

Modélisation et étude histologique de gliomes diffus de bas grade

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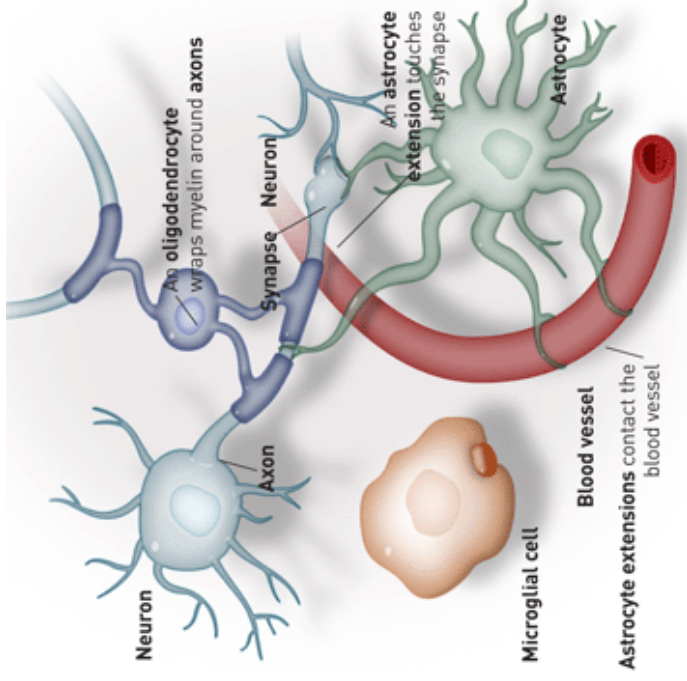
Direction : M. Badoual



Le système nerveux central

Les principaux types cellulaires du SNC sont :

- les neurones,
- les cellules gliales :
 - ▶ les astrocytes,
 - ▶ les oligodendrocytes,
 - ▶ les épendymocytes,
 - ▶ la microglie



astrocyte → astrocytome

oligodendrocyte → oligodendroglome

cancer
du sein

cancer
du
poumon

gliomes : 2%

cancer du sein

23 décès

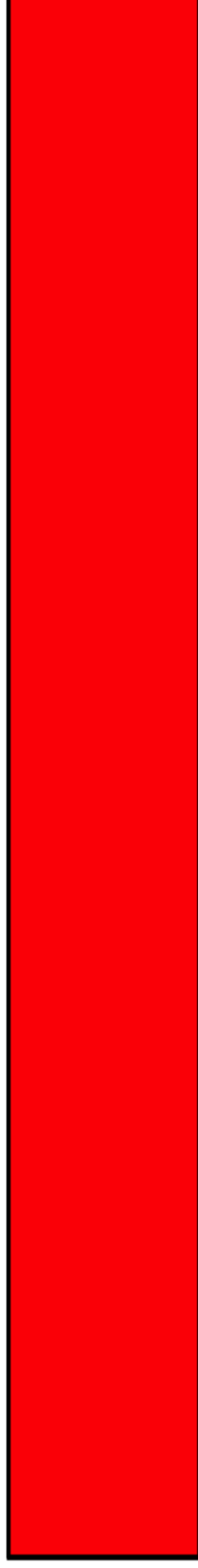
100 patients



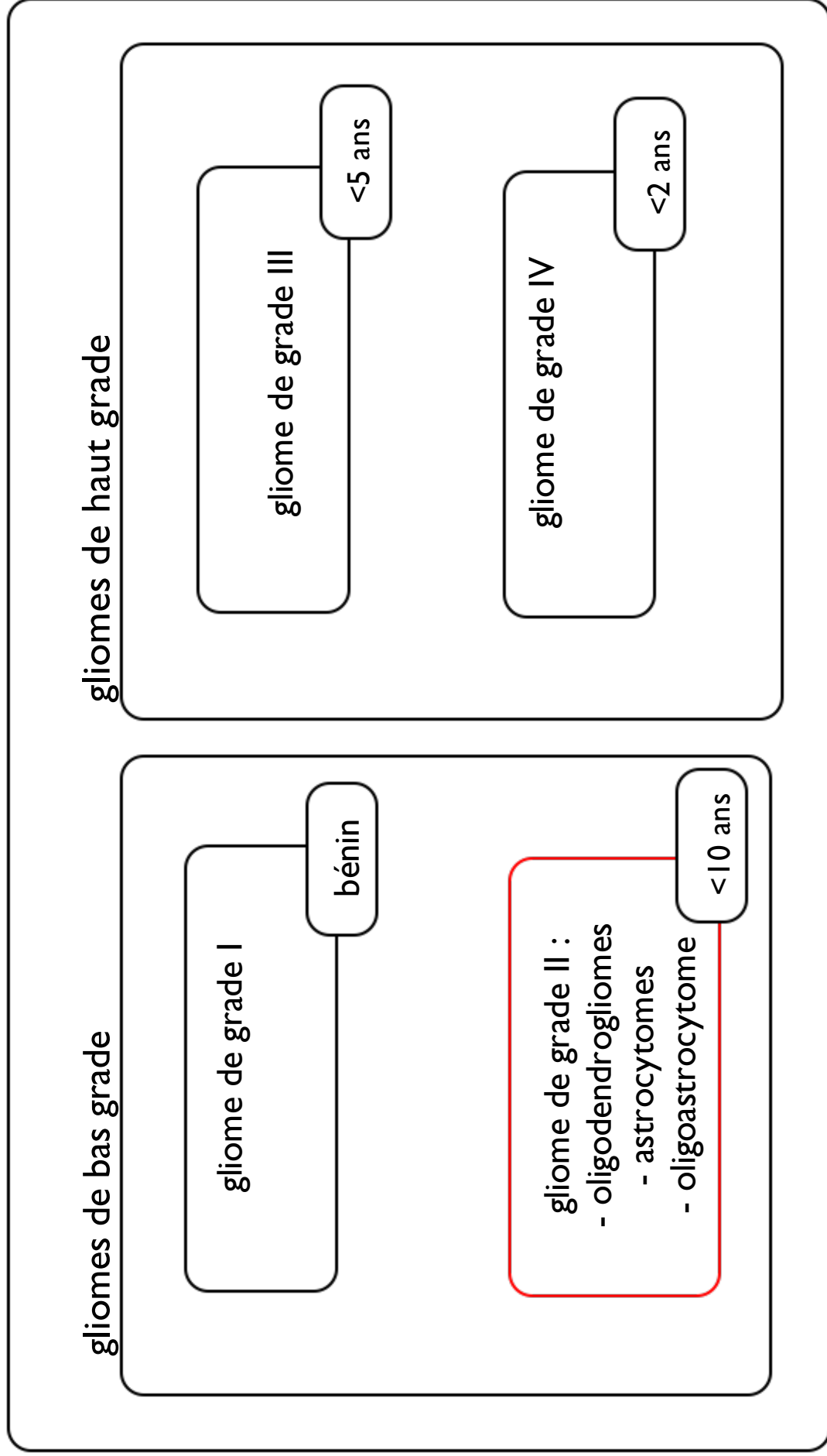
gliome

100 décès

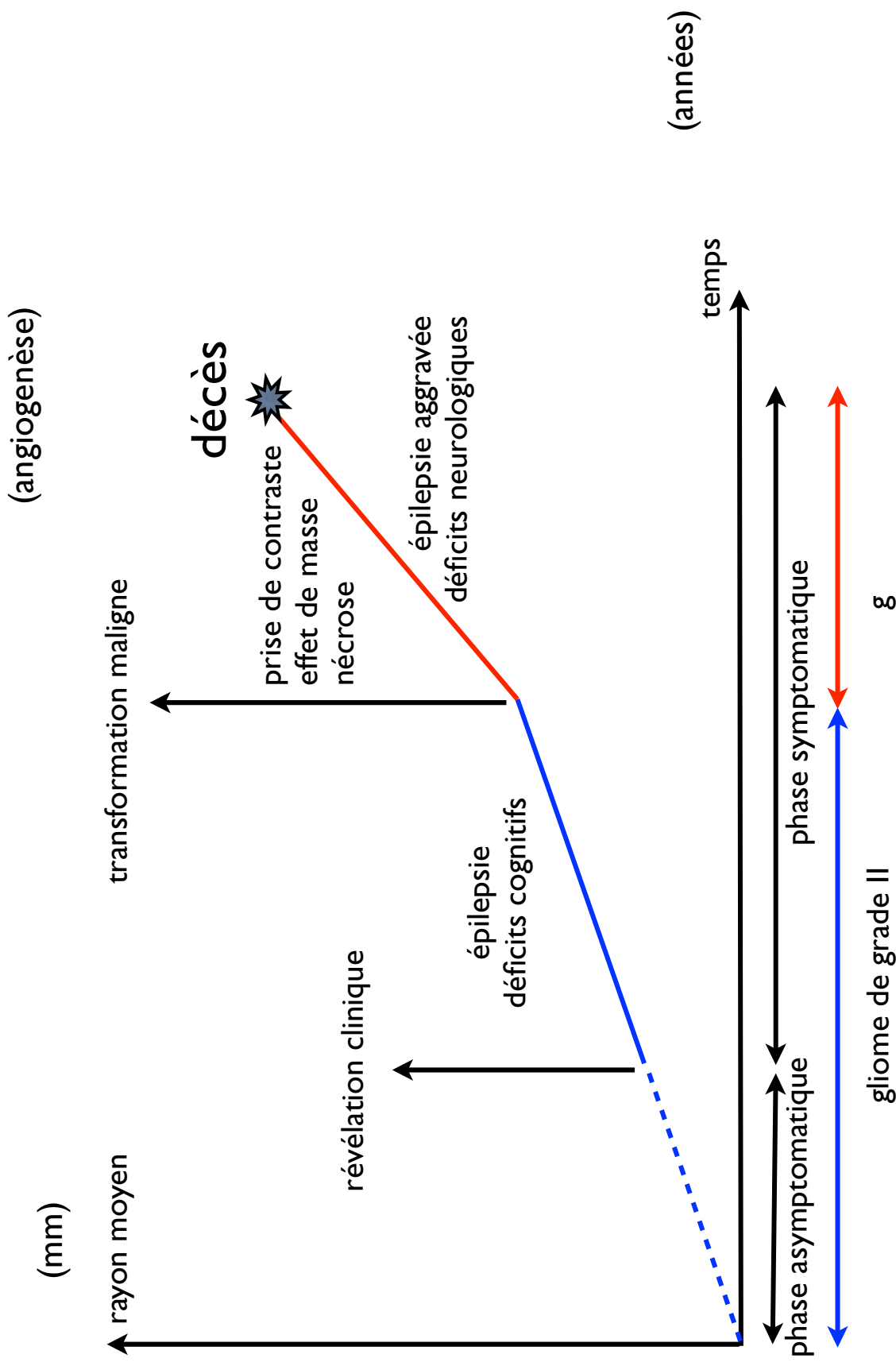
100 patients



Les gliomes



l'évolution d'un GBG

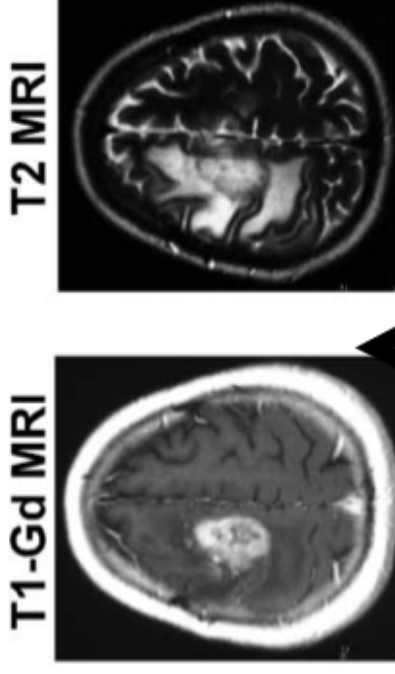


Quelques caractéristiques du gliome de bas grade

- âge médian de 35 ans à la découverte de la tumeur,
- déficit cognitif,
- incurable : transformation maligne (survie à 5 ans 50%),
- **très infiltrant** → problème de visibilité à l'imagerie

Problème de la sensibilité de l'imagerie

gliome de grade IV

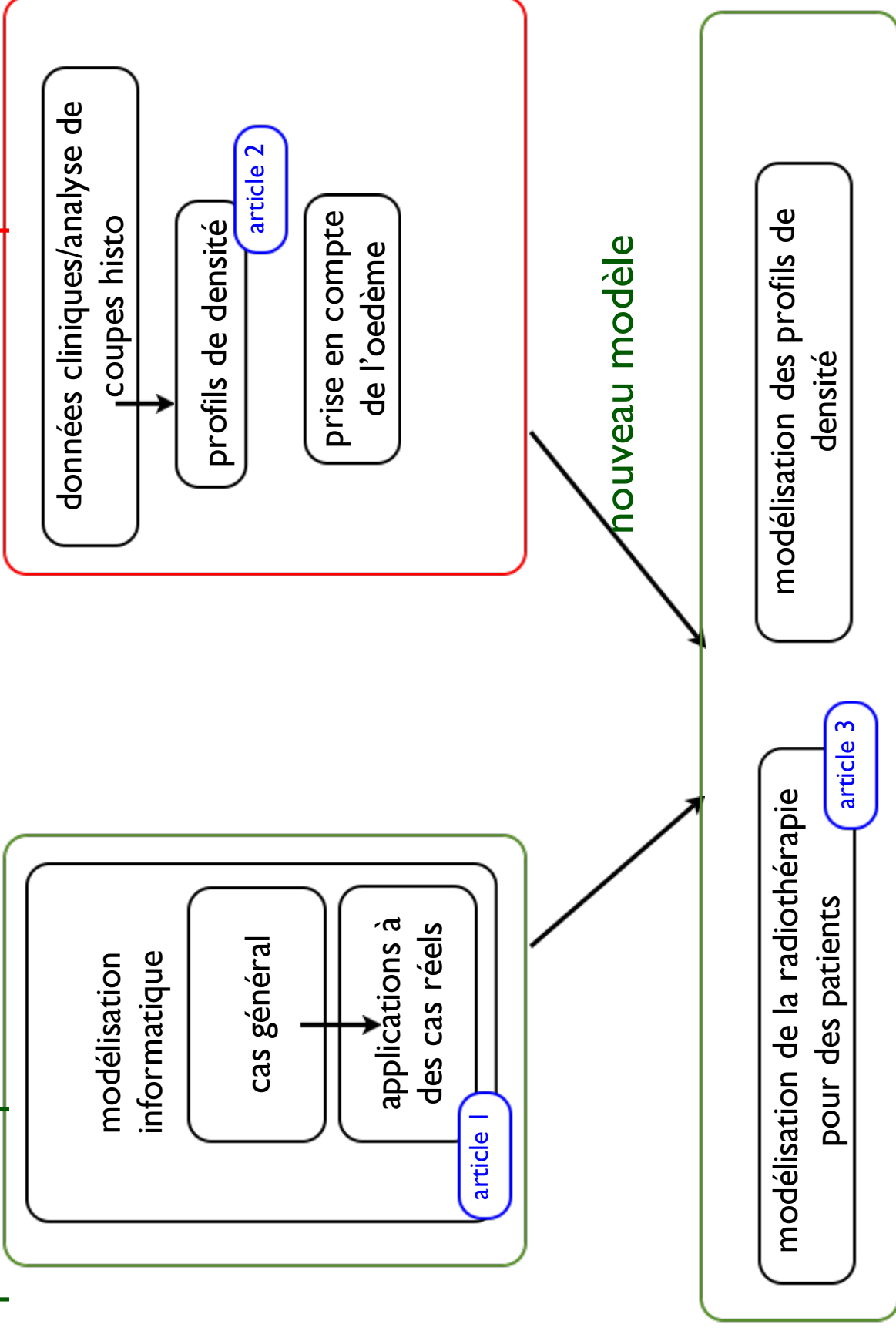


Prise en charge du gliome de bas grade

- Diagnostiquer un gliome :
 - ▶ les symptômes (épilepsie inaugurale)
 - ▶ l'imagerie (IRM multimodale, scanner, TEP, ...)
 - ▶ la biopsie
- Traiter un gliome :
 - ▶ chirurgie en première intention
 - ▶ sinon chimiothérapie et/ou radiothérapie

physique théorique

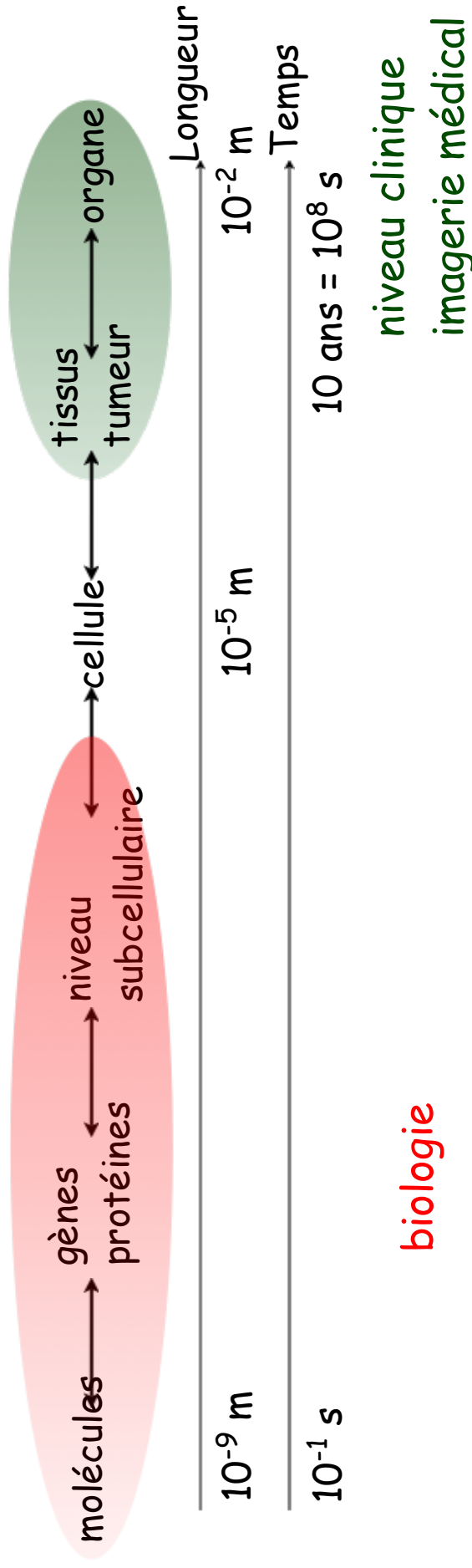
recherche de données pour le modèle




Partie I

un modèle bio- mathématique classique

La tumeur : un système complexe



+ les traitements, l'angiogenèse, le système immunitaire, ...

 **modèle simple**

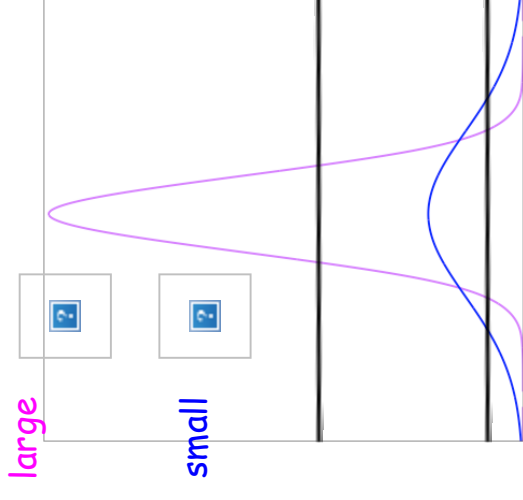
Modèle existant : modèle diffusion-prolifération

$$\frac{\partial C(\vec{r}, t)}{\partial t} = \nabla(D(\vec{r}, t)\nabla C(\vec{r}, t)) + \kappa(\vec{r}, t)C(\vec{r}, t)$$

Si D et K sont uniformes et

$$\frac{\partial C(r, t)}{\partial t} = D\nabla^2 C(r, t) + \kappa C(r, t)$$

symétrie sphérique :



Le modèle diffusion-prolifération

Postulat : $R(t)$ = courbe d'isodensité de cellules tumorales C^*

$$\sqrt{4Dt(\kappa t + \ln(\frac{N_0}{C^*(4\pi Dt)^{3/2}}))}$$

$$\sqrt{4D\kappa t}$$

⇒ vitesse radiale constante

la vitesse permet de remonter à $2\sqrt{\kappa D}$

Données cliniques

- suivi sans traitement
- patients recalés
- évolution linéaire dès R=15mm
- $\langle v_{\text{rayon}} \rangle \approx 2\text{mm/an}$

rayon (mm)

40

30

20

10

temps

Quantitative Imaging Biomarker
 The number of MRI studies per patient was 4 on average, with a range of 2–7. The average age was 4.75 years (range, 3.52–7.98 years) at the time of the first MRI. The average age at the time of the last MRI was 7.30 years (range, 3.0–11.000 days).
 Evolution of the mean diameter over time for each patient is shown in Figure 2. These observations can be compared with the theoretical evolution of a spherically growing tumor, from 2.1 to 10.5 mm, over a 3-year period. The average diameter of these tumors grows noticeably above the theoretical prediction, especially in the last 2 years of observation. The average slope of evolution of the mean diameter is $\langle v_{\text{rayon}} \rangle = 0.11\text{mm/year} (0.53\text{cm}^3/\text{year})$. The correlation coefficient is $r = 0.91$.
 The average diameter of the tumors at the time of the last MRI is $\langle R \rangle = 15.5\text{mm}$.
 $v_t = v_0 + \alpha x / R$
 For all curves are aligned along the common tangent line, the average behavior are shown in Figure 3.
 The average diameter of the tumors at the time of the last MRI is $\langle R \rangle = 15.5\text{mm}$.
 The average slope of evolution of the mean diameter is $\langle v_{\text{rayon}} \rangle = 0.11\text{mm/year} (0.53\text{cm}^3/\text{year})$.
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rayon (mm)

40

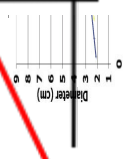
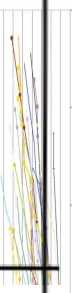
30

20

10

0

temps



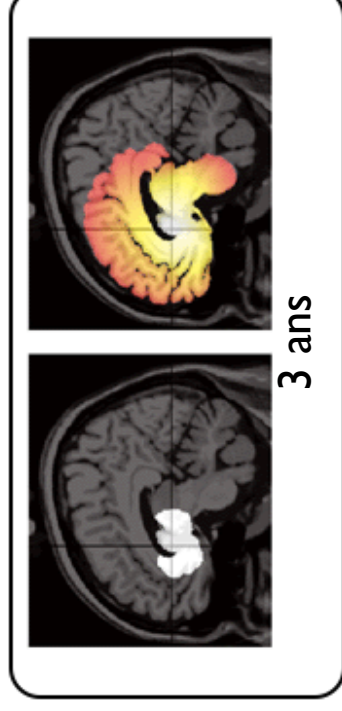
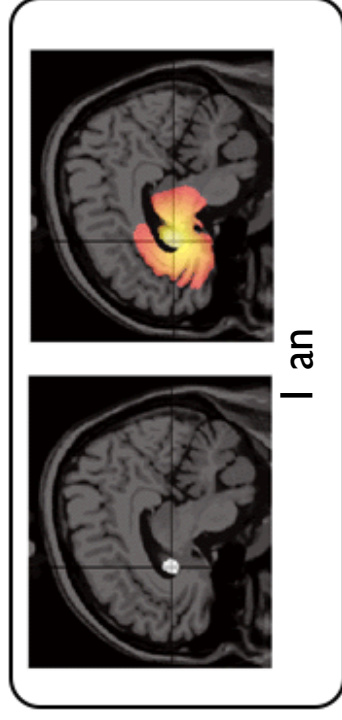
Quelques exemples avec le modèle DP

- 1995, Tracqui, Murray : gliome de haut grade et chimiothérapie

bonne reproduction des résultats cliniques et in vitro

12 paramètres libres, 1 seul patient

- années 2000, Swanson : gliome de haut grade



- 2005, Jbabdi, Clatz : gliome de haut grade, prise en compte de l'hétérogénéité des tissus/effet de masse

Tracqui et al. (1995) *Cell Proliferation*, **28**(1):17–31

<http://depts.washington.edu/krs/lab/wp-content/uploads/2010/07/brainslides.gif>

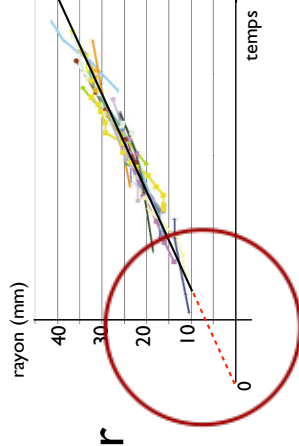
Jbabdi et al (2005) *Magnetic Resonance in Medicine*, **54**(3):616–624

Clatz et al (2005) *IEEE Transactions on Medical Imaging*, **24**(10):1334–1346

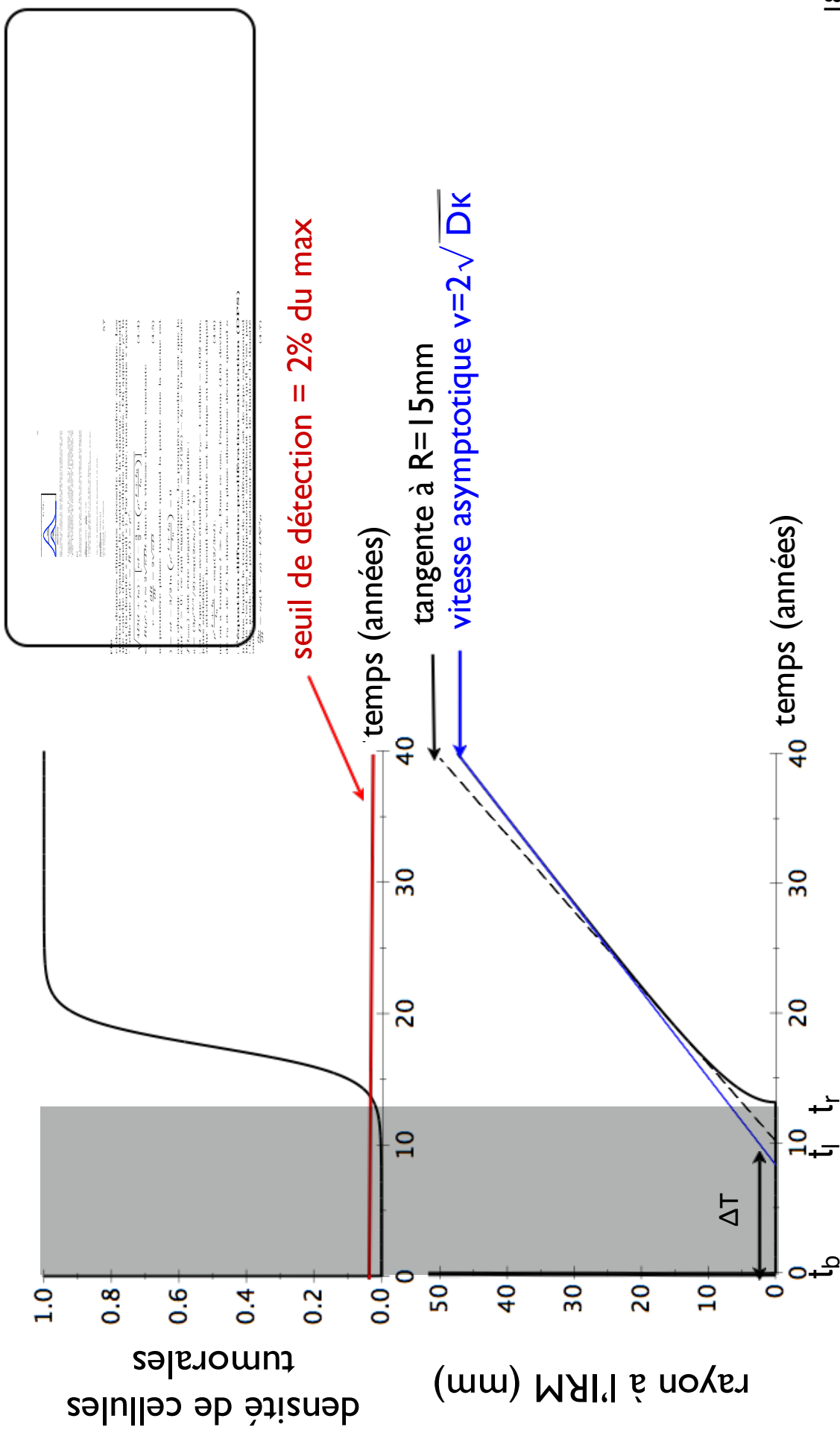
Objectif :

naviguer dans le temps pour comprendre l'évolution du gliome.

- Nos questions:
 - connaître l'âge moyen des patients à l'apparition de la tumeur
 - déterminer l'erreur due à l'approximation linéaire
- Nos postulats :
 - que des cellules cancéreuses
 - isotropie dans l'espace
 - pas de communication entre cellules

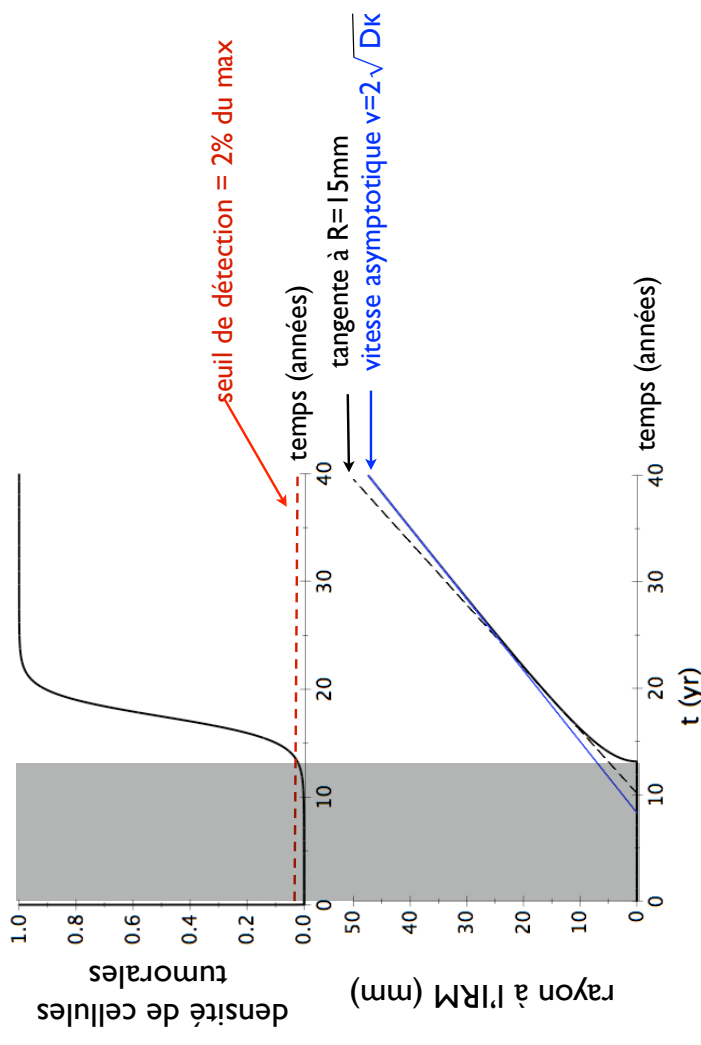


Modèle diffusion-prolifération-saturation



Application du modèle diffusion-prolifération-saturation

- Nos critères:
 - ▶ $R_{lin} < 15$ mm
 - ▶ saturation < 5 ans
 - ▶ $t_{tum} < \text{âge patient}$
- Application aux patients :
 - ▶ 120 patients
 - ▶ âge, rayon et vitesse connus
 - ▶ plage de (k,D) par patient



données initiales

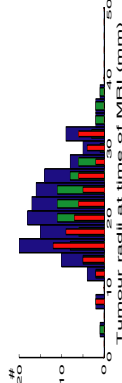
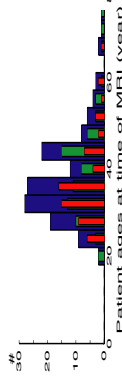
$v < 4 \text{ mm/an}$ █
 $v > 4 \text{ mm/an}$ █

- 120 patients adultes, $v < 8 \text{ mm/an}$

Improving the time-machine 81

m. Difference in mean tumour diameter on the estimate of the diametric velocity (i.e. 20%). We analysed data of patients using the model in which patient diffusion-proliferation equation was numerically solved for proliferation coefficient k between 0.1 and 1.0. For each patient, one value of the proliferation coefficient leads to a unique value of the diffusion coefficient of the tumour as a function of time. We imposed several constraints for one of them was not satisfied, the value of biological birthrate of the tumour, estimated with the proliferation-diffusion model, should not precede the birthrate of the patient.

1 proliferation-diffusion model, should not precede the birthrate of the patient.
 2 radius values larger than 15 mm by comparing value of the slope at 15 mm with half the theoretical value of the proliferation coefficient. Values of velocity of the proliferation coefficient was rejected (value of 20% experimental error) was chosen, consistent with cell density should not have reached saturation more than 15 mm (tumour being saturated when density at centre of the tumour exceeds 0.99). This is justified by absence of definite contrast enhancement on T2-enhanced image and thus absence of angiogenesis (the value of k of each patient was not very restrictive, imposing this constraint was not very restrictive, imposing this



Résultats

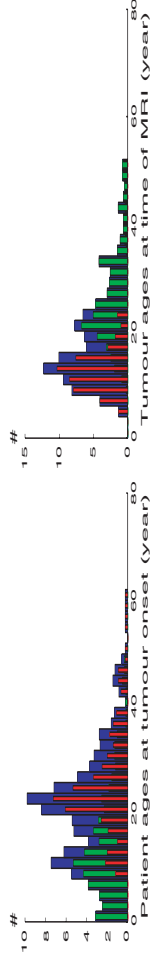
v < 4mm/an



v > 4mm/an



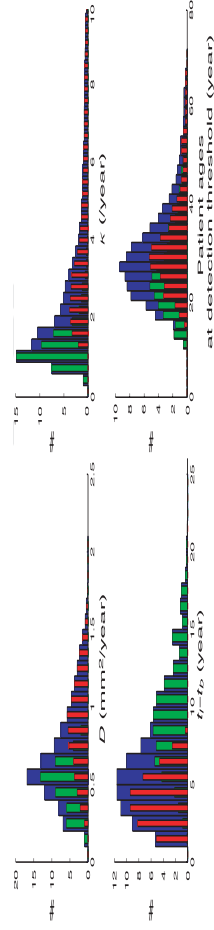
CHAPITRE 5. REMONTER LE TEMPS D'UN GLIOME DE BAS GRADE 85



- $t_{\text{tum}} = (10 + R_{\text{IRM}}) / v$

- âge radio ≈ 30 ans

CHAPITRE 5. REMONTER LE TEMPS D'UN GLIOME DE BAS GRADE 86



Gerin C, et al. (2012) Cell Proliferation, 45(1):76–90

un cas fortuit

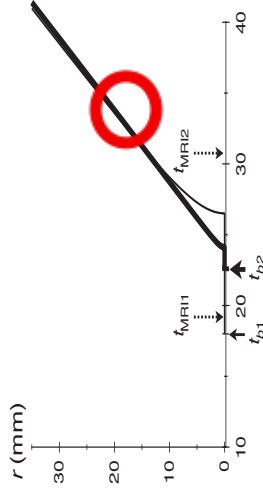
rayon IRM (mm)



MONTER LE TEMPS D'UN GLIOME DE BAS GRADE

89

âge du patient (années)



Gerin C, et al. (2012) *Cell Proliferation*, **45**(1):76–90
d'après les données de Pallud et al. (2011) *Acta Neurochir* 153(3):473-7

Conclusion

- 2 populations de tumeurs selon la vitesse
- date de naissance différente → sens biologique ?

from radiological diagnosis was 96, 80, and 68% at 5, 10, and 15 years, respectively, for the LR group and was 57% at 5 years for the HR group. The median survival was 5.16 years in the HR group and was greater than 15 years in the LR group.

In univariate analysis, there is an inverse correlation between ICR and survival: the higher the ICR, the lower the survival (Fig. 2). In multivariate analysis, regarding the risk factors commonly admitted,⁶ histological diagnosis ($p = 0.415$), tumor volume (cutoff at 6cm in diameter; $p = 0.063$), age at radiological diagnosis (cutoff at 40 years; $p = 0.822$), presence of neurological deficit ($p = 0.087$), and the Ki-67 proliferation index (cutoff at 5%; $p = 0.862$) did not reach statistical significance. In multivariate analysis, ICR ($p < 0.0001$) and tumor volume ($p = 0.054$) proved to be independent prognostic factors significantly associated with survival.

Discussion

This study indicates that ICR measurements before treatment of supratentorial grade II gliomas are predictive of prognosis. Survival times for patients with an ICR 8mm/year or more are indeed significantly reduced compared with those with an ICR less than 8mm/year. The biological diversity of grade II gliomas results in a great heterogeneity of prognosis, both within and be-

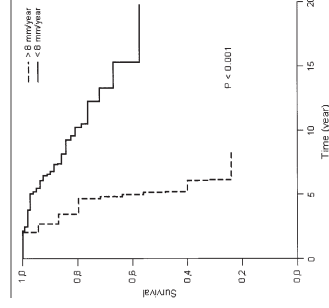
tween series.⁷⁻¹³ European Organisation for Research and Treatment of Cancer (EORTC) prospective randomized studies have allowed to define five risk factors (age >40 years, histological diagnosis of astrocytoma, largest tumor diameter >6 cm, presence of a neurological deficit, midline crossing) independently correlated to a worsened prognosis. When these five risk factors are present, the median survival is estimated at 4.5 years, 1 year and survival times of such grade II gliomas are similar to those of high-grade gliomas. This heterogeneity of prognosis could be explained, at least in part, by the limitations of the histological diagnosis. Indeed, the method relies on a "static" analysis at the cellular scale of an often limited part of the tumor, especially on biopsy or partial resection specimen. Anaplastic areas may be missed, leading to an "undergrading" of the tumor. In fact, anaplastic areas may be missed on paraffin-embedded and dynamic scales are required to refine the prognostic evaluation, and thus to overcome this eventual undergrading. Indeed, immunohistochemical and molecular analyses are known to add a prognostic value^{6,14-16} to the WHO classification. Moreover, combination of histology and imaging is known to be more informative than the sole histological analysis in the grading of oligodendrogliomas.^{17,18} A multiscale approach is thus the only biological parameter that can be used to overcome the biological heterogeneity of the tumor.

The aim of this study was to determine whether tumor growth, a dynamic macroscopic parameter measured before any treatment, could be contributive to the prognostic evaluation of patients who harbor a grade II glioma. In this study, only 15.5% of patients presented an ICR of 8mm/year or more. This group had a statistically significant lower length of survival than the group with ICRs less than 8mm/year. We are thus able to identify a subgroup of patients with a biological heterogeneity that is similar to that of anaplastic gliomas. The HR group is closer to that of anaplastic gliomas with a median survival at 5.16 years.

The results suggest the strong statistical influence of ICR on survival in this selected population. The absence of statistical significance for several known risk factors⁶ may be due to the small size of the studied population. Thus, ICR measurements may be useful to overcome biological diversity of grade II gliomas.

Conclusion and Perspectives

In this study, we have shown that the clinical outcomes of histologically proved grade II gliomas growing faster than 8mm/year are similar to those of anaplastic gliomas. On a practical view, estimation of ICR from only two MRI is probably not systematically reliable. Nev-



Conclusion

- mais même âge à la détection IRM
- plage de paramètres en accord avec K. Swanson et al

mais

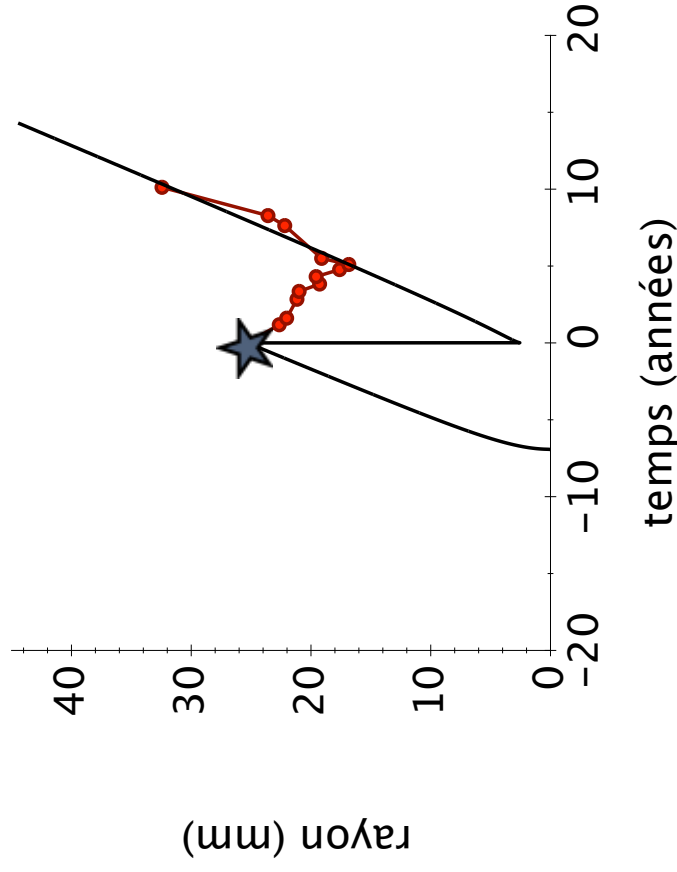
- des patients dont la vitesse est faible ($v < 0,5$ mm/an) sans solution
- le seuil C* paramètre caché inconnu

Pallud, J., et al (2006) *Annals of Neurology*, **60**(3):380–383.

Les limites du modèle

- RT en l'ère intention
- traitement pendant 6 semaines
- 60 Gy

La décroissance longue de la radiothérapie est mal modélisée...



Partie II

Analyse histologique

corrélation micro/macroscopique

histologie des gliomes

organisation microscopique

- 1940, Scherer : observation spatiale, tri, début de modèle
- 1987, Kelly, Daumas-Duport : infiltration du tissu sain
- 2010, Pallud : étude quantitative

Scherer (1940) *Brain*, **63**(1):1

Kelly et al (1987) *Journal of Neurosurgery*, **66**(6):865–874

Pallud et al (2010) *Neurology*, **74**(21):1724

Que détecte l'IRM ?

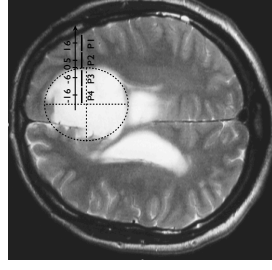
- l'IRM est sensible à l'«eau libre».
- 1994, Tovi : l'oedème
 - oedème = perte de tissus et vacuolisation
 - oedème → lames H&E pâles
 - ➡ quantifions l'oedème pour vérifier

Les données cliniques

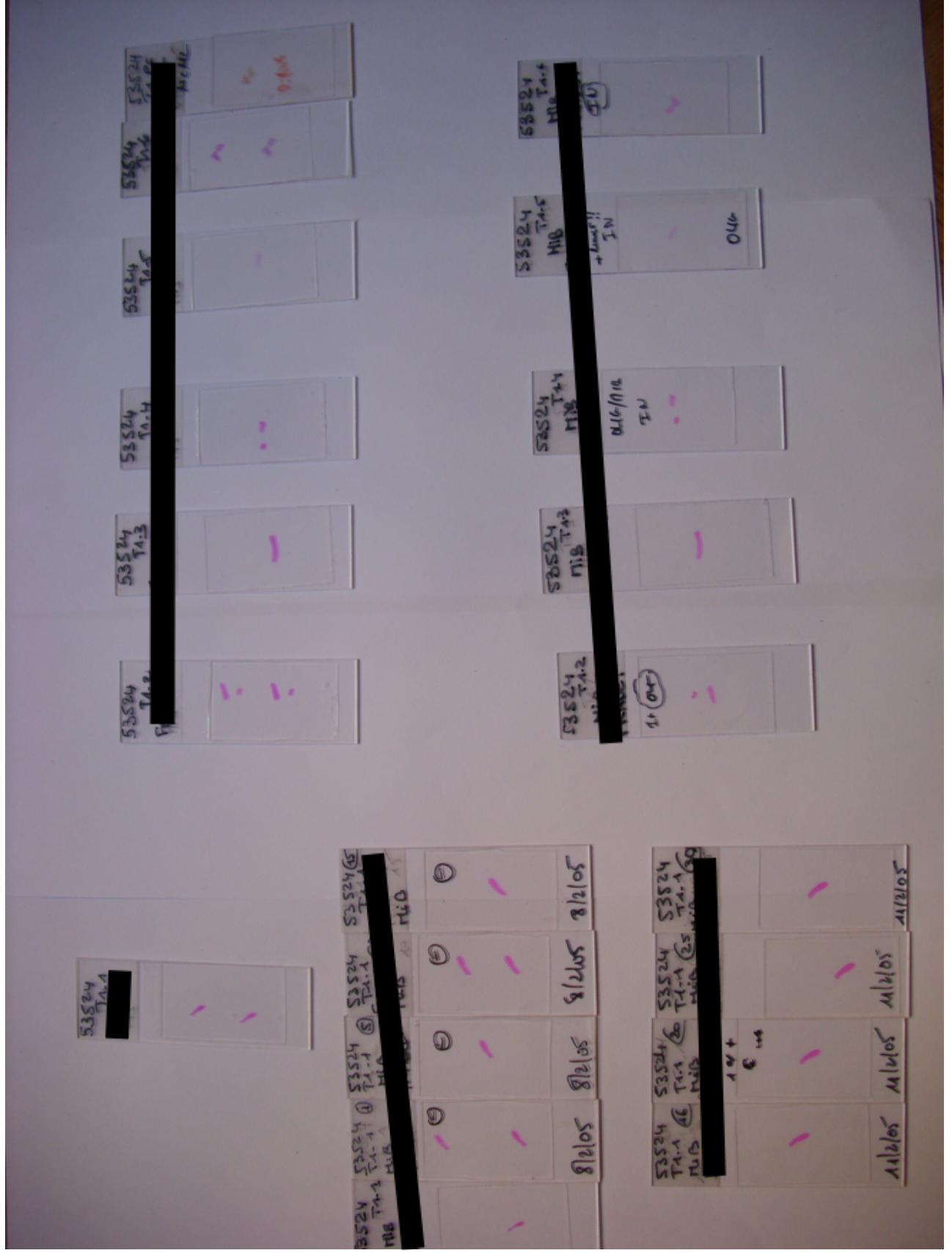
- Sélection des 9 patients
 - adultes
 - biopsie stéréotaxique fondée sur l'IRM
 - suivis à Sainte-Anne entre 1992 et 2001
 - pas de traitement antérieur à la biopsie
- Un exemple de patient :
 - 1 biopsie
 - 1 trajet
 - 4 prélèvements

low-grade gliomas

13



Lien histologie-imagerie



Évolution de nos méthodes...

env. 200 lames colorées en H&E



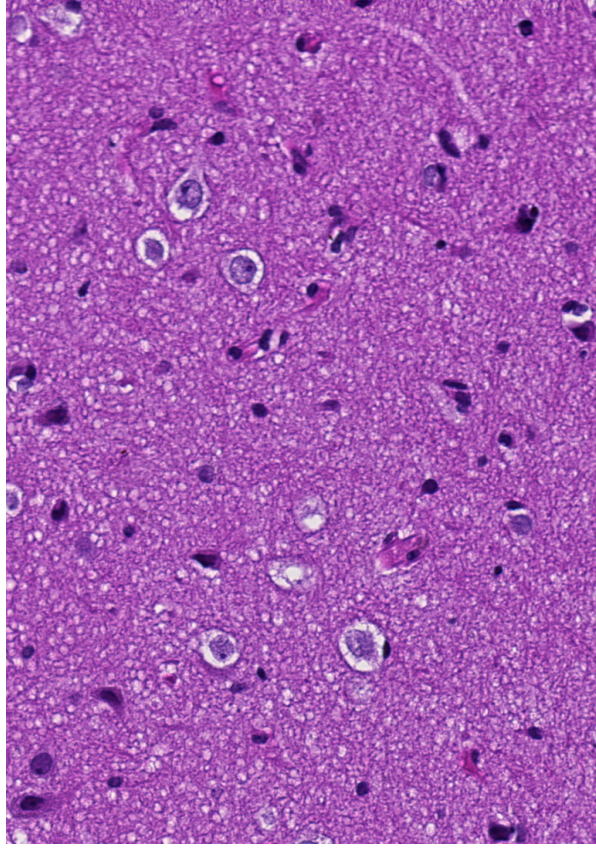
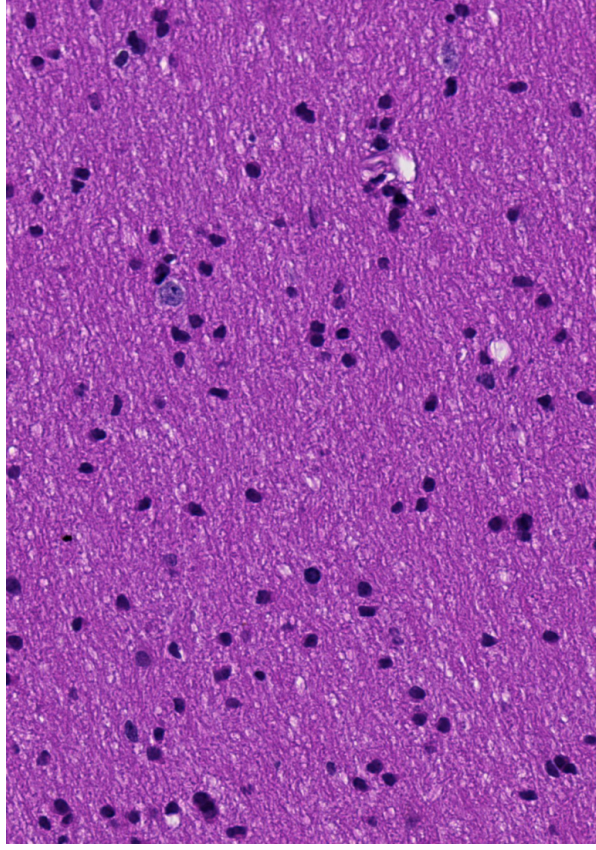
2h/lame



5min/lame



Apprentissage



sélection de la substance blanche

Les données initiales

IX



400X

tissu sain

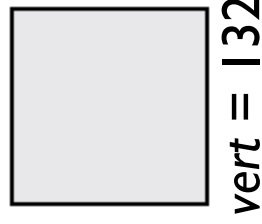
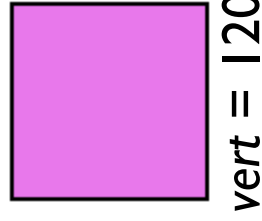
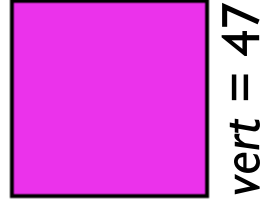
tissu tumoral

description d'une image numérique

- un pixel = un triplet (R,V,B)
- Une composante va du noir (0) au blanc (255) en passant par toutes les intensités



- Exemple de coloration d'une lame (*rouge* = *bleu* = 135)



→ rouge-vert

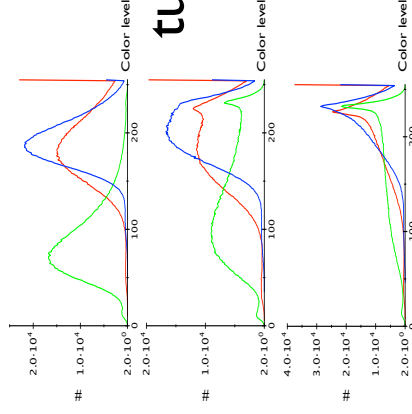
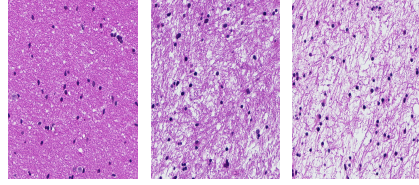
Quantification de l'oedème

sain



histology, imaging and modeling of low-grade gliomas

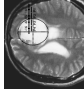
15



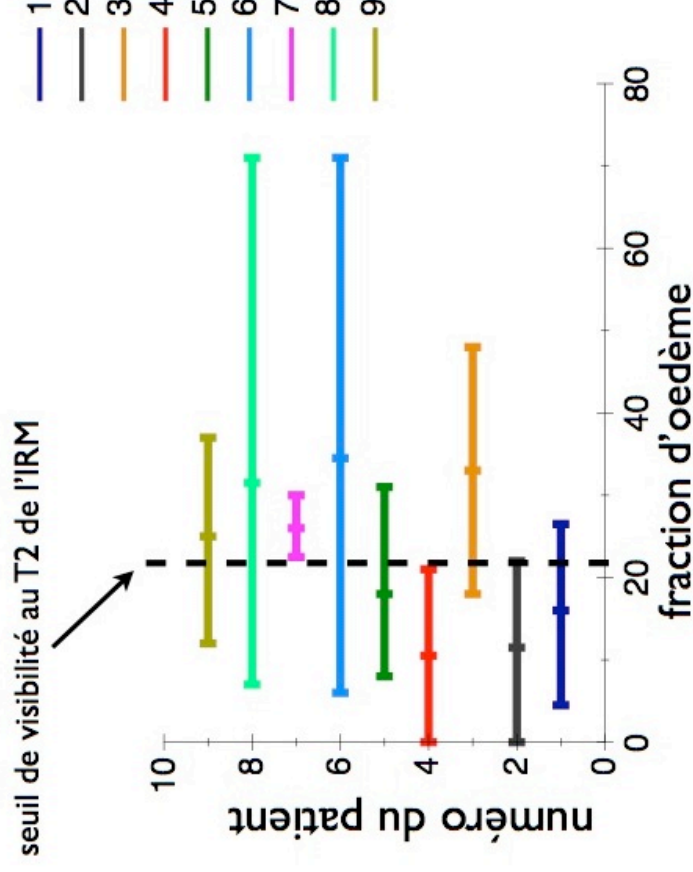
rouge-vert \propto fraction d'oedème

Profil de densité d'oedème

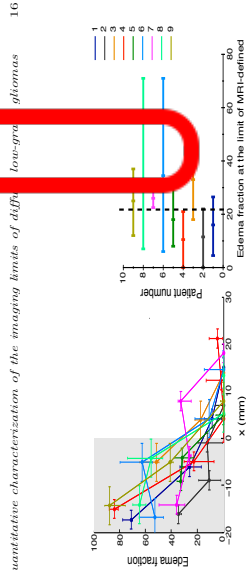
10



intérieur extérieur



quantitative characterization of the imaging biomarkers of diffuse low-grade gliomas



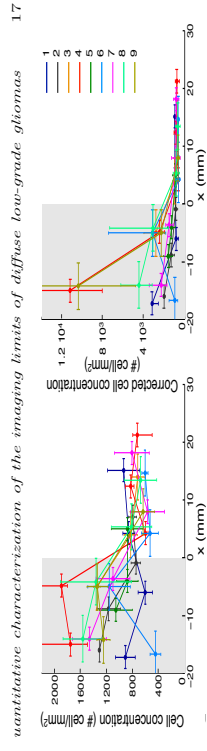
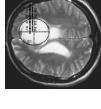
seuil=20% d'oedème

Profil de densité de cellules

intérieur

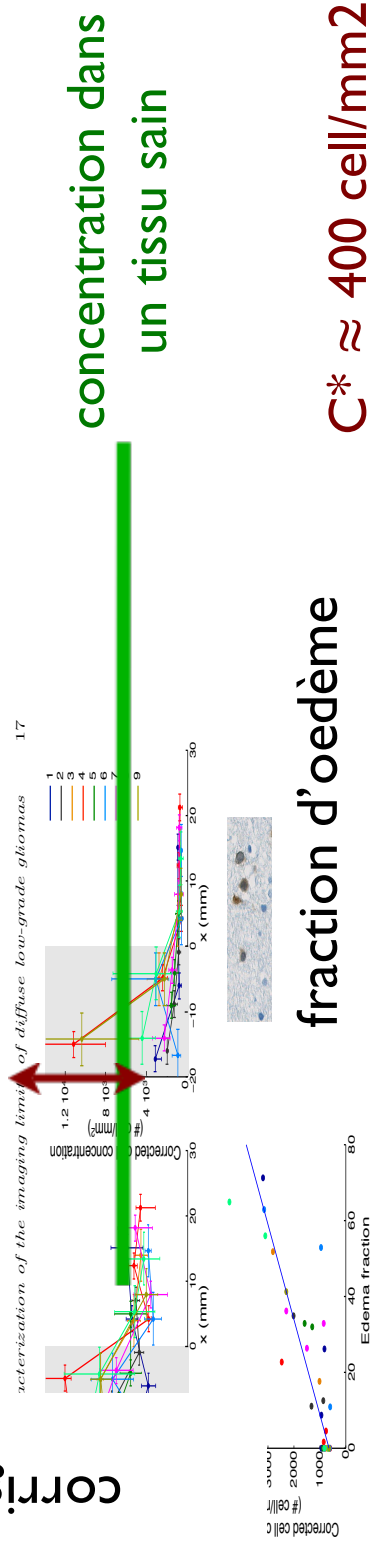
extérieur

Dr. J. P. L. G. G. G.



Connaitre la densité de cellules grâce à l'oedème

Concentration cellulaire
corrigée (cell/mm²)



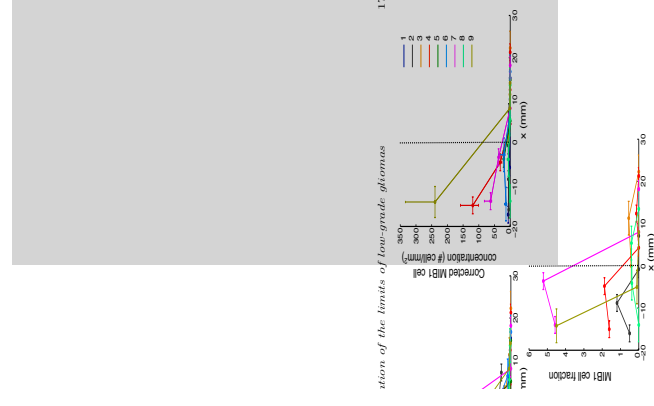
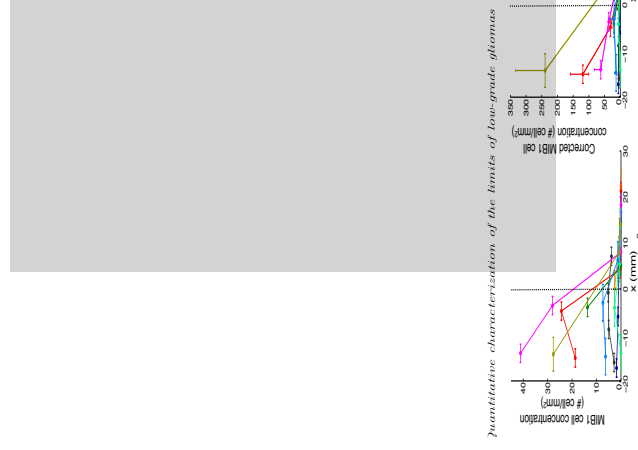
Les cellules en cycle

intérieur

extérieur

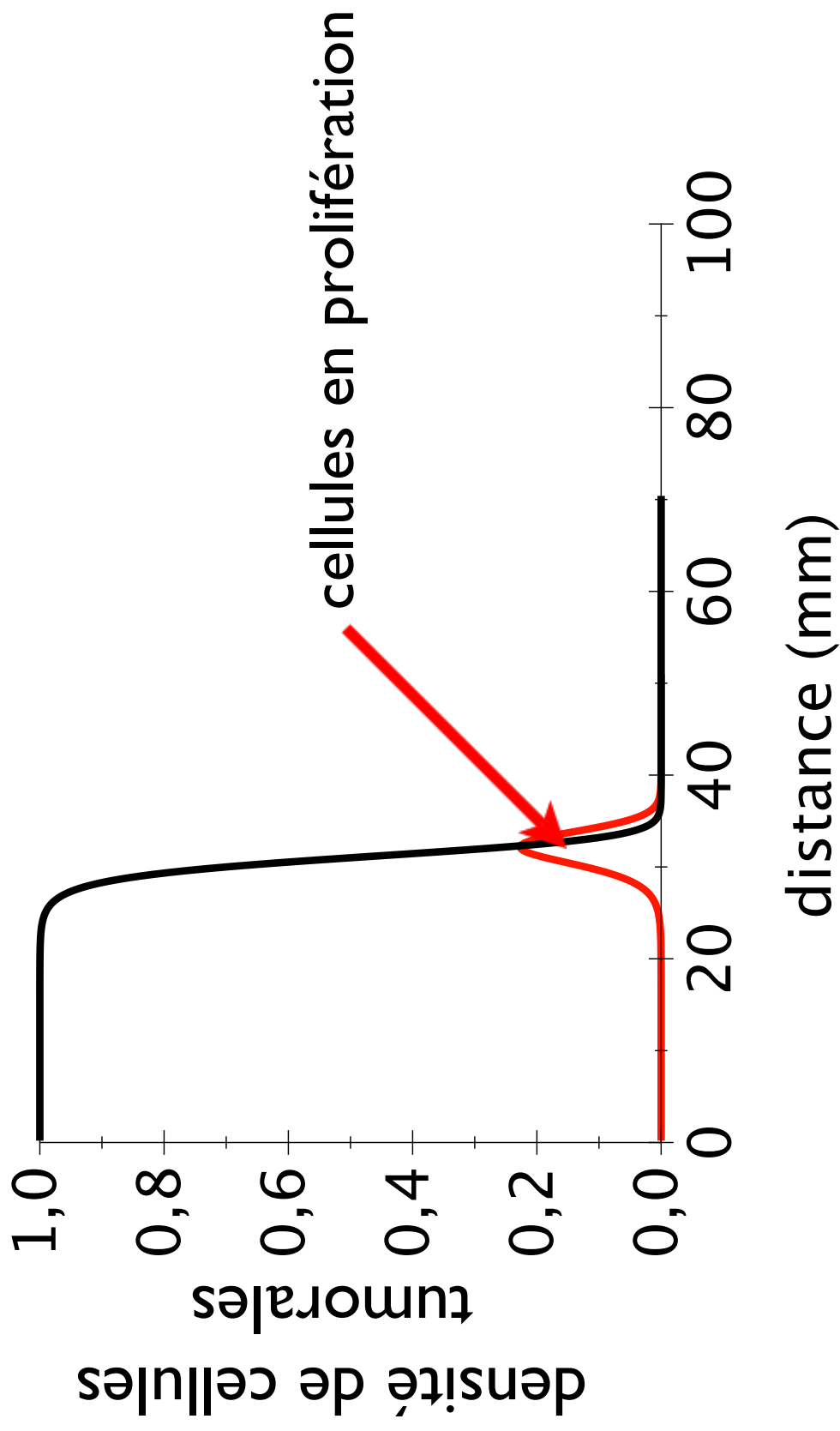
intérieur

extérieur



- concentration supérieure dans le signal
- pourtour actif
- en accord avec les modèles diffusion-prolifération

les cellules en cycle : le modèle DPS



Conclusion de l'histologie

- L'oedème est responsable du signal IRM-T2
- Étendue de la tumeur à l'imagerie non significative
- Présence de beaucoup de cellules en cycle proche de la frontière de l'anomalie de signal

Partie III

Nouveau modèle

Radiothérapie

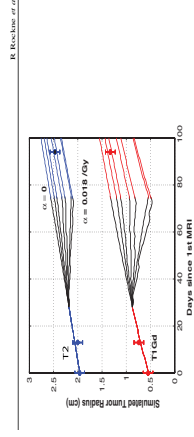
Un modèle de radiothérapie : Rockne et al

- gliome de grade IV
- modèle diffusion-prolifération-saturation
- modèle pour la RT: linéaire quadratique



Mais

impossible de reproduire la longue décroissante des gliomes de bas grade



Un modèle de radiothérapie : Ribba et al

- équations différentielles ordinaires
- modèle pour le cancer colorectal
- 2 populations cellulaires : proliférantes et quiescentes

reproduit assez bien les données

reproduit l'effet retard

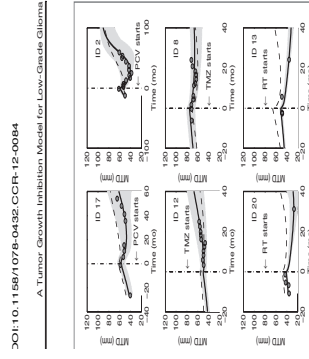
Mais

6 paramètres/2 conditions initiales

pas d'aspect spatial

pas de migration cellulaire

if? entre concentration cellulaire et IRM ?

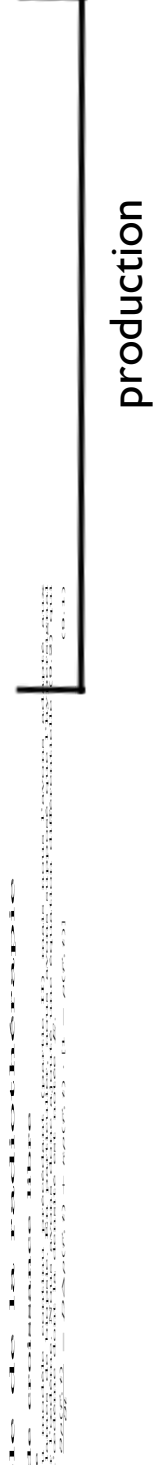


DOI:10.1158/1078-0432.CCR-12-0084

A. Tumor Growth Inhibition Model for Low-Grade Glioma

Proposition d'un nouveau modèle

cellules :



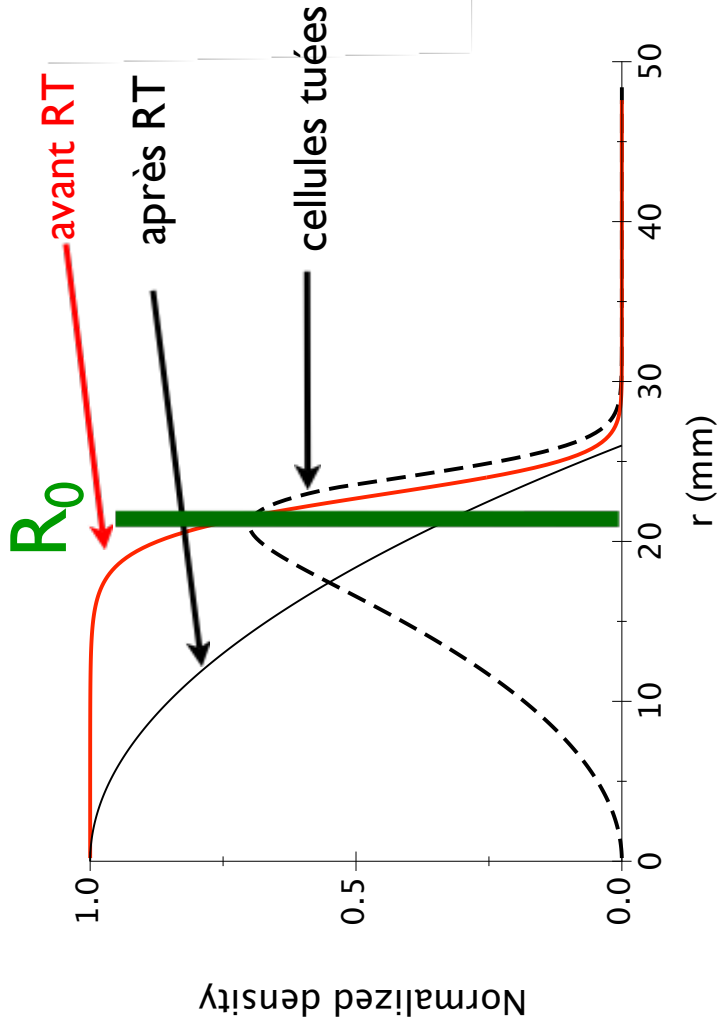
oedème :



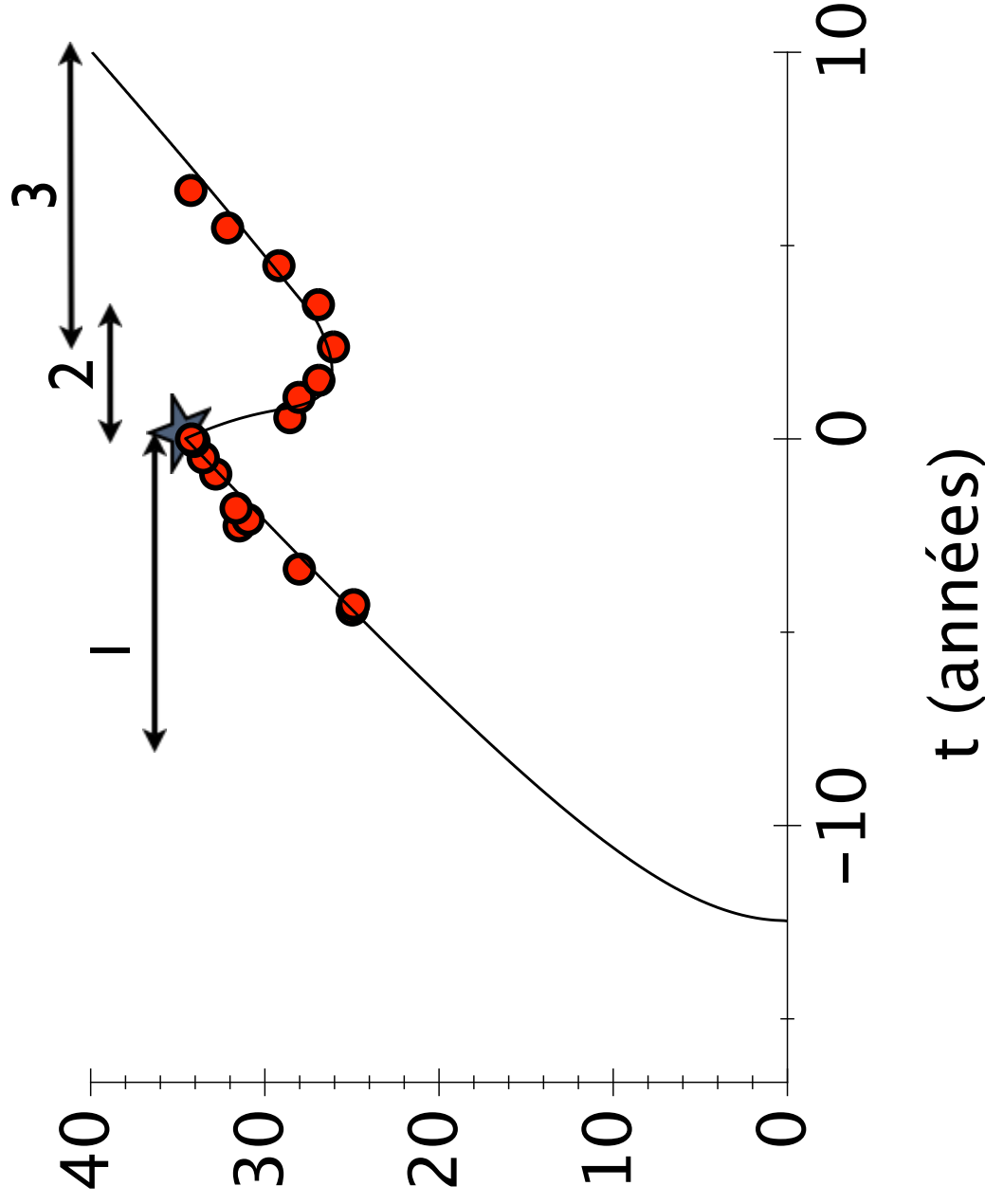
Effets de la radiothérapie

postulat : la radiothérapie est instantanée

Figure 10.10. Effets de la radiothérapie sur la densité cellulaire et la densité de cellules tuées. La courbe en pointillés représente la densité cellulaire avant la radiothérapie (RT), la courbe en trait plein représente la densité cellulaire après RT, et la courbe en trait rouge représente la densité de cellules tuées. La densité cellulaire après RT est plus faible que celle avant RT, et la densité de cellules tuées est plus élevée que celle avant RT. La densité cellulaire après RT est plus élevée que celle avant RT dans la région où la densité de cellules tuées est plus élevée que celle avant RT.



⇒ pic d'efficacité au maximum de cellules en prolifération



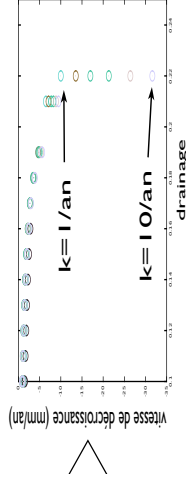
- seuil fixé par l'œdème
- $\mu = \mu(v_d, \lambda)$
- $R_{lin} < 15 \text{ mm si } v < 4 \text{ mm/an}$

v_{init} et v_d connues \rightarrow 3 paramètres libres : D, λ, r_0

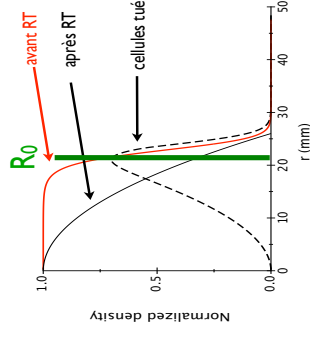
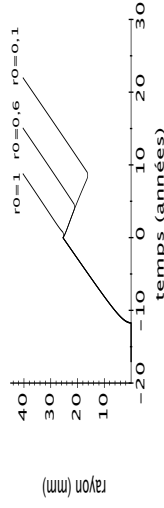
r_0 contrôle la durée de la décroissance

DIOTHÉRAPIE

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dimensions l'influence sur la vitesse de décroissance λ . Puisque la vitesse de croissance $2\sqrt{RD}$ est fixée, le profil de densité de cellules. Le graphique de droite est en 2 dimensions où λ est représenté par une couleur. n/an pour les très grands λ . En d'autres termes, pour $r_d \leq 20 \text{ mm}/\text{an}$, il faut $\lambda \geq 5/\text{an}$.

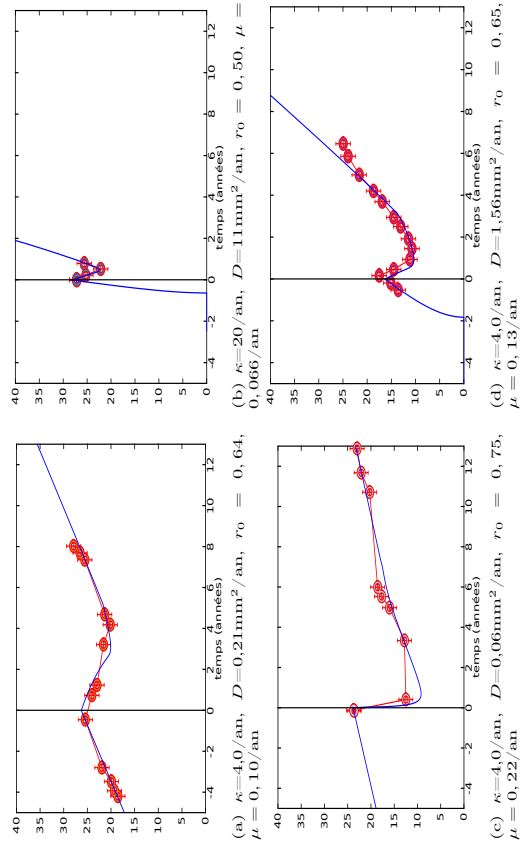


Validation du modèle

- 25 patients
- grande variété de comportements

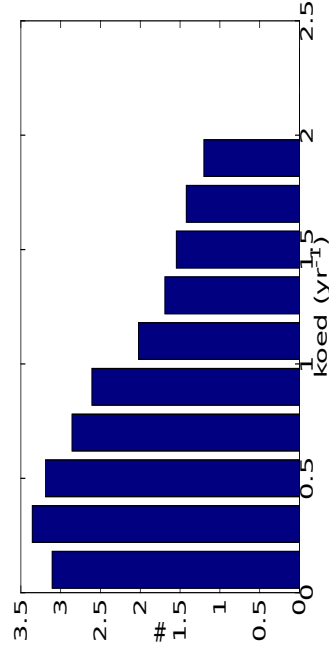
FIGURE 10. APPLICATION AUX CAS CLINIQUES

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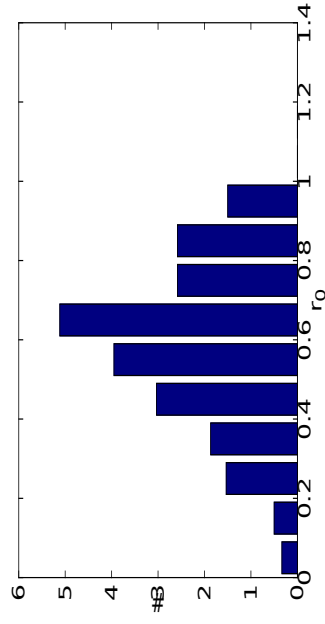


Les plages de paramètres du modèle II

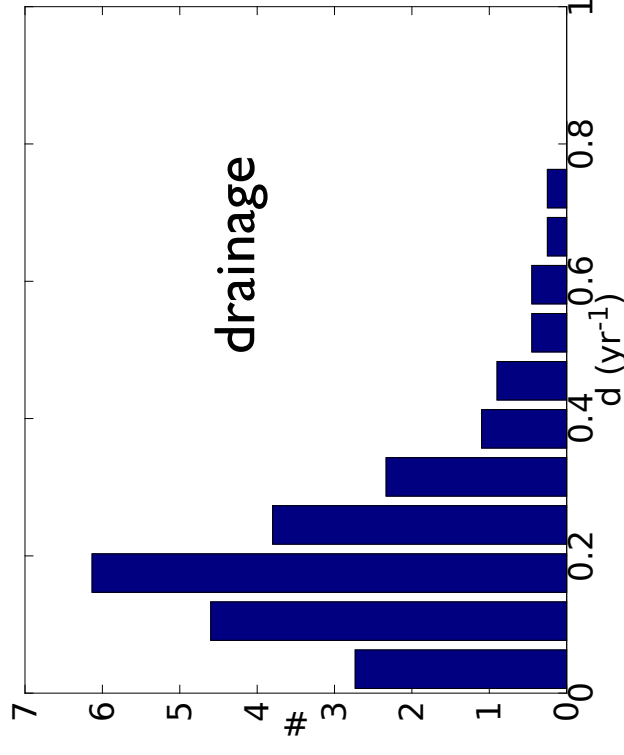
production
d'oedème



efficacité de
la radiothérapie



drainage

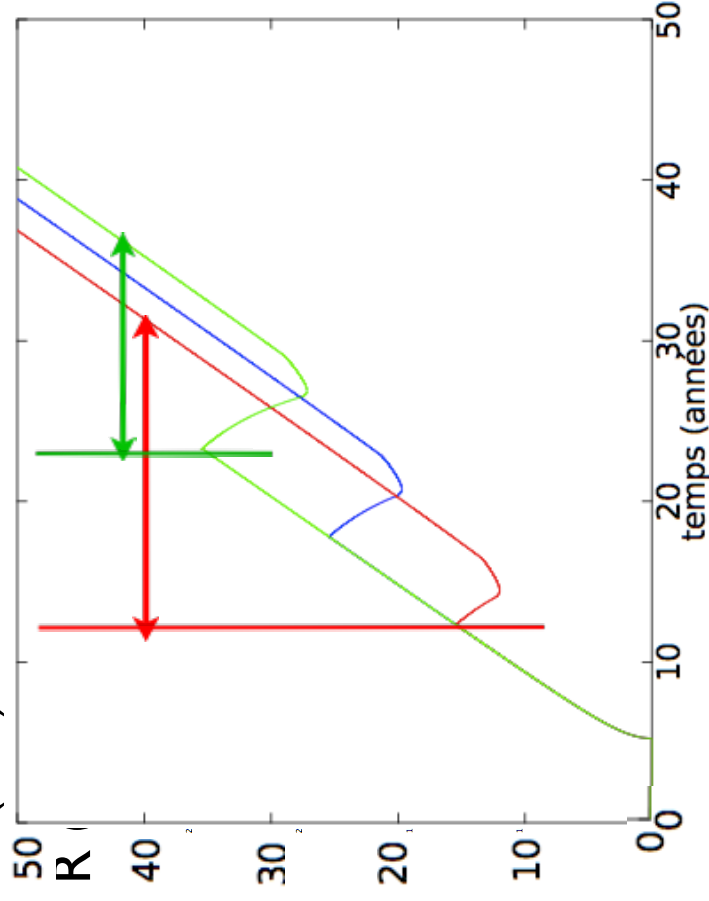


Analyse des cliniques

- coeff prolif k élevé → mauvais pronostic ✓
- rayon initial élevé → mauvais pronostic ✓
- vitesse de décroissance élevée → mauvais pronostic ✗



... en cours...



Soffietti R et al. (2010) *Eur J Neurol.* **17**:1124-1133.
Pallud J, et al. (2012) *Neuro-Oncology*, **14**(4):1-10

Conclusion

Modèle simple avec seulement 3 paramètres libres

- ⊕ Un nouveau modèle en accord avec les données/la littérature

Ce modèle explique l'origine du signal T2

- ⊖ La densité de cellules est saturée depuis longtemps chez la plupart des patients

? Possibilité de prédire la réponse aux traitements ?

Conclusion générale

- **histologie** Oedème pour faire avancer la compréhension du signal IRM
- Profils de concentration → contrôle des modèles
- **modélisation** Possibilité d'estimer l'âge de la tumeur
- Existence de deux types de tumeur ? Génotype ?
- Tumeurs détectables vers 30 ans → dépistage ?
- Nouveau modèle pour les traitements

Perspectives

- À court terme :
 - ▶ Le modèle avec oedème est à continuer
 - ▶ Valider les modèles existants grâce aux données histologiques

- À long terme :
 - ▶ développer le modèle pour la chimiothérapie
 - ▶ obtenir des données plus récentes
 - ▶ prendre en compte le volume de l'oedème

les gens du labo

nos collaborateurs

P.

C. Nioche

D.

Varlet

Ameisen

M. Badoual

J. Pallud

N. Defamie

C. Daumas-
Duport

Merci

C. Deroulers

B. Grammaticos

F.

E. Mandonnet

Bouhidel

le NCT

mes étudiants

Histoire du gliome

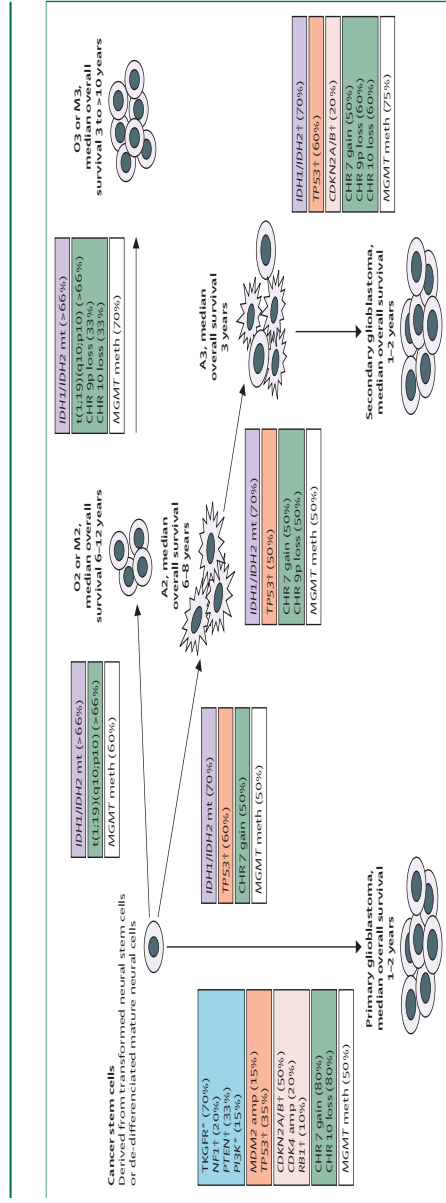
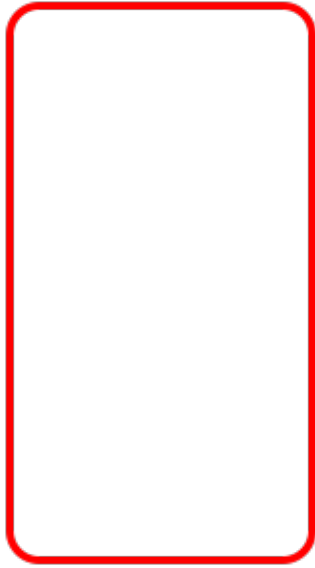


- 1940 : Scherer
- observation spatiale, tri, début de modèle
- années 1980 : Daumas-Duport

lien imagerie/histologie, recommande la prudence avec l'imagerie

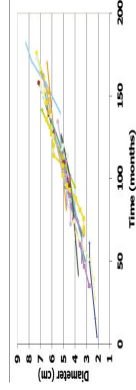
- années 1980: Murray
- premiers modèles mathématiques

Scherer J. (1940) The forms of growth in gliomas and their practical significance. *Brain* part I, vol 63
Daumas-Duport et al (1988) Serial stereotactic biopsies and CT scan in gliomas : correlative study in 100 astrocytomas, oligo-astrocytomas and oligodendrocytomas. *Journal of Neuro-Oncology*, 4(4);317-328, 1987.
Murray J.D. *Mathematical Biology : I. An Introduction (Interdisciplinary Applied Mathematics)*. Springer, 3rd édition

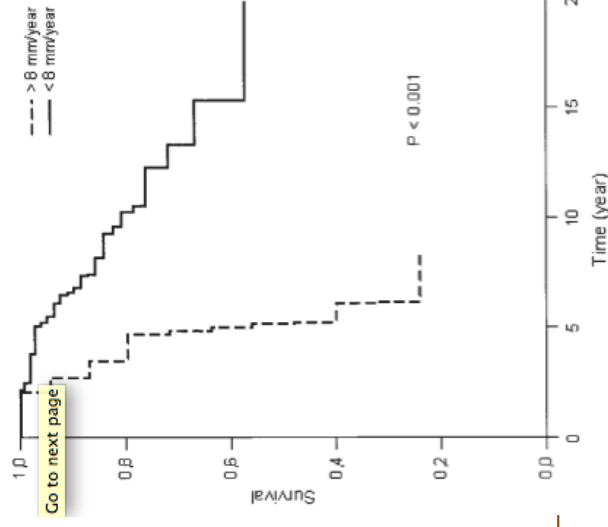


Données cliniques

- $\langle v \rangle = 2 \text{ mm/an}$
 - évolution linéaire dès $R = 10 \text{ mm}$
- \Rightarrow modèle moins contraignant, $R_{\min} = 15 \text{ mm}$



mean diameter over time. B_1 is 0.00113 cm/day (or 0.411 cm/year) with a narrow CI (95% CI: $3.8-4.4 \text{ mm/year}$). Note, again, that this mean line of growth was obtained by excluding rapidly progressing patients (who were excluded because of the small number of cases of anaplastic transformation). Our results are nevertheless relevant for a substantial group of low-grade oligodendrogliomas, which are the most common of the dynamic properties of these tumors are most often comparable between various patients. The underlying biological processes that determine tumor growth therefore



La vitesse de croissance du rayon visible à l'IRM a une valeur pronostic.

Mandonnet E et al (2003) Continuous growth of mean tumor diameter in a subset of grade II gliomas. *Ann Neurol* **53**, 524–528
 Pallud J, et al. (2006) Prognostic value of initial magnetic resonance imaging growth rates for world health organization grade II gliomas. *Annals of Neurology*. 60, 380–383.

validation du protocole

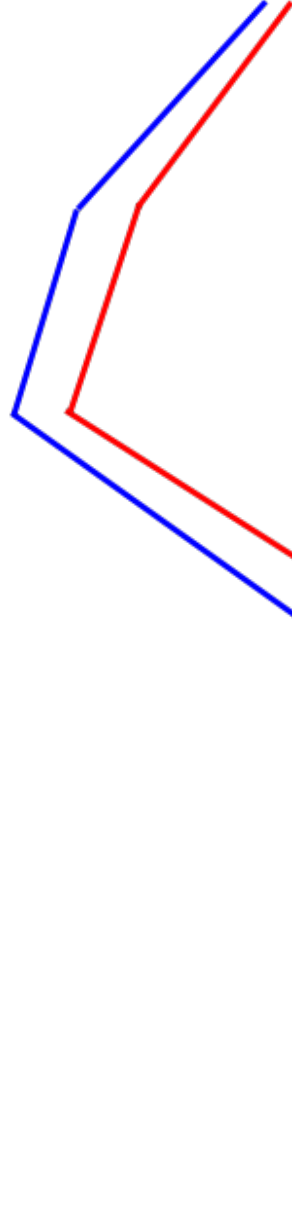
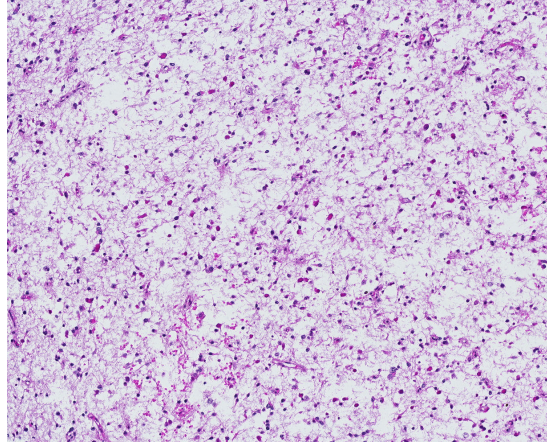
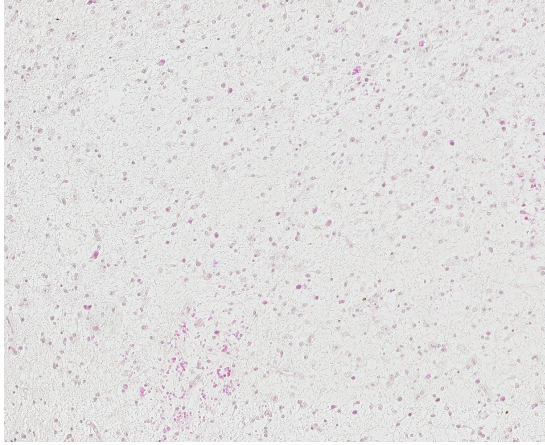


FIGURE 7. NOTRE ANALYSE HISTOLOGIQUE

Effets de la radiothérapie

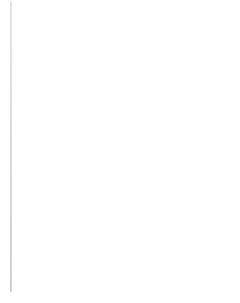
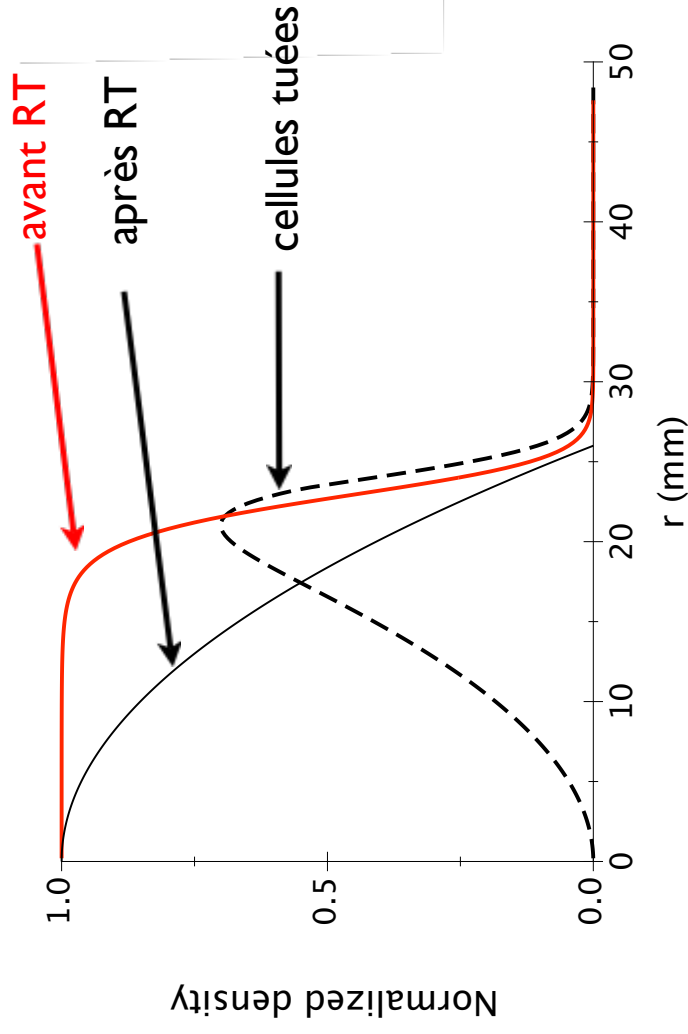


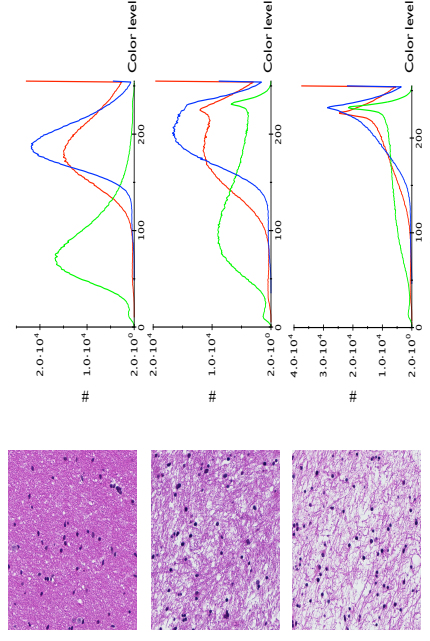
Figure 1. Normalized density profiles of a tumor of radius 50 mm, before and after radiotherapy (RT). The solid line represents the density profile before RT, and the dashed line represents the density profile after RT. The x-axis is the radial distance r (mm) from the center, and the y-axis is the normalized density. The density is 1.0 at the center and decreases to 0.0 at the periphery. After RT, the density profile is shifted towards the center, indicating a decrease in cell density at the periphery.



Quantification de l'oedème II

histology, imaging and modeling of low-grade gliomas

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Gerin et al (2013) Quantitative characterization of the imaging limits of diffuse low-grade gliomas, *sourmis*

Méthode

- essai n° 1 : le maximum de vert

dépend de la coloration -> nécessité de trouver



référence commune.

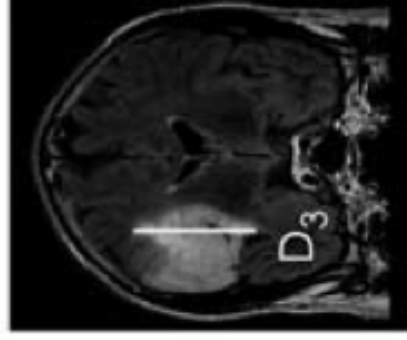
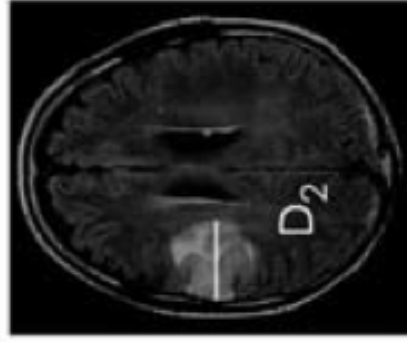
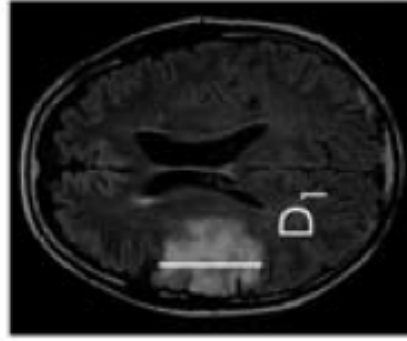
- essai n° 2 : la différence rouge-vert

plus elle est faible, plus l'image est grise (contient de l'oedème non coloré); indépendamment de l'âge de la lame.

Modéliser ?

- La tumeur est un système complexe. On peut la modéliser de plusieurs manières :
 - ▶ **comme un système isolé (croissance, migration, mort des cellules),**
 - ▶ en interaction avec son environnement (communication avec les cellules saines, angiogenèse, système immunitaire, ...),
 - ▶ comme un système couplé aux traitements (radiothérapie, chimiothérapie, ...).

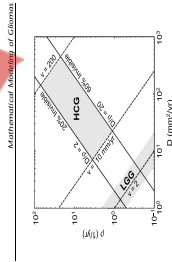
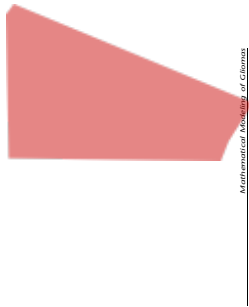
Calcul du rayon moyen



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

$$\text{MTD} = (2 \times V)^{\frac{1}{3}}$$

rayon moyen = MTD/2



Results of variation of $t_1 - t_0$ as a function of t_0 are shown in Fig. 1 bottom right (grey curve). These were obtained from simulation of (5) with $v = 2$ mm/year and $\kappa = 2$ /year. We remark that variations can be quite appreciable when t_0 varies from 1 to 100, but since nothing justifies a choice of a large initial tumour size, in applications the initial conditions corresponding to tumours of radius 1.

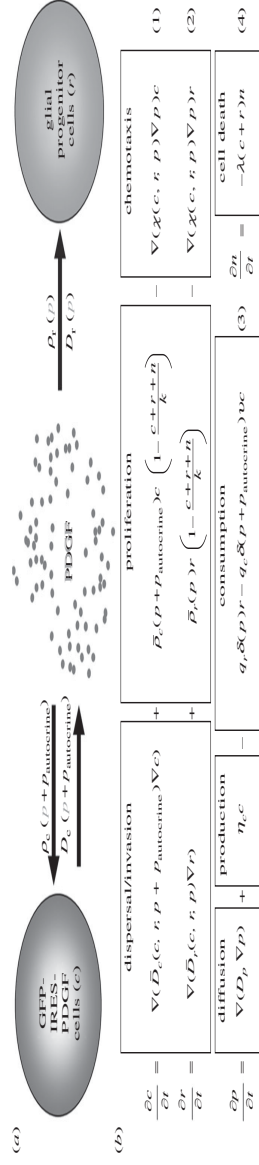
Clearly, parameters D and κ appearing in the model equation are also expected to play an important role in determination of value of the correction. We represent difference $t_1 - t_0$ between time of biological tumour genesis calculated with the diffusion-proliferation model and with linear extrapolation, in (D, κ) Fig. 2. There are two regions where the correction is significant: the grey area of linearity and maximum time evolution (not satisfied) and the grey area (where at least one condition is not satisfied). The frontier at-large diffusion coefficient is related to linearity constraint and its equation is: $\kappa/D = 1.3$ /mm². Frontiers at small diffusion coefficient values are related to radius of 15 mm not being reached after maximum time of 50 years. Minimum value of $t_1 - t_0$ is 0.3 mm²/year. The diagram which roughly corresponds to the equation of the second frontier. The diagram that depicts difference $t_1 - t_0$ between times of radiological tumour genesis calculated with the diffusion-proliferation

model, and tumour onset estimated with linear extrapolation, in the (D, κ) diagram is very similar to diagram of $t_1 - t_0$. Maximum is also reached for small values of κ and D , and its value is around 8 years, compared to 35 years for $t_1 - t_0$ (data not shown). We remark readily that time difference $t_1 - t_0$, on date of birth of the tumour increases with the age of the patient. The correction is significant when it exceeds 2.5 years for $\kappa \approx 0.25$ /year. On the other hand when κ is equal to 10/year, $t_1 - t_0$ is close to zero. When the value of v is taken equal to 4 mm/yr (mean diametric velocity for low-grade gliomas), variations of $t_1 - t_0$ change between 1 year for $\kappa = 10$ /year and 7 years for $\kappa = 1.2$ /year (at the limit of linearity).

Application to cases involving patients

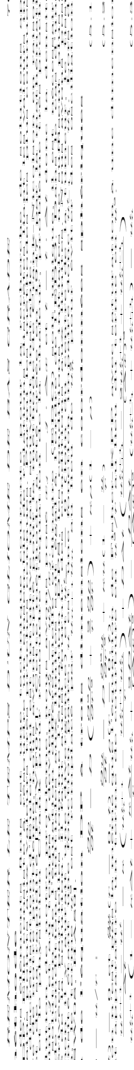
Having established usefulness of estimation of tumour genesis in a generic case, we now turn to applications to cases where we deal with real-life patients. A series of 264 patients with grade II glioma is used, followed up between 1992 and 2009 in a French glioma study group (Réseau d'Etude des Gliomes (REG), France) and subsequently at 18 years at MRI scan: (i) absence of definite contrast enhancement on T1-enhanced image, defined by nodules of high intensity; (ii) histological diagnosis of supratentorial hemispheric WHO grade II gliomas; and (iv) MRI follow-up before treatment, allowing to estimate diametric velocity of expansion of the tumour (a minimum of two available scans). Patients were excluded from the study when the tumour was considered (except for resective biopsy) when radiological information had occurred, either proved histologically or suspected, when a contrast enhancement appeared on MRI. For each MRI, three diameters were manually measured always by the same neurosurgeon who was blind to patient and examination data, and who did not participate in subsequent analysis of the data. In the axial plane, the largest diameters of anterior-posterior axis and perpendicular to it were measured. In the sagittal plane, only T1-weighted images were available and were used to measure largest diameter along the vertical axis. Mean diameter was obtained as geometric mean of the three diameters, that is cube root of their product. For each patient, the curve providing velocity of expansion of mean tumour diameter as function of time was fitted by linear regression

Modèle avec précurseurs

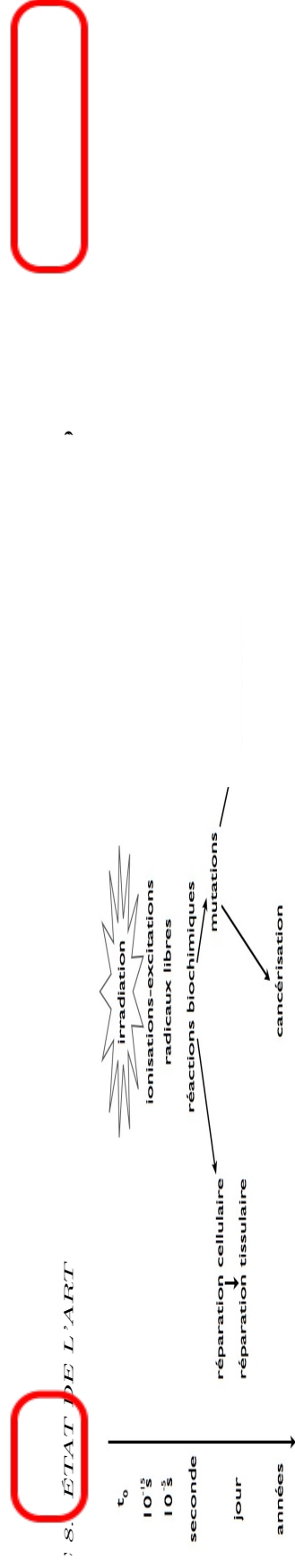


Discrétisation du modèle

- méthode de Crank-Nicholson
- 2 conditions aux limites et 2 conditions initiales
- $\Delta r = 0,02$ mm et $\Delta t = 0,01$ an

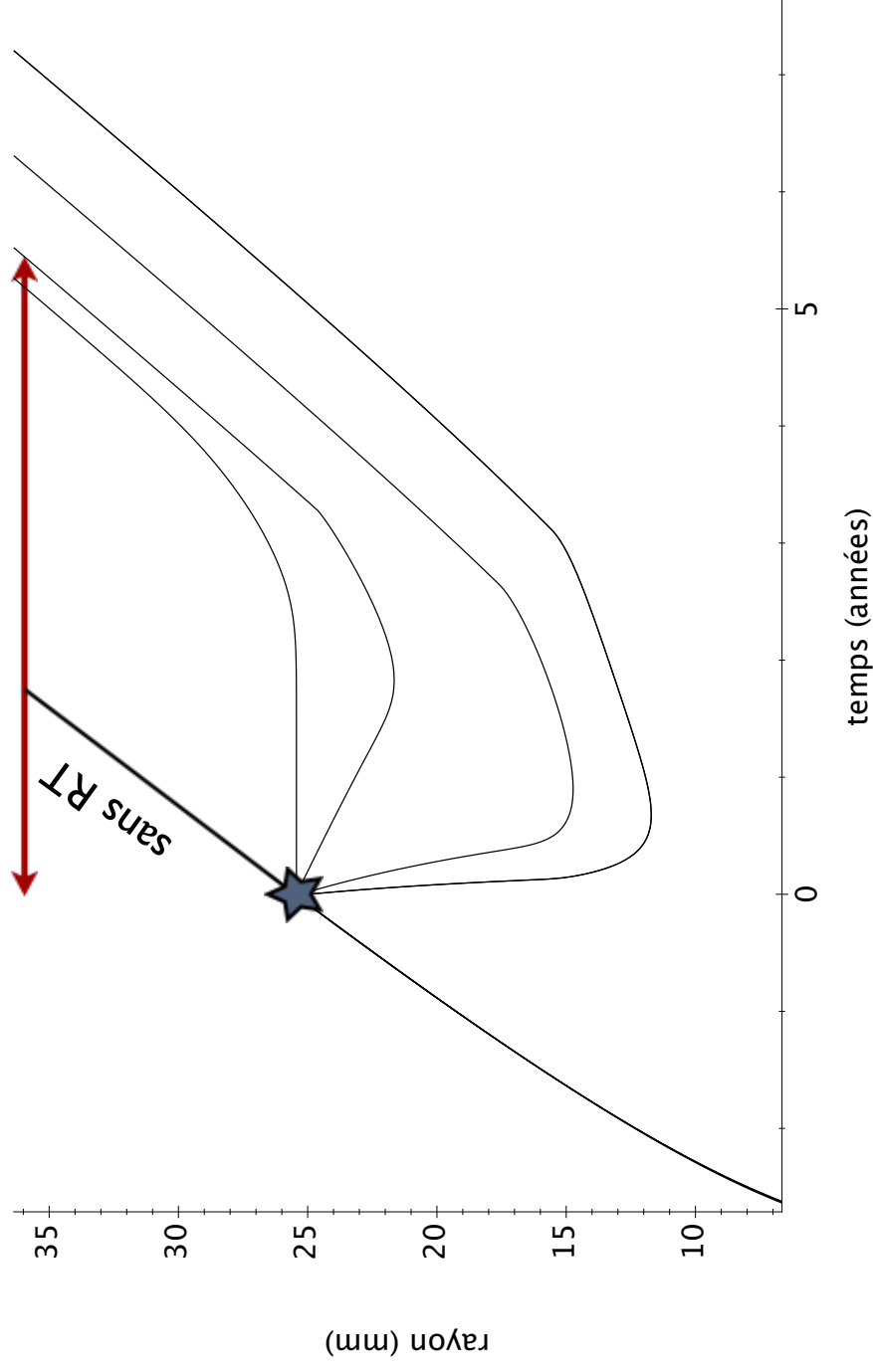


Les effets biologiques de la radiothérapie



Caractériser l'efficacité de la radiothérapie

survie sans transformation maligne



L'œdème contrôlé v_d

