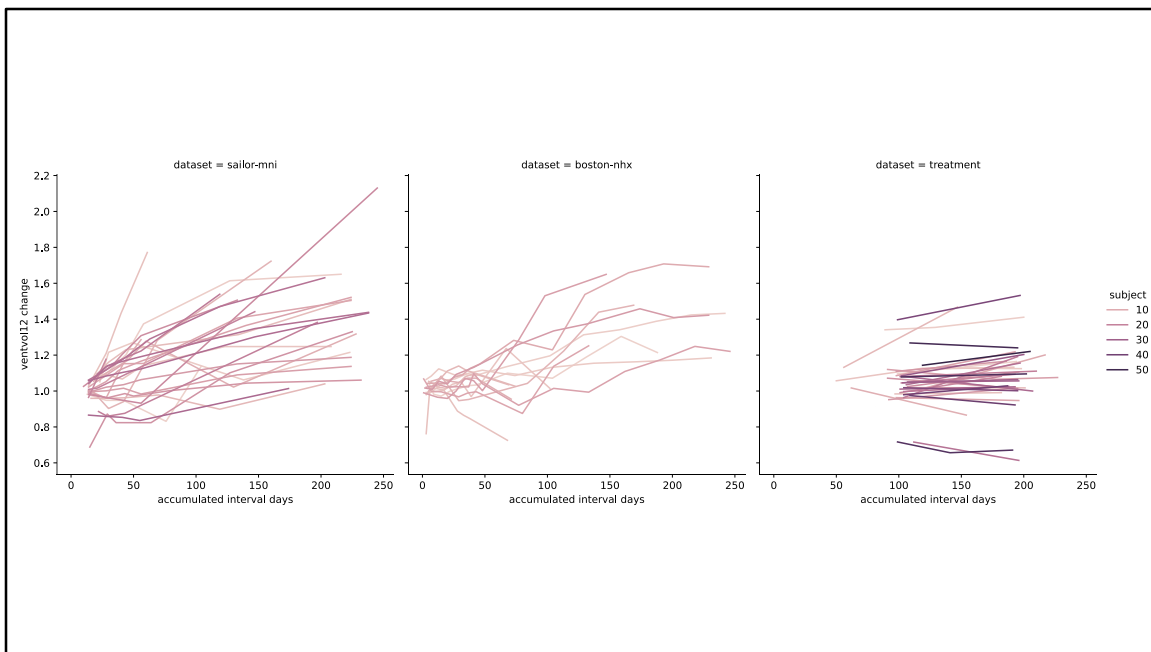
This is clearly another pathology, and the treatment is not the same for this type of cancer, than for glioblastoma

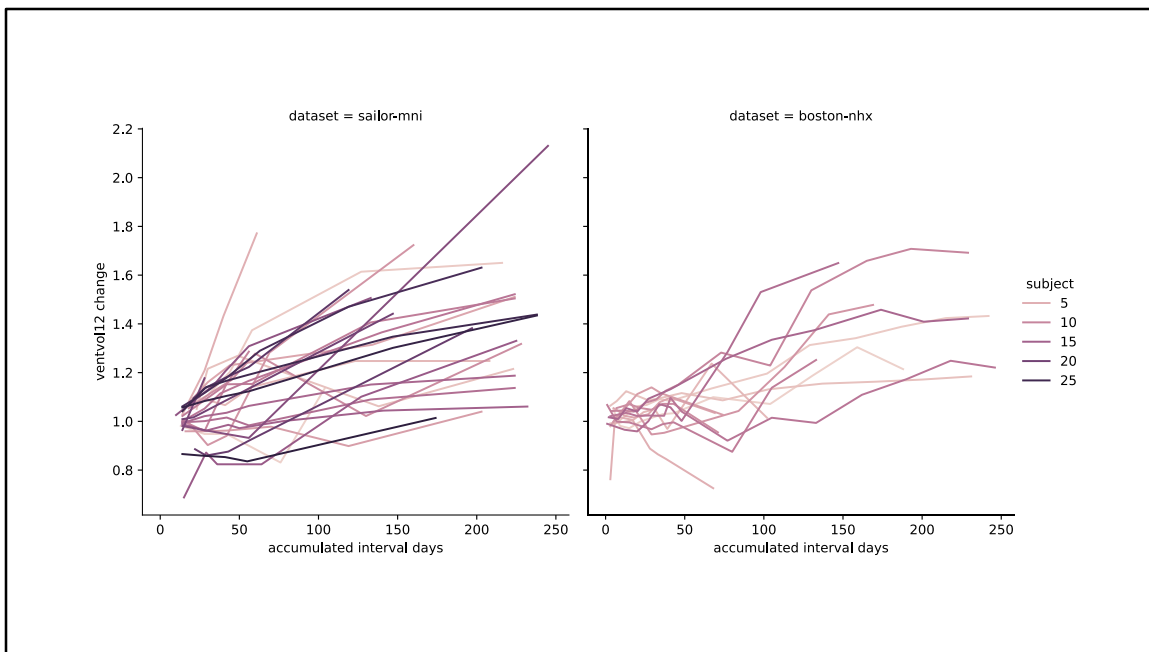




Brain metastases dont give that much ventricle dilation compared to glioblastoma

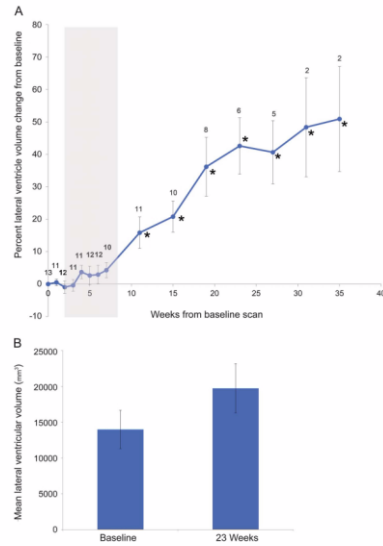






250 days = ~35 weeks

Figure 4 Longitudinal progression of anterior lateral ventricular volume



(A) Lateral ventricular volumes across the treatment period. Data points represent the sample mean of percent volume change from baseline at each time point. Error bars represent the SEM. Sample sizes are indicated at each time point. Gray shading indicates combined chemotherapy and radiation. One participant was excluded because of extensive ventricular tumor involvement. *Time points at which volumetric changes are statistically significant ($p < 0.05$). (B) Lateral ventricular volumes at baseline and 23 weeks in participants remaining on the protocol to this point ($n = 6$). Bars represent sample means at baseline and 23 weeks; error bars represent the SEM.

2015 reference

250 days = ~35 weeks

40 weeks=280 days

Eksperiment 5, observasjoner

- Data fra Boston tilsier at behandlingen er kortere, men med tettere oppfølging i starten under kjemostråle

Eksperiment 5, konklusjon

- Glioblastoma: Data suggests similar ventricle volume increase (compared to baseline ventricle volume) to [Evidence of ventricle expansion as part of brain atrophy \(shrinkage\) as an effect of radiation therapy on glioblastoma \(2015\)](#)

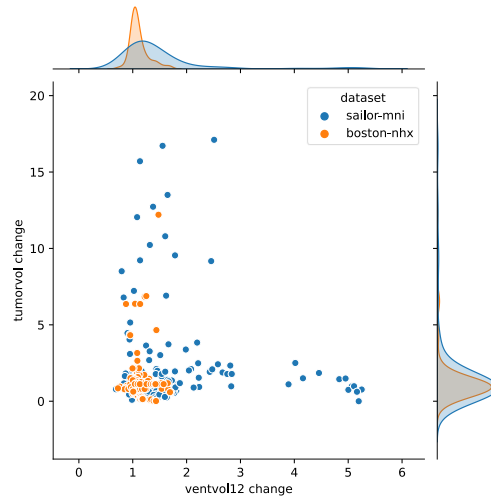
Experiment 6

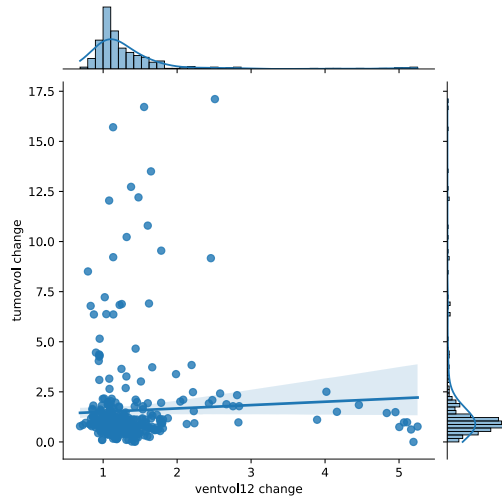
- Goal: Analyze correlation between ventricle and tumor volume change from baseline
- Two datasets, 41 subjects, 387 volume change measurements (intervals)

Experiment 6, method

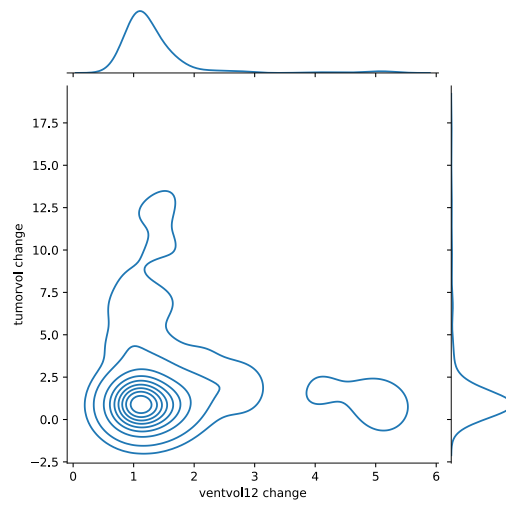
- Computation of total tumor volume [mm³] from segmentation (necrosis, contrast enhanced and edema (sailor) or contrast enhanced (boston)): 'compute-tumor-vols.sh'
- Computation of ventricle volume [mm³] from ventricle masks: compute-vent-vols.sh
- Collection of interval measures relative to baseline: print-from-baseline-interval-measures.sh
- Joint plot with linear regression and marginal distributions
- Pearson correlation

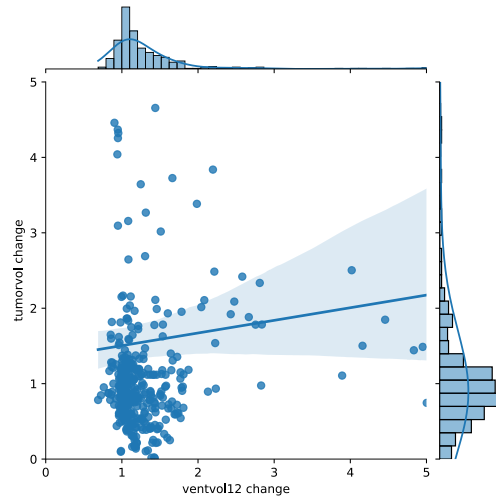
Pearson correlation coefficient: 'bivariate correlation'

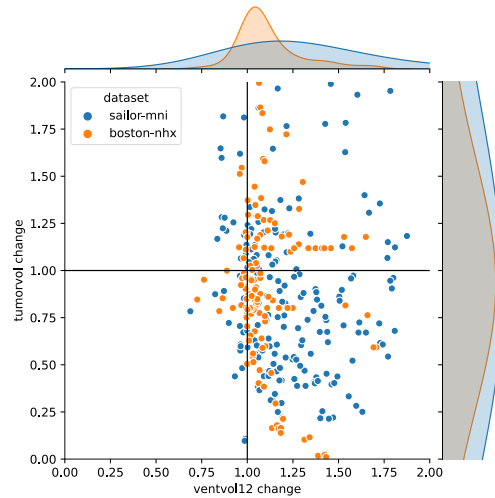




Many outliers



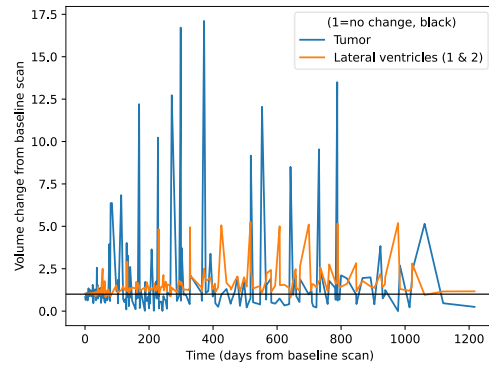


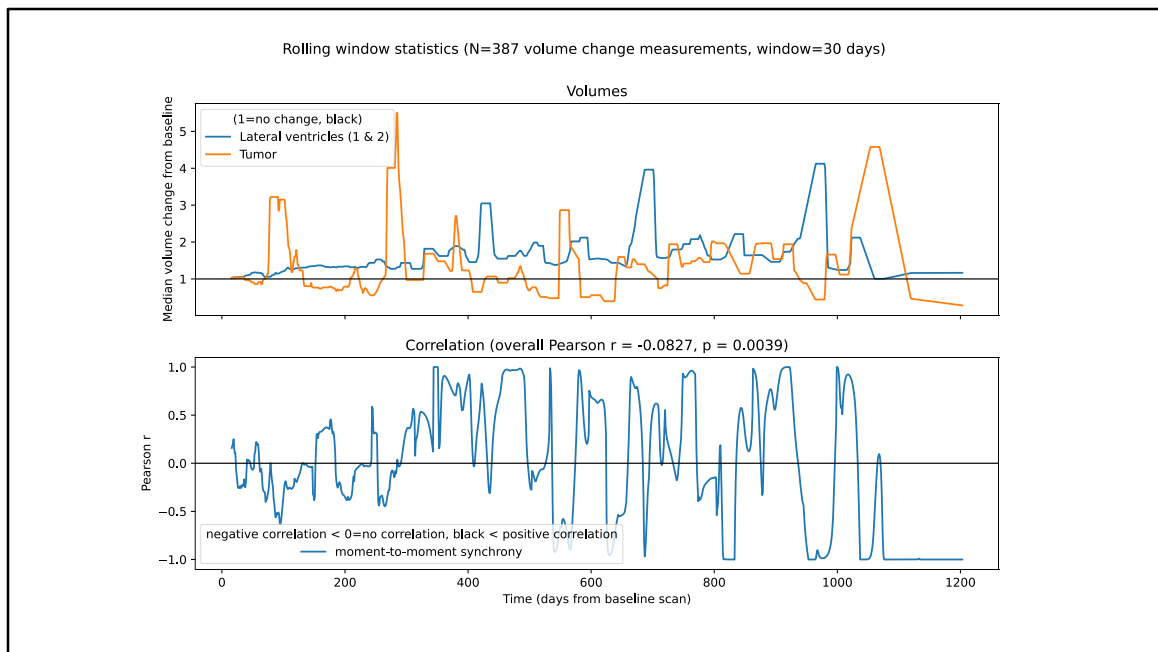


What is a dot:

- For a single patient
- $\text{ventvol12 change} = \frac{\text{volume(a later time point for this patient)}}{\text{volume(baseline time point for this patient)}}$
- $\text{Tumor change} = \frac{\text{volume(a later time point for this patient)}}{\text{volume(baseline time point for this patient)}}$

Opposed to tumor volume change which is both shrinkage and expansion, ventricle change is almost always expansion





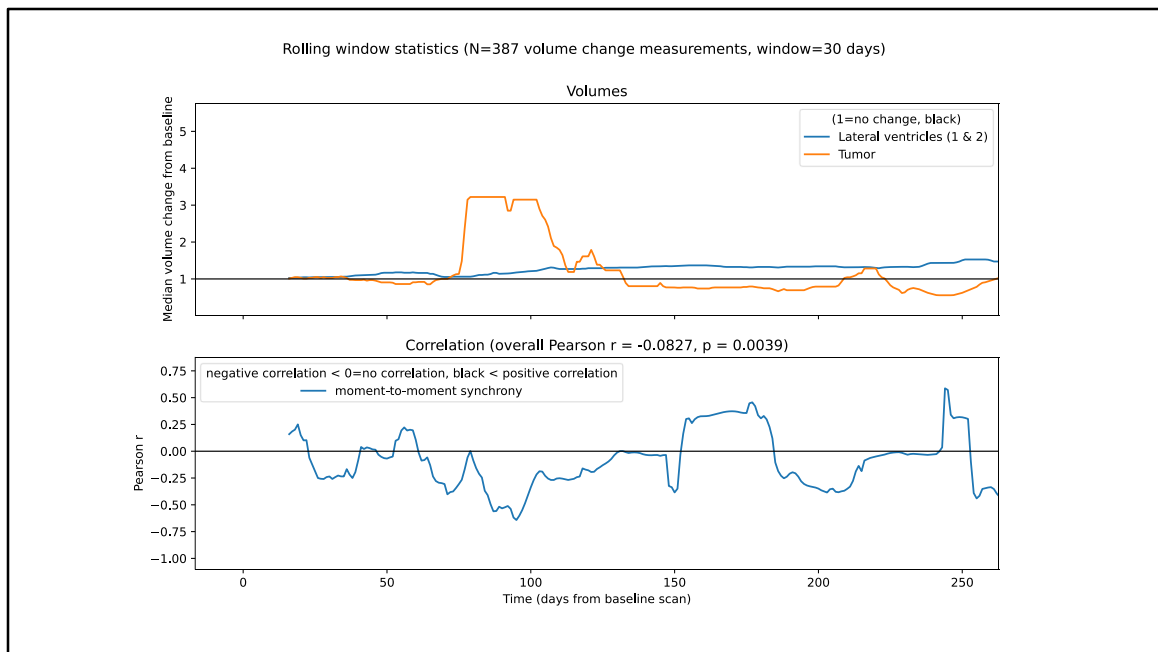
Notice that the colors are swapped for tumor and ventricle compared to the previous slide

Overall pearson returns negative correlation

387 volume change measurements

Median of medians

Then linear interpolation



Sudden increase of median of median tumor volume around 75 days post baseline scan (~10 weeks)

Analysis start at 15 days post baseline because of a rolling window of 30 days (stride of 1 day)

No window function used (just computing median values with equal weighting)

Experiment 6, conclusion

- Overall Pearson: Small, but significant negative correlation between ventricle and tumor volume

Diskusjon

1. Data for både Oslo (SAILOR) og Boston viser klart at ventrikkelvolum øker underveis i behandlingen, i motsetning til tumorvolum som kan både minke og øke.
2. Det er en vesentlig forskjell i ventrikkeløkning mellom glioblastompasienter og metastasepasienter. En forskjell i behandling er om kjemoterapi blir brukt eller ikke. Ellers viser litteratursøk at atrofi, som kan medfølge dilasjon av ventrikler, er en kjent respons på stråleterapi. Begge pasientgrupper mottar strålebehandling, forstår jeg rett.
3. Korrelasjonsanalyse viser en signifikant, men svak negativ korrelasjon mellom endring i ventrikkelvolum og endring i tumorvolum.
4. Alder, overlevelse, bruk av steroider (ja/nei) og tidlig (CRT) vs. sent (kjemo) er mulige oppdelinger i analysen for å markere klinisk relevans.

Thank you!