



BRETAGNE

Ré-irradiation des glioblastomes

SNOB - 2025

Ré-irradiation des GBM

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Guidelines

ESTRO/EANO recommendation on reirradiation of glioblastoma

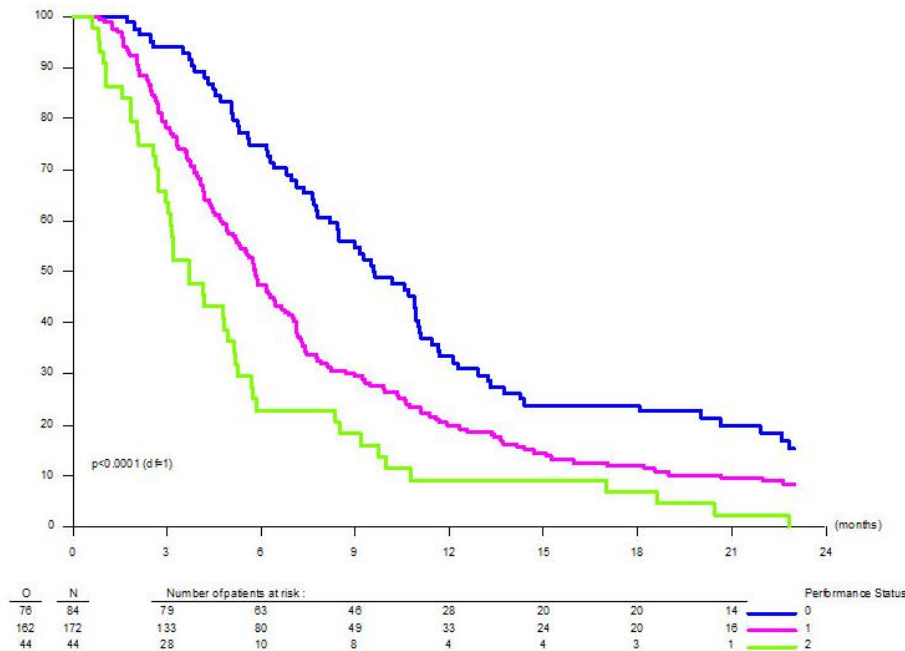


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Rationnel de la réirradiation des GBM récurrents ?

► Pronostic très péjoratif

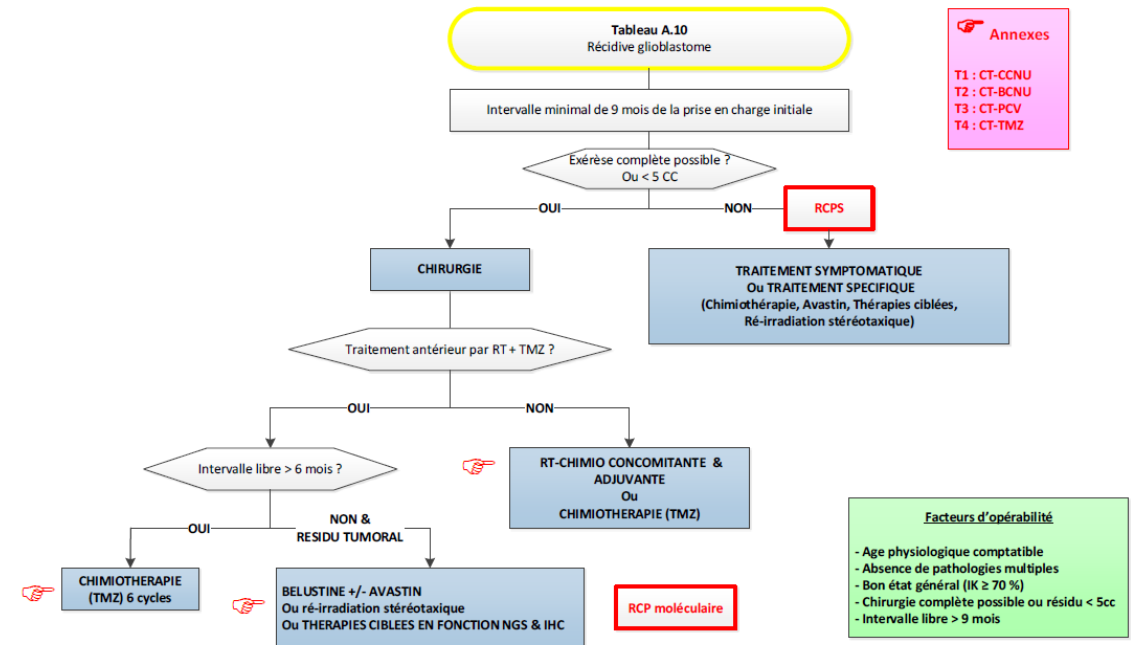
A. PERFORMANCE STATUS



Gorlia et al., EORTC, JCO, 2011

► Options thérapeutiques très limitées

SNOB



► Nombreuses expériences de réirradiation des années 1920 à 1960.

Nieder et al., ARO, 2017

Rationnel de la réirradiation des GBM récurrents ?

- ▶ Gliome infiltrant diffus de la ligne médiane
 - ▶ Bénéfice de la réirradiation : clinique et réponses radiologiques
 - ▶ Doses de 20 à 24 Gy
 - ▶ Contraintes spécifiques à la réirradiation du tronc
 - ▶ Très peu de toxicité

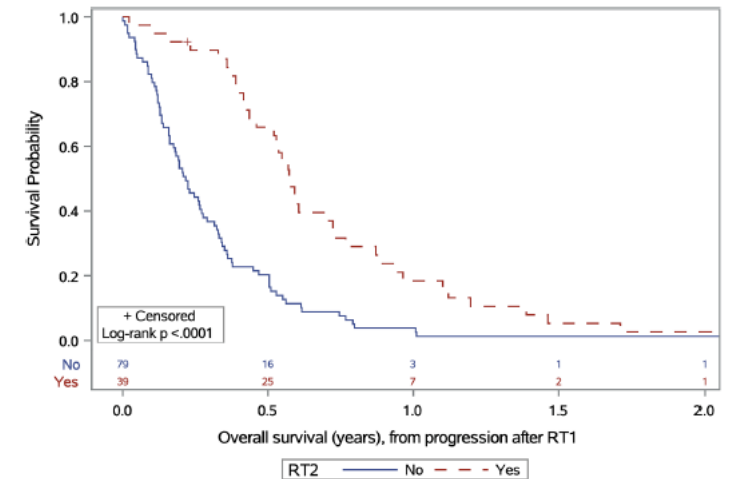
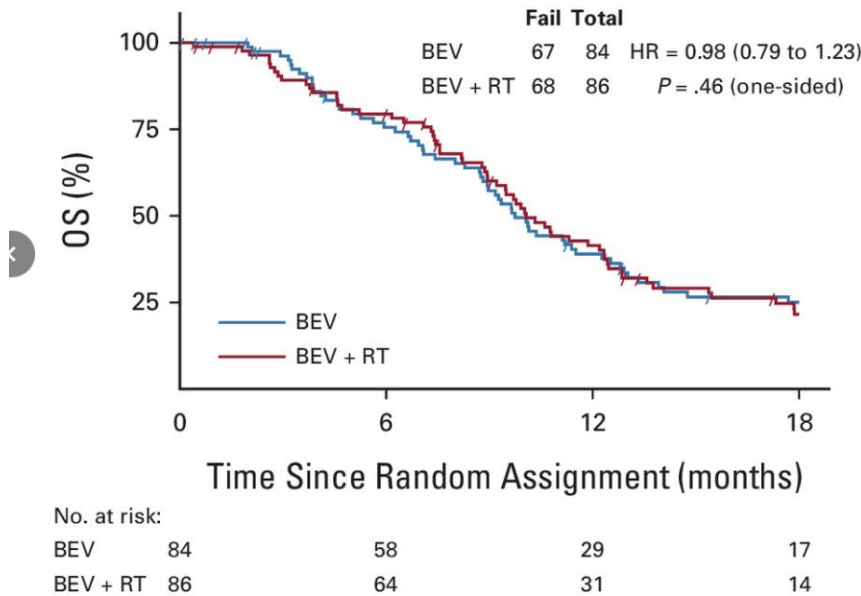


Fig. 1. Overall survival, with index time at progression after RT1.

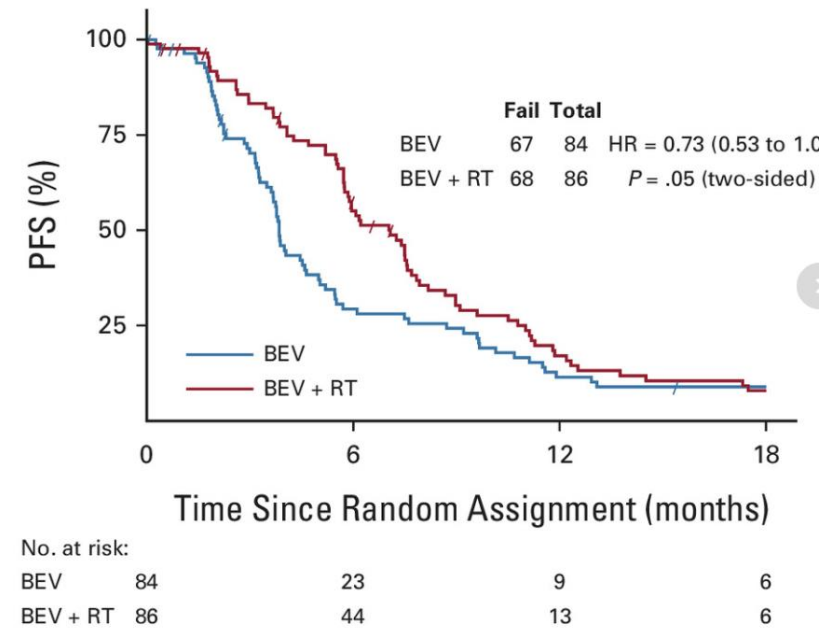
Ré-irradier des GBM, à quoi ça sert ?

- ▶ RTOG 1205, essai phase II : bevacizumab vs bevacizumab + ré-irradiation

A



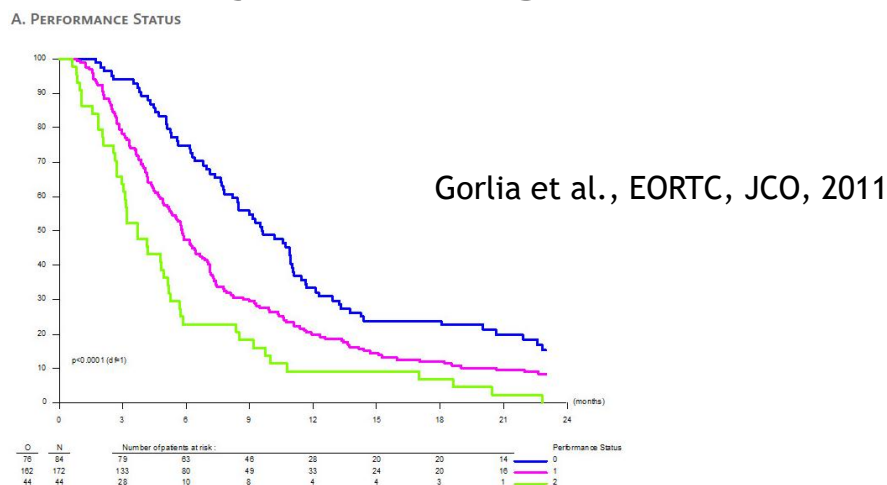
B



- ▶ Bénéfice en PFS mais pas en OS
- ▶ Traitement globalement bien toléré

Ré-irradiation : sélection des patients

► Facteur pronostic majeur : état général



- Délai > 6 mois depuis RT
 - + long recul, moindre risque d'évolution multifocale
 - Délai court = risque de radiorésistance
 - Potentiel de récupération après 6 mois
- Facteurs non démontrés : MGMT, ttt systémique concurrent, taille tumorale, ré-opération

KQ1: Which patients should be considered for reirradiation?	Strength of recommendation	Level of evidence
Recommendations		
1. Reirradiation of patients with recurrent glioblastoma should be based on individual decision making and should only be recommended after careful discussion in an MDT balancing risks, benefits, and treatment alternatives (100 %; 19/19).	Strong	Expert opinion
2. Reirradiation of patients with recurrent glioblastoma may be considered with a KPS ≥ 60 and an interval > 6 months from the previous radiotherapy independent of age or MGMT methylation status (89 %; 17/19).	Conditional	Moderate
3. After gross total resection of recurrent glioblastoma reirradiation may be considered in patients with favorable prognostic factors (84 %; 16/19).	Conditional	Low
Statement		
1. Although reirradiation has not yet been shown to provide an OS benefit, a prolongation of progression-free survival can be expected after careful patient selection (84 %; 16/19).	—	Moderate

Quel bilan avant d'envisager ré-irradiation ?

► Distinguer récurrence lésionnelle de radionécrose.

► IRM multi-modale : T1-gado, T2, T2 FLAIR

► Séquences de perfusion : néo-angiogénèse

► Spectroscopie

► Médecine nucléaire : TEP acides aminés

► Importance de l'expertise locale +++

Table 2

Key question 2 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

<i>KQ2: What imaging is required to assess recurrence after primary treatment of GB?</i>	Strength of recommendation	Level of evidence
Recommendations		
4. To assess recurrence, particularly in-field, contrast-enhanced T1-weighted imaging is required, and the addition of advanced MRI or AA-PET is recommended for its differentiation from pseudoprogression/radiation necrosis (95 %; 19/20).	<i>Strong</i>	<i>Low</i>
Statement		
2. Advanced imaging techniques (i.e., perfusion MRI, MR spectroscopy, AA-PET) increase diagnostic accuracy for differentiation of recurrence from pseudoprogression, but no technique, nor combination of techniques, is clearly superior to the other (95 %; 19/20).	—	<i>Low</i>

Quels volumes cibler lors d'une réirradiation ?

- ▶ Eviter lésions volumineuses > 6 cm, multifocales, avec envahissement lepto-méningé.

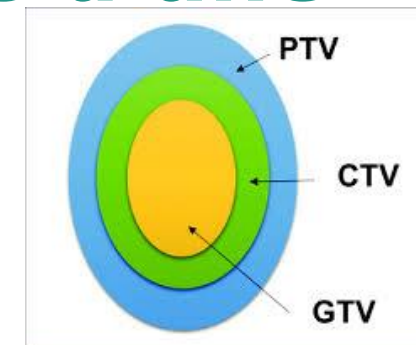
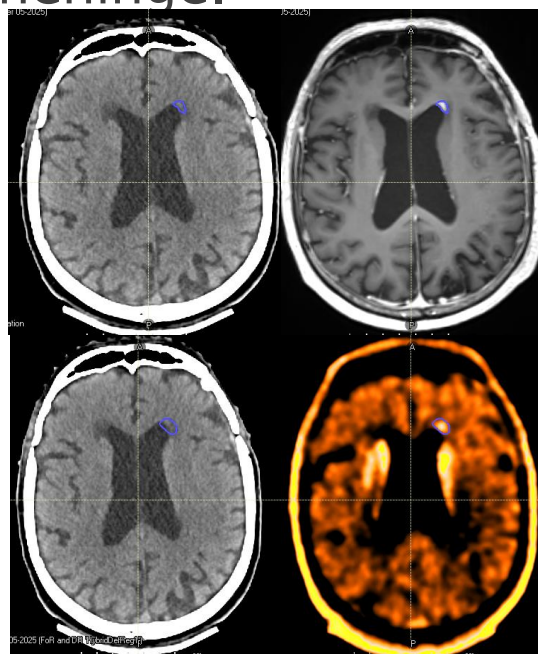
▶ GTV

- ▶ T1 gado
- ▶ T2-FLAIR
- ▶ TEP acides aminés

▶ CTV

- ▶ Marge pas forcément nécessaire notamment en stéréo
- ▶ Pas de consensus. Option 3-5 mm

- ▶ PTV : < 3 mm, selon pratiques du service



KQ3: What are requirements for optimal target definition?	Strength of recommendation	Level of evidence
Recommendations		
5. Rigid image registration for target volume definition and dose accumulation is recommended (89 %; 17/19).	Strong	Moderate
6. CE-T1-weighted contrast enhancing lesions, new or progressive T2-weighted/ T2-weighted FLAIR abnormalities, and AA-PET-avid regions should be included in the GTV (80 %; 16/20).	Strong	Expert opinion
7. A CTV margin is not mandatory, but a GTV to CTV margin of 3–5 mm can be added optionally (depending on overall volume, dose/fractionation and pattern of recurrence), while a maximum CTV to PTV of 3 mm is recommended (80 %; 16/20).	Strong	Expert opinion
Statement		
3. If functional imaging is considered, both AA-PET as well as advanced MRI are valid options, although no consensus could be reached to whether or not to include perfusion suspect regions into the GTV (80 %; 16/20).	—	Expert opinion

Quels schémas de ré-irradiation proposer ?

- ▶ Schémas les plus utilisés : 36 Gy / 18 fx ou 35 Gy / 10 fx > bien toléré
- ▶ De plus en plus de données en stéréotaxie
 - ▶ 25-35 Gy en 5 à 7 séances
 - ▶ Dose unique 16-24 Gy
- ▶ Pratiques très hétérogènes
 - ▶ Globalement même efficacité OS médiane 9 mois
 - ▶ BED10 > 40 Gy en stéréo
 - ▶ BED 10 > 45 Gy en RT fractionnée
 - ▶ Pas de bénéfice à l'escalade de dose > 55 Gy
 - ▶ Privilégier les schémas les plus courts possibles

KQ4: What is the recommended dose and fractionation for reirradiation?

Strength of recommendation

Level of evidence

Recommendations

8. A treatment in which a sufficient dose is delivered is preferred, and therefore, the biologically effective dose measured in EQD2 should be no less than 36 Gy in 2 Gy fractions (84 %; 16/19).

Strong

Moderate

9. Single fraction radiosurgery can be used for smaller lesions (e.g. GTV size up to 3 cm) (100 %; 18/18).

Strong

Expert opinion

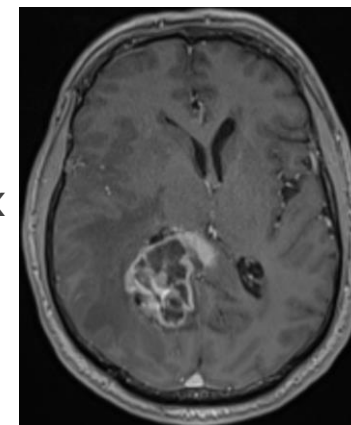
Statement

4. Prospective evidence with regards to safety and efficacy only exists for lesion sizes up to 6 cm (100 %; 18/18).

—

Expert opinion

- Volumineuses lésions :
 - RT fractionnée 36 Gy/18 fx
- Petites lésions :
 - RT stéréo en séance unique
- Entre les deux :
 - Hypofractionnement 35 Gy/10fx
 - Stéréo fractionnée 30 Gy / 3 à 5 fx



Plannification d'une réirradiation

- ▶ Cumul de dose EQD2 ($\alpha/\beta=3$)
- ▶ Contraintes aux OAR :
 - ▶ Pas de consensus en réirradiation
 - ▶ Si possible contraintes primo-irradiation
 - ▶ Contraintes spécifiques en réirradiation de plus en plus souvent proposées

OAR	Objective(s)
BRAINSTEM	$D \leq 54$ Gy [72] $D_{0.03cc} \leq 56$ Gy** $1-10$ cc*** < 59 Gy (periphery) [72] Surface $D_{0.03cc} \leq 60$ Gy [73]** Interior $D_{0.03cc} \leq 54$ Gy [73]
CHIASM	$D_{max} < 55$ Gy [72] $D_{0.03cc} \leq 55$ Gy [73]**
COCHLEA	Ideally one side mean < 45 Gy [74]
EYES	Macula < 45 Gy [75] Eye balls $D_{max} \leq 40$ Gy** (low priority)
LACRIMAL GLANDS	$D_{max} < 40$ Gy [76] Mean ≤ 25 Gy [73]
LENS	Ideally < 6 Gy Max 10 Gy [76]
OPTIC NERVES	$D_{max} \leq 54$ Gy [77] $D_{max} < 55$ Gy [72] $D_{0.03cc} \leq 56$ Gy**
PITUITARY	$D_{max} < 50$ Gy [78] ALARA

TABLE 3 Expert consensus-based cumulative dose guidance for normal tissue in reirradiation.

Organ	Desirable cumulative EQD2Gy ^a	Acceptable cumulative EQD2Gy ^a	α/β value ^a	Reference
Brain stem	$D_{0.03cc} \leq 70.2$ Gy	$D_{0.03cc} < 81$ Gy	Not specified	Ng 2021 ⁴³
Spinal cord	$D_{0.03cc} \leq 58.5$ Gy	$D_{0.03cc} < 67.5$ Gy	Not specified	Ng 2021 ⁴³
Optic chiasma	$D_{0.03cc} \leq 70.2$ Gy	$D_{0.03cc} < 81$ Gy	Not specified	Ng 2021 ⁴³
Optic nerve	$D_{0.03cc} \leq 70.2$ Gy	Unilateral: No dose constraint if the patient accepts Bilateral: $D_{0.03cc} < 81$ Gy	Not specified	Ng 2021 ⁴³
Temporal lobe	$D_{0.03cc} \leq 91$ Gy	$D_{0.03cc} < 105$ Gy	Not specified	Ng 2021 ⁴³

KQ5: What is the preferred treatment planning and delivery method?	Strength of recommendation	Level of evidence
KQ6: How should cumulative doses be assessed with regards to safety?		
Recommendations		
10. Advanced IGRT techniques should be employed for high dose reirradiation (95 %; 18/19).	Strong	Low
11. EQD2 dose recalculation is preferred (over BED and EUD) and should be used for dose accumulation, as it is most commonly used in the literature and easy to interpret (89 %, 16/18).		Moderate
12. PTV prescription and compromise should follow the following cascading steps: 1) No PTV compromise if cumulative OAR doses are deemed safe and/ or acceptable. 2) PTV compromise allowed to keep cumulative OAR doses safe and/ or acceptable. 3) If a reasonable CTV / GTV dose coverage is not to be achieved, dose prescription may be adapted to reach safe or acceptable OAR doses. (88 %; 15/17)	Strong	Expert opinion
13. Recovery from previous irradiation has only consistently been described for brain tissue and spinal cord and thus, should only be considered for assessing cumulative doses in these organs (88 %; 16/17).	Strong	Low
Statement		
5. The minimum set of OAR to evaluate after biological dose accumulation include: brain, brain stem, optic chiasm, optic nerves/ tract, cranial nerves in close proximity to PTV (89 %; 16/18).	—	Expert opinion
6. Both methods of dose accumulation are considered valid when assessing cumulative doses to brain tissue: a) Same OAR constraints as for first course; dose discount for first course considered. b) Cumulative OAR constraints used. (100 %; 17/17)	—	Expert opinion
7. As there is considerable uncertainty about recovery of optic chiasm and optic nerves' function, allowance of cumulative doses should be carefully assessed (100 %; 18/18).	—	Expert opinion

Ré-irradiation : place des traitements systémiques ?

- ▶ Intérêt controversé : manque de données d'essais randomisés
- ▶ Ajout du TMZ :
 - ▶ Comparaison d'essais sembleraient en faveur d'une meilleure PFS et OS
 - ▶ Principalement chez MGMT méthylés : intérêt de la réirradiation ?
 - ▶ Tolérance re-RT + TMZ similaire à re-RT : < 10 % grade III
- ▶ Ajout du bevacizumab
 - ▶ Bevacizumab + re-RT bien tolérée : < 5% tox aigue GIII, pas de tox tardive
 - ▶ Diminue le risque de radionécrose
- ▶ Pas de recommandations d'association

Table 6

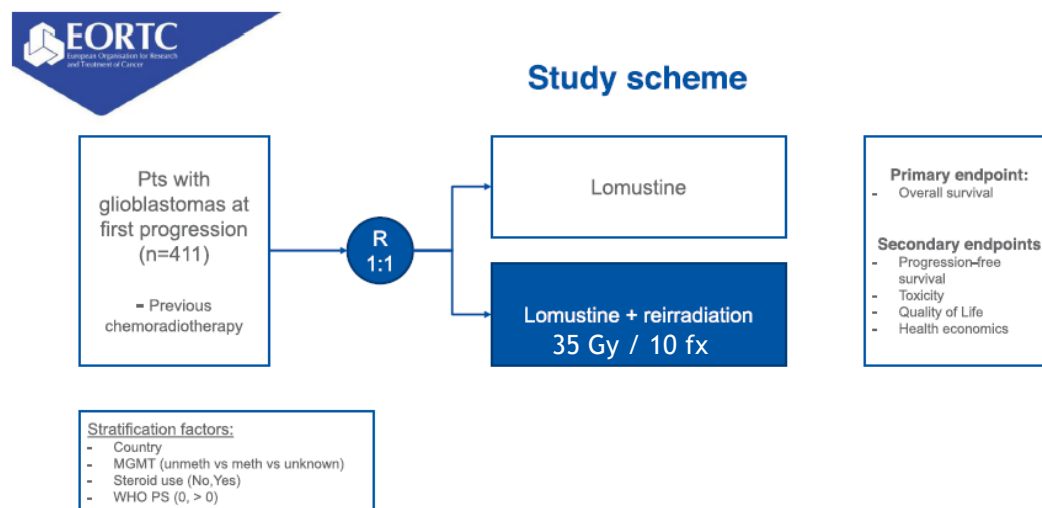
Key question 7 and 8 recommendations and statements with strength of recommendation and level of evidence; level of evidence in parenthesis (percentage; absolute number of votes per total voters).

<i>KQ7: What is the evidence for combined modality reirradiation?</i>	Strength of recommendation	Level of evidence
<i>KQ8: What is the role of maintenance systemic therapy after reirradiation?</i>		
Recommendations		
14. When considering combined modality treatment, there is no need to change target definition, dose and fractionation (94 %; 17/18).	<i>Strong</i>	<i>Expert opinion</i>
15. The use of systemic treatment together with reirradiation of recurrent glioblastoma should be further explored in prospective clinical trials (95 %; 18/19).	<i>Strong</i>	<i>Expert opinion</i>
Statement		
8. A clear recommendation for this approach, especially with respect to a specific drug combination, cannot be given (94 %; 17/18).	—	<i>Moderate</i>
9. Currently, data are insufficient to support the routine use of concurrent or maintenance systemic therapy after reirradiation (89 %; 16/18).	—	<i>Expert opinion</i>

Ré-irradiation des GBM : points clés

- ▶ Objectifs de ces recommandations : harmonisation des pratiques.
- ▶ Niveau de preuve : jamais fort, au mieux modéré, le plus souvent basé sur des opinions d'experts.
- ▶ La réirradiation des glioblastomes fait partie des options de traitement des glioblastomes récidivants chez des patients sélectionnés.
- ▶ Efficacité attendue principalement sur la PFS : importance de la qualité de vie.
- ▶ Toxicité très limitée.
- ▶ Nécessité d'essais prospectifs de phase III pour valider sa place.

LEGATO : essai EORTC phase III



Funded by
the European Union

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Fig. 1 Study scheme of the EORTC-2227-BTG (LEGATO) trial



► Critères inclusion :

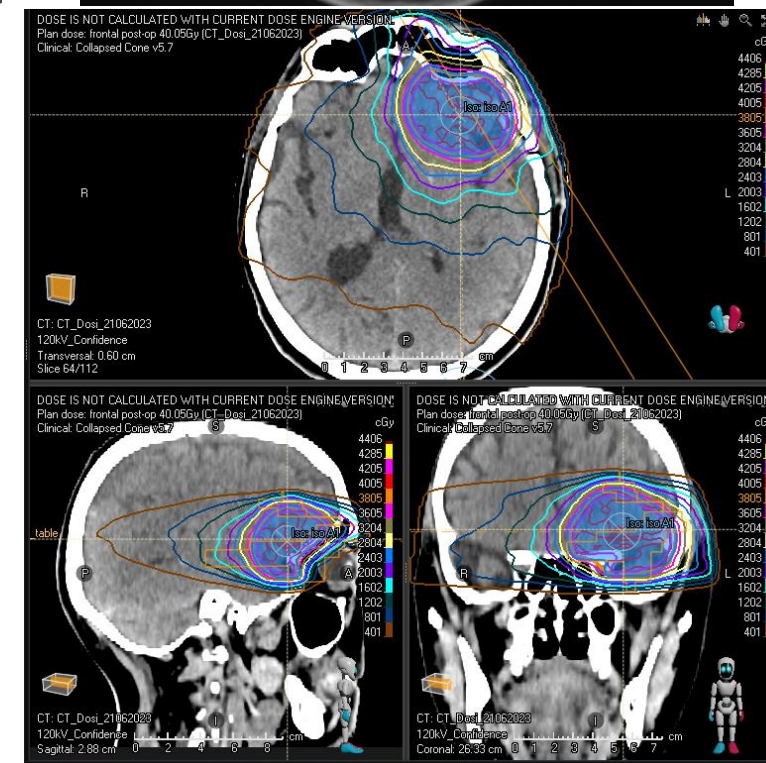
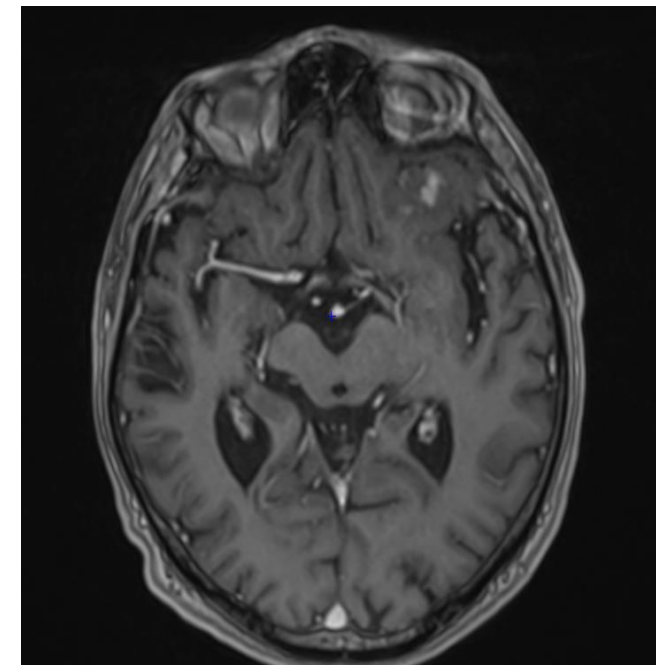
- Progression/récurrence au – 6 mois après RT
- GBM IDH-WT
- CTC stables ou en diminution la semaine avant l'inclusion
- Taille maximum de la lésion < 5 cm
- PS 0-2

Ré-irradiation : pour résumer

- ▶ Le bon patient : volume faible, bon état général, intervalle depuis pec initiale le plus long possible
- ▶ Le bon bilan : multimodal selon expertises locales : IRM multiparametrique + TEP
- ▶ Le bon volume : GTV + marge limitée, maximum 3-5 mm
- ▶ Le bon fractionnement : dépend essentiellement de la taille de la lésion
- ▶ Le moins de risque possible : cumul et respect des contraintes aux OAR (tronc, voies optiques...)
- ▶ Place par rapport à un traitement systémique: très variable, à discuter au cas par cas en RCP

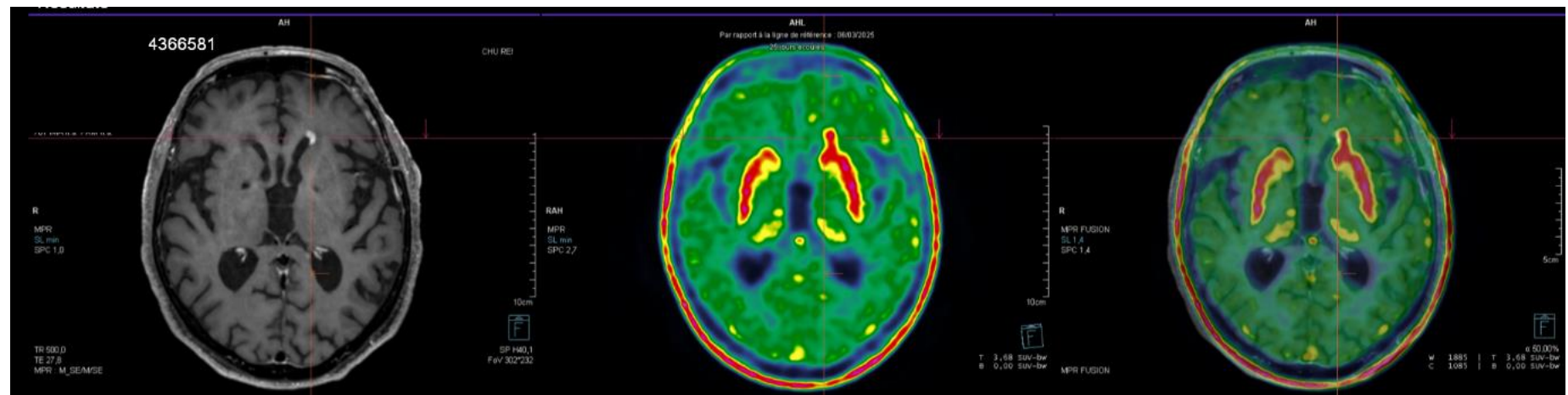
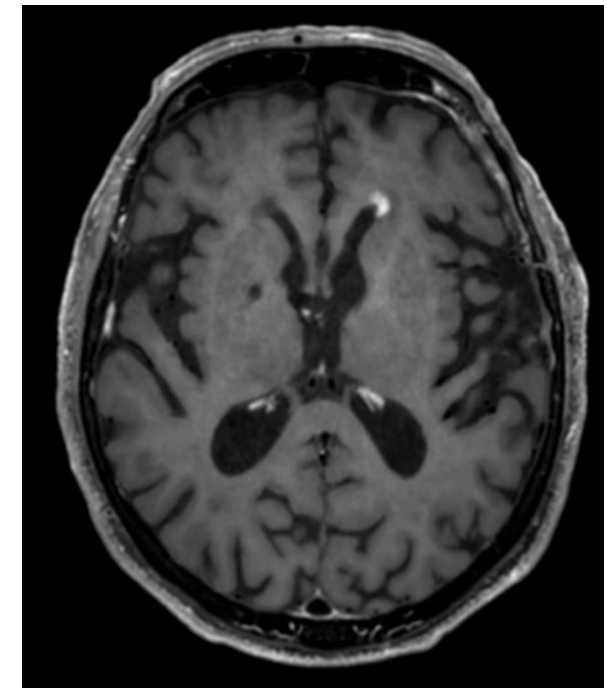
Mr G., 78 ans

- ▶ Février 2023 : crise d'épilepsie généralisée
- ▶ Biopsie : Gliome haut grade, pas d'expression IDH 1
- ▶ Résection neurochirurgicale le 1^{er} juin 2023, exérèse complète sur IRM post-opératoire
- ▶ Radio-chimiothérapie 40 Gy / 15 fractions
- ▶ Temodal adjuvant 6 cycles jusqu'au 22/01/24



Mr G., 78 ans

- ▶ IRM Mars 2025 : majoration d'une pdc nodulaire corne frontale du ventricule latéral gauche, suspecte.
- ▶ TEP-DOPA : hypercaptation suspecte



Mr G. , 78 ans

- ▶ Réirradiation stéréotaxique 20 Gy, 1 fraction, cyberknife le 09/05/2025
- ▶ Bonne tolérance, IRM à 2 mois en juillet 2025 :
 - ▶ Majoration en taille de la pdc au contact de la corne ventriculaire frontale G
 - ▶ Apparition de 2 nouvelles pdc dans la substance blanche adjacente, suspectes
- ▶ Reprise temodal

