Société Française de Neurochirurgie

Club de Neuro-Oncologie

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Chers Amis,

Nous sommes heureux de vous proposer la 4ème lettre d'information du Club de Neuro-Oncologie de la société Française de Neurochirurgie. Cette lettre d'information a pour but de présenter les avancées des travaux du club, de discuter les projets à venir, d'informer sur les évènements touchant à la neuro-oncologie chirurgicale, de mettre en avant les travaux issus du Club via des entretiens avec les participants, de discuter des articles récents pouvant impacter notre pratique via des éditos, et d'échanger entre nous. Nous rappelons que cette lettre constitue un lieu d'échange et une libre tribune pour que vous puissiez y exposer vos idées et projets.

Pour cette 4ème édition, nous vous rapportons un entretien avec le Professeur Alexandre Carpentier qui nous présentera ses travaux sur une approche innovante en neuro-oncologie, l'ouverture de la barrière hémato-encéphalique par l'emploi des ultrasons dans les tumeurs cérébrales. Ensuite, Frédéric Dhermain et Philippe Métellus nous proposerons une analyse critique de deux publications récentes sur les métastases cérébrales rapportées dans Lancet Oncology au mois d'août dernier. Le but de cette revue est d'exposer la vision du radiothérapeute oncologue et du neurochirurgien oncologue sur la stratégie adjuvante optimale après exérèse chirurgicale d'une métastase cérébrale chez le patient oligométastatique. Enfin, nous vous présenterons les derniers travaux et publications scientifiques réalisés sur l'impulsion du Club. .

Nous vous souhaitons une bonne lecture.

Johan Pallud et Philippe Metellus, pour le Club de Neuro-Oncologie de la SFNC

Informations sur la prochaine réunion présentielle du Club de Neuro-Oncologie de la SFNC

Lors du congrès de la SFNC 2018
Réunion du club de Neuro-Oncologie

Vous souhaitez communiquer une information ou intervenir au cours de la réunion présentielle du Club de Neuro-Onco ? Merci de contacter Johan Pallud et/ou Philippe Metellus par courriel.

Appel à communication dans la lettre d'information

Vous souhaitez communiquer une information dans la lettre d'information, présenter une réunion, discuter une publication, proposer un poste dans votre service, nous faire part d'un élément ayant trait à la neuro-oncologie neurochirurgicale ?

Merci de contacter Johan Pallud et/ou Philippe Metellus par courriel.

Sommaire

Actualités sur les travaux et publications scientifiques du Club de Neuro-Oncologie de la SFNC

Publications scientifiques

- **1 article accepté dans Neurochirurgie,** intitulé: « Carmustine wafer implantation for high-grade gliomas : Evidence based safety efficacy and practical recommandations from the neurooncology club of the french society of neurosurgery » par Alexandre ROUX, François CAIRE, Jacques GUYOTAT, Philippe MENEI, Philippe METELLUS et Johan PALLUD. Neurochirurgie. 2017 Dec ;63(6) :433-433. doi: 10.1016/j.neuchi.2017.07.003.

Abstract: There is a growing body of evidence that Carmustine wafer implantation during surgery is an efficient therapeutic adjunct to the standard combined radio-chemotherapy regimen using Temozolomide in newlydiagnosed and recurrent high-grade glioma patient's management with a statistically significant survival benefit demonstrated across several randomized clinical trials, prospective and retrospective studies (grade A recommendation). Compelling clinical data also support the safety of Carmustine wafer implantation (grade A recommendation) in these patients and suggest that observed adverse events can be avoided in experienced neurosurgeon hands. Furthermore, Carmustine wafer implantation does not seem to impact negatively the quality of life and the completion of adjuvant oncological treatments (grade C recommendation). Moreover, emerging findings support the potential of high-grade gliomas molecular status, especially the O(6)-Methylguanine-DNA Methyltransferase promoter methylation status, in predicting the efficiency of such a surgical strategy, especially at recurrence (grade B recommendation). Finally, Carmustine wafer implantation appears to be cost-effective in high-grade glioma patients when performed by experienced team and when total or subtotal resection can be achieved. Altogether, these data underline the actual need for a new randomized clinical trial to assess the impact of a maximal safe resection with Carmustine wafer implantation followed by the standard combined chemoradiation protocol stratified by molecular status in high-grade glioma patients.

Nous rappelons que ce travail du Club de Neuro-Oncologie est la réalisation d'un de nos engagement, à savoir de produire des articles de recommandations sous l'égide de la SFNC et écrits par nos plus jeunes collègues.
La version finale PDF est jointe à cette lettre d'information

- **1 article accepté dans Journal of Neuro-Oncology,** intitulé: « Prognostic factors for survival in adult patients with recurrent glioblastoma : a decision-tree-based model » par Etienne AUDUREAU, Anais CHIVET, Renata URSU, Robert CORNS, Philippe METELLUS, Georges NOEL, Sonai ZOUAOUI, Jacques GUYOTAT, Pierre-Jean LE RESTE, Thierry FAILLOT, Fabien LITRE, Nicolas DESSE, Antoine PETIT, Evelyne EMERY, Emmanuelle LECHAPT-ZALCMAN, Johann PELTIER, Julien DUNTZE, Edouard DEZAMIS, Jimmy VOIRIN, Philippe MENEI, François CAIRE, Phong DAM HIEU, Jean-Louis BARAT, Olivier LANGLOIS, Jean-Rodolphe VIGNES, Pascale FABBRO-PERAY, Adeline RIONDEL, Elodie SORBETS, Marc ZANELLO, Alexandre ROUX, Antoine CARPENTIER, Luc BAUCHET, Johan PALLUD for the Club de Neuro-Oncologie of the Société Française de Neurochirurgie. J Neurooncol. 2017 Nov 20. doi: 10.1017/s11060-017-2685-4.

Abstract: We assessed prognostic factors in relation to OS from progression in recurrent glioblastomas. Retrospective multicentric study enrolling 407 (training set) and 370 (external validation set) adult patients with a recurrent supratentorial glioblastoma treated by surgical resection and standard combined chemoradiotherapy as first-line treatment. Four complementary multivariate prognostic models were evaluated: Cox proportional hazards regression modeling, single-tree recursive partitioning, random survival forest, conditional random forest. Median overall survival from progression was 7.6 months (mean, 10.1; range, 0–86) and 8.0 months (mean, 8.5; range, 0–56) in the training and validation sets, respectively ($p = 0.900$). Using the Cox model in the training set, independent

predictors of poorer overall survival from progression included increasing age at histopathological diagnosis (aHR, 1.47; 95% CI [1.03–2.08]; p = 0.032), RTOG–RPA V–VI classes (aHR, 1.38; 95% CI [1.11–1.73]; p = 0.004), decreasing KPS at progression (aHR, 3.46; 95% CI [2.10–5.72]; p < 0.001), while independent predictors of longer overall survival from progression included surgical resection (aHR, 0.57; 95% CI [0.44–0.73]; p < 0.001) and chemotherapy (aHR, 0.41; 95% CI [0.31–0.55]; p < 0.001). Single-tree recursive partitioning identified KPS at progression, surgical resection at progression, chemotherapy at progression, and RTOG–RPA class at histopathological diagnosis, as main survival predictors in the training set, yielding four risk categories highly predictive of overall survival from progression both in training (p < 0.0001) and validation (p < 0.0001) sets. Both random forest approaches identified KPS at progression as the most important survival predictor. Age, KPS at progression, RTOG–RPA classes, surgical resection at progression and chemotherapy at progression are prognostic for survival in recurrent glioblastomas and should inform the treatment decisions.

- **1 article accepté dans Journal of Neuro-Oncology,** intitulé: « Recurrent glioblastomas in the elderly after maximal first-line treatment : does preserved overall condition warrant a maximal second-line treatment ? » par Marc ZANELLO, Alexandre ROUX, Renata URSU, Sophie PEETERS, Luc BAUCHET, Georges NOEL, Jacques GUYOTAT, Pierre-Jean LE RESTE, Thierry FAILLOT, Fabien LITRE, Nicolas DESSE, Evelyne EMERY, Antoine PETIT, Johann PELTIER, Jimmy VOIRIN, François CAIRE, Jean-Luc BARAT, Jean-Rodolphe VIGNES, Philippe MENEI, Olivier LANGLOIS, Edouard DEZAMIS, Antoine CARPENTIER, Phong DAM HIEU, Philippe METELLUS, Johan PALLUD for the Club de Neuro-Oncologie of the Société Française de Neurochirurgie. J Neurooncol. 2017 Nov;135(2) :285-297. doi: 10.1017/s11060-017-2573-y.

Abstract: A growing literature supports maximal safe resection followed by standard combined chemoradiotherapy (i.e. maximal first-line therapy) for selected elderly glioblastoma patients. To assess the prognostic factors from recurrence in elderly glioblastoma patients treated by maximal safe resection followed by standard combined chemoradiotherapy as first-line therapy. Multicentric retrospective analysis comparing the prognosis and optimal oncological management of recurrent glioblastomas between 660 adult patients aged of < 70 years standard group) and 117 patients aged of ≥70 years (elderly group) harboring a supratentorial glioblastoma treated by maximal first-line therapy. From recurrence, both groups did not significantly differ regarding Karnofsky performance status (KPS) (p = 0.482). Oncological treatments from recurrence significantly differed: patients of the elderly group received less frequently oncological treatment from recurrence (p < 0.001), including surgical resection (p < 0.001), Bevacizumab therapy (p < 0.001), and second line chemotherapy other than Temozolomide (p < 0.001). In multivariate analysis, Age ≥70 years was not an independent predictor of overall survival from recurrence (p = 0.602), RTOG-RPA classes 5–6 (p = 0.050) and KPS at recurrence <70 (p < 0.001), available in all cases, were independent significant predictors of shorter overall survival from recurrence. Initial removal of ≥ 90% of enhancing tumor (p = 0.004), initial completion of the standard combined chemoradiotherapy (p = 0.007), oncological treatment from recurrence (p < 0.001), and particularly surgical resection (p < 0.001), Temozolomide (p = 0.046), and Bevacizumab therapy (p = 0.041) were all significant independent predictors of longer overall survival from recurrence. Elderly patients had substandard care from recurrence whereas age did not impact overall survival from recurrence contrary to KPS at recurrence <70. Treatment options from recurrence should include repeat surgery, second line chemotherapy and anti-angiogenic agents.

- **1 article en préparation** concernant la présentation à usage neurochirurgical de la nouvelle classification des gliomes diffus de l'adulte, version 2016, de l'OMS, intitulé : « Implication of the revised WHO 2016 Classification of gliomas from a neurosurgical perspective : Evolving concepts and pratical applications » par Philippe METELLUS, Johan PALLUD et Dominique FIGARELLA-BRANGER.

Abstract: A large body of literature indicates that certain glioma molecular alterations define subgroups that are prognostic and can be used in the clinical management of infiltrating glioma patients. This has led to repparaise the purely morphologically based concepts that were used as exclusive defining criteria in the WHO 2007 classification. Recently, the 2016 World Health Organization (WHO) classification of tumors of the central nervous system (CNS) has promoted the pathology into a molecular era as the result of integration of relevant biomarkers. The 2016 CNS WHO remarkably redefined the diffuse gliomas based on the traditional histology features and molecular parameters centered around isocitrate dehydrogenase (IDH) and 1p/19q diagnostics. Apart from assessment of IDH mutational status and 1p/19q testing, several other markers can be considered for routine testing, including assessment of copy number alterations of chromosome 7 and 10 and of TERT promoter, BRAF, and H3F3A mutations.
We performed here a review of the WHO 2016 classification with a focus on adult brain gliomas as well as a search and review of publications in the literature relevant for glioma classification from 2007 up to now has been performed. This work will also include a recommendation of genes of which routine testing is clinically useful.
The idea of incorporating the molecular features in classifying tumors of the central nervous system has led to raise actual conceptual diagnostic process issues, particularly with respect to linking morphology to molecular alterations. As a solution the concept of a "layered diagnosis" has been introduced. This still allows at a lower level a purely « morphologically based diagnosis » and also at a higher level an « integrated diagnosis » incorporating molecular characteristics of the tumor.
We propose here a comprehensive analysis of the 2016 WHO revised classification from a neurosurgical perspective with a focus on tissue sampling process and efficient integration of the molecular findings into final diagnosis and glioma patient management strategy.

Vous souhaitez proposer une idée d'article à publier dans Neurochirurgie concernant l'harmonisation des pratiques en neurochirurgie oncologique ?
Merci de contacter Johan Pallud et/ou Philippe Metellus par courriel.
TOUTES LES IDEES SONT BIENVENUES

➢ <u>Organisation de Réunion scientifique</u>

Table ronde sur les Métastases cérébrales en coordination avec l'ANOCEF lors du dernier congrès de la SNCLF, Paris, Novembre 2017. Philippe Métellus, Philippe Cornu, Khê-Hoang Xuang.

- Chirurgie des métastases cérébrales : actualités et nouveaux concepts – Ph. Métellus.
- Radiochirurgie stéréotaxique dans les métastases cérébrales : y-a-t-il encore une place de l'encéphale in toto ? – CA Valery
- Immunothérapie et thérapie ciblées combinées au traitement local des métastases cérébrales : efficacité et critères d'évaluation – F Dhermain
- Prise en charge des métastases cérébrales : stratégie globale et recommandations – E Le Rhun
- Session interactive / Cas Clinique – A Roux

Prochains congrès impliquant la neuro-oncologie chirurgicale

- **SFNC**
  Congrès Annuel, 28 au 30 mars 2018, Grenoble
  (http://congres.neurochirurgie.fr)

- **JNLF**
  Journées de Neurologie de Langue Française, 10 au 13 avril 2018, Bordeaux
  (http://www.jnlf.fr/congres-jnlf-2018/mot-du-president)

- **AANS annual meeting**
  Du 28 avril au 2 mai 2018, New Orleans, USA
  (http://www.aans.org/en/Annual-Scientific-Meeting/2018)

- **ASCO**
  American Society of Clinical Oncology annual meeting, 1 au 5 juin 2018 Chicago, USA
  (http://am.asco.org)

- **2nd Edition of International Conferences on Clinical Oncology and Molecular Diagnostics**
  Du 11 au 13 juin 2018, Dublin, Irelande
  (http://oncology.euroscicon.com/)

- **BRAIN METS**
  8th Annual Brain Metastases Research and Emerging Therapy Conference, les 21 et 22 Septembre 2018, Marseille
  (http://brain-mets.com/)

- **CNS annual meeting**
  Congress of Neurological Surgeons 2018 Annual Meeting, 6 au 10 octobre 2018, Houston, USA
  (https://www.cns.org/meetings/2018-cns-annual-meeting)

- **EANO annual meeting**
  European Association of Neuro-Oncology (EANO), 11 au 14 octobre 2018, Stockholm, Suede
  (https://www.eano.eu/eanomeetings/eano-2018-meeting/eano-2018-meeting-welcome/

- **EANS**
  Annual Meeting, 21 au 25 octobre 2018, Brussels, Belgique
  (http://eans2018.com)

- **SNO**
  Society for Neuro-Oncology congress, 15 au 18 novembre 2018, New Orleans, USA
  (http://www.soc-neuro-onc.org)

Entretiens avec le Professeur Alexandre Carpentier à propos de ses récents travaux scientifiques sur l'ouverture de la barrière hémato-encéphalique par l'emploi des ultrasons

Bonjour Alexandre Carpentier, merci de nous accorder cet entretien pour la lettre d'information du Club de Neuro-Oncologie de la Société Française de Neurochirurgie.

Tu as publié une série de travaux originaux de recherche translationnelle traitant de l'ouverture de la barrière hémato-encéphalique par l'emploi des ultrasons dans des revues internationales, dont un article intitulé « *Clinical trial of Blood-Brain Barrier disruption by pulsed ultrasound* » dans la prestigieuse revue Science Translational Medicine (Sci Trans Med. 2016;15;8(343) :342re2. doi: 10.1126/scitranslmed.aaf6086) et un article intitulé « *Safe long-term repeated disruption of the Blood-Brain Barrier using an implantable device : a multiparametric study in a primate model* » publié dans la revue Journal of Neurosurgery (J Neurosurg. 2017 ;126(4) :1351-1361. doi: 10.3171/2016.3.JNS151635).

Au nom du Club de Neuro-Oncologie de la Société Française de Neurochirurgie, nous t'adressons nos sincères félicitations pour la qualité et la constance de tes travaux

Johan Pallud (JP) : Peux-tu te présenter en quelques mots ? Peux-tu également présenter ton environnement de recherche ?

Après le Lycée Louis Le Grand, cursus habituel d'internes des Hôpitaux de Paris, puis escapade d'un an à Yale University pour un post-doc recherche pendant 6 mois, suivi d'un fellowship clinique en épileptologie chirurgicale pendant 6 mois avec le Pr Spencer. Retour sur Paris comme chef de clinique à la Pitié-Salpêtrière, puis comme Praticien Hospitalier à Lariboisière avec Bernard George, puis nommé PU-PH sur la Pitié-Salpêtrière-Université Paris VI par le Pr van Effenterre. Je suis chef de service de neurochirurgie de la Pitié-Salpêtrière depuis Septembre 2017.

Au niveau de la recherche fondamentale, j'ai fondé mon propre laboratoire de recherche en 2006 (Labo de Recherche en Technologies Chirurgicales Avancées), qui me permet d'embaucher des profils inhabituels, tels que des ingénieurs, mais aussi de contractualiser rapidement des collaborations avec les USA et des réalisations d'expérimentations dans diverses plateformes ou laboratoires d'accueil français équipés des outils/modèles animaux souhaités pour chaque expérimentation. Ainsi, en sus des expérimentations que l'on mène à l'Institut du Cerveau et de la Moelle Epinière (plateforme imagerie avec Stéphane Lehericy, Labo GlioTex avec l'exceptionnel Ahmad Idbaih, etc...), mon équipe et moi-même réalisons des expérimentations à l'extérieur (HEGP, CEA Orsay, INSERM Lyon, ..) au gré des besoins. Au sein de mon équipe, je garde toujours une place prioritaire pour deux neurochirurgiens (en M2 ou en thèse) en les plaçant comme manager de projet. Il y a eu par exemple Kevin Beccaria et Catherine Horodyckid qui ont fait un travail exemplaire.

Depuis 2011 pour la thématique d'ouverture de la BHE par ultrasons, j'ai mis en place une structure supplémentaire (CarThera) composée de cinq ingénieurs pour la réalisation de mes dispositifs ultrasonores selon les normes drastiques réglementaires afin de transférer mes résultats pré-cliniques vers des essais cliniques.

Au niveau de la recherche clinique, le site de la Pitié-Salpêtrière est optimal avec une équipe de neuro-oncologues dynamiques, une URC, plusieurs IRM, une PET-IRM, etc ....

JP : Comment t'es venue l'idée de travailler sur l'ouverture de la barrière hémato-encéphalique à l'aide d'ultrasons ? Quelles furent la genèse et l'évolution de ces travaux ?

En 2010, travaillant à l'époque sur la technologie laser pour détruire des tumeurs métastatiques sous IRM, j'ai été invité à un congrès de physiciens sur les ultrasons. Ils souhaitaient que je leur rapporte mon expérience sur les tous premiers patients avec destruction tumorale par hyperthermie laser, puisqu'eux même envisageaient d'utiliser les ultrasons pour induire une hyperthermie similaire. J'ai assisté à tout le congrès, fasciné par le potentiel des ultrasons en thérapie même s'il ne s'agissait que des premières expérimentations animales à l'époque. Je découvrais alors que des études pré-cliniques toutes récentes au Canada montraient que des ultrasons pulsés pouvaient temporairement perméabiliser la BHE chez l'animal. Ceci était réalisé par des émetteurs ultrasonores focalisés extérieurs au crâne. Les animaux ayant un crâne tout fin, les ultrasons le traversent sans soucis. Mais chez l'homme, l'épaisseur importante de l'os crânien fait que 90% de l'énergie ultrasonore est absorbée et dispersée. Un problème sérieux de faisabilité chez l'homme, mais à cette époque, le concept physique du « retournement temporel » dicté par Mathias Fink devait potentiellement résoudre ce problème.

Néanmoins, à l'issue de cet évènement, m'est venue l'idée de simplifier cette problématique physique liée au crâne : il suffirait d'implanter un émetteur ultrasonore miniaturisé directement dans le crâne des patients, au sein des trous de trépans, évitant ainsi aux ultrasons d'avoir besoin de franchir l'os. Nous, neurochirurgiens, réalisons tous les jours ces trous de trépans pour réaliser les biopsies ou les chirurgies d'exérèse, étape indispensable avant tout autre traitement, on pratique au moins un orifice dans la boîte crânienne, on peut introduire facilement un émetteur ultrasonore dans l'épaisseur de l'os. C'est ainsi que je me suis lancé dans les ultrasons de contact et non focalisés, donc tout l'inverse de ce que faisaient mes amis physiciens. Je concrétise très vite mon idée avec le SonoCloud®, un implant IRM compatible, de dix millimètres de diamètre, émetteur d'ultrasons. Le dispositif est implanté directement dans l'épaisseur de l'os pour délivrer par la suite une dose d'ultrasons dans le cerveau à chaque cure de chimiothérapie.

JP : Les étapes de progression de ton projet, des modèles pré-cliniques aux applications cliniques sont bien visibles dans tes travaux. Peux-tu expliquer le rationnel sous-tendant cette progression par étapes successives ?
C'est là toute la méthode de la recherche translationnelle. Instinctivement, on pense qu'elle démarre de la paillasse pour aller au malade. C'est vrai en pratique, mais intellectuellement l'exercice doit être inversé : il faut d'abord penser à la problématique chez nos patients (unmet need) et imaginer le tout premier protocole clinique qu'il faudrait réaliser. Ensuite, ma méthode est de dérouler le tapis à l'envers : en fonction de ce protocole clinique rêvé, je définis le protocole de recherche pré-clinique d'efficacité nécessaire (preuve du concept chez l'animal), sans oublier le protocole de recherche pré-clinique d'absence de toxicité car ce sera la préoccupation principale des instances autorisant les essais cliniques futurs (ANSM, comité d'éthique, conseil scientifique indépendant). C'est ce dernier point qui nous a orienté vers l'utilisation concomitante du Carboplatine IV, puisque cette chimiothérapie avait prouvé son innocuité neuronale en injection intracérébrale directe à forte dose par convection enhanced delivery. En parallèle, il faut produire le dispositif médical ou le médicament objet de la recherche, et ce dans le respect de plus de 15 règles CE, ISO, stérilisation, etc.... Début des expérimentations au laboratoire début 2011, et début du premier essai clinique fin 2014 sur des glioblastomes en récidives, avec l'implication exemplaire d'Ahmed IDBAIH.

JP : Peux-tu nous résumer les principaux résultats de ces travaux ?
Sur cerveau sain, nous avons montré que les ultrasons de contact non focalisés émis pendant deux minutes seulement, étaient capables d'ouvrir le BHE chez la souris, le lapin, le chien, le primate, le babouin, et ce de façon temporaire pendant six heures, et façon répétée tous les quinze jours. Ceci a été montré en bleue d'Evans (50kDa), en IRM gadolinium (1kDa), en microscopie confocale avec Dextran fluorophore (2000kDa), en immunohistochimie avec des anticorps de Lama (150kDa) et en microscopie électronique. Nous avons trouvé une pression acoustique efficace sans entraîner la moindre toxicité neuronale, gliale ou endothéliale en IRM (T2SWI, FLAIR, Diffusion), PET (glucose, dopa), EEG, PES, PEM, examen et échelle neurologique, histologie immédiate et retardée. Nous avons retrouvé une biodisponibilité cérébrale accrue pour les trois drogues choisies : Irinotecan (+260%), TMZ (+25%), Carboplatine

(+550%). Sur modèle U87 de gliome murin traité par Carboplatine, nous obtenons un meilleur contrôle tumoral et une survie significativement meilleurs.
Chez l'homme, nous avons montré que l'ouverture temporaire de la BHE associée au Carboplatine IV est rapide (12 min), indolore, reproductible, sans toxicité et sans atténuation d'efficacité même au bout de 10 cures mensuelles. Nous avons traité 25 patients et réalisé plus de 80 séances d'ultrasons. Il semblerait que la PFS et l'OS soient améliorés de façon significative, mais cet essai de phase 1, qui vient de se terminer, ne nous permet pas méthodologiquement de conclure sur ce point. Le but était de montrer la tolérance. Nous gardons une avance nette par rapport aux équipes étrangères.

JP : Formé à partir de dispositifs implantables, le faisceau d'ultrasons semble assez focalisé. As-tu prévu un outil de modélisation de la couverture optimale pour définir la meilleure position du(es) dispositif(s) chez nos patients ?
Le faisceau est non focalisé, et c'est là toute la distinction qui me sépare de mes amis qui travaillent sur les ultrasons focalisés externes. C'est d'ailleurs la raison principale de notre complémentarité : les ultrasons focalisés externes sont adaptés au traitement des pathologies ciblées des noyaux gris (Parkinson, douleur, ...), tandis que les ultrasons de contact non focalisés sont adaptés aux pathologies corticale/sous corticale et diffuses. J'ai opté d'emblée pour l'option NON focalisation puisque les tumeurs cérébrales sont des pathologies diffuses du cerveau. La couverture ultrasonore actuelle située entre 15 et 45 cm^3 sera en effet augmentée pour le prochain essai clinique à 135 cm^3, ce qui permettra de traiter des régions de 7 cm de côté sur 5 cm de profondeur. Le positionnement des émetteurs se fait tout simplement via la neuronavigation avec une compatibilité pour tous les systèmes existants.

JP : En tant que neurochirurgien, devons-nous déjà nous préparer à anticiper, pour les patients que nous opérerons, à réaliser des trous de trépan, non seulement pour lever un volet, mais aussi pour permettre l'implantation optimale des dispositifs ?
Rien à prévoir actuellement, c'est trop tôt. La prochaine étape c'est l'essai clinique randomisé de phase 2b pour prouver que cela sert à quelque chose en termes de PFS et d'OS.

JP : En amont des applications thérapeutiques, l'étude du signal ultrasonore, au plus près de la lésion, permet-elle d'obtenir une signature ultrasonore de la lésion, permettant de faire un équivalent de « biopsie ultrasonore » sans avoir recours à l'analyse anatomo-pathologique ?
La signature ultrasonore de la lésion n'est pas informative, car elle est très variable au sein même d'une tumeur et entre les patients. La signature ultrasonore utile serait celle de l'endothélium du cerveau infiltré ne prenant pas le contraste, mais c'est un signal acoustique imperceptible et en fait sans grand intérêt.
Par contre, entre chaque pulse d'ultrasons qui dure 20 ms, on dispose de 80 ms durant lesquels on enregistre la cavitation des microbulles, c'est-à-dire leur intensité de vibration/résonnance induite par ultrasons. Cela permet de s'assurer du bon fonctionnement, de la sécurité et de faire des corrélations entre signal acoustique réfléchi et qualité de l'ouverture de la BHE visible en IRM.

JP : Quelle sera la prochaine étape pour faire évoluer ce projet ? Comment le Club de Neuro-Oncologie pourra t'il t'aider ?
La prochaine étape est la mise en place de l'essai clinique multicentrique international avec trois centres en France, deux en Europe et trois aux USA. Nous sommes en discussion actuellement avec la FDA. De toute façon, l'essai en France devrait commencer dans six mois quelle que soit la durée de mise en route dans les autres pays. On pourrait en effet se centrer majoritairement sur la France en ouvrant plus de centres ce qui permettrait d'aller plus vite.

JP : Peut-on imaginer des applications au-delà du champ de la neuro-oncologie, notamment en tant que thérapie de neuro-modulation à visée symptomatique pour les épilepsies pharmacorésistantes ou les maladies neurodégénératives ?

J'ai beaucoup de sollicitation pour cela. Nous allons probablement démarrer un essai clinique sur les métastases de mélanomes pour faire pénétrer des anticorps inhibiteurs de checkpoint. Car les métastases possèdent une barrière hémato-tumorale. Il faut bien comprendre qu'une prise de contraste en IRM signifie que la BHE laisse passer le gadolinium. Mais c'est une molécule très petite de 1kDa (comme repère, la BHE ne laisse normalement passer que les molécules inférieures à 0.5kDa). Les chimiothérapies sont souvent au-delà de 5kDa, et les anticorps sont 150kDa. Donc voir une prise de contraste en IRM ne signifie pas que la BHE est suffisamment ouverte. C'est un gradient.

Parallèlement, nous débutons un essai de phase 1 dans la maladie d'Alzheimer car, chose inattendue, la simple ouverture de BHE par ultrasons permet une diminution de 80% des plaques extracellulaires et de 40% des agrégats Tau intracellulaires. L'albumine (50kDa) tout comme nos anticorps endogènes, profite de l'ouverture de la BHE pour rentrer, et elle se colle aux plaques. Or l'albumine est un puissant activateur des cellules microgliales, qui phagocytent alors le complexe Albumine-plaque pour l'externaliser. On analysera en PET IRM si cet effet est retrouvé chez l'homme. Je reste très prudent car entre les modèles animaux et la réalité chez l'homme il y a toujours un gap important.

JP : enfin, pour une parfaite clarté, peux-tu nous détailler d'éventuels conflits d'intérêt au sein de ton activité de recherche ?

L'Université et l'APHP ont breveté tout le concept, le dispositif et ses variantes. Je suis l'inventeur, mais c'est l'APHP et l'Université qui sont propriétaires des brevets. La start-up CarThera a été créée sur l'impulsion du président de l'Université afin de financer la production des dispositifs, les mises aux normes, les certifications extérieures par les organismes notifiés, bref tout le translationnel nécessaire qui est d'ailleurs beaucoup plus onéreux que la recherche elle-même. La loi Allègre sur l'Innovation et la Recherche de 1999 me permet de détenir quelques actions de cette société. Tout ceci est visé et validé par le Commission Nationales de Déontologie.

JP : Bravo une nouvelle fois pour cet excellent travail récompensé par des publications de haut niveau. Au nom du Club de Neuro-Oncologie de la Société Française de Neurochirurgie, merci Alexandre Carpentier d'avoir accepté mon invitation d'entretien.

Merci Johan. Tes questions étaient parfaites et m'ont permis de bien montrer l'ampleur de l'effort fourni et l'état d'esprit de la recherche translationnelle avec son impératif de partenariat public-privé.

Editorial par Frédéric DHERMAIN et Philippe METELLUS concernant les articles « Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-center, randomised, controlled, phase 3 trial » et « Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicenter, randomised, controlled, phase 3 trial »

Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-center, randomised, controlled, phase 3 trial

Mahajan et al., Lancet Oncol. 2017;18(8):1040-1048

Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicenter, randomised, controlled, phase 3 trial

Brown et al., Lancet Oncol. 2017;18(8):1049-1060

Frédéric DHERMAIN, Philippe METELLUS

La chirurgie représente un traitement local efficace dans les métastases cérébrales (MC), particulièrement pour les lésions volumineuses, responsables d'un effet de masse et symptomatiques. Elle est également associée à une amélioration significative de la survie globale (SG) chez les patients atteints de métastase unique, comparé à la radiothérapie pan-encéphalique seule (RTPE) (Patchell, Tibbs et al. 1990). Cependant, malgré l'amélioration des techniques et des modalités de résection, la chirurgie seule est associée à un taux de rechute locale important (Kocher, Soffietti et al. 2011). La réalisation d'une RTPE adjuvante après un traitement local permet une amélioration significative du contrôle local et du contrôle intra-crânien mais est associée à une détérioration cognitive et de la qualité de vie sans gain en terme de SG (Kocher, Soffietti et al. 2011, Soffietti, Kocher et al. 2013, Brown, Jaeckle et al. 2016). Dans le but d'éviter cette toxicité neurocognitive de la RTPE, la radiochirurgie (RC) du lit opératoire s'est progressivement substituée à cet ancien « standard » sans pour autant être basé sur un niveau d'évidence fort (Roberge, Parney et al. 2012). Ainsi, la stratégie thérapeutique adjuvante optimale au décours de l'exérèse chirurgicale d'une métastase cérébrale n'était, jusqu'à récemment, pas encore clairement établie. Afin d'apporter une réponse à ce questionnement, deux études prospectives randomisées ont été conduites aux USA et récemment rapportées dans Lancet Oncology au mois d'août dernier (Brown, Ballman et al. 2017, Mahajan, Ahmed et al. 2017).

La première publication que nous analyserons ici est celle de Mahajan et al. menée par l'équipe du MD Anderson (Houston, Texas), il s'agit d'un essai randomisé de phase 3 monocentrique.

La question posée était : chez des patients en bon état général, naïfs de toute irradiation préalable, après exérèse 'complète' (validée par une revue centralisée de l'IRM post-opératoire) de 1 à 3 MC, une RC de la cavité opératoire (de *moins de 4 cm* et délivrée *dans les 30 jours* de l'exérèse) prolonge-t-elle le 'délai à la rechute locale' (critère principal) ? Les autres critères de jugement (secondaires) étaient : le délai à la rechute 'à distance' (en intra-crânien) et la SG. Trois points à noter : (1) *une marge de (seulement) 1 mm* autour de la cavité pour définir le 'volume microscopique à risque de rechute' (le CTV – ou Clinical Target Volume - pour les onco-radiothérapeutes) ; (2) des doses de RC *décroissantes avec l'augmentation de la taille* de la cavité, ex. 16 Gy si < 10 cc, mais 12 Gy si > 15 cc

(toujours au Gamma-Knife), afin de limiter le risque de radionécrose (RN) et (3) tout traitement 'systémique' était autorisé au décours de la RC.
La population étudiée comptait 132 patients respectivement 68 et 64 patients dans chaque bras (RC *vs* Observation), avec IRM de suivi à 5-8 semaines puis toutes les 6-9 semaines, la répartition des histologies était la suivante : *20% mélanome*, 20% poumon, 22% sein, 38% autres. La faible prévalence des métastases d'origine bronchique est un peu étonnante dans cette population (en général plutôt autour des 60-70%). 63% des patients n'avaient qu'une MC, des *métastases extra-SNC* et *progressives* notées dans plus de 40% des cas et surtout la taille médiane des MC en préopératoire était de 3 cm, près de 70% des cavités faisant plus de 2.5 cm.

Au final, en 7 ans et avec un suivi médian de 11,1 mois, 48% des patients sans RC (groupe observation) rechutaient localement, versus 24% seulement après RC (groupe RC), ce qui se traduisait par 72% de contrôle local à 1 an dans le groupe RC versus 43% dans le groupe observation (après chirurgie complète seule). Le contrôle intracrânien à 1 an était de 60 - 65% et la *SG de 17-18 mois* était non différente entre les 2 groupes. A noter : *16 à 28% de maladie leptoméningée* (!), aucune radionécrose (?) mais surtout une grosse différence de contrôle local à 1 an *selon la taille* de la MC : 91% si la MC faisait moins de 2.5 cm *versus* (seulement) 40 à 46% de contrôle si la MC faisait (respectivement) entre 2.5 et 3.5 ou plus de 3.5 cm. Moins de 50% de contrôle local à 1 an dès que la MC fait plus de 2.5 cm, après exérèse complète <u>et</u> RC adjuvante, *des résultats bien médiocres* que les auteurs expliquent par la décroissance (contre-intuitive en cancérologie) de la dose de RC 'obligée par la dose unique' avec l'augmentation de taille de la MC et préconisent pour les MC > 2.5 cm, (qui forment une majorité des pts) une RT Stéréotaxique 'hypofractionnée' (RTSHF) type 5 X 6 Gy en 1 semaine, *ce qui remet potentiellement en cause la RC 'historique' (dose unique*) et le Gamma-Knife classique. Les onco-radiothérapeutes pourraient même ajouter *qu'une marge de 1 mm autour de la cavité* opératoire (souvent bien délicate à définir 'au mm près') est optimiste, beaucoup d'équipes (y compris dans le second papier, de Brown) recommandant une zone 'à risque' de *2 à 3 mm* autour de la cavité, surtout pour les plus grosses MC.

On peut soulever 2 points 'dérangeants', même si les auteurs concluent 'en faveur de la RC systématique' puisque leur objectif principal a été atteint (et sans toxicité clinique) : (1) pour les opérés (vraiment) complets d'une *MC de moins de 2 à 2.5 cm* (une minorité), on pourrait *identifier un sous-groupe* de pts ne nécessitant <u>pas</u> de RC adjuvante et (2) *pour ceux dont la MC fait plus de 2.5 à 3 cm*, recommander une RTSHF type 3 x 9 Gy ou 5 x 6 Gy… Lo et al , dans leur éditorial publié dans le même numéro de Lancet Oncology posent aussi d'autres questions: pourquoi *l'étude des marges de résection* n'a pas été rapportée (à la différence de Brown où 55-64% des résections étaient 'en bloc'), quel timing pour la RC (les contours de la cavité se modifient dans le temps), quelle *définition de la 'rechute locale'* après exérèse (risque de confondre 'modifications post-RC' avec une vraie rechute focale), modes de rechute autour de cette cavité, etc… (Lo, Chang et al. 2017).

Le second papier analysé ici est un essai multicentrique randomisé de phase 3 publié par Brown P et al.

Les questions posées étaient : chez des patients adultes atteints de 1 à 4 métastases cérébrale, naïfs de toute irradiation préalable et opérés d'une métastase cérébrale avec une cavité de résection post-opératoire de moins de 5cm, (1) la survenue d'une détérioration cognitive (critère de jugement principal n°1) est-elle supérieure chez les patients traités par RTPE postopératoire que chez les patients ayant bénéficiés d'une radiochirurgie du lit tumoral ? (2) La RTPE adjuvante est-elle associée à une amélioration significative de la SG (critère de jugement principal n°2) ? Les critères de jugement secondaires étaient, la qualité de vie, l'indépendance fonctionnelle, le contrôle local (rechute dans le lit tumoral), le contrôle à distance (intra-crânien), la toxicité et la survenue d'une dissémination leptoméningée. Les patients du groupe RC bénéficiaient d'une RC du lit tumoral dont la dose variait de 20 à 12 Gy en fonction du volume de la cavité chirurgicale avec une marge de 2mm. Les autres métastases non opérées (si présentent) étaient traitées par RC en une seule fraction avec des doses variant de 24 à 20 Gy en fonction de leur diamètre maximal.

Les patients du groupe RTPE bénéficiaient d'une irradiation selon un schéma 30 Gy en 10 fractions ou 37.5 Gy en 15 fractions (5 jours par semaines). Les autres métastases non opérées (si présentent) étaient traitées par RC en une seule fraction avec des doses variant de 22 à 18 Gy en fonction de leur diamètre maximal. Tout traitement systémique n'était autorisé qu'après RC ou RTPE mais pas pendant.

La population étudiée était de 194 patients, 98 dans le groupe RC et 96 dans le groupe RTPE. Le suivi clinique et radiologique était effectué tous les 3 mois après la chirurgie. L'évaluation neurocognitive utilisait des tests bien établis (Chang, Wefel et al. 2009): Hopkins Verbal Learning Test-Revised (HTLV-R) pour la mémoire, Controlled Oral Word Association Test (COWAT) pour la fluence verbale, Trail Making Test A (TMT-A) pour la vitesse de traitement des informations et B (TMT-B) pour les fonctions exécutives. Dans 77% des cas les patients avaient une seule métastase cérébrale, la taille de la cavité de résection était supérieure à 3 cm dans 40% des cas, l'exérèse était jugée complète (évaluée par IRM sans relecture centralisée par le clinicien de chaque centre) dans environ 90% des cas et réalisée en bloc dans 60% des cas. Enfin, l'histologie était bronchique dans 59% des cas.

Après un suivi médian de 11.1 mois, le délai médian de détérioration cognitive était significativement plus long (3.7 mois) dans le groupe RC que dans le groupe RTPE (3.0 mois) et le taux de déclin cognitif moins fréquent à 6 mois 52% (groupe RC) vs 85% (groupe RTPE). Par ailleurs la qualité de vie était meilleure dans le groupe RC que le groupe RTPE. Enfin il n'y avait pas de différence significative en termes de SG.

Cette étude démontre pour la première fois avec un tel niveau d'évidence (niveau 1) que la RC adjuvante après chirurgie chez des patients atteints d'une maladie oligométastatique est associée à une détérioration neurocognitive moins importante et une meilleure qualité de vie que la RTPE adjuvante. Il est intéressant de noter dans cette étude que le contrôle local à 1 an est supérieur dans le bras RTPE (81%) à celui du bras RC (61%) et que le contrôle local dans le bras RC est particulièrement faible. En effet dans le papier précédemment analysé le taux de contrôle à 1 an est de 72%. Les auteurs explique cela par le fait que leur étude inclue des résections incomplètes, bien que rare (8% dans le bras RC), et que l'évaluation radiologique a été faite localement, pas de manière centralisée et inclue probablement de fausses progressions (remaniements post-thérapeutiques ou radionécrose) d'autant plus que les doses utilisées dans cette étude sont supérieures (donc potentiellement plus pourvoyeuses de radionécrose) à celles de l'étude du MD Anderson (12-20 Gy vs 12-16Gy). Cela souligne l'extrême importance de l'évaluation rigoureuse de la qualité de la chirurgie. On peut regretter l'absence d'analyse du contrôle local en fonction de la taille de la lésion. En effet, il y a probablement une sous population de patients qui pourraient bénéficier d'une chirurgie d'exérèse seule associée à une surveillance. L'importance de la taille de la cavité et le mauvais contrôle local rapporté ici dans le bras RC adresse, comme dans l'étude du MD Anderson, la question de l'intérêt potentiel de l'hypofractionnement. Enfin, une étude de phase 2 portant sur l'apport de l'épargne hippocampique dans la RTPE a rapporté un réel impact favorable sur la survenue de troubles cognitifs (Gondi, Pugh et al. 2014). Ceci a motivé la réalisation d'un essai de phase 3 évaluant cette stratégie d'épargne hippocampique chez les patients traités par RTPE. En l'absence de résultats définitifs et probant sur cette approche la RC, constitue à ce jour, sous réserve d'une plus grande précision de ses modalités de prescription, la stratégie thérapeutique adjuvante la plus efficace et la moins délétère sur le plan cognitif chez les patients opérés de MC.

En conclusion, les données rapportées dans ces deux publications constituent une réelle avancée dans la prise en charge des patients atteints d'une maladie oligométastatique cérébrale. Les enseignements clairs sont que (1) il faut envisager un traitement adjuvant après exérèse chirurgicale d'une métastase cérébrale mais que probablement dans certains cas (lésion de petite taille, exérèse en bloc avec marge saine) il y a une place pour l'observation et cela souligne l'importance de l'évaluation chirurgicale et radiologique de la qualité de résection ; (2) le traitement adjuvant optimal post-opératoire est très probablement la RC plus la RTPE mais on ne peut pas cependant parler de standard car il existe encore trop points à éclaircir sur la dose à utiliser, le timing de la RC, le type de RC (hypofractionnement/ fraction unique) et enfin sur l'intérêt et la meilleure tolérance potentielle de la RTPE avec épargne hippocampique dans certains sous-types histomoléculaires à fort tropisme cérébral. Finalement, on peut également relever que dans ces deux études, le sous-type moléculaire des néoplasies primitives n'ait pas été pris en compte puisque l'on sait qu'il peut impacter non seulement le pronostique globale de la maladie, l'incidence des métastases cérébrales mais aussi l'efficacité du traitement local sur ces dernières (Johung, Yao et al. 2013, Sperduto, Jiang et al. 2017, Sperduto, Yang et al. 2017)et constitue donc un outil qui devra, à l'avenir s'intégrer dans la prise en charge de ces patients.

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Présentation des résumés de deux Master 2 soutenus par deux internes en Neurochirurgie en 2017

• Projet GLIOTRAP - François-Xavier FERRACCI – Service de Neurochirurgie ROUEN, Inserm 1239

Introduction : Le pronostic sombre des Glioblastomes (14,6 mois de médiane de survie) est lié en partie au potentiel proliférant et migratoire de néo-vaisseaux intra-tumoraux et au caractère invasif des cellules tumorales gliales qui envahissent le parenchyme nerveux *via* les vaisseaux sanguins et les axones myélinisés. Nous avons proposé de détourner la capacité neurobiologique de chimio-attraction des cellules tumorales pour les attirer dans des «pièges» biologiques, utilisant l'introduction d'un hydrogel biocompatible dans lequel serait ajouté des chimiokines à l'intérieur de la cavité d'exérèse dans le but de rediriger la migration des cellules tumorale, les piéger pour mieux les cibler au sein de l'hydrogel.

Matériel et méthodes : Pour cela nous avons réalisé dans un premier temps, in vitro, des mesures de viabilité et de migration des cellules gliales dans cet hydrogel. Puis nous avons mis en place un modèle d'exérèse microchirurgicale de Glioblastome injectés par xénogreffe orthotopique, chez la souris Nude, avec 2 lignées de cellules gliales (U87-GFP et 42MG-GFP). Et ce afin de tester l'impact de notre gel en termes de tolérance, de chimio attraction de cellules gliales et de réaction astrocytaire au contact, dans 3 conditions : contrôle (exérèse seule), hydrogel seul (exérèse + hydrogel), hydrogel avec molécule chimiokines.

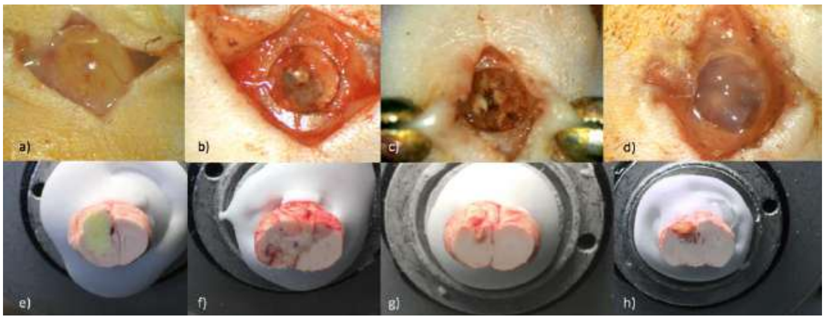


Figure 1. ***Photographies des tumeurs greffées au cours de la résection chirurgicale, et des cerveaux en coupe présentant les tumeurs.*** *a) Tumeur U87 non réséquée, portion exophytique extra-crânienne, vue per opératoire; b) Tumeur 42MG non réséquée, visible au travers de la rondelle de craniectomie, vue per opératoire; c) Tumeur 42MG réséquée, vue per opératoire; d) Tumeur 42MG réséquée, avec colle (polymérisée) dans la cavité opératoire, vue per opératoire; e) Tumeur U87 non réséquée, auto-fluorescence visible des cellules GFP; f) Tumeur 42MG non réséquée, infiltration du parenchyme visible jusqu'en contro-latéral; g) Tumeur 42MG réséquée, sans colle dans la cavité opératoire; h) tumeur 42MG réséquée, avec colle dans la cavité opératoire.*

Résultats : L'analyse des coupes de cerveaux nous a permis de constater dans un premier temps, deux phénotypes de tumeurs gliales.
Les cellules U87, produisent une tumeur à profil angiogénique, avec une vraie masse tumorale et un effet de masse important. Les cellules 42MG, ont un profil plus invasif, avec volontiers une atteinte contro latérale via le corps calleux. Nous avons également pu mettre en évidence, au vu des analyses immuno histochimiques, la capacité des astrocytes à venir en bordure de la cavité d'exérèse, d'autant plus que des molécules chimio attractantes se trouvent dans l'hydrogel. La présence de molécules chimio attractantes dans l'hydrogel semble permettre de faire migrer les cellules exprimant le récepteur de ces molécules aux bordures de la cavité d'exérèse.

Discussion : Ce travail de Master 2 a permis de mettre en évidence la capacité des cellules gliales à se mouvoir et traverser des interfaces d'hydrogel. Il sera nécessaire à l'avenir d'arriver à mettre clairement en évidence la présence de cellules tumorales dans l'hydrogel. Puis d'évaluer sur de plus grands effectifs un bénéfice en termes de survie globale et sans progression chez l'animal.

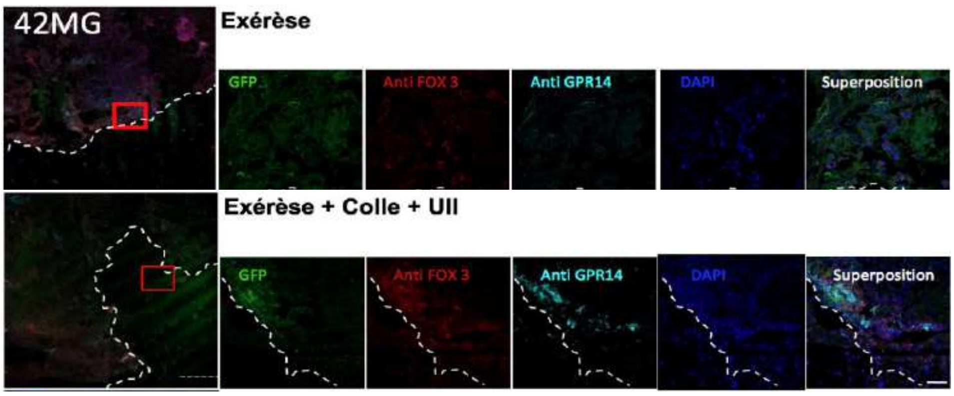
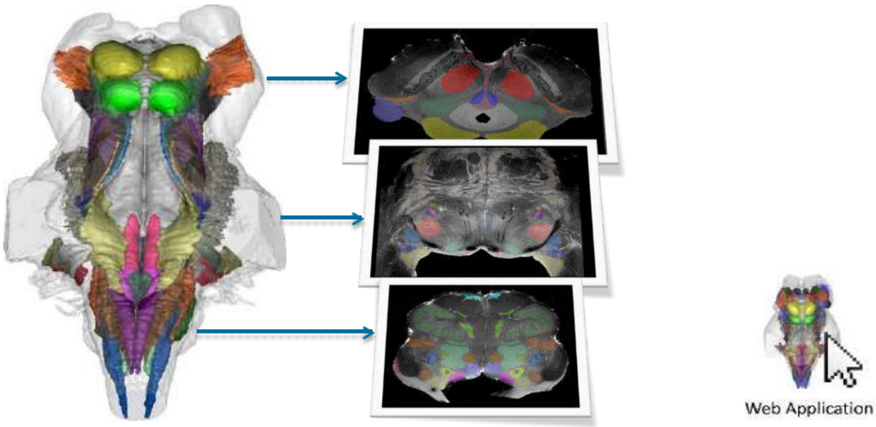


Figure 2. Immuno-marquage sur coupe de cerveaux de souris xénogreffés à l'aide par des anticorps dirigés contre FOX 3 et UT. *42MG; B, U87. En vert, les cellules tumorales GFP+; en rouge, l'anticorps dirigé contre FOX3 montrant les neurones matures, en bleu clair, les cellules UT+, en bleu foncé, les noyaux, DAPI). Le marquage de l'UT (bleu ciel) est diffus et isolé dans les conditions sans exérèse, exérèse sans hydrogel ou avec hydrogel seul. On constate une augmentation du marquage dans les conditions de tumeurs en présence d'hydrogel + UII.*

• <u>Projet « </u>**Etude *ex vivo* des noyaux du tronc cérébral humain en IRM à très haut champ magnétique (11,7 Tesla) et très haute résolution » - François LECHANOINE – Service de Neurochirurgie Tours, Université François-Rabelais de Tours-Laboratoire d'informatique, EA6300**



INTRODUCTION : Comprendre comment le cerveau réalise une tâche donnée nécessite une bonne connaissance de l'anatomie du réseau fonctionnel impliqué dans cette tâche. La représentation tridimensionnelle des structures internes du tronc cérébral est peu connue, leur connaissance reposant principalement sur des travaux histologiques de sections bidimensionnelles. Les connaissances sur la connectivité fonctionnelle sont-elles, essentiellement extrapolées des études électro physiologiques animales. Nous exposons le développement d'un protocole original de segmentation *ex vivo* du tronc cérébral humain en Imagerie par Résonance Magnétique (IRM) à très haut champ magnétique (11,7 Tesla) et très haute résolution, première étape vers l'étude de sa microstructure et de sa connectivité à une échelle mésoscopique

MÉTHODES : Un spécimen de tronc cérébral humain, obtenu à partir du programme de dons du corps de notre établissement, a été préparé puis scanné dans l'IRM préclinique Bruker 11,7T de Neurospin (CEA, Gif-sur-Yvette). Ceci a fourni des séquences anatomiques 3D en pondération T2 avec une résolution spatiale isotrope maximale de 100µm et des séquences de diffusion avec une résolution spatiale isotrope de 300µm. Une classification inédite hautement détaillée a été créée incluant les 73 structures et 43 sous-structures connues du tronc cérébral. Nous avons par la suite segmenté manuellement toutes les structures identifiables à cette résolution, et nous avons généré des règles strictes de segmentation pour chacune d'elles.

RÉSULTATS : 52 classes anatomiques et 19 sous-classes ont ainsi pu être segmentées sur l'ensemble des données, auxquelles ont été rajoutées 3 structures du diencéphale et 4 du cervelet. Des tables de règles de segmentation ont été produites pour chaque classe. Ainsi, 18 noyaux propres du tronc cérébral, 13 noyaux des nerfs crâniens et 21 noyaux de la substance réticulée ont été segmentés.

CONCLUSION : Ce travail constitue une avancée importante dans la création de protocoles d'acquisition et de segmentation de spécimens anatomiques de tronc cérébral analysés en IRM à 11,7T. Il constitue la première étape vers la création d'un atlas multi-sujets du tronc cérébral, utilisable tant pour une segmentation automatique à haute résolution que pour un recalage sur des images cliniques. Cette dernière application pourrait avoir d'importants bénéfices cliniques et pédagogiques. En effet, cela pourrait aider à localiser précisément des lésions du tronc cérébral (vasculaires, traumatiques, tumorales…), aider les neurochirurgiens dans les approches difficiles de cette structure, évitant ainsi d'irréversibles lésions des noyaux ou des faisceaux. Un atlas pourrait fournir des cibles anatomiques précises à l'implantation stéréotaxique d'électrodes dans le cadre de la stimulation cérébrale profonde pour le traitement de la maladie de Parkinson, d'autres mouvements anormaux ou de maladies psychiatriques. Nous avons créé une application web qui sera en accès gratuit, permettant une visualisation et une utilisation de nos résultats par la communauté scientifique.

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CLINICAL STUDY

Prognostic factors for survival in adult patients with recurrent glioblastoma: a decision-tree-based model

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Abstract

We assessed prognostic factors in relation to OS from progression in recurrent glioblastomas. Retrospective multicentric study enrolling 407 (training set) and 370 (external validation set) adult patients with a recurrent supratentorial glioblastoma treated by surgical resection and standard combined chemoradiotherapy as first-line treatment. Four complementary multivariate prognostic models were evaluated: Cox proportional hazards regression modeling, single-tree recursive partitioning, random survival forest, conditional random forest. Median overall survival from progression was 7.6 months (mean, 10.1; range, 0–86) and 8.0 months (mean, 8.5; range, 0–56) in the training and validation sets, respectively ($p = 0.900$). Using the Cox model in the training set, independent predictors of poorer overall survival from progression included increasing age at histopathological diagnosis (aHR, 1.47; 95% CI [1.03–2.08]; $p = 0.032$), RTOG–RPA V–VI classes (aHR, 1.38; 95% CI [1.11–1.73]; $p = 0.004$), decreasing KPS at progression (aHR, 3.46; 95% CI [2.10–5.72]; $p < 0.001$), while independent predictors of longer overall survival from progression included surgical resection (aHR, 0.57; 95% CI [0.44–0.73]; $p < 0.001$) and chemotherapy (aHR, 0.41; 95% CI [0.31–0.55]; $p < 0.001$). Single-tree recursive partitioning identified KPS at progression, surgical resection at progression, chemotherapy at progression, and RTOG–RPA class at histopathological diagnosis, as main survival predictors in the training set, yielding four risk categories highly predictive of overall survival from progression both in training ($p < 0.0001$) and validation ($p < 0.0001$) sets. Both random forest approaches identified KPS at progression as the most important survival predictor. Age, KPS at progression, RTOG–RPA classes, surgical resection at progression and chemotherapy at progression are prognostic for survival in recurrent glioblastomas and should inform the treatment decisions.

Keywords Cox model · Conditional random forest · Decision tree · Glioblastoma · Karnofsky performance status · Overall survival · Prognostic models · Random survival forest · Recurrence · Recursive partitioning analysis · Surgery

Abbreviations

CRF	Conditional random forest
IQR	Inter quartile range
KPS	Karnofsky performance status
OS	Overall survival
PFS	Progression-free survival
RPA	Recursive partitioning analysis
RSF	Random survival forest
RTOG	Radiation Therapy Oncology Group
VIMP	Variable IMPortance
WHO	World health organization

Etienne Audureau and Anaïs Chivet have contributed equally to this work.

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Introduction

Despite maximal first-line treatment for glioblastoma (World Health Organization WHO grade IV astrocytoma), including maximal safe resection followed by concomitant chemoradiotherapy, then adjuvant Temozolomide (i.e. standard combined radiochemotherapy) [1], tumour progression or recurrence almost inevitably occurs. At glioblastoma recurrence, there is no universally accepted standard treatment [2, 3]. Treatment is decided on an individual basis and includes: repeat surgical resection with or without carmustine wafer implantation [1, 4–15], chemotherapy using Temozolomide or other agent, bevacizumab therapy, radiotherapy, all of these possibly in combination and, finally, best supportive care [1, 4, 5, 9, 10, 16–20]. In addition, many patients are considered for experimental therapy [2, 21, 22].

Therapeutic decisions should be guided by clinically relevant prognostic factors. Some studies suggest that patients receiving combined treatments at the time of recurrence have better Overall Survival (OS) from progression [5, 9, 10, 18, 20], while patients in good clinical condition with a preserved Karnofsky Performance Status (KPS) are also the most likely to receive more aggressive and effective treatments [2, 16, 23–25]. Yet, there still remains uncertainty as to whether such prognostic factors may operate in combination or independently. While conventional approaches to survival analysis such as Cox proportional hazard modeling have provided useful information to identify single independent predictors, such methods are generally less suitable to detect more complex relationships or interactions relevant in subgroups of patients, e.g. to examine the prognostic value of KPS in specific patients receiving specific treatments. In this regard, machine learning techniques based on decision trees can prove useful to identify high-order interactions between predictors that may have been overlooked otherwise, even in situations of relatively small sample size with a large number of covariates [26]. Consequently, the aim of this study was to evaluate the prognostic significance of intrinsic (patient- and glioblastoma-related), and extrinsic (treatment-related) factors in adult patients with recurrent supratentorial glioblastoma, so as to develop, validate, and compare novel prognostic models based on conventional and decision-tree-based survival analyses.

Materials and methods

Study population

Two study populations were considered: a training set for deriving the initial predictive algorithms and an independent validation set to externally validate the models. Both the training and the validations sets were obtained through a multicentric retrospective study on the behalf of the Club de Neuro-Oncologie of the Société Française de Neurochirurgie. The training set was obtained using a first-round patient screening of voluntary neurosurgical and neurooncological centers in France and the validation set was obtained using a second-round patient screening restricted to non-participating voluntary neurosurgical and neurooncological centers during the first-round screening. Inclusion criteria were: (i) patients aged ≥ 18 at diagnosis, (ii) newly diagnosed glioblastoma [3], (iii) supratentorial hemispheric location, (iv) surgical resection followed by standard combined radiochemotherapy without bevacizumab as first-line treatment [1, 27], (v) tumour progression as defined by the Macdonald criteria (25% increase in total perpendicular diameters of an enhancing lesion, any new lesion, or clinical deterioration) [2, 28, 29], (vi) available KPS at the time of histopathological diagnosis and at tumour progression and, (vii) available follow-up at tumour progression. For the training set, an additional criterion was the KPS at the end of first-line oncological treatment.

Patient flow charts are illustrated in Fig. 1. A total of 407 patients from 16 centres were available for full analyses in the training set (La Timone Hospital—University Aix-Marseille, n = 96; Paul Strauss Cancer Centre—University of Strasbourg, n = 60; Pierre Wertheimer Hospital—University of Lyon, n = 42; Pontchaillou Hospital—University of Rennes, n = 41; Beaujon Hospital—University Paris Diderot, n = 36; Maison Blanche Hospital—University of Reims, n = 34; Sainte-Anne Military Teaching Hospital in Toulon, n = 24; Caen University Hospital—University Caen Lower-Normandy, n = 21; Jean-Minjoz Hospital—University of Besançon, n = 19; Amiens University Hospital—University of Amiens, n = 13; Pasteur Hospital in Colmar, n = 9; Limoges Hospital—University of Limoges, n = 5; Clairval Clinic in Marseille, n = 3; Pellegrin Hospital—University Victor Segalen Bordeaux 2, n = 2; Angers University Hospital—Angers University, n = 1; Rouen University Hospital—Rouen University, n = 1). A total of 370 patients from three centres were available for full analyses in the validation set (Sainte-Anne Hospital Centre—University Paris Descartes, n = 180; Guy de Chauliac Hospital—University of Montpellier, n = 98; Assistance Publique-Hôpitaux de Paris Avicenne Hospital—University Paris 13, n = 91). The local institutional review board approved the study protocol (Protocol number AC036).

Data collection

Data were obtained from the patients' medical records using a protocol designed for the study. Patient- and tumour-related characteristics collected at the time of histopathological diagnosis included: gender, age, KPS, tumour location, the revised Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG–RPA) classification system for glioblastoma [30]. KPS was further collected at the end of first-line oncological treatment. Patient-related characteristics collected at the time of tumour progression included:

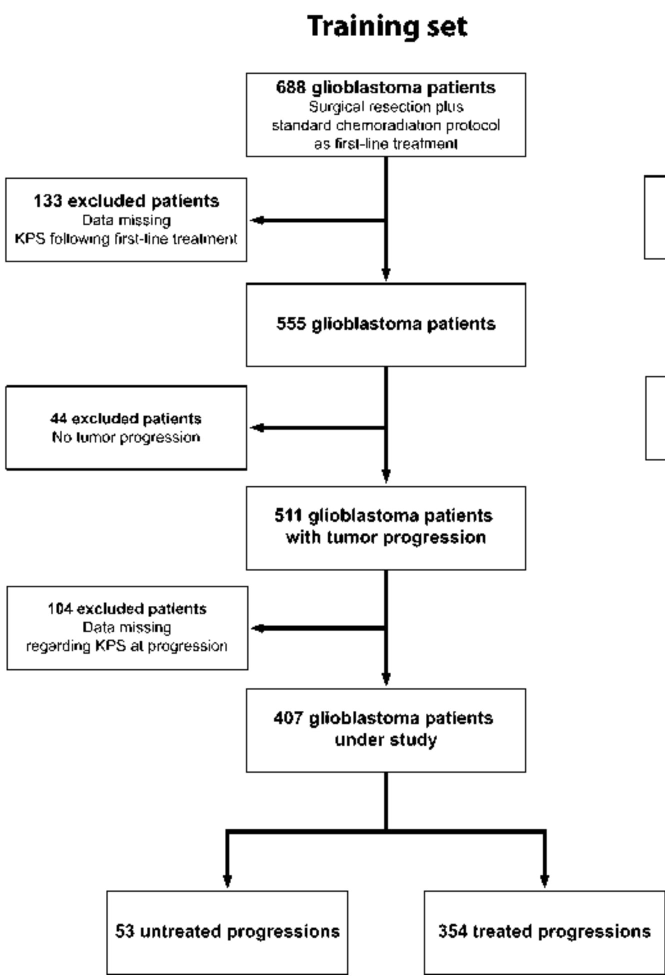


Fig. 1 Recruitment and inclusion of patients in the study

duration of the progression-free survival (PFS) following first-line oncological treatment, KPS, oncological treatments at progression [none, surgical resection with or without carmustine wafer implantation, chemotherapy (Temozolomide or other chemotherapy agents), radiotherapy, bevacizumab therapy].

Endpoints

The primary endpoint was OS from glioblastoma progression measured from the date of tumour progression to the date of death from any cause.

Statistical analyses

Descriptive results are given as means (± standard deviation) or medians [interquartile range (IQR)] for continuous variables, and counts (%) for categorical variables. Survival curves for OS from progression were plotted by the Kaplan–Meier method, using logrank tests to assess significance for group comparison.

Four complementary statistical approaches were carried out to establish multivariate prognostic models of OS from progression and compare their discriminative ability and clinical significance. First, Cox proportional hazards regression modeling was performed, following a stepwise backward approach for multivariate analysis by entering predictors previously associated with OS in univariate analysis at the p-value < 0.2 level, sequentially removing not significant predictors at the $p < 0.05$ level until reaching the final model. KPS was analyzed as a categorical variable to account for its semi-quantitative nature (< 70, 70, 80, 90, 100) and continuous variables were re-categorized into binary factors using the best discriminant cut-off points. Based on Schoenfeld residuals, all the covariates were tested for the proportional hazards assumption, which was not found to be violated. Second, we used RPA to derive a decision tree for OS from progression prediction. Briefly, a typical RPA algorithm recursively examines all possible binary splits across observed values of the input predictors and selects the optimal value to partition the population into groups with differentiated survivals. Starting with all observations, the process is repeated recursively until a stopping criterion is met. We used the conditional inference tree methodology which offers several advantages, including unbiased variable selection (conventional methods are biased towards continuous variables with many possible splits), the non-necessity of pruning the tree given the split selection process based on statistical tests, and the fact that the algorithm provides p-values helpful to quantify the level of confidence that can be achieved at each split [31]. Finally, we established prognostic models using two random forests approaches for censored data: random survival forests (RSF) and conditional random forests (CRF). Random survival forests combine the results obtained from a large ensemble of trees, thus avoiding the difficulty of selecting one single tree of appropriate size and often producing more powerful and stable predictive models. Random survival forest corresponds to the direct application to survival analysis of the general random forest principle [32], while CRF is based on the aggregation of conditional inference trees [31]. We used 1000 trees for both approaches, using the logrank splitting criterion for RSF. Variable importance measures (VIMP) were computed to help quantifying a given variable importance within a random forest, by examining the increase in prediction error when perturbation is added to the variable. High positive importance values hence indicate informative and influential variables. We calculated VIMP using Breiman–Cutler permutation principle for RSF and its implementation for CRF approaches [33]. Discrimination performance of the prognostic models was assessed and compared across the four approaches by the Harell's concordance index (C-index), which measures the probability of concordance between predicted and observed survival [34]. C-indexes were computed after derivation on the training set, after internal validation by 10-fold cross-validation repeated 20 times, and after applying the prognostic models to the external validation set.

All data were complete to the exception of two variables in the validation set, namely KPS at the end of first-line treatment ($n = 275$ complete, 74.3%) and tumor main lobar location ($n = 279$, 75.4%). Those variables were neither identified as predictors in Cox proportional hazards modeling nor in the single decision tree and external validation were thus possible on complete cases; for CRF and RSF approaches, imputation of those two variables was performed using the built-in procedures.

Cox proportional hazards analyses were performed using Stata v14.2 (StataCorp, TX, USA), and decision tree and random forests with R v3.2.4 (R Foundation for Statistical Computing, Vienna, Austria; packages *party, partykit, randomForestSRC*) [31, 35].

Results

Study population

The patients' main characteristics are summarized in Table 1. Clinically relevant differences in the validation set as compared to the training set include a higher prevalence of RTOG–RPA III–IV classes [38.8% (training) vs. 67.3% (validation)], and a higher proportion of patients with a KPS ≥ 70 at diagnosis, at the end of first line treatment, and at progression (89.9 vs. 92.4%, 77.9 vs. 92.0%, 64.6 vs. 80% in the training and validation sets, respectively).

Oncological treatments performed at first-line treatment included a subtotal or total resection in 60 and 58.4% in the training and validation sets, respectively. After concomitant chemoradiotherapy, patients received a mean of 5.7 ± 3.4 cycles and 4.5 ± 3.4 cycles of adjuvant Temozolomide in the training and validation sets, respectively. Additionally, 62.2 and 44.4% of patients completed at least six cycles of adjuvant Temozolomide in the training and validation sets, respectively. Regarding oncological treatments at progression, similar rates of radiotherapy were found in the two cohorts [4.9% (training) vs. 7.0% (validation)], while slightly lower rates of surgery [28.3% (training) vs. 21.9% (validation)], chemotherapy [81.6% (training) vs. 70.8% (validation)], and carmustine wafers implantation [18.7% (training) vs. 9.5% (validation)] were observed in the validation set.

Re-presentation with disease progression was at a median 9.5 months (mean, 12.1; range 3–76) in the training set (histopathologically proven in 115 cases, 28.5%) and 10.0 months (mean, 11.7; range 1–41) in the validation set (histopathologically proven in 81 cases, 21.9%). Death rates over the follow-up period were 88.5% (training set) and 77.6% (validation set). Median OS from progression was 7.6 months (mean, 10.1; range 0–86) in the training set and 8.0 months (mean, 8.5; range 0–56) in the validation set ($p = 0.900$) (Fig. 2a).

Prognostic model by Cox proportional hazards regression

Unadjusted and adjusted prognostic factors for OS from progression identified from the training set are summarized in Table 2. After stepwise multivariate analysis, independent predictors of poorer OS from progression included increasing age at histopathological diagnosis ($p = 0.032$), RTOG–RPA V–VI classes ($p = 0.004$), decreasing KPS at progression ($p < 0.001$), while independent predictors of longer OS from progression included surgical resection ($p < 0.001$), and chemotherapy ($p < 0.001$). Kaplan–Meier curves of overall survival from progression according to

Table 1 Clinical and treatment patient characteristics by cohort

		Training set (n = 407) N (%)	Validation set (n = 370) N (%)
Gender, Men		268 (65.8%)	236 (63.8%)
Age, years	Median (IQR)	58.0 (51.0; 64.0)	59.0 (52.0;67.0)
	≥ 70	41 (10.1%)	76 (20.5%)
Progression free survival, months	Median (IQR)	9.5 (6.4; 14.0)	10.0 (6.5;14.9)
	< 18	339 (83.3%)	304 (82.2%)
RTOG–RPA class	III–IV	158 (38.8%)	249 (67.3%)
	V–VI	249 (61.2%)	121 (32.7%)
Tumor main lobar location	Deep-seated	42 (10.3%)	82 (29.4%)
	Frontal	150 (36.9%)	122 (43.7%)
	Parietal	66 (16.2%)	15 (5.4%)
	Temporal	149 (36.6%)	60 (21.5%)
KPS at diagnosis	100	78 (19.2%)	59 (15.9%)
	90	81 (19.9%)	126 (34.1%)
	80	105 (25.8%)	99 (26.8%)
	70	102 (25.1%)	58 (15.7%)
	< 70	41 (10.1%)	28 (7.6%)
KPS at the end of first-line treatment	100	54 (13.3%)	15 (5.5%)
	90	67 (16.5%)	127 (46.2%)
	80	123 (30.2%)	73 (26.5%)
	70	73 (17.9%)	38 (13.8%)
	< 70	90 (22.1%)	22 (8.0%)
KPS at progression	100	29 (7.1%)	19 (5.1%)
	90	49 (12.0%)	99 (26.8%)
	80	85 (20.9%)	101 (27.3%)
	70	100 (24.6%)	77 (20.8%)
	< 70	144 (35.4%)	74 (20.0%)
Treatments at progression	Surgical resection	115 (28.3%)	81 (21.9%)
	Carmustine wafer implantation	76 (18.7%)	35 (9.5%)
	Chemotherapy	332 (81.6%)	262 (70.8%)
	Temozolomide	100 (24.6%)	74 (20.0%)
	Bevacizumab	254 (62.4%)	153 (41.4%)
	Other chemotherapy	202 (49.6%)	196 (53.0%)
	Radiotherapy	20 (4.9%)	26 (7.0%)

KPS Karnofsky performance status, *IQR* interquartile range, *SD* standard deviation

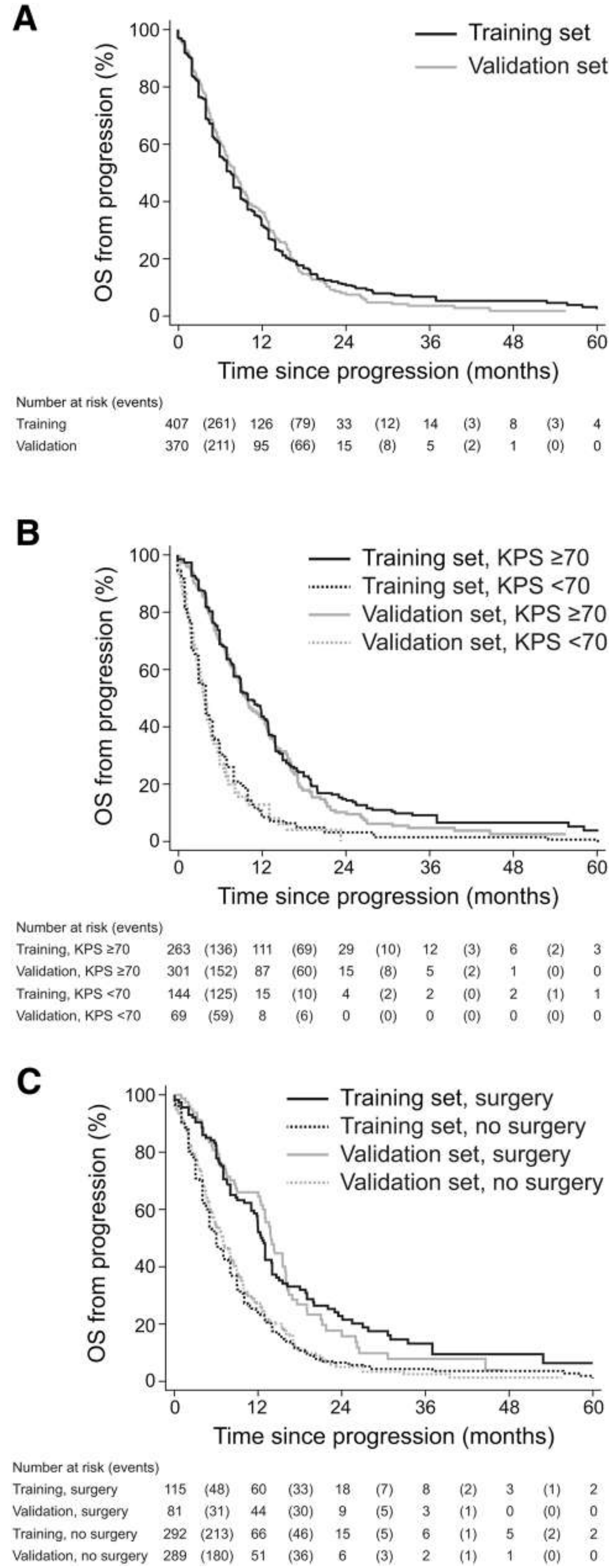
KPS at progression and according to surgical resection at progression are presented in Fig. 2b, c.

Prognostic model by single tree recursive partitioning

The single tree recursive partitioning applied on the training set identified four main predictors of OS from progression, namely KPS at progression, surgical resection at progression, chemotherapy at progression, and the RTOG–RPA class at histopathological diagnosis, yielding seven groups with differentiated survival as shown by the corresponding Kaplan–Meier curves depicted at each end node (Fig. 3a). The best predictor in the root node was the KPS at progression, using a < 70 versus ≥ 70 threshold for the first step. Group 3 had the best predicted OS from progression (median, 14 months [CI 95% 12.4–18.8]) with the following characteristics: KPS at progression of 70–80, surgical resection at progression, and an RTOG–RPA III–IV class. Group 1 had the worst predicted OS from progression [median, 2 months (CI 95% 1.4–2.4)] with the following characteristics: KPS at progression < 70 without any treatment at progression.

Four risk categories were then computed from the seven terminal nodes, merging groups with overlapping survival profiles as indicated by the absence of statistically significant

Fig. 2 Kaplan–Meier curves of overall survival from progression of ▸ patients with supratentorial newly diagnosed glioblastomas all treated with surgical resection and standard combined radiochemotherapy as first-line treatment. Results are given for the training set (black lines) and the validation set (grey lines); overall (**a**), according to KPS at progression (**b**), and according to surgical resection at progression (**c**). **a** Overall survival from progression in the training set (n = 407) and in the validation set (n = 370). **b** Overall survival from progression according to KPS at progression. The unadjusted hazard ratio for overall survival from progression in the subgroup of patients with a KPS at progression < 70 as compared with the subgroup of patients with a KPS at progression ≥ 70 was 2.46 [95% confidence interval (95% CI), 1.98–3.06; p < 0.001] in the training set and was 2.71 (95% CI, 2.03–3.58; p < 0.0001) in the validation set. **c** Overall survival from progression according to surgical resection at progression. The unadjusted hazard ratio for overall survival from progression in the subgroup of patients with a surgical resection at progression as compared with the subgroup of patients without a surgical resection at progression was 0.52 [95% confidence interval (95% CI) 0.41–0.66; p < 0.0001] in the training set and was 0.52 (95% CI 0.39–0.69; p < 0.0001) in the validation set



difference in their corresponding hazard ratios when entered in Cox analysis: very high risk (merging groups 1 and 5), high risk (group 2), intermediate risk (merging groups 4 and 6), and minimal risk (merging groups 3 and 7). Those four risk categories were highly predictive of subsequent OS from progression, as shown in Fig. 3b, c, in the training set (p < 0.0001) and in the validation set (p < 0.0001).

Prognostic models by survival random forests

Random forests were finally fitted on the training set using two complementary approaches: RSF and CRF and VIMP were calculated to provide the relative importance of the predictors for establishing the model. Rankings of variables in order of relative importance are shown in Fig. 3d, e. Both random forest approaches identified KPS at progression as the most important variable predicting OS from progression. Following covariates in ranking predicting OS from progression were surgical resection at progression, chemotherapy at progression, and KPS at the end of first-line treatment, with subtle variations in ranking between RSF and CRF.

Validation and comparison of discriminative ability across approaches

Table 3 compares the discrimination performance of the four statistical approaches used for building the prognostic models (Cox, single decision tree, RSF, and CRF), contrasting the concordance indexes achieved after derivation on the original training set, after internal validation by 10-fold cross-validation, and after external validation by applying the prognostic models to the independent validation set. C-indexes derived from the original training set ranged from 69.80 to 71.96%, with the highest values obtained from CRF

Table 2 Predictors for overall survival from progression: univariate and multivariate Cox proportional hazard model, training set (N = 407)

		Univariate analysis		Multivariate analysis	
		HR (CI 95%)	P values	aHR (CI 95%)	P values
Gender, Men		1.18 (0.94; 1.47)	0.150	–	
Age, years	Per 1-year increase	1.02 (1.01; 1.03)	**0.001**	–	
	≥ 70	1.59 (1.13; 2.24)	**0.008**	1.47 (1.03; 2.08)	**0.032**
Progression Free Survival, months	per 1-month increase	0.99 (0.98; 1.00)	0.078	–	
	< 18	1.29 (0.96; 1.74)	0.090	–	
RTOG–RPA classes	III–IV	1(ref)	**<0.001**	1(ref)	**0.004**
	V–VI	1.49 (1.20; 1.86)		1.38 (1.11; 1.73)	
Tumor main lobar location	Deep-seated	1(ref)	0.747	–	
	Frontal	1.19 (0.82; 1.73)		–	
	Parietal	1.05 (0.69; 1.59)		–	
	Temporal	1.10 (0.76; 1.60)		–	
KPS at diagnosis	100	1(ref)	0.080	–	
	90	1.03 (0.73; 1.45)		–	
	80	1.36 (0.99; 1.85)		–	
	70	1.11 (0.81; 1.53)		–	
	< 70	1.56 (1.05; 2.32)		–	
KPS at the end of first-line treatment	100	1(ref)	**<0.001**	–	
	90	1.29 (0.85; 1.95)		–	
	80	1.42 (0.99; 2.03)		–	
	70	2.10 (1.42; 3.10)		–	
	< 70	3.37 (2.30; 4.92)		–	
KPS at progression	100	1(ref)	**<0.001**	1(ref)	**<0.001**
	90	1.30 (0.73; 2.29)		1.65 (0.93; 2.92)	0.088
	80	1.79 (1.07; 2.99)		2.05 (1.22; 3.45)	**0.007**
	70	2.20 (1.33; 3.65)		2.31 (1.39; 3.84)	**0.001**
	< 70	4.23 (2.58; 6.94)		3.46 (2.10; 5.72)	**<0.001**
Treatments at progression	Surgical resection	0.52 (0.41; 0.66)	**<0.001**	0.57 (0.44; 0.73)	**<0.001**
	Chemotherapy	0.41 (0.32; 0.54)	**<0.001**	0.41 (0.31; 0.55)	**<0.001**
	Temozolomide	0.59 (0.46; 0.76)	**<0.001**	–	
	Bevacizumab	0.66 (0.53; 0.82)	**<0.001**	–	
	Other chemotherapy	0.65 (0.53; 0.80)	**<0.001**	–	
	Carmustine wafersimplantation	0.58 (0.44; 0.76)	**<0.001**	–	
	Radiotherapy	0.63 (0.39; 1.02)	0.061	–	

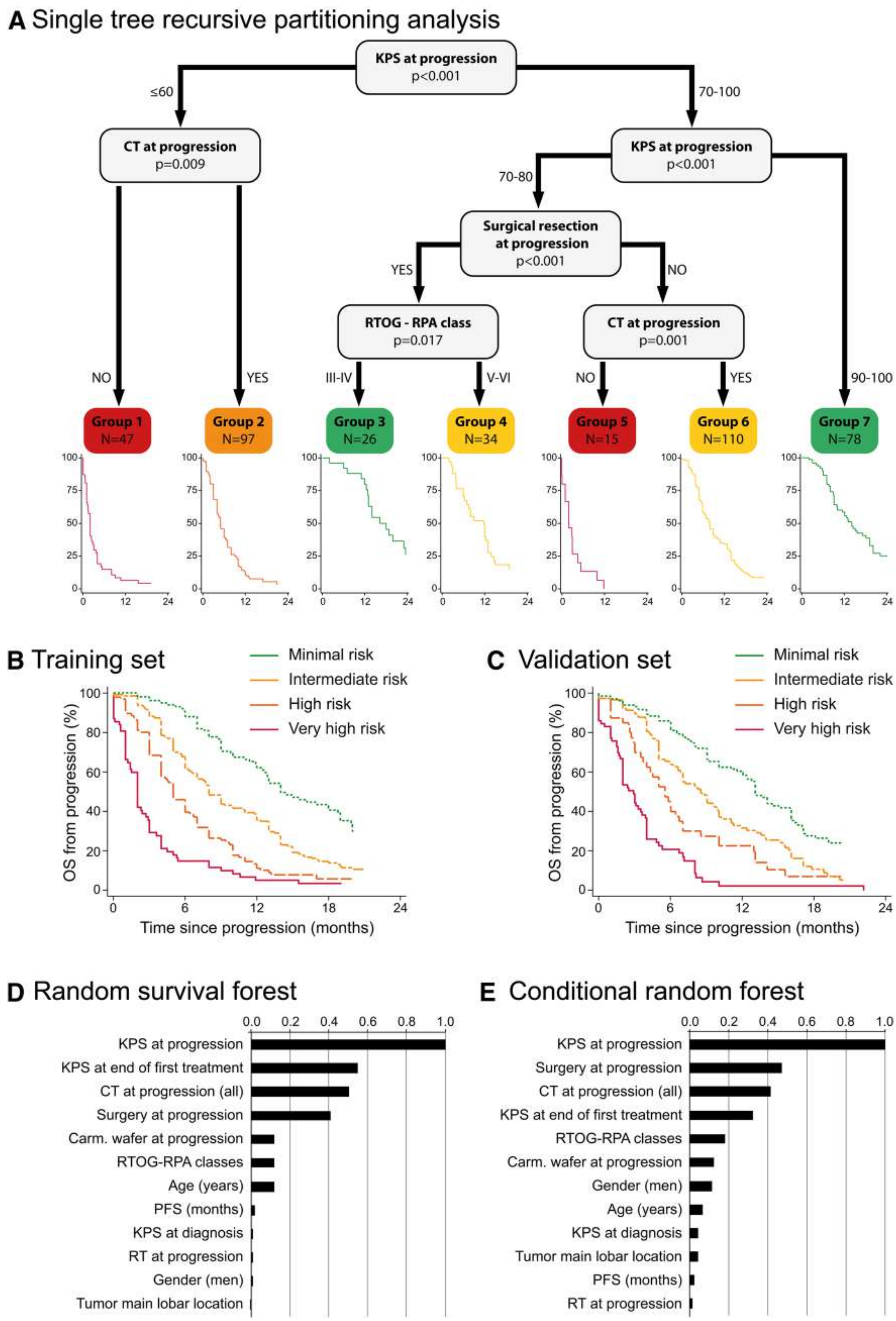
Bold reflects the statistical significance of p-values

HR Hazard ratio, *a HR* adjusted HR by stepwise multivarite analysis

and Cox analysis, followed by the single tree approach. As expected, decreased C-indexes were generally found after cross-validation and external validation, indicating possible slight overfitting in the development of the prediction models, as indicated by the limited magnitude of the differences, e.g. difference in C-indexes between external validation and training sets: − 2.09% (Cox), − 1.59% (CRF), − 0.96% (single tree). To the exception of the Cox proportional hazards modeling, all approaches yielded concordance indexes superior to 70.0% in the external validation set. Of note, while the best result was achieved by CRF (70.37%), a very close C-index value was obtained by the single decision tree (70.15%), demonstrating a remarkably stable discriminative performance in the external validation set with increased usability for clinical practice.

Discussion

The determination of strong predictors of OS from progression is crucial to guiding therapeutic decisions for recurrent glioblastoma. We confirm age, RTOG–RPA classes, KPS at progression, surgical resection at progression, and chemotherapy at progression as independent single predictors of


A Single tree recursive partitioning analysis
KPS at progression p<0.001
≤60
70-100
CT at progression p=0.009
KPS at progression p<0.001
70-80
90-100
Surgical resection at progression p<0.001
YES
NO
RTOG - RPA class p=0.017
CT at progression p=0.001
NO
YES
III-IV
V-VI
NO
YES
Group 1 N=47
Group 2 N=97
Group 3 N=26
Group 4 N=34
Group 5 N=15
Group 6 N=110
Group 7 N=78
B Training set
C Validation set
Minimal risk
Intermediate risk
High risk
Very high risk
OS from progression (%)
Time since progression (months)
D Random survival forest
KPS at progression
KPS at end of first treatment
CT at progression (all)
Surgery at progression
Carm. wafer at progression
RTOG-RPA classes
Age (years)
PFS (months)
KPS at diagnosis
RT at progression
Gender (men)
Tumor main lobar location
E Conditional random forest
KPS at progression
Surgery at progression
CT at progression (all)
KPS at end of first treatment
RTOG-RPA classes
Carm. wafer at progression
Gender (men)
Age (years)
KPS at diagnosis
Tumor main lobar location
PFS (months)
RT at progression

◂**Fig. 3** **a** Results for single decision tree by recursive partitioning analysis. The terminal nodes are represented by squares, which contain the number of patients in each group. Four risk categories were computed from the seven group: very high risk (merging groups 1 and 5, red), high risk (group 2, orange), intermediate risk (merging groups 4 and 6, yellow), and minimal risk (merging groups 3 and 7, green). *CT* chemotherapy, *KPS* Karnofsky performance status, *RPA* recursive partitioning analysis, *RTOG* radiation therapy oncology group. **b** Kaplan–Meier curves for overall survival from progression in the training set according to risk categories computed from classification and regression tree analysis: very high risk group (red), high risk group (orange), intermediate risk group (yellow), and minimal risk group (green). **c** Kaplan–Meier curves for overall survival from progression in the validation set according to risk categories computed from classification and regression tree analysis: very high risk group (red), high risk group (orange), intermediate risk group (yellow), and minimal risk group (green). **d** Selected predictors of overall survival from progression ranked by variable importance measure using a random survival forest algorithm. **e** Selected predictors of overall survival from progression ranked by variable importance measure using a conditional random forest algorithm

OS from progression in recurrent glioblastomas. Interestingly, we demonstrated complex interactions between those prognostic factors, which allowed the establishment of a new decision-tree-based algorithm that proved to be highly predictive both of training and independent external validation sets.

Our results are in-keeping with the current literature, which suggests that age and KPS at diagnosis are the two strongest independent predictors of OS from progression [2, 16, 23, 24]. We found that KPS at progression was even a stronger predictor of OS from progression, which has not been identified in previous studies due to incomplete data precluding its incorporation in survival models. As previously reported, we identified surgical resection at progression as an independent predictor of OS from progression [4, 9, 13–15, 36, 37]. We also found chemotherapy at progression, regardless of the regimen used, and repeated oncological treatments to be independent predictors of OS from progression. These observations support the usefulness of combined treatments for each patient, in accordance with previous reports [5, 9, 10, 16, 18, 20].

We performed decision-tree based analyses to build a novel prognostic model both highly predictive and practical for daily clinical use. The current recursive partitioning analysis complements and does not subtitute the seminal RTOG–RPA classes established for high-grade gliomas at initial diagnosis, suggesting that the overall condition of the patient should be considered at first-line treatment and at progression. Indeed, we highlight that both baseline parameters, including KPS at diagnosis and age at diagnosis that are captured in the RTOG–RPA classes, and KPS at progression are required for an optimal therapeutic decision making for recurrent glioblastoma. Single tree analysis confirmed KPS at progression as the most important predictor, finding worse survival in patients with KPS < 70, and improved outcomes in those with KPS ≥ 90. In the latter group, no additional node was found beyond KPS, e.g., involving therapeutic modalities, which possibly reflects that most patients with optimal clinical status at progression benefit from surgical resection and adjuvant chemotherapy. Interestingly, the most complex were found in patients with intermediate KPS at progression (70–80), in whom RTOG–RPA class, surgical resection at progression, and chemotherapy at progression determined subgroups with highly differentiated outcomes: patients benefiting neither from surgery nor chemotherapy had the worst survival; conversely, RTOG III–IV class patients benefiting from surgical resection at progression demonstrated similar outcomes than patients with KPS ≥ 90.

The strengths of this study are: (1) the multicentre and large study population; (2) a similar first-line treatment precluding biases in survival analyses at progression by varying first-line treatments; (3) available KPS at progression allowing its incorporation in survival models; (4) a starting time for calculating OS at the time of progression preventing biases in estimation of OS from progression [38]; and (5) the use of advanced statistical approaches based on decision trees in complement to conventional Cox modeling that allowed automatic determination of the optimal cut-off values for quantitative predictors and identification of prognostic subgroups based on complex combinations between predictors. Weaknesses of this study include the lack of central histopathological, molecular, and imaging

Table 3 Discrimination C-indexes performance indices by modeling approach

	Training set (%)	Internal validation[a] (%)	External validation set (%)
Cox model	71.89	69.91	69.80
Single tree by recursive partitioning	71.11	70.76	70.15
Survival random forest	69.80[b]	70.17	70.14
Survival conditional random forest	71.96[b]	70.22	70.37

[a] 10-fold cross-validation with ten replications

[b] Based on out-of-bag (OOB) predictions

reviews. Our findings may be reassessed in future studies by addressing other potentially relevant prognostic factors not available in our database, such as the extent of resection at progression, the MGMT promoter methylation status, and the IDH mutation status. Finally, interpretation of our findings should consider the observational nature of the present retrospective study, allowing the identification of prognostic factors but preventing direct conclusions to be drawn on the causal effects. This especially applies to therapeutic modalities whose indications depend on patients' characteristics at progression.

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Compliance with ethical standards

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Update

Carmustine wafer implantation for high-grade gliomas: Evidence-based safety efficacy and practical recommendations from the Neuro-oncology Club of the French Society of Neurosurgery

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ABSTRACT

There is a growing body of evidence that carmustine wafer implantation during surgery is an effective therapeutic adjunct to the standard combined radio-chemotherapy regimen using temozolomide in newly diagnosed and recurrent high-grade glioma patient management with a statistically significant survival benefit demonstrated across several randomized clinical trials, as well as prospective and retrospective studies (grade A recommendation). Compelling clinical data also support the safety of carmustine wafer implantation (grade A recommendation) in these patients and suggest that observed adverse events can be avoided in experienced neurosurgeon hands. Furthermore, carmustine wafer implantation does not seem to impact negatively on the quality of life and the completion of adjuvant oncological treatments (grade C recommendation). Moreover, emerging findings support the potential of high-grade gliomas molecular status, especially the O(6)-Methylguanine-DNA Methyltransferase promoter methylation status, in predicting the efficacy of such a surgical strategy, especially at recurrence (grade B recommendation). Finally, carmustine wafer implantation appears to be cost-effective in high-grade glioma patients when performed by an experienced team and when total or subtotal resection can be achieved. Altogether, these data underline the current need for a new randomized clinical trial to assess the impact of a maximal safe resection with carmustine wafer implantation followed by the standard combined chemoradiation protocol stratified by molecular status in high-grade glioma patients.

1. Introduction

High-grade gliomas (HGGs) (World Health Organization [WHO] grade III and IV gliomas) are the most aggressive primary brain tumors. They are more common in men, and their incidence increases with age. The incidence rate of HGGs, within the French population, varies between 3.34 and 6.09 per 100 000 inhabitants per year [1].

Maximal safe resection, whenever possible using intraoperative imaging navigation tools and functional monitoring, is recommended as the first treatment for newly diagnosed and recurrent HGG and has been shown to reduce symptoms, improve survival, and increase the efficacy of adjuvant therapies [1–11]. During surgical resection, biodegradable wafers releasing the cytotoxic agent Carmustine (1,3-bis(2-chloroethyl)-1-nitrosourea, BCNU), can be implanted in the surgical bed on the walls of the resection cavity [12–14]. Carmustine wafer implantation is proposed for newly diagnosed and recurrent HGG when subtotal (>90% of contrast enhancement) or total resection is performed [15–17]. This local chemotherapy treatment offers a theoretical therapeutic bridge

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during the regular off-period treatment that lies after surgery and before the beginning of adjuvant oncological therapy [4]. Although the efficacy of carmustine wafer implantation is well established, its safety remains a matter of debate, with varying results regarding toxicity, maintaining of the quality of life, and feasibility of adjuvant oncological treatments [18].

On the behalf of the Neuro-Oncology Club of the Société française de neurochirurgie, we aimed to perform an evidence-based analysis of carmustine wafer implantation safety and efficacy in newly diagnosed and recurrent HGG to help in providing practical recommendations for this patient population.

1.1. Standard of care for newly diagnosed HGG

Each oncologic decision should be discussed in a multidisciplinary staff meeting. Following surgery, the current standard of care for newly diagnosed grade IV glioma (glioblastomas) patients under 70-years-old with preserved overall condition consists of radiotherapy (60 Gy, 30 fractions over 6 weeks) with concomitant and adjuvant temozolomide, the standard combined chemoradiotherapy, (level of evidence 1, grade A recommendation) [19,20]. Recently, two randomized controlled trials (RCTs) conducted in Europe and US showed that adding bevacizumab to the standard combined chemoradiotherapy protocol in newly diagnosed WHO grade IV glioma patients, was not associated with an improvement of overall survival (OS) [21,22].

Following surgery, the current standard of care for newly diagnosed grade III gliomas (anaplastic gliomas) for patients under 70-year-old depends on glioma molecular subtype. For isocitrate dehydrogenase (IDH)-mutated 1p19q codeleted WHO grade III oligodendrogliomas, the current standard of care consists of sequential radiotherapy and chemotherapy using procarbazine, lomustine and vincristine (PCV) [23,24] (level of evidence 1, grade A recommendation). For IDH-mutated WHO grade III astrocytomas without 1p19q codeletion, there is currently no standard of care. Standard combined chemoradiotherapy, radiotherapy followed by adjuvant chemotherapy using temozolomide or PCV can be proposed [25] (level of evidence 3, grade C recommendation). For IDH-wild-type WHO grade III astrocytomas without 1p19q codeletion, there is also no standard of care. Standard combined chemoradiotherapy or radiotherapy followed by adjuvant chemotherapy with Temozolomide could be proposed [25] (level of evidence 3, grade C recommendation).

For patients over 70-years-old, the current standard of care for newly diagnosed grade IV glioma (glioblastomas) with preserved overall condition consists of short-course radiotherapy (40 Gy, 15 fractions over 3 weeks) with concomitant and adjuvant temozolomide (level of evidence 1, grade A recommendation) [26]. For other high-grade glioma subtypes, there is no standard of care and oncological treatment depends on a multidisciplinary discussion, which takes into account the global condition of the patient [27–31].

1.2. Standard of care for recurrent HGG

For recurrent grade III or IV gliomas, whatever the patient's age and overall condition, there is currently no standard of care. The choice of the oncological treatment depends on a multidisciplinary discussion, which takes into account the previous therapeutic modalities, and the global condition of the patient. Surgical resection, radiotherapy, chemotherapy or supportive care could be proposed (level of evidence 2–3, grade B–C recommendation) [32–41].

2. Carmustine wafer technology

Carmustine wafer (Gliadel®, Kyowa Hakko Kirin Co) is a biodegradable copolymer disc releasing the alkylating agent Carmustine (1,3-bis(2-chloreoethyl)-1-nitrosourea, BCNU). Each implant contains 7.7 mg of Carmustine and 192.3 mg of polifeprosan 20 (inactive ingredient), which induce cell-cycle arrest and apoptosis by alkylating DNA and inhibiting nucleic acid synthesis [42]. Carmustine wafers delivers chemotherapy directly into the surgical cavity. Pharmacological studies in rabbit models showed that the delivery of carmustine inside the brain tissue is extended at high concentrations up to 12 mm from the wafer site [43]. Beyond this, the brain tissue is exposed to lower concentrations of carmustine [42]. The carmustine release time is 21 days but the majority is released between 5 and 7 days [43,44] and complete degradation of the wafers occurs between the 6th and 8th weeks [43,45,46].

3. Search methodology

A literature search was conducted on PubMed to identify phase I and II studies, randomized clinical trials (RCTs), prospective cohort studies, and retrospective studies concerning carmustine wafer implantation (case reports excluded) in English language. The inclusive search dates were from January 1992 through October 2016. Specific search terms included Gliadel® and carmustine wafer. Relevant studies were classified according to the level of evidence (1, 2, 3-4) and to the grade of recommendation (A, B or C) in accordance with the French National Authority for Health - Haute Autorité de santé (HAS) (Table 1). We used the RIGHT reporting tool for practice guidelines in health care to strengthen the methodology [47].

4. Evidence-based data of carmustine wafers efficacy for newly diagnosed HGG

4.1. Highest level of evidence (level 1) with grade A recommendation

Two multicenter RCTs [13,14] and one long-term follow-up analysis of the largest RCT [41] assessed the efficacy of carmustine wafer implantation in newly diagnosed HGG. In both studies, patients were randomized to carmustine or placebo wafers implantation followed by adjuvant radiotherapy, which was the standard of care at that time for grade III and grade IV gliomas. These two RCTs showed that carmustine wafer implantation significantly improved OS.

The first RCT assessing carmustine wafer implantation in newly diagnosed HGG was performed in 1997 by Valtonen et al., who conducted a multicenter Finnish RCT, which included 32 patients with newly diagnosed HGG – 16 in each group – (27 grade IV gliomas, 5 grade III gliomas) [13]. The small number of included patients, due to the fact that Carmustine wafers were no longer available,

Table 1
Grades of recommendation and levels of evidence according to the French National Authority for Health (Haute Autorité de santé).

Grade of recommendation	Level of evidence	Study types
A - scientific evidence	1	Well-conducted randomized controlled trials Meta-analysis including randomized controlled trials Decision analysis based on well-conducted studies
B - scientific presumption	2	Randomized controlled trials with biases Well-conducted non-randomized comparative studies Cohort studies
C - low level of scientific evidence	3–4	Case-control studies Comparative studies with significant biases Retrospective studies Descriptive epidemiological studies

questions the level of evidence of this trial (level 1 that can be lowered to level 2). The median overall survival (OS) was 58.1 weeks in the carmustine wafer implantation group and was 39.9 weeks for the placebo group ($P = 0.012$). There was no statistically significant difference in progression-free survival (PFS) between both groups. Westphal et al., in 2003 performed a multicenter international study, which included 240 patients, 120 in each group (207 grade IV gliomas, 21 grade III gliomas, and 12 other diagnoses) [14]. The median OS was 13.9 months in the carmustine wafer implantation group and was 11.6 months in the placebo group ($P = 0.03$), with a 29% reduction in the risk of death in the carmustine wafer implantation group. There was no statistically significant difference in PFS between both groups. In 2006, Westphal et al. published a long-term follow-up analysis of patients previously included in the RCT conducted by Westphal et al. in 2003 [48]. Of the 59 patients available for long-term follow-up, 11 were alive at 56 months: 9 in the carmustine wafer implantation group and 2 in the placebo group. Median OS of patients in carmustine wafer implantation group was 13.8 months vs 11.6 months in placebo group ($P = 0.017$), representing a 27% significant risk reduction. This survival advantage was maintained at 1, 2, and 3 years and was statistically significant ($P = 0.01$) at 3 years. These authors concluded that carmustine wafer implantation in combination with radiation therapy demonstrated a survival advantage at 2 and 3 years follow-up compared with placebo for newly diagnosed HGG [48].

Eight systematic reviews, including RCT and retrospective studies in their analyses, assessed the efficacy of carmustine wafer implantation in newly diagnosed HGG and all showed that carmustine wafer implantation improved survival when subtotal or total resection was performed [15–17,49–53].

In 2007, the National Institute for Health and Care Excellence (NICE) published a systematic review and economic evaluation in the United Kingdom of carmustine wafer implantation for newly diagnosed HGG [17]. They concluded that carmustine wafer implantation represented a cost-effective use, which statistically improved the OS, the PFS and the time to functional decline for both grade III and IV gliomas after a subtotal or total resection (defined by a resection of more than 90% of the contrast enhancement on magnetic resonance imaging [MRI]). They recommended the use of carmustine wafers in specific experienced centers [17]. The Cochrane Database systematic review assessed the clinical effectiveness of chemotherapy wafers for patients with HGG in 2008, which was subsequently updated in 2011 [15,16]. They concluded that carmustine wafer implantation resulted in a significant improvement in OS ($P = 0.003$) without an increased incidence of adverse events over placebo for newly diagnosed HGG but there was no evidence of benefit with regards to PFS or quality of life. They recommended an individual analysis in a multidisciplinary team for carmustine wafer implantation decision-making process [15,16]. Dixit et al. performed a clinical review in 2011, to assess the efficacy and toxicities for patients who were treated by carmustine wafer implantation after surgical resection followed by the standard combined chemoradiotherapy [49]. Twelve phase II and retrospective studies were included. The median survival has been reported from 12.7 to 22 months and 2-year survival ranged from 13% to 47%. This review indicated that the sequential combination of the two regimens was safe and efficient with 2–3 months incremental gain in median OS. Bregy et al. performed a meta-analysis including 19 studies involving a total of 795 patients with newly diagnosed HGG in 2013 [50]. Fourteen of the studies used the standard combined chemoradiotherapy and three used adjuvant radiotherapy only. Survival ranged from 8.7 to 22.6 months with a mean OS of 16.2 months in the carmustine wafer implantation group and 14 months in the non-carmustine wafer implantation group. They concluded that carmustine wafers as an adjuvant therapy along with standard combined chemoradiotherapy could lead to an increase in OS. In 2014, Zhang et al., performed a systematic review of carmustine wafer implantation clinical trials in newly diagnosed and recurrent glioblastoma patients [51]. Six trials were included, four were RCTs and two were retrospective studies. Carmustine wafer implantation significantly improved OS, did not significantly improve PFS and did not increase adverse events. This review suggested that carmustine wafer implantation was an effective and safe treatment in comparison to other treatment strategies in glioblastoma patients. Chowdhary et al. performed the largest meta-analysis in 2015 including 62 publications, which reported data from 60 studies (3162 patients with carmustine wafer implantation and 1736 without for newly diagnosed and recurrent HGG) [52]. For newly diagnosed HGG, 1-year OS was 67% in carmustine wafer implantation group and 48% in the non-carmustine wafer implantation group; 2-year OS was 26% and 15%, respectively. The median OS was significantly increased in the carmustine wafer implantation group (16.4 ± 21.6 months) compared to the non-carmustine wafer implantation group (13.1 ± 29.9 months) ($P = 0.043$). They concluded a significant survival benefit for carmustine wafer implantation for newly diagnosed and recurrent HGG. Ashby et al., in 2016, performed a systematic literature review of 11 studies (3 prospective trials and 8 retrospective studies) including 411 patients who received carmustine wafers after surgical resection followed by the standard combined chemoradiotherapy protocol [53]. The median OS was 18.2 months and the median PFS was 9.7 months. They concluded that carmustine wafer implantation followed by the standard combined chemoradiotherapy improved median OS by 3 to 4 months compared to carmustine wafer implantation or temozolomide when used alone in the respective phase III trials [13,14,19]. They stated that a RCT of carmustine wafer implantation followed by combined chemoradiotherapy using temozolomide compared to the current standard of care was actually needed.

4.2. Level of evidence 2 with grade B recommendation

Three prospective cohort studies assessed the efficacy of carmustine wafer implantation in newly diagnosed HGG [54,55,56]. Two of them showed a significant improvement in OS [55,56]. In 2013 Salmaggi et al., performed an Italian prospective study that assessed the safety efficacy of carmustine wafer implantation after surgical resection followed by the standard combined chemoradiotherapy in 35 newly diagnosed glioblastoma patients [55]. The observed median OS was 17.8 months, actually superior to the 14.6 months reported in the study of Stupp et al. [19]. Duntze et al., in 2013 reported, a French prospective multicenter (17 centers) cohort of 92 HGG patients treated by surgical resection with carmustine wafer implantation followed by the standard combined chemoradiotherapy [56]. Median OS and PFS were 18.8 months and 10.4 months respectively and greater than those reported by Westphal et al., in 2003. During the same period, a Spanish prospective study reported by Catalán-Uribarrena et al., in 110 HGG newly diagnosed patients treated with or without carmustine wafer implantation after surgery did not find any significant difference in OS between the implanted (13.4 months) and non-implanted-group (11.0 months; $P = 0.856$).

4.3. Level of evidence 3 and 4 with grade C of recommendation

Twelve retrospective studies assessed the efficacy of carmustine wafer implantation in newly diagnosed HGG [4,10,18,57–65]. Nine of them showed that carmustine wafer implantation during surgery was independently associated with a better OS and/or PFS [4,10,18,57,58,60–63] whatever the extent of surgical resection and the Karnofsky performance status (KPS) at diagnosis HGG [4,18].

Pallud et al. performed a French retrospective multicenter national study (18 centers) in 2015, including 787 adult patients with newly diagnosed glioblastoma that were treated with surgical resection with ($n=354$) or without ($n=433$) carmustine wafer implantation followed by the standard combined chemoradiotherapy as first-line treatment [4]. Carmustine wafer implantation followed by the standard combined chemoradiotherapy was independently associated with longer PFS (12.0 vs 10.0 months) in patients with subtotal/total surgical resection for the whole series ($P=0.005$) and after propensity matching ($P=0.008$), whereas no significant difference was found for OS (20.4 vs 18.0 months) in both sub-analyses ($P=0.570$ and $P=0.561$). Roux et al., in 2017 performed a retrospective monocentric study which assessed together safety, tolerance, and efficacy of carmustine wafer implantation and of extent of resection for newly diagnosed glioblastoma at the era of the standard combined chemoradiotherapy [18]. Carmustine wafer implantation was independently associated with longer OS (19.0 versus 17.8 months, $P=0.029$) and PFS (10 versus 8 months, $P=0.043$).

Three retrospective studies did not show significant survival benefit from carmustine wafer implantation in newly diagnosed HGG at the era of standard combined chemoradiotherapy [59,64,65]. Noël et al. performed a French prospective single center study in 2012 to assess the efficacy of carmustine wafer implantation in 65 patients with HGG (28 patients with carmustine wafer implantation, 37 without) [59]. There was no significant survival difference between patients who received carmustine wafer implantation and those who did not. However, in the glioblastoma subgroup ($n=36$), the median OS was higher (20.8 vs 13.8 months) when carmustine wafer implantation was performed, with no statistical significance ($P=0.067$).

5. Evidence-based data of carmustine wafers efficacy for recurrent HGG

5.1. Highest level of evidence (level 1) with grade A of recommendation

Only one multicenter RCT assessed the efficacy of carmustine wafer implantation in recurrent HGG patients versus placebo [12]. Brem et al., conducted a North American multicenter RCT in 1995, which assessed the safety efficacy of carmustine wafer implantation in recurrent HGG. They included 222 patients with recurrent HGG requiring surgical resection from 27 medical centers. The median survival was significantly longer ($P=0.006$) in the carmustine wafer implantation group (31 weeks) compared with the placebo wafer implantation group (23 weeks).

Three systematic reviews assessed the efficacy of carmustine wafer implantation in recurrent HGG [15,16,52]. One of them showed that carmustine wafer implantation improved survival when subtotal or total resection was performed [52]. The median OS was significantly longer in the carmustine wafer implanted-group (9.7 months) than in the non-implanted one (8.6 months) ($P=0.043$) [52]. The Cochrane Database systematic review published in 2008 and updated in 2011 reported that carmustine wafer implantation did not confer significant survival benefit for recurrent HGG patients [15,16].

5.2. Level of evidence 2 with grade B recommendation

Three prospective cohort studies assessed the efficacy of carmustine wafer implantation in recurrent HGG [66,67,68]. Two studies showed that carmustine wafer implantation improved survival when subtotal or total resection was performed [67,68].

Metellus et al. performed a prospective single center study, in 2009, and assessed, for the first time, the prognostic impact of carmustine wafers implantation in recurrent glioblastoma multiforme (GBM) according to the methylguanine-DNA methyltransferase (MGMT) status [67]. MGMT promoter hypermethylation was associated with a statistically significant improvement in both OS and PFS ($P=0.019$ and $P=0.0012$, respectively). Dörner et al. performed a German prospective study, in 2013, which assessed the efficacy of carmustine wafer implantation in HGG after surgical resection at recurrence [68]. Their findings suggested that carmustine wafer implantation could not be employed as a "stand-alone" modality but could provide a perioperative link between surgery and adjuvant oncological treatments.

Subach et al. reported their experience of carmustine wafer implantation in 62 patients with recurrent glioblastoma [66]. They compared their results with a cohort of 45 patients treated by surgery alone for recurrent HGG during the same time period. They did not find any survival benefit for recurrent glioblastoma patients treated with carmustine wafer implantation.

5.3. Level of evidence 3 and 4 with grade C recommendation

Three retrospective studies assessed the efficacy of carmustine wafer implantation in recurrent HGG [4,57,65]. Two studies showed that carmustine wafer implantation improved survival when subtotal or total resection was performed [4,57]. Menei et al. assessed the efficacy of carmustine wafer implantation at the era of the standard combined chemoradiotherapy for newly diagnosed and recurrent HGG and compared the results with those of RCTs for these two groups [57]. Median survival in the recurrent HGG was seven months. Their findings suggested that carmustine wafer implantation in recurrent HGG was safe but also underlined the current need for further evaluation of their efficacy in phase II and III trials. Pallud et al. demonstrated that surgical resection at progression, whether alone or combined with carmustine wafer implantation, was independently associated with longer OS in the entire series ($P=0.0001$) and after propensity matching ($P=0.0001$) [4]. De Bonis et al. assessed the efficacy of carmustine wafer implantation in 88 patients with recurrent glioblastoma and did not find any significant survival benefit [65].

6. Evidence-based data of carmustine wafers safety

The safety of carmustine wafer implantation was analyzed in 23 studies which are summarized in Table 2 [4,12–16,49–53,55–57,60,61,65,66,69–73].

The reported morbidity of carmustine wafer implantation varied in the literature. Carmustine wafer implantation could increase postoperative adverse events, including postoperative infectious complications (7.1% in implanted-group versus 1.5% in non-implanted-group) (level of evidence 3–4) [4], cerebrospinal fluid leak (5% versus 0.8%, respectively) and intracranial hypertension (9.1% versus 1.7%, respectively) (level of evidence 1) [14]. These data support the fact that carmustine wafer implantation in fact increases local complication rates, even if this does not impact survivals. However, systemic therapies also carry actual and significant rates of systemic complications that could potentially affect the quality of life and survival, but it has never been an argument to prevent their use. Thus, it is necessary to put in balance the safety/efficacy impact of carmustine wafer implantation in treatment strategy. Also, one should keep in mind that neurosurgeon's experience actually impact complication occurrence rate and has to be taken into account in the treatment decision-making process.

Table 2
Evidence-based data of carmustine wafer safety.

Studies, year	Level of evidence	Study type	Country	Patients (n)	Postoperative infection	Raised intracranial pressure	Healing defect	Epileptic seizure	Neurological worsening	Author's conclusion
Ashby et al., 2016	1	Systematic review	USA	411	N/A n = 18; 4.8%	N/A n = 11; 3.0%	N/A n = 16; 4.3%	N/A n = 11; 3.0%	N/A n = 29; 7.8%	CWI combined with Stupp regimen improved survival without increasing toxicity
Chowdhary et al., 2015	1	Meta-analysis	USA	4898	N/A n = 11; 0.36%	N/A	N/A n = 6; 0.2%	N/A	N/A	Good surgical practice lowering the risk of known postoperative adverse events
Aoki et al., 2014	1	Phase I/II	JAP	24	No increase n = 0; 0%	N/A	No increase n = 0; 0%	No increase n = 0; 0%	No increase n = 6; 25%	There are no major safety concerns associated with CWI
Zhang et al., 2014	1	Systematic review	CHI	N/A	N/A	N/A	N/A	N/A	N/A	CWI did not increase postoperative adverse events
Bregy et al., 2013	1	Systematic review	USA	795	N/A n = 33; 14.4%	N/A n = 11; 4.8%	N/A n = 7; 3.1%	N/A n = 19; 8.2%	N/A n = 35; 15.3%	CWI followed by Stupp regimen was associated with a higher risk of toxicity
Dixit et al., 2011	1	Systematic review	UK	N/A	No increase 6–12%	No increase 7–10%	No increase 2–16%	No increase 5–16%	No increase 6–16%	Postoperative adverse events rate was comparable to the results published in literature
Hart et al., 2011	1	Systematic review	UK	N/A	N/A	N/A	N/A	N/A	N/A	CWI increase survival without a significant increase in adverse events
La Rocca et Mehdorn, 2009	1	Systematic review	USA	N/A	N/A	N/A	N/A	N/A	N/A	CWI was well-tolerated treatment for newly diagnosed or recurrent HGG
Hart et al., 2008	1	Systematic review	UK	N/A	N/A	N/A	N/A	N/A	N/A	CWI increase survival without a significant increase in adverse events
Sabel et Giese, 2008	1	Systematic review	GER	230	No increase 3.9% vs 3.0%	Increase 5.7% vs 3.5%	Increase 13% vs 7.4%	No increase 22.6% vs 24.8%	N/A	Healing abnormalities was higher in patients with CWI than in the literature
Westphal et al., 2003	1	RCT	GER	240	No increase	Increase 9.1% vs 1.7%	Increase 5% vs 0.8%	No increase 33.3% vs 37.5%	No increase	CWI did not increase postoperative adverse events except ICH and CSF fluid leak
Valtonen et al., 1997	1	RCT	FIN	32	No increase	No increase	No increase	No increase	No increase	Postoperative adverse events with CWI were consistent with those expected in HGG
Brem et al., 1995	1	RCT	USA	222	No increase 3.6% vs 0.9%	No increase	No increase	No increase	No increase	There were no adverse events related to CWI. CWI was a safe and effective treatment

Table 2 (*Continued*)

Studies, year	Level of evidence	Study type	Country	Patients (n)	Postoperative infection	Raised intracranial pressure	Healing defect	Epileptic seizure	Neurological worsening	Author's conclusion
Duntze et al., 2013	2	Prospective	FR	92	No increase $n=5$; 5.4%	No increase $n=2$; 2.2%	No increase $n=3$; 3.3%	No increase $n=3$; 3.3%	No increase $n=9$; 9.8%	CWI improved survival without increased adverse events
Salmaggi et al., 2013	2	Prospective	ITA	35	No increase $n=1$; 2.9%	No increase $n=1$; 2.9%	N/A	N/A	N/A	Postoperative adverse events were similar than those in the literature
Subach et al., 1999	2	Prospective	USA	62	Increase 23.5% vs 2.2%	Increase 5.9% vs 0%	Increase 11.8% vs 2.2%	Increase 11.8% vs 6.7%	N/A	The rate of postoperative adverse events was higher with CWI than surgery alone
Roux et al., 2017	3	Retrospective	FR	340	No increase 4.9% vs 2.3%	N/A	N/A	No increase 2.4% vs 0.9%	No increase 7.3% vs 6.9%	CWI was not associated with an increased incidence of adverse postoperative events
Chaichana et al., 2015	3	Retrospective	USA	401	No increase $n=21$; 5.5%	N/A	N/A	N/A	N/A	CWI was not associated with an increased rate of postoperative infections
Pallud et al., 2015	3	Retrospective	FR	787	Increase 7.1% vs 1.5%	Increase 3.1% vs 0.3%	No increase 1.3% vs 0.3%	No increase 5.3% vs 2.9%	No increase 7.6% vs 8.5%	Postoperative infections and raised intracranial pressure were significantly higher in CWI group
Samis Zella et al., 2014	3	Retrospective	GER	95	Increase 3.1% vs 0%	N/A	Increase 14.2% vs 6.2%	N/A	N/A	Postoperative adverse events were slightly higher with CWI but clinically acceptable
De Bonis et al., 2012	3	Retrospective	ITA	165	Increase $n=1$; 2.1%	Increase $n=7$; 14.9%	Increase $n=3$; 6.4%	Increase $n=4$; 8.5%	N/A	CWI increased toxicity for patient with newly diagnosed or recurrent glioblastoma
Menei et al., 2010	3	Retrospective	FR	163	No increase $n=8$; 4.9%	No increase $n=12$; 7.3%	No increase $n=8$; 4.9%	No increase $n=12$; 7.3%	No increase $n=28$; 17.1%	Complications rate was not statistically associated with CWI
Affronti et al., 2009	3	Retrospective	USA	85	N/A $n=4$; 11%	N/A	N/A	N/A $n=4$; 11%	N/A	Toxicities with CWI combined with Stupp regimen were higher but tolerable
Attenello et al., 2008	3	Retrospective	USA	1013	No increase 2.8% vs 1.8%	No increase 2.1% vs 2.3%	No increase 0.7% vs 0.4%	No increase 14.6% vs 15.7%	N/A	CWI was not associated with higher perioperative morbidity of any measure

CWI: carmustine wafer implantation; RCT: randomized clinical trial; USA: United States of America; JAP: Japan; CHI: China; UK: United Kingdom; GER: Germany; FIN: Finland; FR: France; ITA: Italy. N/A: not available.

7. Carmustine wafer implantation and quality of life analysis

Only one retrospective study (level 3–4 of evidence) assessed the quality of life after carmustine wafer implantation in newly diagnosed glioblastoma [18].

Roux et al., in 2017 reported, for the first time, that carmustine wafer implantation did not significantly reduce the early postoperative KPS ($P = 0.402$) and the KPS at the end of first-line oncological treatment ($P = 0.636$) [18]. Their findings suggest that the quality of life, as estimated by the KPS, is maintained in the months following carmustine wafer implantation and thus that carmustine wafer implantation could help improve survival with acceptable functional independence in these patients.

8. Impact of the molecular status on carmustine wafer implantation

Three retrospective studies assessed the impact of the MGMT promoter methylation status in newly diagnosed glioblastomas treated by surgical resection and carmustine wafer implantation at the era of the standard combined chemoradiotherapy [74–76]. These studies showed a significant survival benefit for carmustine wafer implantation in patients with a MGMT-methylated tumor. Lechapt-Zalcman et al. analyzed the MGMT promoter methylation status and MGMT protein expression in formalin-fixed, paraffin-embedded tumor specimens obtained from 111 patients with newly diagnosed glioblastoma treated by surgical resection, carmustine wafer implantation and followed by the standard combined chemoradiotherapy [74]. They showed that patients with MGMT-methylated glioblastomas had a significantly longer OS compared with patients who had wild-type MGMT glioblastomas (21.7 vs 15.1 months; $P = 0.025$). Similarly, patients who had low MGMT protein expression (MGMT-methylated tumors) had a significantly improved OS compared with patients who had high MGMT expression (27.0 vs 15.1 months; $P = 0.021$). Grossman et al. assessed the impact of MGMT promoter methylation status on clinical outcomes in 122 newly diagnosed glioblastoma patients who were treated by carmustine wafer implantation and did not find any survival benefit in the MGMT-methylated group ($P = 0.860$) [75]. Conversely, Gutenberg et al. reported in 2013 a significant longer OS (21.0 vs 11.1 months, $P = 0.013$) in MGMT-methylated tumor patients among 37 newly diagnosed glioblastoma treated by surgical resection and carmustine wafers implantation followed by the standard combined chemoradiotherapy [76].

Two retrospective studies assessed the impact of the MGMT promoter methylation status in recurrent glioblastomas treated by surgical resection and carmustine wafer implantation at the era of the standard combined chemoradiotherapy [67,76].

Metellus et al., in 2009, reported 22 patients with recurrent glioblastoma treated by surgical resection with carmustine wafer implantation and found that carmustine wafer implantation was significantly associated with a better OS in recurrent glioblastoma patients with MGMT-methylated tumors [67]. Gutenberg et al. in 2013 reported a series of 17 patients who underwent surgery with carmustine wafer implantation for recurrent glioblastoma but failed to show any significant difference in OS for both MGMT-methylated and non-methylated tumors groups ($P = 0.680$) [76].

9. Carmustine wafer implantation in elderly patients

Only one retrospective study assessed the efficacy of carmustine wafer implantation in elderly patients with newly diagnosed glioblastoma [77].

In 2011, Chaichana et al. performed an American retrospective monocentric study, which assessed the efficacy of carmustine wafer implantation in elderly patient with a newly diagnosed glioblastoma between 1997 and 2007 [77]. The median OS was significantly higher for patients with carmustine wafer implantation (8.7 months) compared to those without carmustine wafer implantation (5.5 months; $P = 0.007$). The 3-, 6-, 9-, and 12-month OS rates were significantly higher for patients with carmustine wafer implantation (89, 62, 47, and 33%, respectively) than those without carmustine wafer implantation (71, 40, 24, and 9%, respectively; $P = 0.007$). The same significant results were observed after subgroup analysis stratified by age (patients older than 70 and patients older than 75). Their results in fact support the use of carmustine wafer implants in elderly glioblastoma patients, which could prolong survival up to 3.2 months.

10. Cost-effectiveness

The NICE guidance conducted an economic evaluation, which was designed to estimate the cost-effectiveness of carmustine wafer implantation in the United Kingdom [17]. It was estimated that the cost of surgery, oncological treatment, follow-up, treatment of adverse effects, and end of life care was approximately £16,000 per patient. Carmustine wafer implantation added an additional £6,000. Across the modelled cohort of 1000 patients, carmustine wafer implantation costs an additional £6.1 million and confers an additional 107 Quality Adjusted Life Years, which was a generic measure of disease burden, including both the “quality of life” and the “quantity of life” lived. On average, that is £6,100 per patient for 0.107 quality adjusted life years (5.6 quality adjusted life weeks). The base case incremental cost-effectiveness ratio is £57,000 per quality adjusted life year gained. The NICE committee concluded that carmustine wafer implantation represented a cost-effective use for the treatment of HGG in specialized centers by neuro-oncological surgeons which have intraoperative technology that aid in judging the extent of resection only for patients in whom 90% or more tumor resection could be performed.

To date, there is no reported cost-effectiveness study of carmustine wafer implantation available in France.

11. Interpretation by the Neuro-oncology Club of the Société française de neurochirurgie

RCTs providing the prognostic value of carmustine wafer implantation for newly diagnosed and recurrent HGGs [12–14] were performed before the era of the standard combined chemoradiotherapy [19], and even if they are positive in terms of OS, no definitive recommendation on carmustine wafer implantation use can be drawn for today’s practice.

A RCT assessing the safety efficacy of carmustine wafer implantation in patients treated by the standard combined chemotherapy protocol after surgical resection with histomolecular stratification would be of great practical interest.

The NICE and the Cochrane Database systematic reviews of carmustine wafer implantation for newly diagnosed and recurrent HGG have shown a significant improvement in survival following carmustine wafer implantation in newly diagnosed HGG, which supports the evidence of its efficiency (level of evidence 1, grade A recommendation) [15–17].

The NICE guidance showed a significant improvement in survival following carmustine wafer implantation in recurrent HGG (level of evidence 1, grade A of recommendation) [17], but not The Cochrane Collaboration [15,16].

The survival benefit of carmustine wafer implantation appears to occur when a subtotal or total resection (> 90% or more of the

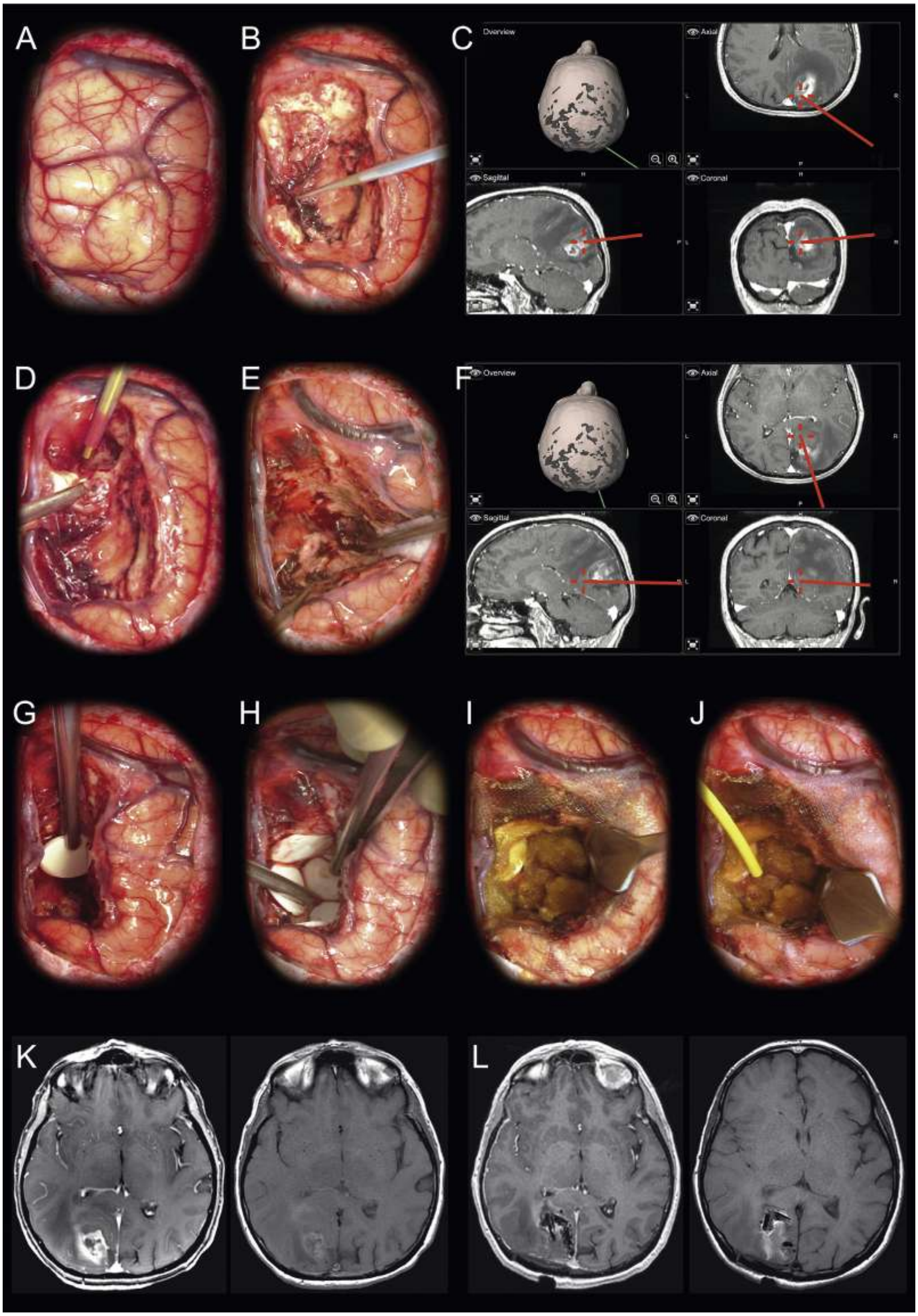

Fig. 1. Carmustine wafer implantation in high-grade glioma surgery. Intraoperative photographs (A–J) showing the surgical field in an adult patient who underwent surgical resection with carmustine wafer implantation for a right parietal IDH-wildtype glioblastoma and corresponding preoperative (K) and postoperative (L) MR examinations. On opening the dura, the tumor infiltration component appeared cortically as pale, hypertrophied and distended gyri (A). After corticectomy, the contrast-enhanced tumor component appeared as dark red, purple and brown (B) as ascertained by the projection of the intraoperative tool on the MRI-based intraoperative neuronavigation system (C). A safe surgical removal was performed using an ultrasonic surgical aspirator (D) beyond MRI-defined abnormalities with preservation of functional boundaries (E), as ascertained by the projection of the intraoperative tool on the MRI-based intraoperative neuronavigation system (F). Then, after achieving hemostasis with no residual bleeding and removed every haemostatic material, carmustine wafers were implanted directly in contact with the brain surface (G) along the whole tumor bed (H). Carmustine wafers were then stabilized and secured by a single layer of cellulose absorbable hemostat (I) and covered by biological glue application (J). Preoperative (K) axial pre- (right) and post-contrast (left) T1-weighted sequence demonstrating a right parietal contrast-enhanced tumor. Postoperative day one (K) axial pre- (right) and post-contrast (left) T1-weighted sequence demonstrating the carmustine wafers lying over the surgical cavity. In (C) and (F) images, the side is reversed for navigation planning purposes.

contrast-enhanced area) is performed (level of evidence 1, grade A of recommendation) [4,17].

The Cochrane Collaboration rigorous systematic review did not observe a significant increase in postoperative morbidity (level of evidence 1, grade A recommendation) [15,16] but the initial RCT demonstrated increased adverse effects [14]. Varying experiences have been reported, including an increase in postoperative adverse events (level of evidence 2, grade B recommendation) [4,65,66], suggesting a possible impact of the institution practice and of neurosurgeon's practice of postoperative adverse effects.

Carmustine wafer implantation does not seem to negatively impact the efficacy and the completion of the standard combined chemoradiotherapy (level of evidence 2, grade B recommendation) [4,53].

Carmustine wafer implantation does not seem to negatively impact the postoperative health-related quality of life as estimated by the KPS (level of evidence 3, grade C recommendation) [18].

Intraoperative extemporaneous pathological examination appears to be a useful tool to prevent carmustine wafers to be implanted in non-HGG patients (level of evidence 1, grade A recommendation) [13,14].

Contrarily to newly diagnosed HGG for which molecular status is unknown at the time of surgery, the knowledge of the MGMT promoter methylation status should be analyzed for recurrent HGG, as carmustine wafer implantation appears more effective in MGMT-methylated glioblastomas (level of evidence 2, grade B recommendation) [67,74].

The specific impact of carmustine wafer implantation on gliomas by WHO grade and subtype is unknown. In the molecular era and in the light of the 2016 WHO Classification of Tumors of the Central Nervous System, several suggestions can be made. Carmustine wafer implantation should be of relevant survival benefit for glioblastomas regardless of isocitrate dehydrogenase (IDH) status (mutated or wild-type) and for "glioblastoma-like" WHO grade III gliomas sharing a poor prognosis (IDH-wild-type, no 1p19q codeletion). In contrast, carmustine wafer implantation is probably not of relevant survival benefit for WHO grade III gliomas sharing a good prognosis (IDH-mutated, with or without 1p19q codeletion).

As for other oncological treatment, carmustine wafer implantation should be discussed in a multidisciplinary staff meeting before surgical resection, if possible, because this would prevent patient inclusion in a great majority of clinical trials.

12. Practical aspects: carmustine wafer implantation techniques in HGG surgery

12.1. Indications of carmustine wafer implantation

Treatment of newly diagnosed and suspected glioblastoma (grade IV glioma) where a subtotal, total or supratotal resection appears achievable.

Treatment of newly diagnosed and suspected grade III glioma where a subtotal, total or supratotal resection appears achievable:

- highly recommended for "glioblastoma-like" grade III gliomas with ring-like contrast enhancement and necrosis on MRI;
- not recommended for non-enhancing and non-necrotic glioma on MRI;
- to be discussed for other cases.

Treatment of recurrent glioblastomas and of recurrent poor prognosis grade III gliomas in whom a subtotal, total or supratotal resection appears achievable:

- highly recommended for MGMT-methylated glioblastomas;
- to be discussed for wild-type MGMT glioblastomas.

12.2. Requirements

Obtained informed consent before surgery.

Preoperative estimation of the extent of resection using multimodal MRI in a multidisciplinary discussion at specialized centers.

Intraoperative histopathological diagnosis of HGG.

Knowledge of the MGMT promoter methylation status for recurrent HGG.

Maximize the extent of the resection while preserving eloquent brain areas with appropriate surgical tools and conceptual approaches: intraoperative ultrasound, intraoperative MRI-based neuronavigation, intraoperative fluorescence using 5-Amino-levulinic acid (5-ALA), intraoperative MRI, intraoperative functional brain mapping using direct cortical and subcortical electrical stimulation with functional monitoring under awake condition [78–83].

12.3. Relevant points

Maximize the extent of the resection while preserving eloquent brain areas with appropriate surgical tools and conceptual approach [78–83] (Fig. 1).

Ventricular opening is not a contraindication for carmustine wafer implantation but in the case of a wide opening the risk of obstructive hydrocephalus must be considered and prevented by a closure of the ventricle opening using layers of cellulose absorbable hemostat covered by biological glue application [57].

Carmustine wafer should be manipulated and maintained in required temperature according to the manufacturer recommendations and the package should be opened at the very last moment.

Achieve complete hemostasis before carmustine wafer implantation.

Implant carmustine wafer directly on the surgical bed without the interposition of cellulose absorbable hemostat.

Carmustine wafers can be stabilized and secured with a single layer of cellulose absorbable hemostat covered by a biological glue application.

Watertight closure of the dura is mandatory to reduce the risk of cerebrospinal fluid leak and to reduce the subsequent risk of postoperative wound defect and infection.

In case of imperfect sealing, a watertight closure of the dura can be obtained using a duraplasty with autologous epicranius or synthetic dura.

Postoperative systemic corticotherapy should be administrated and maintained.

Postoperative MRI must be performed within two postoperative days to quantify the extent of resection.

Disclosure of interest

J. Pallud, P. Menei, and P. Metellus have received honoraria for consultancy from Kyowa Hakko Kirin Co. J. Pallud, P. Menei, P. Metellus and A. Roux have received honoraria for speaking engagements (including travel and accommodation) from Kyowa Hakko Kirin Co.

F. Caire and J. Guyotat declare that they have no competing interest.

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CLINICAL STUDY

Recurrent glioblastomas in the elderly after maximal first-line treatment: does preserved overall condition warrant a maximal second-line treatment?

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Abstract A growing literature supports maximal safe resection followed by standard combined chemoradiotherapy (i.e. maximal first-line therapy) for selected elderly glioblastoma patients. To assess the prognostic factors from recurrence in elderly glioblastoma patients treated by maximal safe resection followed by standard combined chemoradiotherapy as first-line therapy. Multicentric retrospective analysis comparing the prognosis and optimal oncological management of recurrent glioblastomas between 660 adult patients aged of <70 years (standard group) and 117 patients aged of ≥70 years (elderly group) harboring a supratentorial glioblastoma treated by maximal first-line therapy. From recurrence, both groups did not significantly differ regarding Karnofsky performance status (KPS) ($p=0.482$). Oncological treatments from recurrence significantly differed: patients of the elderly group received less frequently oncological treatment from recurrence ($p<0.001$), including surgical resection ($p<0.001$), Bevacizumab therapy ($p<0.001$), and second line chemotherapy other than Temozolomide ($p<0.001$). In multivariate analysis, Age ≥70 years was not an independent predictor of overall survival from recurrence ($p=0.602$), RTOG-RPA classes 5–6 ($p=0.050$) and KPS at recurrence <70 ($p<0.001$), available in all cases, were independent

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significant predictors of shorter overall survival from recurrence. Initial removal of ≥90% of enhancing tumor (p=0.004), initial completion of the standard combined chemoradiotherapy (p=0.007), oncological treatment from recurrence (p<0.001), and particularly surgical resection (p<0.001), Temozolomide (p=0.046), and Bevacizumab therapy (p=0.041) were all significant independent predictors of longer overall survival from recurrence. Elderly patients had substandard care from recurrence whereas age did not impact overall survival from recurrence contrary to KPS at recurrence <70. Treatment options from recurrence should include repeat surgery, second line chemotherapy and anti-angiogenic agents.

Keywords Aged patients · Glioblastoma · Recurrence · Karnofsky performance status · Geriatric assessment

Abbreviations

PFS	Progression-free survival
EFGR	Epidermal growth factor receptor
HR	Hazard ratio
KPS	Karnofsky performance status
OS	Overall survival
RTOG-RPA	Radiation therapy oncology group recursive partitioning analysis

Introduction

Glioblastoma (World Health Organization WHO grade IV astrocytoma) is the most common malignant primary brain tumor in adults [1]. Its frequency increases with age, the average annual incidence rate of glioblastoma ranging from 0.4 per 100,000 for patients aged 20–34 years to more than 15.0 per 100,000 for patients aged 75–84 years [1]. In parallel, the senior population (aged 65 and over) will grow in the next decades, from 15 to 24% of the United State's overall population between 2015 and 2060 [2]. It is thus expected that the number of glioblastomas in the elderly population will increase. In France, one-third of the population will likely be over 60 years in 2060 whereas median age at diagnosis for glioblastoma is currently of 63 years [3].

Age is a strong prognostic factor for glioblastoma [4–6]. Due to their worse prognosis, the optimal treatment of elderly patients with a glioblastoma is still being debated, since the benefit-to-risk ratio remains to be determined [7]. However, several studies have showed the positive impact of surgical resection [8–10], radiotherapy [11], and chemotherapy [12] on the survival of these patients. The role for current standard of oncological care, consisting of combined chemoradiotherapy with concomitant Temozolomide followed by adjuvant Temozolomide, the so-called standard combined chemoradiotherapy [13], had not yet been evaluated for elderly patients with newly diagnosed glioblastomas until recently [14]. In clinical practice, elderly patients are frequently undertreated [15–17]. However, promising studies suggested a survival benefit associated with the use of surgical resection followed by standard combined chemoradiotherapy (i.e. maximal first-line therapy) in elderly patients with good overall condition [7, 10, 16, 18–25]. Based on a practical approach, a growing number of patients aged 70 years or more are currently treated with the standard combined chemoradiotherapy with an age-matched appropriate radiotherapy schedule with or without surgical resection as first-line therapy, as long as their overall condition allows it [17, 25, 26].

At glioblastoma recurrence, there is no universally accepted standard treatment [27]. This issue is critical concerning elderly patients, especially in those with preserved physical condition and quality of life, who benefited from maximal first-line oncological treatment. Their preserved general condition, which allowed aggressive first-line oncological treatment, is encouraging for a maximal treatment from recurrence. To our knowledge, no study explored the optimal treatment strategy for recurrent glioblastoma in elderly patients previously treated with a maximal first-line oncological treatment, defined as surgical resection followed by standard combined chemoradiotherapy whatever the number of Temozolomide cycles received. The aim of this multicentric retrospective study was to assess the prognosis and optimal oncological management of recurrent glioblastomas in elderly patients who were initially treated with maximal first-line oncological treatment.

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Materials and methods

Study population

This multicentric retrospective study was conducted in 20 institutions in France. Inclusion criteria were: (1) patients older than 18 at diagnosis; (2) newly diagnosed glioblastoma; (3) supratentorial hemispheric tumor location; (4) surgical resection followed by adjuvant treatment according to the combined standard chemoradiotherapy, without bevacizumab, as first-line treatment [13], even if not completed (less than six cycles of adjuvant Temozolomide); (5) recurrence as defined by the Macdonald criteria for tumor progression (25% increase in total perpendicular diameters of an enhancing lesion, any new lesion, or clinical deterioration) [28]; (6) available KPS at diagnosis and at recurrence and; (7) available follow-up data from recurrence.

The institutional review board of the University Paris Descartes (CPP Ile de France 3) approved the study protocol (Approval No. S.C. 3458).

Data sources

Data were obtained from the medical records using a protocol designed for this study. The data collected at the time of histopathological diagnosis included the following: gender, age, KPS, tumor location, the revised Radiation Therapy Oncology Group recursive partitioning analysis (RTOG-RPA) classification system for glioblastoma, [5, 29] Carmustine wafer implantation, extent of surgical resection based on early postoperative MRI (within 48 h) on contrast-enhanced T1-weighted sequence (subtotal and total resections defined by removal of ≥90% of enhancing tumor), postoperative complications (neurological deficit, epileptic seizures, infection), first-line oncological treatment modalities (time to initiation of standard combined chemoradiotherapy, radiotherapy dose, number of adjuvant Temozolomide therapy cycles). The data collected at the time of glioblastoma recurrence included the following: duration of the progression-free survival following first-line oncological treatment, KPS, number of treated recurrences, number of treatment modalities from recurrence, oncological treatments from recurrence [none, surgical resection with or without Carmustine wafer implantation, chemotherapy (Temozolomide or other chemotherapy), radiotherapy, Bevacizumab therapy].

Study size

Supplementary Fig. 1 is the flow diagram of the studied cohort. Between January 2005 and December 2015, a total of 1102 patients were screened. We excluded 325 patients (29.4%) from the cohort: 272 with no available KPS during follow-up, 44 without available tumor progression, and 9 without documented standard combined chemoradiotherapy. There were no significant statistical difference between included and excluded patients concerning KPS at diagnosis ($p = 0.372$), sex ($p = 0.493$), age at diagnosis ($p = 0.413$; excluded patients: mean age at diagnosis of 58.1 ± 11.2 years; range 21–72), and extent of resection ($p = 0.187$). A total of 777 cases were available for survival analysis from recurrence.

Endpoints

The aim of the study was to assess survival by age (cutoff 70 years) in a homogeneous glioblastoma population. The primary endpoint was overall survival (OS) from recurrence in adult patients harboring a supratentorial glioblastoma treated with surgical resection and the standard chemoradiotherapy protocol as first-line treatment. The secondary endpoints were OS and progression-free survival (PFS) in that same patient population. Progression-free survival was measured from the date of histopathological diagnosis to the date of evidence of recurrence or to the date of death. Glioblastoma recurrence was defined according to the Macdonald criteria as previously defined [28, 30]. Overall survival was measured from the date of histopathological diagnosis to the date of death from any cause. Overall survival from recurrence was measured from the date of tumor progression to the date of death from any cause. Surviving patients were censored at the date of last follow-up.

Statistical methods

Univariate analyses were carried out using the Chi-square or Fisher's exact tests for comparing categorical variables, and the unpaired t-test or Mann–Whitney rank sum test for continuous variables, as appropriate. Unadjusted survival curves for PFS, OS, and OS from recurrence were plotted by the Kaplan–Meier method, using log rank tests to assess significance for group comparison. For PFS, OS, and OS from recurrence, multivariate analyses were carried out using Cox proportional hazards regression models using a backward stepwise approach, entering the predictors previously associated with tumor progression or mortality in univariate analysis using a p-value <0.2 level. A p-value of <0.05 was considered significant. Statistical analyses were performed using JMP software (version 12.1.0, SAS Institute Inc).

Table 1 Main characteristics of the study sample

Series	Whole (n = 777)		Standard patient < 70 years (n = 660)		Older patient ≥ 70 years (n = 117)		p-value
Parameters	n	%	n	%	n	%	
Clinical parameters at diagnosis							
Age (mean ± SD)	58.0 ± 11.1		55.2 ± 9.6		73.6 ± 3.5		
<70 years	660	84.9	–		–		
≥70 years	117	15.1					
Gender							0.691
Female	273	35.1	230	34.8	43	36.8	
Male	504	64.9	430	65.2	74	63.2	
KPS at diagnosis (mean ± SD)	82.0 ± 13.1		82.0 ± 13.1		82.2 ± 13.1		0.789
≥70	709	91.2	603	91.4	106	90.6	
<70	68	8.8	57	8.6	11	9.4	
RTOG-RPA class							**<0.001**
3–4	410	52.8	369	55.9	41	35.0	
5–6	367	47.2	291	44.1	76	65.0	
First-line oncological treatments							
Extent of resection							0.302
Subtotal/total	458	58.9	384	58.2	74	63.2	
Partial	319	41.1	276	41.8	43	36.8	
Carmustine wafer implantation							0.522
Yes	194	25.0	162	24.5	32	27.4	
No	583	75.0	498	75.5	85	72.6	
Adjuvant Temozolomide cycles (mean ± SD)	5.1 ± 3.4		5.2 ± 3.3		4.7 ± 4.0		**0.043**
Completion of the standard combined radiochemotherapy[a]							0.396
Yes	360	46.3	307	51.3	53	46.9	
No	352	45.3	292	48.7	60	53.1	
Characteristics at progression							
KPS at progression (mean ± SD)	72.7 ± 17.2		73.2 ± 17.1		69.8 ± 17.8		0.482
≥70	559	71.9	478	72.4	81	69.2	
<70	218	28.1	182	27.6	36	30.8	
Oncological treatment at progression							**<0.001**
Yes	661	85.1	575	87.1	86	73.5	
No	116	14.9	85	12.9	31	26.5	
Surgical resection at progression							**<0.001**
Yes	179	23.0	163	24.7	16	13.7	
No	598	77.0	497	75.3	101	86.3	
Carmustine wafer implantation at progression							0.274
Yes	111	14.3	98	14.8	13	11.1	
No	666	85.7	562	85.2	104	88.9	
Radiotherapy at progression							0.975
Yes	46	5.9	39	5.9	7	6.0	
No	731	94.1	621	94.1	110	94.0	
Temozolomide at progression							0.961
Yes	174	22.4	148	22.4	26	22.2	
No	603	77.6	512	77.6	91	77.8	
Bevacizumab at progression							**<0.001**
Yes	407	52.4	365	55.3	42	35.9	
No	370	47.6	295	44.7	75	64.1	

Table 1 (continued)

Series	Whole (n = 777)		Standard patient < 70 years (n = 660)		Older patient ≥ 70 years (n = 117)		p-value
Parameters	n	%	n	%	n	%	
Another chemotherapy at progression							**<0.001**
Yes	398	51.2	359	54.4	39	33.3	
No	379	48.8	301	45.6	78	66.7	

p-values in bold are statistically significant

KPS Karnofsky performance status, *RPA* recursive partitioning analysis, *RTOG* Radiation Therapy Oncology Group, *SD* standard deviation

[a]Combined radiochemotherapy with Temozolomide followed by, at least, six cycles of adjuvant Temozolomide (712 patients with available data)

Results

Patient characteristics

Patient and treatment characteristics are summarized in Table 1. Seven hundred-and seventy-seven glioblastoma patients with surgical resection followed by standard combined chemoradiotherapy as first-line treatment were enrolled (mean age at diagnosis of 58.0 ± 11.1 years; 64.9% were men), 117 patients (15.1%) were at least 70 years of age (elderly group). In detail, elderly group was composed of 82 patients ≥70 years and <75 years, 29 patients ≥75 years and <80 years, 4 patients ≥80 years and <85 years, and 2 patients ≥85 years. The elderly group did not significantly differ regarding KPS at diagnosis, available in all cases (p = 0.789). The elderly group did not significantly differ regarding extent of resection (p = 0.302), Carmustine wafer implantation (p = 0.522) and completion of standard combined chemoradiotherapy, namely at least 6 cycles of adjuvant Temozolomide (p = 0.396), compared to the standard group.

At glioblastoma recurrence, the standard and the elderly groups did not significantly differ regarding KPS at recurrence, available in all cases (p = 0.482). Six hundred- and sixty-one patients (85.1%) received an oncological treatment. Oncological treatments from recurrence differ between standard and elderly groups. Significantly more patients of the standard group compared to the elderly group received an oncological treatment from recurrence (87.1 vs. 73.5%, p < 0.001), surgical resection (24.7 vs. 13.7%, p < 0.001), Bevacizumab therapy (55.3 vs. 35.9%, p < 0.001), and second line chemotherapy other than Temozolomide (54.4 vs. 33.3%, p < 0.001).

Survival analyses

The median follow-up period was 18.0 months (range, 3–95). Six hundred and forty-three patients (82.8%) died during the follow-up period and all patients (100%) experienced tumor progression, which was subsequently proven histopathologically in 179 cases (23.0%) following a second surgical resection.

The median PFS was 9.7 months (95% CI, 9.0–10.0). Kaplan–Meier curves of PFS are presented in Fig. 1, stratified by age. Unadjusted and adjusted predictors of PFS are detailed in Supplementary Table 1. After multiple adjustments using Cox models, age of ≥70 years was independently associated with shorter PFS (median of 10.0 months vs. 9.0 months, adjusted Hazard Ratio (aHR), 1.24 [95% CI: 1.01–1.50], p = 0.040). Initial removal of ≥90% of enhancing tumor (aHR, 0.86 [95% CI: 0.74–0.99], p = 0.044), and Carmustine wafer implantation (aHR, 0.82 [95% CI: 0.69–0.97], p = 0.018) were independently associated with longer PFS.

The median OS was 19.0 months (95% CI, 18.0–20.5). Kaplan–Meier curves of OS are presented in Fig. 1, stratified by age. Unadjusted and adjusted predictors of OS are detailed in Table 2. After multiple adjustments using Cox models, male gender (aHR, 1.35 [95% CI: 1.13–1.60], p < 0.001), RTOG-RPA classes 5–6 (aHR, 1.25 [95% CI: 1.06–1.48], p = 0.009), and KPS less than 70 from recurrence (aHR, 1.83 [95% CI: 1.50–2.23], p < 0.001) were independently associated with shorter OS. Initial removal of ≥90% of enhancing tumor (aHR, 0.80 [95% CI: 0.68–0.95], p = 0.011), Carmustine wafer implantation (aHR, 0.71 [95% CI: 0.58–0.86], p < 0.001), completion of the standard combined chemoradiotherapy, namely at least six cycles of adjuvant Temozolomide (aHR, 0.66 [95% CI: 0.56–0.78], p < 0.001), and oncological treatment at tumor progression (aHR, 0.41 [95% CI: 0.32–0.53], p < 0.001) were independently associated with longer OS. Age of ≥70 years was not a significant independent predictor of OS (median 19.6 vs. 17.0 months, aHR, 1.17, [95% CI: 0.93–1.46], p = 0.190).

The median OS from recurrence was 8.0 months (95% CI, 7.0–14.0). Kaplan–Meier curves of OS from recurrence are presented, stratified by age, by KPS at recurrence and oncological treatments from recurrence in

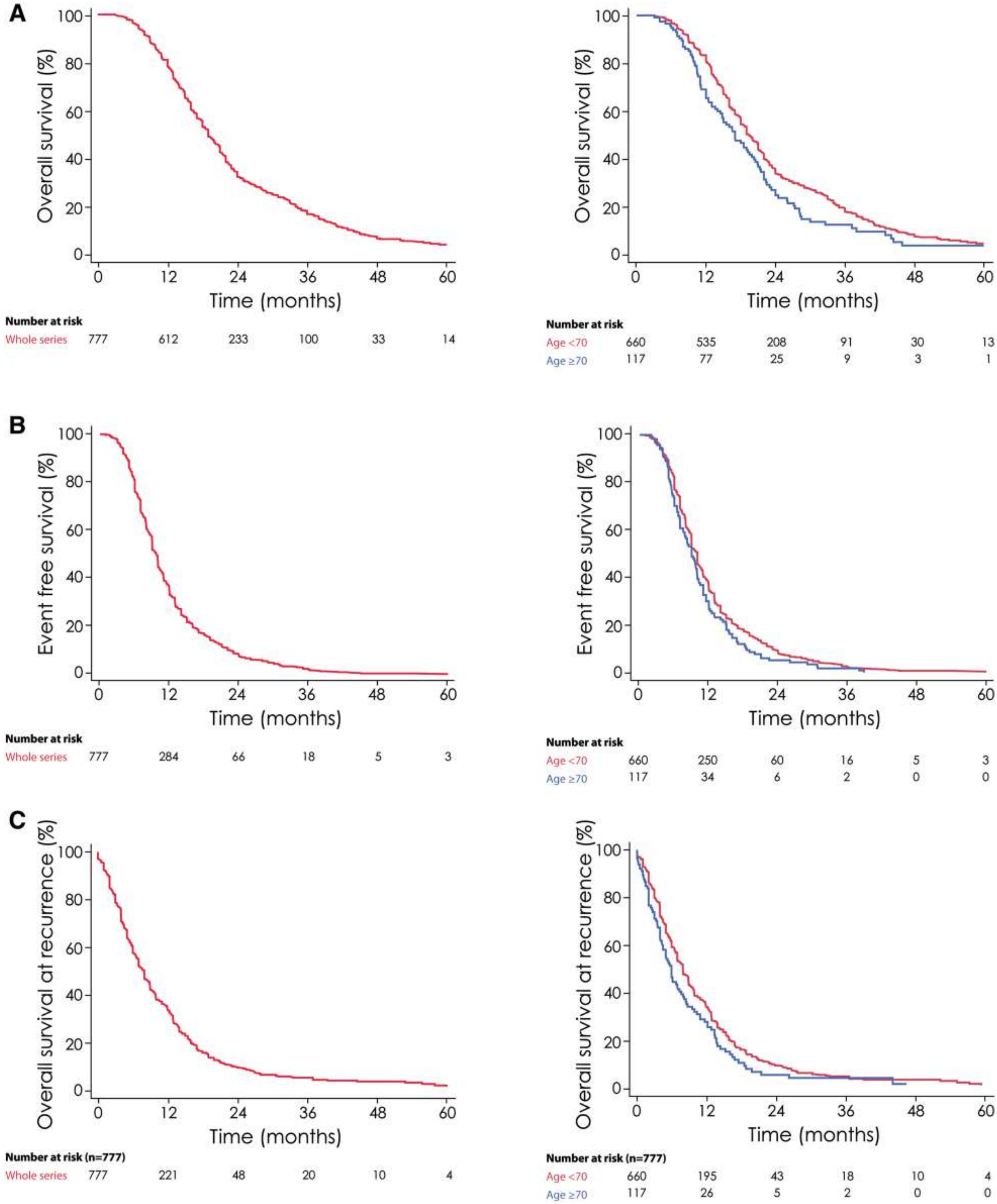


Fig. 1 Kaplan–Meier estimates of overall survival, progression-free survival, and overall survival from recurrence in the whole series and according to age. **a** Overall survival in the whole series (*left*) and stratified according to age (*right*) of glioblastoma patients treated with surgical resection followed by standard combined chemoradiotherapy at first-line treatment. **b** Progression-free survival in the whole series (*left*) and stratified according to age (*right*) of glioblastoma patients treated with surgical resection followed by standard combined chemoradiotherapy at first-line treatment. **c** Overall survival from recurrence in the whole series (*left*) and stratified according to age (*right*) of glioblastoma patients treated with surgical resection followed by standard combined chemoradiotherapy at first-line treatment

Table 2 Overall survival. Unadjusted and adjusted prognostic factors by Cox proportional hazards model

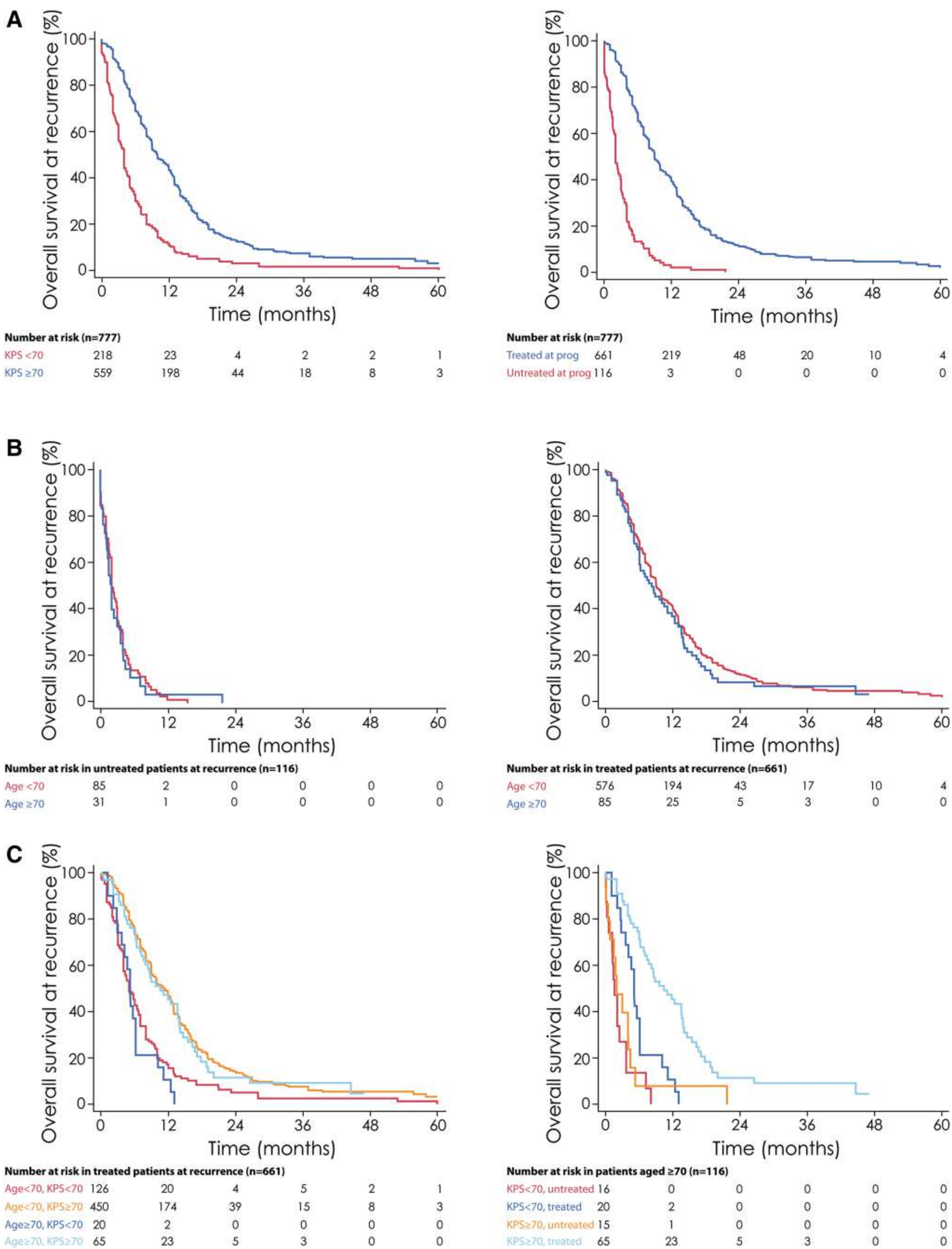
Parameters	Median	95% CI	Unadjusted hazard ratio			Adjusted hazard ratio		
			uHR	95% CI	p-value	aHR	95% CI	p-value
Clinical characteristics at diagnosis								
Age								
<70 years	19.6	18.7–21.0	1 (Ref)			1 (Ref)		
≥70 years	17.0	14.5–20.3	1.33	1.07–1.65	**0.011**	1.17	0.93–1.46	0.190
Gender								
Female	20.0	18.0–22.0	1 (Ref)			1 (Ref)		
Male	19.0	18.0–20.2	1.20	1.02–1.42	**0.027**	1.35	1.13–1.60	**<0.001**
KPS at diagnosis								
≥70	19.6	18.7–21.0	1 (Ref)					
<70	16.0	13.0–19.0	1.37	1.04–1.77	**0.024**			
RTOG-RPA class								
3–4	21.6	20.3–22.7	1 (Ref)			1 (Ref)		
5–6	17.1	16.0–19.0	1.52	1.30–1.78	**<0.001**	1.25	1.06–1.48	**0.009**
First-line oncological treatments								
Extent of resection								
Partial	18.0	16.0–19.4	1 (Ref)			1 (Ref)		
Subtotal/total	20.9	19.0–21.6	0.82	0.70–0.96	**0.012**	0.80	0.68–0.95	**0.011**
Carmustine wafer implantation								
No	19.0	17.8–19.9	1 (Ref)			1 (Ref)		
Yes	21.9	19.0–24.1	0.77	0.64–0.93	**0.006**	0.71	0.58–0.86	**<0.001**
Completion of the standard combined radiochemotherapy[a]								
No	16.0	15.0–17.4	1 (Ref)			1 (Ref)		
Yes	22.6	21.0–24.0	0.64	0.55–0.76	**<0.001**	0.66	0.56–0.78	**<0.001**
Characteristics at progression								
KPS at progression								
≥70	22.0	21.0–23.0	1 (Ref)			1 (Ref)		
<70	13.0	12.2–14.3	2.33	1.96–2.75	**<0.001**	1.83	1.50–2.23	**<0.001**
Oncological treatment at progression								
No	10.3	9.0–12.0	1 (Ref)			1 (ref)		
Yes	21.0	19.8–21.9	0.31	0.25–0.39	**<0.001**	0.41	0.32–0.53	**<0.001**

p-values in bold are statistically significant

KPS Karnofsky performance status, *RPA* recursive partitioning analysis, *RTOG* Radiation Therapy Oncology Group, *SD* standard deviation

[a]Combined radiochemotherapy with Temozolomide followed by, at least, six cycles of adjuvant Temozolomide (712 patients with available data)

Figs. 1 and 2. Unadjusted and adjusted predictors of OS from recurrence are detailed in Table 3. Unadjusted and adjusted predictors of OS from recurrence for treated patients are detailed in Supplementary Table 2. After multiple adjustments using Cox models, RTOG-RPA classes 5–6 (aHR, 1.16 [95% CI: 1.00–1.35], p = 0.050) and KPS <70 from recurrence (aHR, 1.52 [95% CI: 1.27–1.82], p < 0.001) were independently associated with shorter OS from recurrence. Initial removal of ≥90% of enhancing tumor (aHR, 0.80 [95% CI: 0.69–0.93], p = 0.004), completion of the standard combined chemoradiotherapy, namely at least six cycles of adjuvant Temozolomide (aHR, 0.81 [95% CI: 0.70–0.94], p = 0.007), oncological treatment from recurrence (aHR, 0.45 [95% CI: 0.34–0.59], p < 0.001), surgical resection from recurrence (aHR, 0.67 [95% CI: 0.56–0.81], p < 0.001), Temozolomide from recurrence (aHR, 0.70 [95% CI: 0.58–0.84], p < 0.001), other chemotherapy than Temozolomide from recurrence (aHR, 0.84 [95% CI: 0.71–0.99], p = 0.046), and Bevacizumab therapy from recurrence (aHR, 0.83 [95% CI: 0.70–0.99], p = 0.041) were independently associated with longer OS from recurrence. Age of ≥70 years was not a significant independent predictor of OS from recurrence (median 8.0 vs. 6.0 months, aHR, 1.06, [95% CI: 0.85–1.31], p = 0.602).


A
B
C
Overall survival at recurrence (%)
Time (months)
0 12 24 36 48 60
Number at risk (n=777)
KPS <70 218 23 4 2 2 1
KPS ≥70 559 198 44 18 8 3
Number at risk (n=777)
Treated at prog 661 219 48 20 10 4
Untreated at prog 116 3 0 0 0 0
Number at risk in untreated patients at recurrence (n=116)
Age <70 85 2 0 0 0 0
Age ≥70 31 1 0 0 0 0
Number at risk in treated patients at recurrence (n=661)
Age <70 576 194 43 17 10 4
Age ≥70 85 25 5 3 0 0
Number at risk in treated patients at recurrence (n=661)
Age<70, KPS<70 126 20 4 5 2 1
Age<70, KPS≥70 450 174 39 15 8 3
Age≥70, KPS<70 20 2 0 0 0 0
Age≥70, KPS≥70 65 23 5 3 0 0
Number at risk in patients aged ≥70 (n=116)
KPS<70, untreated 16 0 0 0 0 0
KPS<70, treated 20 2 0 0 0 0
KPS≥70, untreated 15 1 0 0 0 0
KPS≥70, treated 65 23 5 3 0 0

◂**Fig. 2** Kaplan–Meier estimates of overall survival from recurrence according to age, to Karnofsky performance status at recurrence, and to oncological treatment from recurrence. **a** Overall survival from recurrence in the whole series stratified according to Karnofsky performance status at progression (*left*) and according to treatment from recurrence (*right*) of glioblastoma patients treated with surgical resection followed by standard combined chemoradiotherapy at first-line treatment. **b** Overall survival from recurrence in the subgroup of untreated recurrence stratified according to age (*left*) and in the subgroup of treated recurrence according to age (*right*) of glioblastoma patients treated with surgical resection followed by standard combined chemoradiotherapy at first-line treatment. **c** Overall survival from recurrence in the subgroup of treated recurrence stratified according to age and to Karnofsky performance status at recurrence (*left*) and in the subgroup of patients aged of ≥70 years stratified according to Karnofsky performance status from recurrence and to treatment from recurrence (*right*) of glioblastoma patients treated with surgical resection followed by standard combined chemoradiotherapy at first-line treatment

Discussion

Key results

In this multicentric series of 777 adult patients, we analyzed the impact of age (117 patients aged of ≥70 years) on OS from recurrence of glioblastoma patients treated with a maximal first-line oncological treatment, including surgical resection followed by standard combined chemoradiotherapy. We show in this specific population that: (1) elderly patients received substandard care at glioblatoma recurrence; (2) despite this fact, age ≥70 did not significantly nor independently impact OS from recurrence; (3) when treated from recurrence, elderly patients with a KPS at recurrence ≥70 shared similar OS from recurrence than younger patients; and (4) treatment options at glioblastoma recurrence should include repeat surgery, second line chemotherapy and anti-angiogenic agents, as these were found to impact OS from recurrence.

Limitations

Limitations of this study include its retrospective design, the lack of central histopathological review, and molecular analyses including MGMT testing and epidermal growth factor receptor (EGFR) gene amplification, the lack of central imaging review, including the extent of resection for surgery from recurrence [31], the lack of data concerning patients' quality of life throughout glioblastoma evolution, and the use of The MacDonald criteria to assess glioblastoma recurrence, which cannot exclude pseudoprogression to occur in the recurrence group. Of note, glioblastoma recurrence was histologically proven in 179 cases (23%) following surgical resection at progression and no pseudoprogression was observed in this subgroup. WHO 2016 classification included numerous molecular parameters and MGMT testing is now recommended for elderly patients [32], however at the starting point of this retrospective study (January 2005) and until the 2010's, none clear recommendation existed concerning MGMT testing [32, 33]. In addition, we were unable to address the prognostic impact of the EGFR gene amplification in elderly patients, which may explain a better survival in response to aggressive treatments [16, 34]. It was impossible to determine MGMT status and EGFR gene amplification status retrospectively in all the screened patients so they were was not included in this work. Last, patient and family choice is another issue that cannot be controlled: possibly some elderly patients and their family declined oncological treatment offered given their limited impact, even in patients with the best prognostic factors.

Interpretation

Age is a major prognostic factor for glioblastoma due to changes in the glioma's biology (decreased isocitrate dehydrogenase mutations in older patients [35] but equal proportion of MGMT promoter methylation [36] compared to their younger counterparts), and reduced administration of combined oncological treatments [37], as well as possibly a lower level of treatment activity, worse treatment tolerance and poor general condition [21]. However, the prognostic significance of the age per se is debatable, as elderly glioblastoma patients survive longer when treated aggressively [17, 25, 38]. Since the late 90s [39], numerous studies have reported outcomes related to elderly glioblastoma patients. Despite some advocating comfort care only [40], a vast majority identified surgical resection as a favorable prognostic factor and recommended not excluding elderly glioblastoma patients from aggressive treatment [9, 10, 17–21, 25, 41–43]. It should be noted that the threshold used to define elderly patients varied widely across studies, probably in part explaining the differences in statistical significance regarding age [16, 25, 26]. Another difficulty is the definition of aggressive therapy for elderly patients: if addition of Temozolomide to radiotherapy seems to provide a clear benefit [14, 22, 25], the most appropriate radiotherapy schedule, including short-course scheme, is still debated [44–46]. In accordance with previous reports, the present study demonstrated that general condition (RTOG-RPA classes, KPS at recurrence) and oncological treatments (including extent of first surgical resection, and surgical resection from recurrence), but not age, were independent predictors of OS and of OS from recurrence. We observed that oncological treatments and KPS at recurrence significantly and independently impacted OS from recurrence, with no significant impact of age. In the subgroup of 661 patients treated from recurrence, survival varied with KPS at recurrence but not with age (Fig. 2).

Table 3 Overall survival at progression. Unadjusted and adjusted prognostic factors by Cox proportional hazards model

Parameters	Median	95% CI	Unadjusted hazard ratio			Adjusted hazard ratio		
			uHR	95% CI	p-value	aHR	95% CI	p-value
Clinical characteristics at diagnosis								
Age								
<70 years	8.0	7.0–9.0	1 (Ref)			1 (Ref)		
≥70 years	6.0	4.5–7.7	1.28	1.02–1.57	**0.032**	1.06	0.85–1.31	0.602
Gender								
Female	7.0	6.0–9.3	1 (Ref)					
Male	8.0	7.0–8.6	1.12	0.95–1.32	0.173			
KPS at diagnosis								
≥70	8.0	7.0–8.9	1 (Ref)					
<70	4.5	3.6–8.0	1.33	1.02–1.72	**0.039**			
RTOG-RPA class								
3–4	9.7	8.9–10.6	1 (Ref)			1 (Ref)		
5–6	6.0	5.2–7.0	1.51	1.29–1.77	**<0.001**	1.16	1.00-1.35	**0.050**
First-line oncological treatments								
Extent of resection								
Partial	6.6	5.8–8.0	1 (Ref)			1 (Ref)		
Subtotal/total	8.5	7.7–9.6	0.79	0.68–0.93	**0.004**	0.80	0.69–0.93	**0.004**
Carmustine wafer implantation								
No	7.7	7.0–8.0	1 (Ref)					
Yes	8.9	7.0–10.0	0.86	0.71–1.03	0.107			
Completion of the standard combined radiochemotherapy[a]								
No	6.6	5.5–7.5	1 (Ref)			1 (Ref)		
Yes	9.0	8.0–10.6	0.80	0.68–0.94	**0.007**	0.81	0.70–0.94	**0.007**
Characteristics at progression								
KPS at progression								
≥70	9.9	9.0–11.5	1 (Ref)			1 (Ref)		
<70	4.0	3.0–4.3	2.51	2.12–2.97	**<0.001**	1.52	1.27–1.82	**<0.001**
Oncological treatment at progression								
No	2.0	1.8–2.9	1 (Ref)			1 (Ref)		
Yes	9.0	8.0–10.0	0.21	0.17–0.26	**<0.001**	0.45	0.34–0.59	**<0.001**
Surgical resection at progression								
No	6.7	5.9–7.2	1 (Ref)			1 (Ref)		
Yes	13.0	12.0–14.0	0.54	0.45–0.65	**<0.001**	0.67	0.56–0.81	**<0.001**
Carmustine wafer implantation								
No	7.0	6.0–8.0	1 (Ref)					
Yes	13.0	11.9–14.0	0.58	0.46–0.73	**<0.001**			
Radiotherapy at progression								
No	7.4	6.8–8.0	1 (Ref)					
Yes	16.0	12.4–21.0	0.54	0.38–0.75	**<0.001**			
Temozolomide at progression								
No	6.7	6.0–7.4	1 (Ref)			1 (Ref)		
Yes	13.0	11.5–15.4	0.56	0.46–0.68	**<0.001**	0.70	0.58–0.84	**<0.001**
Bevacizumab at progression								
No	5.4	4.5–6.7	1 (Ref)			1 (Ref)		
Yes	9.2	8.9–10.5	0.71	0.61–0.83	**<0.001**	0.83	0.70–0.99	**0.041**

Table 3 (continued)

Parameters	Median	95% CI	Unadjusted hazard ratio			Adjusted hazard ratio		
			uHR	95% CI	p-value	aHR	95% CI	p-value
Another chemotherapy at progression								
No	5.5	5.0–7.0	1 Ref)			1 (Ref)		
Yes	9.0	8.5–10.6	0.68	0.58–0.79	**<0.001**	0.84	0.71–0.99	**0.046**

KPS Karnofsky performance status, *RPA* recursive partitioning analysis, *RTOG* Radiation Therapy Oncology Group, *SD* standard deviation

[a]Combined radiochemotherapy with Temozolomide followed by, at least, six cycles of adjuvant Temozolomide (712 patients with available data)

The present results reflect clinical practice with the elderly glioblastoma patients, selected mainly based on their general condition, undergoing maximal first-line treatment, but subsequently treated significantly less frequently and less aggressively treated from recurrence than younger patients, despite their KPS at recurrence not being significantly different from their younger counterparts. The observations stating that age is a statistically significant predictor of shorter OS from recurrence in unadjusted survival analyses, but not in multivariate modeling, illustrates the fact that the elderly population was undertreated in clinical practice. This is reinforced by the observation that on the 34 elderly patients who survived at least 1 year after glioblastoma progression, 31 (91%) presented with a KPS at recurrence higher than 70 and received oncological treatments from recurrence. This subgroup of elderly patients clearly benefited from longer OS from recurrence compared to the other subgroups. There is no standard treatment at glioblastoma recurrence [27] but age does not appear to be a major prognostic factor for OS from recurrence [47]. In a recent series considering recurrent glioblastomas in selected elderly patients, active oncological treatment from recurrence was a significant prognostic factor for OS from recurrence, whereas elderly patients with a KPS at recurrence of 60 or less did not benefit from surgery or radiotherapy at that time compared with chemotherapy instead [48]. The fact that age appears statistically significant in unadjusted analysis but is not significant in adjusted analysis seems to reveal a favorable impact of aggressive therapy on survival in the elderly population. The prognostic significance of KPS at diagnosis and KPS at recurrence was stressed in other studies [49, 50]. Nevertheless, in the present study as in those by Stark et al. [41], KPS at recurrence, though not KPS at diagnosis, was significantly associated with a longer survival. This emphasizes the need for a global geriatric evaluation prior to treatment of a glioblastoma in an elderly patient [51], for instance with minimum dataset data from Elderly Task Force of European Organisation for Research and Treatment of Cancer [52] and clinical trials developed specifically for this population [53]. KPS at recurrence is a key clinical feature of elderly glioblastoma patients, as a part of a prognostic scale [54] or even used alone as an independent prognostic factor, as in the present study.

Generalisability

The strengths of this study are: (1) the multicentric and large study population; (2) the homogeneity of first-line oncological treatment, all patients being treated by surgical resection and standard combined chemoradiotherapy, thus precluding biases in survival analyses from recurrence from varying first-line treatments; (3) available KPS at recurrence, thus allowing its incorporation into the survival models; (4) survival analyses performed with as starting time for OS calculation the time of recurrence and not at the first surgery, thus preventing biases in estimation of OS from recurrence. Altogether, the present results suggest that, in the specific population of glioblastoma patients treated with maximal first-line oncological treatment, including surgical resection followed by standard combined chemoradiotherapy, the glioblastoma recurrence should be: (1) managed aggressively with additional and combined oncological treatments in elderly patients with a good overall condition (KPS at recurrence of at least 70), as in younger patients; (2) managed more conservatively in elderly patients with a poor or unstable general condition (KPS at recurrence <70). The present findings should be confirmed in future randomized controlled trials focused on glioblastoma recurrence in this specific patient population, in order to answer these clinically relevant questions.

Conclusion

The elderly patients with KPS at recurrence ≥70 demonstrated similar overall survival from recurrence than the younger patients. The KPS at recurrence appears to be a stronger predictor of overall survival from recurrence than age and oncological treatments at glioblastoma recurrence should include the options of repeat surgery, second line chemotherapy and anti-angiogenic agents.

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Compliance with ethical standards

Conflict of interest Johan Pallud has received honoraria for consultancy from Kyowa Hakko Kirin Co. Johan Pallud and Alexandre Roux have received honoraria for speaking engagements (including travel and accommodation) from Kyowa Hakko Kirin Co.

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