Automatic extraction and classification of tumor image features from multimodal MRI for prognosis predictive modeling in GBM

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Context

Quantitative imaging features useful for:

- stratifying patients / prognosis (prognostic value)
- selecting therapeutic options / identifying patients at risk (response to therapy / disease progression)

Gliobastoma multiforme (GBM):

- most malignant and commonly diagnosed primary brain tumor [1]
- prognosis is poor, with median survival of 15 months
- currently there is no effective long-term treatment
- therapeutic options: surgical resection, chemotherapy, radiotherapy
- clinical decisions depend on prognosis

Objective: Developing a prognostic model based on image-derived features

[1] Matthias Preusser et el., “Current concepts and management of glioblastoma,” Annals of neurology, 2011.

State-of-the-art

Quantitative metrics currently used by clinicians:

- tumor volume [1]
- major axis length [1]
- ”VASARI”-community derived visual observations familiar to neuroradiologists [2]
- standardized uptake values (SUV) (PET imaging with radio tracer 18F-FLT, L-[methyl-11C]-methionine...)[3]
- apparent diffusion coefficient (ADC) (Diffusion Weighted Imaging)[4]

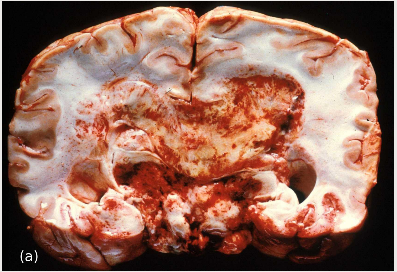
Limitations:

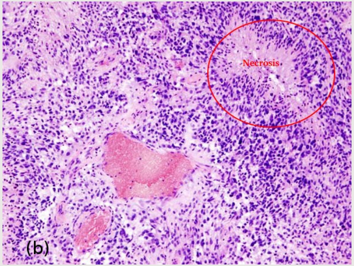
- limited prognostic power
- do not incorporate the heterogeneity characteristics imaged through multimodal MRI

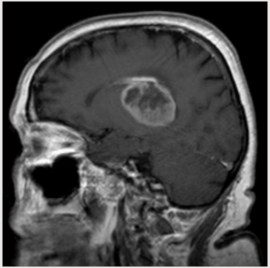
[1] Maciej A Mazurowski et al., “Computer-extracted mr imaging features are associated with survival in glioblastoma patients,” Journal of neuro-oncology, 2014.
[2] David A Gutman et al., “Mr imaging predictors of molecular profile and survival: multi-institutional study of the tcga glioblastoma data set,” Radiology, 2013.
[3] La Fougère et al. ”Molecular imaging of gliomas with PET: opportunities and limitations.” Neuro-oncology,2011).
[4] Waldman, Adam D., et al. ”Quantitative imaging biomarkers in neuro-oncology.” Nature Reviews Clinical Oncology, 2009

Glioblastoma Multiforme

- GBM are highly heterogeneous tumors consisting of:
  - active tumor showing angiogenesis and blood-brain barrier rupture
  - necrosis
  - surrounded by peritumoral edema
  - intratumoral haemorrhage



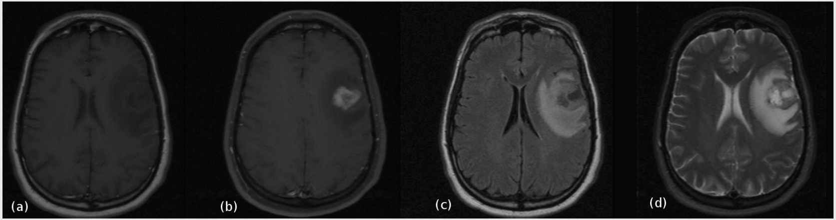




(a) Cross-sectional photographs, (b) histopathology image, and (c) MRI

Patients data

- 40 patients datasets [1]
- Multimodal MRI includes:
  - T1 pre and post-contrast
  - T2
  - FLAIR



(a) T1 pre-contrast, (b) T1 post-contrast, (c) FLAIR and (d) T2 weighted

[1] www.cancerimagingarchive.net

Patients data

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- Multimodal MRI includes:
  - T1 pre and post-contrast
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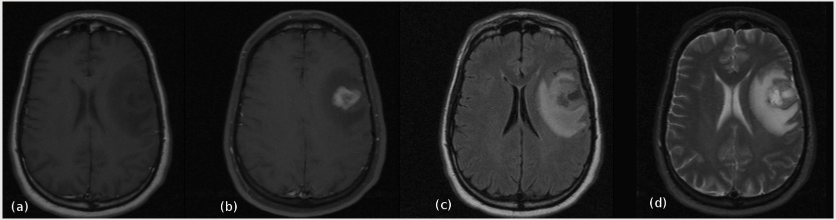


(a) T1 pre-contrast, (b) T1 post-contrast, (c) FLAIR and (d) T2 weighted

- Binary classification problem:
  - median survival is 15 months [2], aim is to classify patients into either worse or better prognosis (survival shorter or longer than median)

[1] www.cancerimagingarchive.net

[2] Dietmar Krex et al.,"Long-term survival with glioblastoma multiforme," Brain, 2007.

Quantifying heterogeneity characteristics in multimodal MRI:

- global scale (first order statistics)
- local scale (second order statistics) [1]
- regional scale (higher order statistics) [2][3]

Multivariate analysis using pattern recognition and machine learning:

- support vector machine (SVM algorithm) [4]
  - exploiting mutual information among features
  - selecting optimal number and combination of features

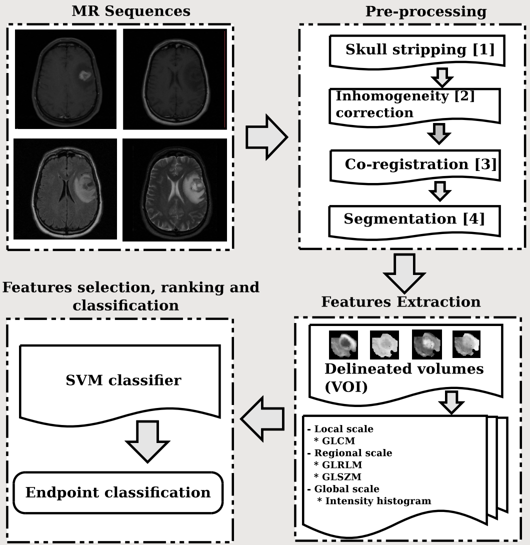
[1] Robert M Haralick et al., "Textural features for image classification," IEEE Transactions on Systems, Man and Cybernetics, 1973.

[2] Horng-Hai Loh et al.,"The analysis of natural textures using run length features," IEEE Transactions on Industrial Electronics, 1988.

[3] Guillaume Thibault et al., "Texture indexes and grey level size zone matrix application to cell nuclei classification," Pattern Recognition and Information Processing, 2009.

[4] Burges, Christopher JC., "A tutorial on support vector machines for pattern recognition." Data mining and knowledge discovery, 1998.

Framework



[1] Stefan Bauer et al., ”A Skull-Stripping Filter for ITK”, 2012.

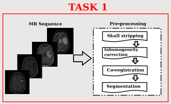
[2] Tustison, Nicholas J., et al. ”N4ITK: improved N3 bias correction.” IEEE Transactions on Medical Imaging, 2010).

[3] Ibanez L et al.,” The ITK software guide,” 2nd ed. Kitware.

[4] Stefan Bauer et al., Nolte L-P, Reyes M (2011) Fully automatic segmentation of brain tumor images using support vector machine classification in combination with hierarchical conditional random field regularization. MICCAI, 2011.

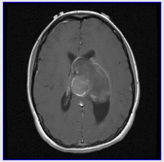
Proposed workflow for Multimodal MRI processing and analysis to extract, rank and combine features for the classification problem: here survival prediction

Task 1: Pre-processing

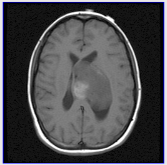


- automatic skull-stripping based on atlas image[1]:
  - to get rid of the skull and consider brain tissue only for further analysis

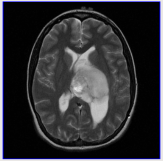
Orginal MRI of the patients



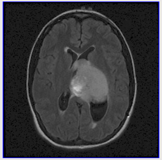
T1 post-contrast



T1 pre-contrast

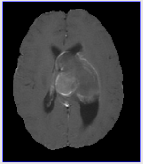


T2

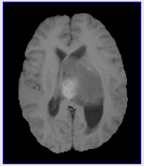


FLAIR

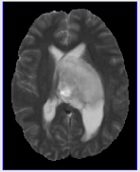
Skull Stripped MRI of the patients



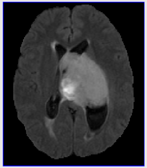
T1 post-contrast



T1 pre-contrast



T2



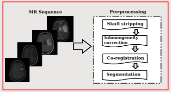
FLAIR

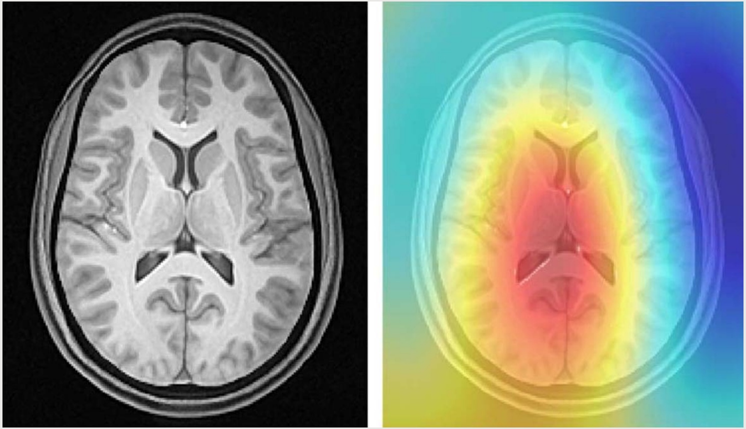
[1] Stefan Bauer et al., "A Skull-Stripping Filter for ITK", 2012.

Task 1: Pre-processing

- Inhomogeneity correction[1]:
  - to correct intensities nonuniformity in similar tissue types

TASK 1

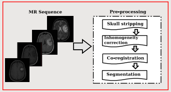




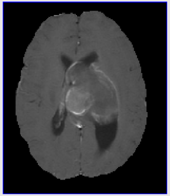
[1] Tustison, Nicholas J., et al. ”N4ITK: improved N3 bias correction.” IEEE Transactions on Medical Imaging, 2010.

- Rigid Registration [1]:
  - mutual information similarity metric which can handle several modalities in order to align them all

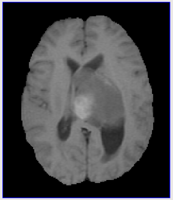
TASK 1



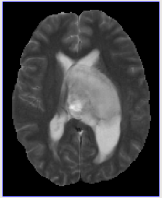
MRI of the patients



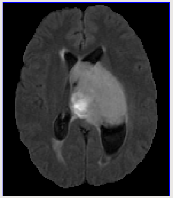
T1 post-contrast



T1 pre-contrast



T2



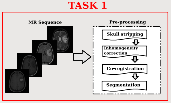
FLAIR

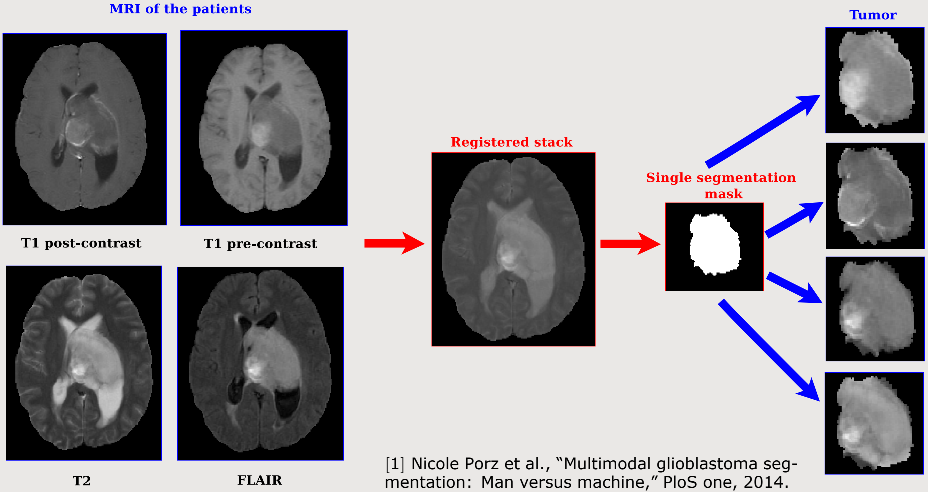
Registration

[1] J. Pluim et al."Mutual-information-based registration of medical images: a survey." IEEE Transactions on Medical Imaging,2003.

Task 1: Pre-processing

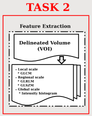
- Brain Tumor Image Analysis (BraTumIA) software [1]:
  - segmentation of a single tumor volume by exploiting all four MRI modalities



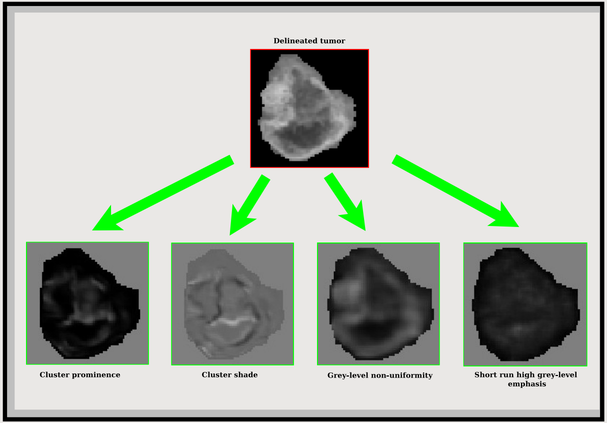


[1] Nicole Porz et al., "Multimodal glioblastoma segmentation: Man versus machine," PloS one, 2014.

Task 2: features extraction



- 3D Image-derived heterogeneity using textural features analysis:
  - global scale (Intensity histogram, no spatial correlation)
  - local scale (spatial correlation at the scale of a voxel and its neighbors)
  - regional scale (spatial correlation at the scale of groups of voxels)



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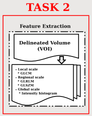

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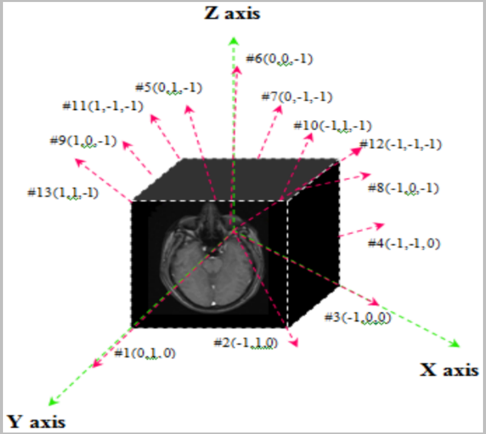
  - global scale (Intensity histogram, no spatial correlation)
  - local scale (spatial correlation at the scale of a voxel and its neighbors)
  - regional scale (spatial correlation a the scale of groups of voxels)
- accounting for all the 13 directions in 3D around a given voxel



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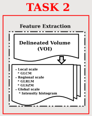
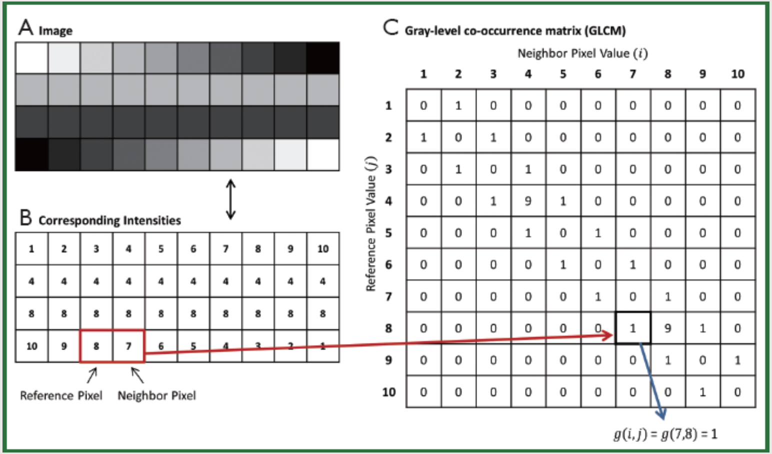


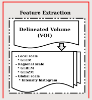
- Image-derived heterogeneity in local scale:
  - GLCM [1] (Grey-level co-occurrence matrix)



[1] Robert M Haralick et al.,"Textural features for image classification", IEEE Transactions on Systems, Man and Cybernetics, 1973.

Task 2: features extraction

TASK 2



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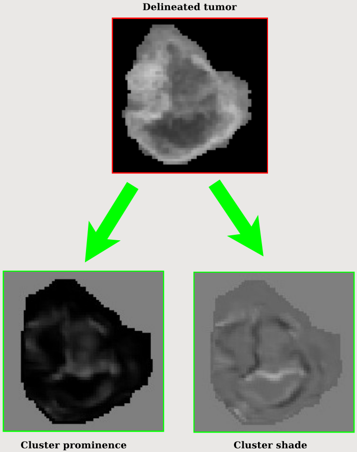
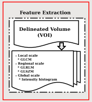


[1] Robert M Haralick et al.,"Textural features for image classification", IEEE Transactions on Systems, Man and Cybernetics, 1973.

Task 2: features extraction

TASK 2



- Image-derived heterogeneity in regional scale:
  - GLRLM (Grey-level run length matrix) [1]
  - GLSZM (Grey-level size zone matrix) [2]

Corresponding intensities

1	2	3	4
1	3	4	4
3	2	2	2
4	1	4	1

GLSZM

Level	*Size zone, s*		
g	1	2	3
1	2	1	0
2	1	0	1
3	0	0	1
4	2	0	1

GLRLM

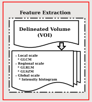
Gray Level	Run Length(j)			
	1	2	3	4
1	4	0	0	0
2	1	0	1	0
3	3	0	0	0
4	3	1	0	0

[1] Horng-Hai Loh et al.,"The analysis of natural textures using run length features, IEEE Transactions on Industrial Electronics 1988.

[2] Guillaume Thibault et al.,"Texture indexes and grey level size zone matrix application to cell nuclei classification", Pattern Recognition and Information Processing 2009.

Task 2: features extraction

TASK 2



- Image-derived heterogeneity in regional scale:
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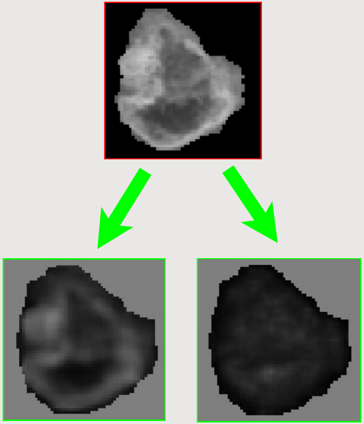
Delineated tumor



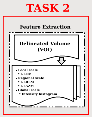
Grey-level non-uniformity

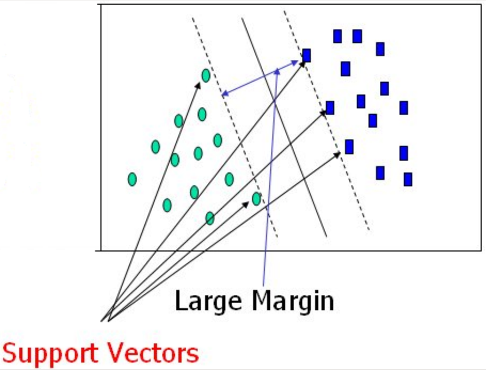
Short run high grey-level emphasis

[1] Horng-Hai Loh et al.,"The analysis of natural textures using run length features, IEEE Transactions on Industrial Electronics 1988.

[2] Guillaume Thibault et al.,"Texture indexes and grey level size zone matrix application to cell nuclei classification", Pattern Recognition and Information Processing 2009.

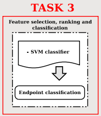
- Support Vector Machine (SVM)
  - maximum margin classifier
- SVM-RFE (Recursive Feature Elimination) [1]
  - rank the features based on weighted magnitude
- Kernel trick
  - helps classification by projecting features into a different space



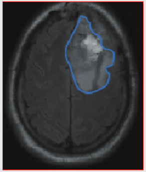


[1] Isabelle Guyon et al., "Gene selection for cancer classification using support vector machines," Machine learning, 2002.

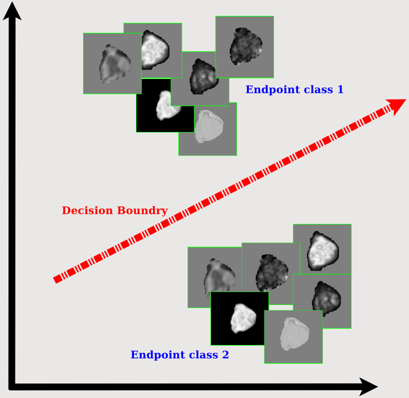
Task 3: classification



- Model building:
  - binary classification (LOS / SOS): SVM using linear kernel
  - features selections: SVM-RFE (Recursive Feature Elimination)[1] with nested k-fold cross-validation scheme
  - combining features from 1 or 2 modalities at most
- Model testing:
  - leave-one-out cross-validation
  - 40 patients



Endpoint classification ?

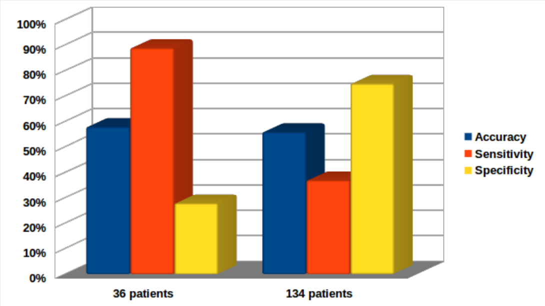


[1] Isabelle Guyon et al., “Gene selection for cancer classification using support vector machines,” Machine learning, 2002.

Preliminary results using contextual features

GBM patients contextual features:

- categorical features
  - therapy options: radiotherapy and/or chemotherapy
  - gender: male or female
- continuous features
  - age
  - Karnofsky's score

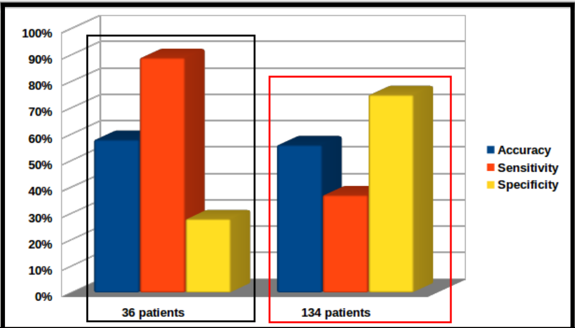


Preliminary results using contextual features

GBM patients contextual features:

- categorical features
  - therapy options: radiotherapy and/or chemotherapy
  - gender: male or female
- continuous features
  - age
  - Karnofsky's score

36 patients
Accuracy 58%
Sensitivity 89%
Specificity 28%

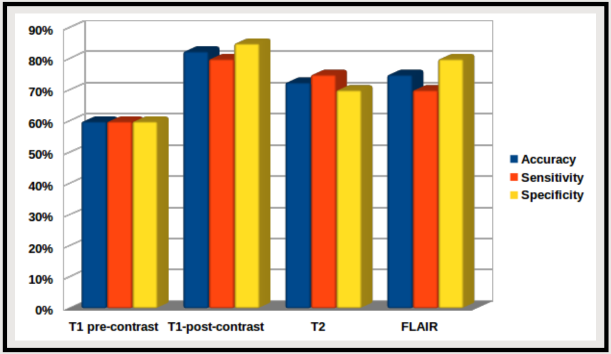


134 patients
Accuracy 56%
Sensitivity 37%
Specificity 75%

Preliminary results using only 1 modality

Retained features from T1 post-contrast:

- 4 regional features
- 1 local feature

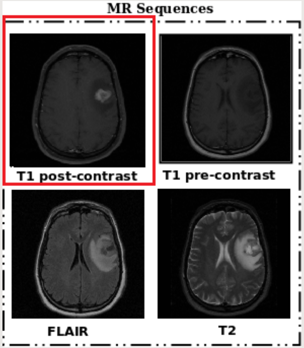


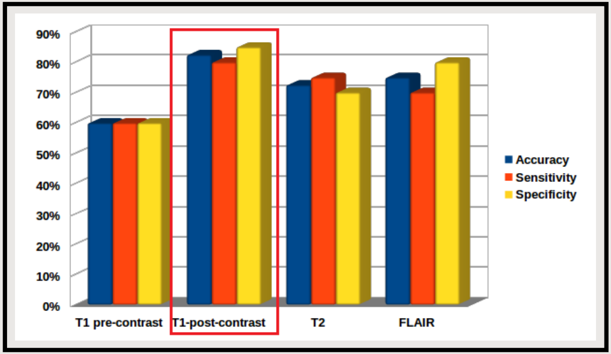
T1-C
Accuracy 82.5%
Sensitivity 80%
Specificity 85%

Preliminary results using only 1 modality

Retained features from T1 post-contrast:

- 4 regional features
- 1 local feature



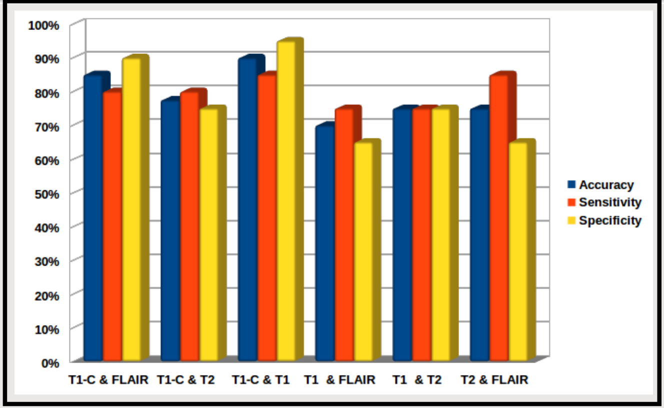


T1-C
Accuracy 82.5%
Sensitivity 80%
Specificity 85%

Preliminary results using combination of 2 modalities

Retained features:

- 2 global features (T1 pre-contrast & T1 post-contrast)
- 3 regional features (1 ∈ T1 pre-contrast & 2 ∈ T1 post-contrast)
- 1 local feature (T1 post-contrast)

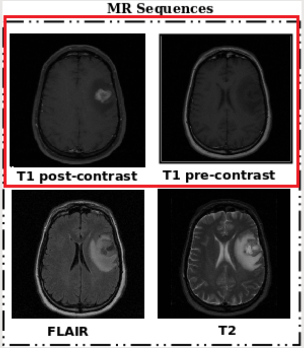


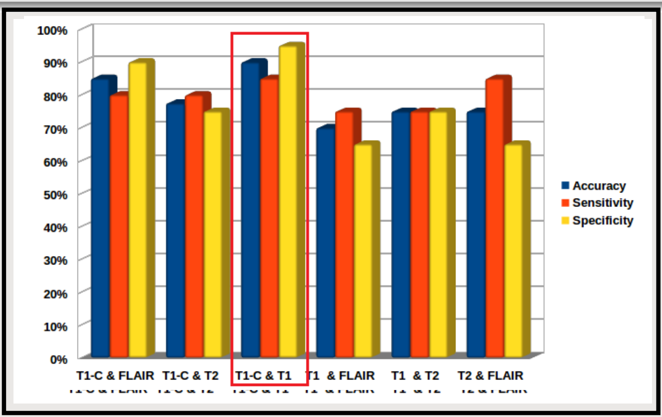
T1-C & T1
Accuracy 90%
Sensitivity 85%
Specificity 95%

Preliminary results using combination of 2 modalities

Retained features:

- 2 global features (T1 pre-contrast & T1 post-contrast)
- 3 regional features (1 $\in$ T1 pre-contrast & 2 $\in$ T1 post-contrast)
- 1 local feature (T1 post-contrast)





T1-C & T1
Accuracy 90%
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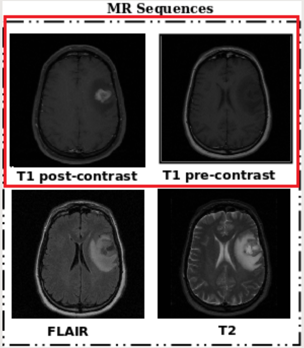
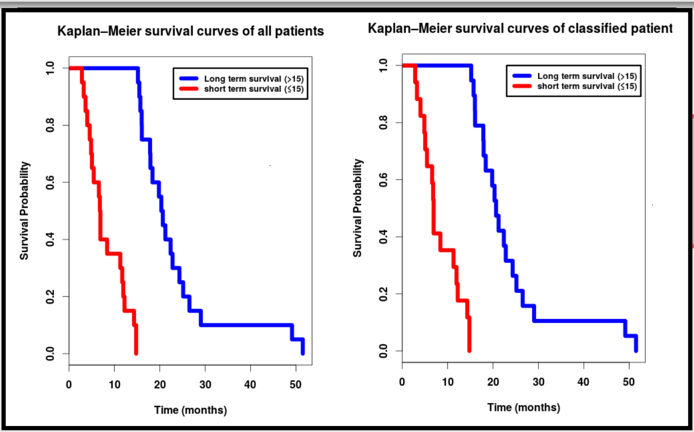
Preliminary results using combination of 2 modalities

Retained features:

- 2 global features (T1 pre-contrast & T1 post-contrast)
- 3 regional features (1 $\in$ T1 pre-contrast & 2 $\in$ T1 post-contrast)
- 1 local feature (T1 post-contrast)





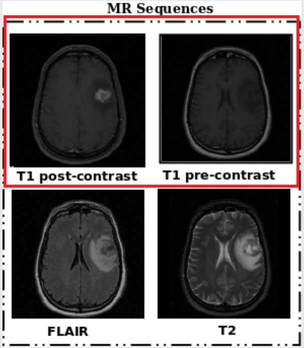
T1-C & T1
Accuracy 90%
Sensitivity 85%
Specificity 95%

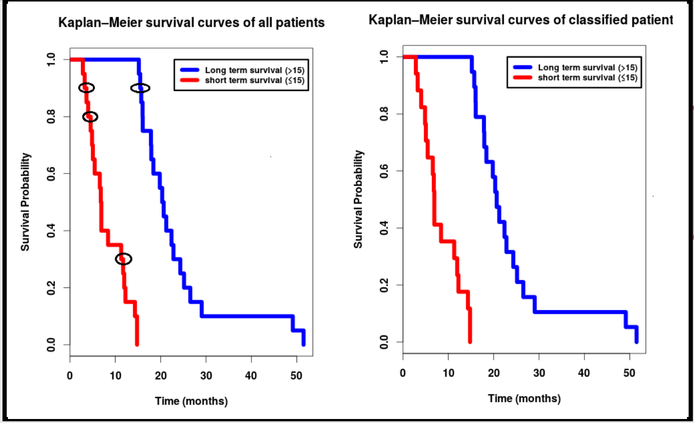
b com

Preliminary results using combination of 2 modalities

Retained features:

- 2 global features (T1 pre-contrast & T1 post-contrast)
- 3 regional features (1 $\in$ T1 pre-contrast & 2 $\in$ T1 post-contrast)
- 1 local feature (T1 post-contrast)





T1-C & T1
Accuracy 90%
Sensitivity 85%
Specificity 95%

b com

Conclusions and perspective

Conclusions:

- a framework for multimodal imaging-based prognostic model building
- framework developed integrating
  - image-derived features quantifying tumor heterogeneity
  - machine learning technique using SVM for multivariate classification
- characterization of GBM based on multimodal MRI (4 different modalities)
- combining T1-pre and T1-post contrast MRI in 40 patients resulted in an accuracy of 90%, sensitivity of 85% and specificity of 95%

Perspective:

- Extend the analysis to the entire dataset (> 100 patients)
- additional / complementary value of other features: spectral analysis, geometrical features...
- considering survival as a continuous variable (instead of binary classification)
- building and comparing models with various other machine learning based classifier techniques like random forests and artificial neural network

Merci / Thank you