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► To cite this version:

Sophie Wantz Mézières, Meriem Ben Abdallah, Marie Blonski, Jean-Marie Moureaux, Yann Gaudeau, et al.. Towards a decision-aid tool in the case of chemotherapy treatment for low-grade glioma. 17th Annual Conference of the European Network for Business and Industrial Statistics, ENBIS'17, Sep 2017, Naples, Italy. hal-02055217

HAL Id: hal-02055217

<https://inria.hal.science/hal-02055217v1>

Submitted on 7 Mar 2019

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Towards a decision-aid tool in the case of chemotherapy treatment for low-grade glioma

Interdisciplinary project:

CRAN

Jean-Marie Moureaux

Yann Gaudeau

Meriem Ben Abdallah (PhD 12/2016)

new PhD from 10/17 ?

IECL - Inria-team BIGS

Sophie Mézières

C.H.R.U. Nancy

Luc Taillandier (neuro-oncologist)

Marie Blonski (hospital practitioner,
PhD)

11/09/17 ENBIS-2017 Napoli

Medical context: Diffuse Low-Grade Glioma

asymptomatic ↔

few symptoms ↔

functional prognosis ↔

bad vital prognosis ↔

Grade(ANOCEF)	
Low-Grade	I II
High-Grade	III IV

↔ slow growth: 4 mm/year ED

↔ quick growth : > 8 mm/year

- ▶ Cerebral tumor
- ▶ median age : 35 years, survival median : 15 years, (*Duffau & al 04, Cancer*)
- ▶ 750 new cases by year in France (*Blonski 11, thèse de médecine*)
- ▶ **diffuse** aspect (*ANOCEF 12*)
- ▶ slow evolution with 4 mm/year **spontaneous linear growth** of equivalent diameter (*Mandonnet 03, Ann Neurol*)
- ▶ no treatment ⇒ anaplastic transformation (evolution to high-grade) (*Bracard, Taillandier & al 06, Jour Radio*)

Therapeutic strategy

surgery
and/or chemotherapy TMZ, PCV
and/or radiotherapy



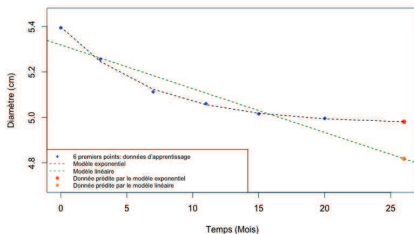
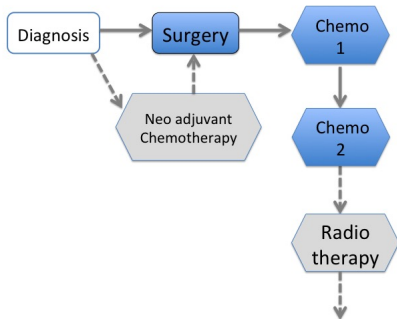
Aim: control of the tumor
evolution in order to extend
patient's lifetime
tumor diameter = good predictor
of the evolution of DLGGs
(*Mandonnet 08 Neurosurgical rw*)



longitudinal supervision of tumor's
diameter evolution



volume estimation from MRI
datasets: security ?



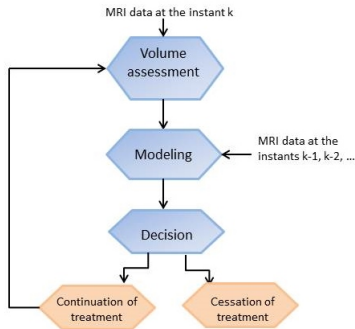
Our aim

Crucial questions posed by the oncologists to be answered:

- ▶ identifying subgroups of patients for chemotherapy
- ▶ determining the best time to initiate or stop chemotherapy
- ▶ evaluating the optimal time to perform surgery, or otherwise radiotherapy

personalised treatment \Rightarrow tool for the current medical practice

proposed procedure to determine
the best time to stop chemotherapy



First phase: tumor volume estimation

still in progress

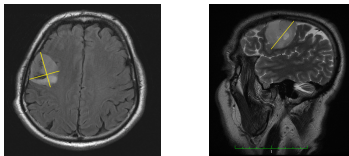
Reliability of the methods used to estimate the volume :

- ▶ 3-diameter method
- ▶ software-based reconstruction from manual segmentation
- ▶ semi-automatic method

Questions: reliability and reproducibility

Impact on the segmentation of the individual practitioner, and of the factors: years of experience, medical speciality ?
with respect to the others methods ?

3-diameter Method

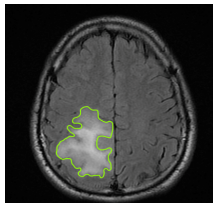


- ▶ 2 largest diameters in axial plane and the largest one in sagittal or coronal plane

- ▶ ellipsoidal approximation of the tumor volume:

$$V \simeq \frac{D_1 \times D_2 \times D_3}{2}$$

Software-based reconstruction from manual segmentation

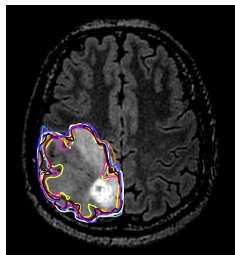


- ▶ digitized MRI, calculus of tumor volume from manual segmentations by Osirix software

Subjective test of reproducibility

Materials:

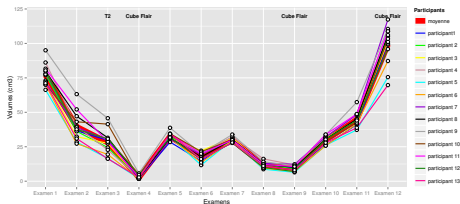
- ▶ one expert neuroradiologist selected 12 longitudinal MRI in the axial plane from 9 patients: 11 FLAIR-weighted (3 Cube-FLAIR), 1 T2-weighted.
- ▶ Osirix software
- ▶ Living Lab PROMETEE, TELECOM Nancy (standardized environment, ITU-BT.500-13 recommendations)
- ▶ panel of 13 participants
- ▶ test procedure: visual test, training dataset, delineation of the 12 exams (5 mn. break in half-time)



Results:

- ▶ variability between participants: one-way analysis of variance \Rightarrow **no significant impact on the tumor volume variable**
- ▶ variability by specialty and years of experience: Fisher's exact test on the standard deviation of the standard volume \Rightarrow **no significant impact on the tumor volume variable**
- ▶ Objective metrics: **Values of COV, AI, pixellic IV confirm the statistical results**

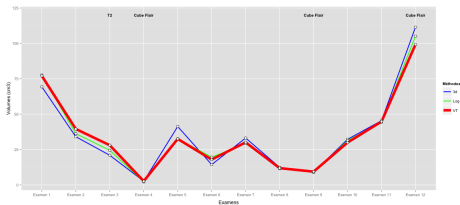
$$COV_j = \frac{\sigma_j}{\bar{X}_j}; AI_{(i,i'),j} = 1 - \frac{2 |x_{i,j} - x_{i',j}|}{x_{i,j} + x_{i',j}}; IV = 1 - \frac{A_{M_i} \cap A_{M'_i}}{A_{M_i} \cup A_{M'_i}}$$



Comparison with the 3-diameter method

Materials:

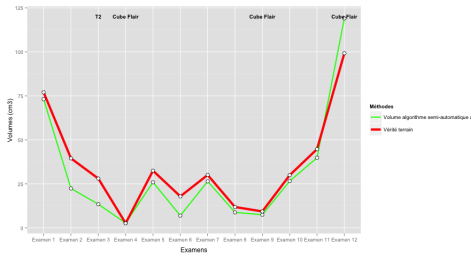
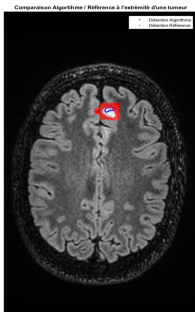
- ▶ preceding 12 exams in the axial plane + sagittal(11) or coronal(1) plane associated
- ▶ 1 participant from the test, close to the average of all the segmented tumor volumes (ground truth)
- ▶ Wilcoxon signed-rank test on all tumor volumes : with a significance level of 5 %, **we do not reject the equality hypothesis** between 3-diameter and manual segmentation methods



	Advantages	Disadvantages
3D	quick, easy for pre-surgery tumor	overestimate the volume, difficult in post-treatment
Osirix	reproducible accurate, easy	time-consuming

First works on semi-automatic segmentation

- ▶ Partnership with LIO Laboratory (C.H.R.U. Montréal, Pr J. De Guise, post-doc MBA)
- ▶ semi-automatic segmentation algorithm from Zhou & al (*EMBC 16*)
- ▶ Procedure: initialization by manual segmentation on 6 MRI in order to generate a 3D mesh, splitting of the mesh in axial slices then 2D delineation in each interest slide, Level-set algorithm applied on the 2D delineations
- ▶ MRI from test, ground truth = mean of the segmented volumes
- ▶ Computation time: 15-185 s



Results:

- ▶ Wilcoxon signed-rank test **rejects equality hypothesis** of the two methods
- ▶ tendency to under-segmentation
- ▶ good result for Cube-Flair 4 and 9
- ▶ segmentation algorithm applied to knees, considered improvements on this application domain

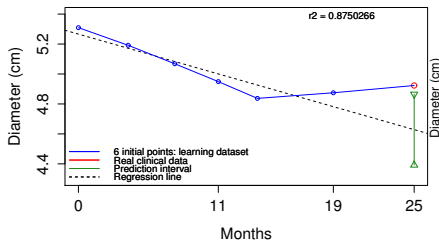
	Advantages	Disadvantages	Recommendations
3D	quick, easy for pre-surgery tumor	overestimate the volume, difficult in post-treatment	no digitised MRI, pre-surgery
Osirix	reproducible accurate, easy	time-consuming	all MRI except Cube-Flair
S-AUTO S	quick, good results on Cube-Flair	post-treatment under-segmentation	Cube-Flair

- ▶ **comparison** between methods to estimate the tumor volume
- ▶ **medical recommendations** to assure a more secure follow-up of the tumor evolution
- ▶ Trials with ITK SNAP: method strongly dependant on initialisation parameters (based on a priori good knowledge of the tumor: localization, shape)

Second phase: modelling of DLGG under chemotherapy

- ▶ tumor diameter: good predictor of the evolution of DLGGs (*Mandonnet 03, Ann Neurol*)
- ▶ state-of-the-art models: microscopic (*Ribba & al 2012, Rojas & al 2016*) or macroscopic (*Swanson & al 2000, Mandonnet & al 2003*) approach
- ▶ Our approach: **data-driven, very simple to implement**
- ▶ Database of 55 patients from both Nancy and Montpellier, France University Hospitals (CHRU)
- ▶ inclusion criteria: established histologic diagnosis of DLGG, first-line TMZ chemotherapy, assessment of the tumor volume with Osirix and manual segmentation method
- ▶ 2 models based on classical regression technics, with AICc criteria for model selection
- ▶ 38 following a **linear model**, 4 an **exponential model**, 13 no identifiable model (hierarchical behaviour)

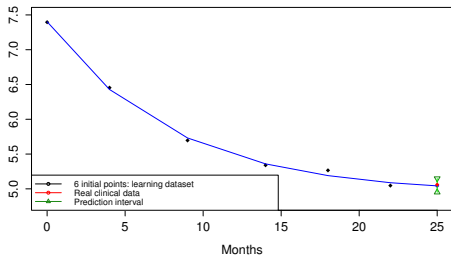
2 examples



linear model

$$D = b_0 + b_1 T + \varepsilon$$

Warning message: alarming regrowth of the tumor, the patient is not reponding any more to treatment



exponential model

$$D = a_0 - a_1 e^{-a_2 T} + \varepsilon$$

Message: expected decrease of the tumor, improved response to treatment

- ▶ encouraging but **multifactorial** problem
- ▶ IDH mutation, 1p19q codeletion are now considered as prognostic and/or predictive factors (*Louis & al 2016, 2016 OMS classification*)
- ▶ identifiable biological, anatomopathological factors ?
- ▶ in the database of 55: only 19 with known mutation and codeletion statuses



Necessity of a bigger database

- ▶ more patients, more molecular's factors, more MRIs
- ▶ difficulty in data collection

Conclusion and Future work

- ▶ First two simple models that operates on 42 patients, encouraging, need to be enhanced
- ▶ **Perspective 1:** Bigger database
 - 30 variables selected by neuro-oncologists: 10 patient variables, 13 treatment variables, 7 tumor variables
 - partnership with Montpellier, NENO base
 - variable selection, unsupervised and/or supervised classification...
- ▶ **Perspective 2:** complete phase 1 with semi-automatic method (future, partnership with Montréal LIO) ; second subjective test to assess intra-participant variability
- ▶ **Perspective 3:** practical tool with additionnal image processing features

References

Meriem Ben Abdallah, Marie Blonski, Sophie Wantz-Mézières, Yann Gaudeau, Luc Taillandier et Jean-Marie Moureaux

Predictive models for diffuse low-grade glioma patients under chemotherapy

Statistical evaluation of manual segmentation of a diffuse low-grade glioma MRI dataset

38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBC-16, Aug 2016, Orlando, Florida, United States

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