

GUIDE MANAGEMENT OF HIGH GRADE GLIOMA

Principles of surgical treatment in high-grade glioma

1. Surgery is commonly the initial therapeutic approach. The surgical procedures are: stereotactic biopsy, open biopsy, partial resection, and complete gross resection.
2. The largest possible surgical removal is recommended; while preserving neurological function. This is to achieve: 1st an accurate histological diagnosis, avoiding underestimates of histology that sometimes can occur with stereotactic biopsy; 2nd to tumour debulking, this improve symptoms caused by mass effect (oedema, hydrocephalus, etc.) and allow chemo-radiotherapy treatment be more effective and 4th a modest but significant impact on survival, so that the extent of resection is part of the classification of RPA prognosis. [1,2] **Evidence level II C.**
3. In tumours involving eloquent areas or near them (patients improve symptoms with corticosteroids), using operative techniques of monitoring (with patients who are awake or not awake) decreases the risk of postoperative complications and increases the degree of resection. [3-4]
4. An increase in the complete resection rate and improvement in progression-free survival (PFS) have been shown when surgery is carried out under blue light with the use of fluorescent marking of the tumour by 5-amino-laevulinic acid (5-ALA) [5] **Evidence Level IIA.** This advantage is only shown with fluorescence obtained with 5-ALA in a specially-trained team with operating limitations stated in data sheet equipment. [6]
5. In case of complete or partial resection, an MRI assessment should be performed within 72 hours after surgery in order to distinguish post-surgical contrast enhancement from residual tumour. It is very important to assess post surgical residual tumour before star chemo-radiotherapy treatments because according to this baseline image is going to take many subsequent treatment decisions. **Evidence Level IVB**

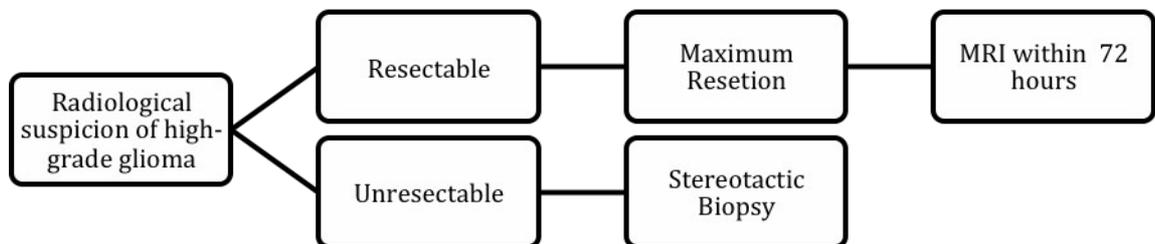


Figure 1: Treatment algorithm to suspicious MRI of high-grade glioma

6. If most of the tumour is unresectable then it is indicated the stereo-tactic biopsy. In heterogeneous tumours, it is necessary to sample multiple areas. Stereo-tactic biopsy indications are: deep tumours, lesions in eloquent areas and multiple or bilateral lesions. It is almost always important to get the tumour histological diagnosis to give

every case the more appropriate therapy. In some cases it may be better to indicate an open biopsy than a stereo-tactic biopsy. In patients with a tumour in a very high risk situation for practicing biopsy (brain stem, etc.) and with a clear image of high-grade glioma it is recommended to start chemo-radiotherapy treatment without a histological sample. Also, in those patients with poor clinical status that are not amenable to any chemo or radiation therapy may obviate the biopsy

1st line treatment of Glioblastoma:

1. Glioblastoma (GBM) includes the following anatomical and pathological diagnoses: IDH- wild type GBM (which includes GBM giant cells, GBM epithelioid and gliosarcoma); IDH-mutated GBM and GBM NOS. [7] Thus with the histological diagnosis of GBM it is very important to carry out the following molecular determinations: IDH1/2 mutations and MGMT Methylation.
2. In patients between 18 and 70 years old the standard treatment is a combination of **radiotherapy (RT) and chemotherapy (CT) with temozolomide (TMZ)** [4]: RT (Fractionated localized in three-dimensional planning up to a total dose of 60 Gy, using a fractionation of 1.8-2 Gy/day, 5 days/week, in a field that includes a 1-2 cm margin around the image pickup defined contrast T1 or all of the abnormal volume defined on T2 or FLAIR image). [5] + TMZ 75 mg/m²/day for 7 days/week, 6 weeks during RT and followed by maintenance TMZ, 6 cycles for 5 days every 28 days (150-200 mg/m²/day) for six cycles (adjuvant) treatment after the end of radiation. **Evidence Level I A**. To enhance absorption fasting is recommended prior and subsequent minimum of 1 hour. The most common acute toxicity are: nausea and vomiting (antiemetic treatment is required); neutropenia and thrombocytopenia (hematologic control is required) and lymphopenia (prophylaxis against pneumocystis is recommended if there is chronic use of corticosteroids). [4] In cases with residual tumor postoperative can be considered to prolong the treatment of TMZ beyond 6 cycles, but this has not been demonstrated in any randomized trial. **Evidence Level V C**
3. In patients > 65 years old:
 - A phase III study presented at the plenary session of the ASCO 2016 meeting has shown that a scheme of hypofractionated RT (40 Gy / 15 sessions) plus TMZ 75 mg/m² /day for 7 days/week, 3 weeks of RT followed by adjuvant TMZ, 12 cycles of 5 days every 28 days at doses of 150-200 mg/m²/day significantly improved both overall survival (OS) and PFS in patients between 66 and 90 years of age with median age of 73. (**Evidence Level IA**) [10]. In the subgroup analysis of patients with MGMT methylation OS it was almost double with RT + QT (13.5m) than with RT alone (7.7m). In patients with unmethylated MGMT no statistical significance (p = 0.055) was achieved but there was a clear trend toward better OS (10m vs 7.9m). The regimen was well tolerated and there were no differences in quality of life test so this scheme can be considered as the new standard in patients > 70 years.
 - Hypo-fractionated RT (10 × 3.4 or 15 × 2.66 Gy) has been shown equivalent to standard fractionated irradiation with 30 fractions (60 Gy) in one trial [11] **Evidence level II, A**
 - A randomized study of ANOCEF showed that a focal RT 1.8 Gy per day, 5 days per week for a total of 50.4 Gy was better than supportive care. [12] **Evidence level II, B**
 - Also a recent retrospective study over 16717 patients > 65 years old, also found an OS superior with the combination of chemoradiation than with either monotherapy (9 months versus 4.7 and 4.5 months (P <.001). [13]
 - A German study has shown that in tumours without methylation of MGMT RT exceeds TMZ instead TMZ is higher in tumours with MGMT methylation [10]. Therefore, it is justified in very fragile elderly patients with MGMT methylation deal with TMZ alone in tumours with MGMT methylation and indicate only RTP in tumours without methylation. [14] **Evidence level II A**
4. Alternating Electric Field Therapy, called Tumor Treating Fields (**TTF**) plus conventional **radio-chemotherapy** have showed in a randomized clinical trial in patients with newly diagnosed GBM a 3 month median survival advantage as well as 3 month PFS advantage. [15] TTF was approved by the FDA for newly diagnosed GBM on Oct. 5, 2015, but still it has not been approved by the EMA. **Evidence Level I B**
5. Two phase III double-blind studies have shown that concomitant use of bevacizumab with RT and TMZ significantly prolonged progression-free survival at 3-4 months but not overall survival (OS). In addition, one of these studies showed quality of life improved and time to neurological

impairment prolonged [16] but not in the other study [17]. The clinical value of the observed prolonged PFS with bevacizumab remains controversial. At the moment this treatment it is not indicated outside clinical study. **Evidence level III C**

6. A meta-analysis showed that the combination of radiotherapy and nitrosoureas (NU) in GBM improved the OS [18]. **Evidence level II B**
7. Implantation of chemotherapy-impregnated wafers (carmustine polymers) into the resection cavity has been shown a significant increase of two months in OS in a study, but this difference was no longer significant after exclusion of cases with anaplastic astrocytoma and an increase in wound healing and infectious complications has been reported [19]. (**Evidence II B**) The combination of carmustine wafers and TMZ/RT has not been assessed in prospective trials, a retrospective comparison failed to demonstrate additive efficacy **Evidence level IV D**
8. Given the incurability of GBM with current treatments, you should always consider the possibility of including these patients in treatment within a controlled clinical trial
9. Supportive care is the best option for patients with PS3 or IK <60. **Evidence Level V C**

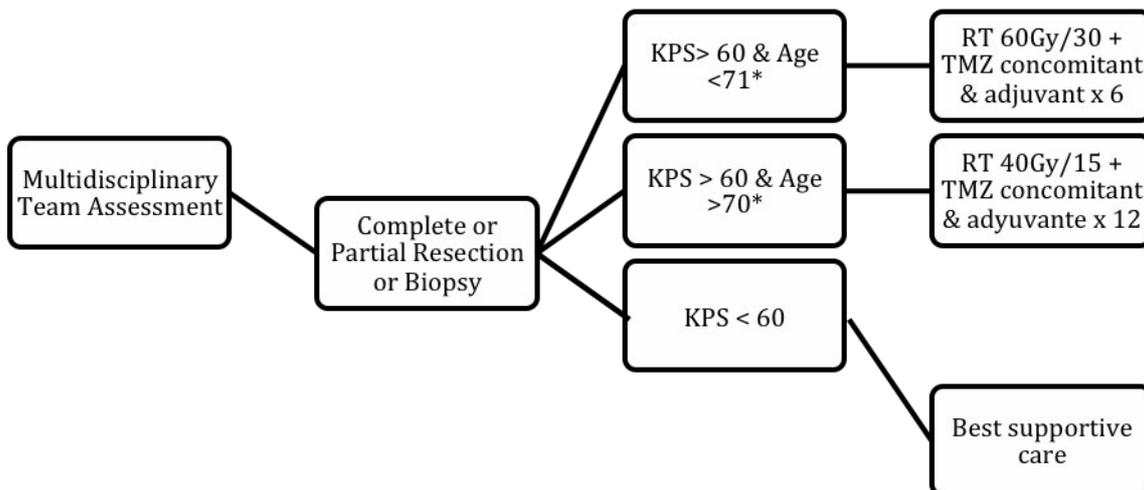
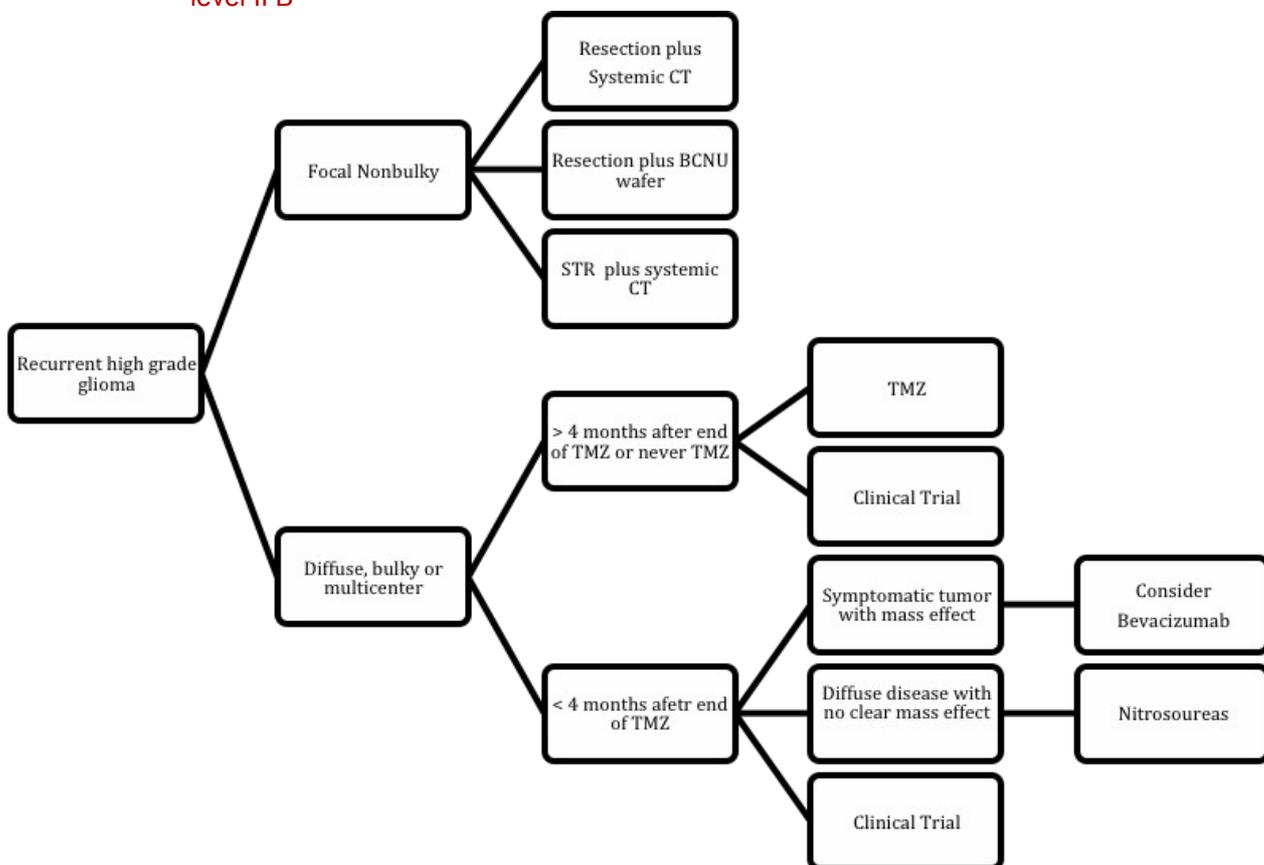


Figure 2: Algorithm for treatment of glioblastoma de novo diagnosis (*always consider clinical trial).

GBM treatment in progression after radiotherapy

1. There is no well-defined standard treatment (all options have shown limited effectiveness) [20] Therapeutic decision will be affected by pretreatment, KPS, age and pattern of relapse.
2. A small percentage of patients are candidates for a second surgery (circumscribed tumors and previous surgery interval > 6-12 months) but there are no randomized studies. Evidence level IV B. When surgery is possible, may be associated with the placement of a biodegradable polymer intracavitary BCNU [21].
3. The role of re-irradiation is uncertain although it has been considering stereo-tactic RT in not very bulky and unresectable tumors by location. [22] (Evidence level IV C)
4. Regardless local rescue is recommended a systemic treatment. (**Evidence level IV C**)
5. Possibilities for systemic treatment are:
 - a. Include the patient in a clinical trial.

- b. Dealing with TMZ 150mg/m²/day x 5 days / 28 days. This option should be considered especially if there is a progression-free interval longer than 4-6 months from the end of the previous TMZ treatment. [23] Evidence level II B
- c. An alternative is to use TMZ 50mg/m²/day continuous dose. Its effectiveness was tested in a phase II trial but there is no comparative studies that have shown this scheme is better than the standard of 150 mg/m²/day x 5 days every 28 [23] Evidence level II B



C T: C hemotherapy; S TR: S tereo-tactic RT; TMZ: Temozolomide

Figure 3: Treatment algorithm for Glioblastoma in progression after RT

- d. Provide a Chemotherapy schedule based on NU, like fotemustine, lomustine, carmustine or PCV [24-26]. Evidence level II B
- e. Dealing with bevacizumab 5-10 mg/kg every 2 weeks, either alone, associated

with NU or CPT11 [27-28]. This treatment may be especially useful in cases of symptomatic tumor with mass effect. **Evidence level II B**

- f. Platinum salts are an alternative for patients with good PS who have shown resistance to TMZ and NU and without possibility to clinical trial. [29] **Evidence level IV D**
- g. Applying electric fields therapy (TTF) on the scalp did not report differences in OS compared with chemotherapy chosen by the investigator in a randomized trial [30] **Evidence level I D**

Chemotherapy regimens commonly used in relapsed Glioblastoma:

• **Temozolomide:**

- Conventional: 150 mg / m² (200 mg/m² if no previous CT) x 5 days every 28 days [31]
- Extended schedules have not proved superiority but more toxic effects than conventional (like 50mg/m² /day continuous [23] or 75-100 mg / m² D1 to D21 every 28 days or 150 mg/m² for 7 days every 14 days).[26-32]

• **BCNU** 200 mg / m² every 6-8 weeks. [33]

• **CCNU:** 100-130 mg / m² every 6 weeks.[24]

• **Fotemustine:**

- 80 mg / m² day 1, 15, 30, 45, 60 followed by a rest lost 4 weeks and a maintenance phase of 80mg / m² every 4 weeks until progression or unacceptable toxicity (Addeo schedule) [34]
- 75 mg / m² days 1,8 and 15 followed by followed by a rest lost 5 weeks and a maintenance phase of 100mg / m² every 3 weeks until progression or unacceptable toxicity or maximum 1 year (Brandes schedule) [35]
- 100 mg / m² days 1,8 and 15 followed by followed by a rest lost 4-6 weeks and a maintenance phase of 100mg / m² every 3 weeks until progression or unacceptable toxicity or maximum 1 year (Fabrini schedule) [36]

• **PCV** every 6 weeks [26]

- Procarbazine 60 mg/m² 2 days 8-21

- CCNU 110 mg/m² 2 day 1

- Vincristine 1.4 mg/m² 2 days 8 and 29

• **Irinotecan** 125 mg /m² (350 if antiepileptic inductors) every 21 days [37].

• **Bevacizumab** 10 mg/kg every 14 days (monotherapy [27] or in combination with CCNU 90 mg/m² every 6 weeks [28] Irinotecan [27] or Fotemustine 75 mg/m² days 1,8 followed after 3 weeks rest 75mg/m² every 3 weeks). [38]

• **Carboplatin** AUC 5 every 4 weeks [29]

References:

1. Vuorinen V, Hinkka S, Färkkilä M, Jääskeläinen J. Debulking or biopsy of malignant glioma in elderly people—a randomised study. *Acta Neurochir (Wien)* 2003; **145**: 5–10.
2. Kreth FW, Thon N, Simon M, et al. Gross total but not incomplete resection of GBM prolongs survival in the era of radiochemotherapy. *Ann Oncol* 2013; **24**: 3117–23.
3. Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med*. 2008;358(1):18.
4. Hervey-Jumper SL, Li J, Lau D, Molinaro AM, Perry DW, Meng L, Berger MS. Awake craniotomy to maximize glioma resection: methods and technical nuances over a 27-year period. *J Neurosurg*. 2015 Aug;123(2):325-39. Epub 2015 Apr 24.
5. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ, and the ALA-Glioma Study Group. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. *Lancet Oncol* 2006; **7**: 392–401.
6. Pichlmeier U, Bink A, Schackert G, Stummer W, ALA Glioma Study Group. Resection and survival in glioblastoma multiforme: an RTOG recursive partitioning analysis of ALA study patients. *Neuro Oncol*. 2008;10(6):1025.
7. Louis DN, Perry A Reifeberger, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. *Acta Neuropathol* 2016; **131**: 803-820.
8. Stupp R, Mason WP, van den Bent MJ, et al, and the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005; **352**: 987–96.
9. Laperriere N, Zuraw L, Cairncross G, and the Cancer Care Ontario Practice Guidelines Initiative Neuro- Oncology Disease Site Group. Radiotherapy for newly diagnosed malignant glioma in adults: a systematic review. *Radiother Oncol* 2002; **64**: 259–73.
10. Perry JR, Laperriere N, O'Callaghan CJ, et al. A phase III randomized controlled trial of short-course radiotherapy with or without concomitant and adjuvant temozolomide in elderly patients with glioblastoma (CCTG CE.6, EORTC 26062-22061, TROG 08.02, NCT00482677). *J Clin Oncol* 34, 2016 (suppl; abstr LBA2)
11. Roa W, Brasher PM, Bauman G et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. *J Clin Oncol* 2004; **2**: 1583-1588
12. Keime-Guibert F, Chinot O, Taillandier L, et al, and the Association of French-Speaking Neuro- Oncologists. Radiotherapy for glioblastoma in the elderly. *N Engl J Med* 2007; **356**: 1527–35.
13. Rusthoven CG, Koshy M, Sher DJ, et al. Combined-Modality Therapy With Radiation and Chemotherapy for Elderly Patients With Glioblastoma in the Temozolomide Era: A National Cancer Database Analysis. *JAMA Neurol*. 2016; doi:10.1001/jamaneurol.2016.0839.
14. Wick W, Platten M, Meisner C, et al, and the NOA-08 Study Group of Neuro-oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. *Lancet Oncol* 2012; **13**: 707–15.
15. Stupp R, Taillibert S, Kanner A, et al. Tumor treating fields (TTFields): A novel treatment modality added to standard chemo- and radiotherapy in newly diagnosed glioblastoma—First report of the full dataset of the EF14 randomized phase III trial. *J Clin Oncol* 33, 2015 (suppl; abstr 2000)
16. Chinot O, Wick W, Mason W, et al. Bevacizumab plus radiotherapy– temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370**: 709–22.
17. Gilbert MR, Dignam J, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014; **370**: 699–708.
18. Stewart LA, and the Glioma Meta-analysis Trialists (GMT) Group. Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. *Lancet* 2002; **359**: 1011–18.
19. Westphal M, Ram Z, Riddle V, Hilt D, Bortey E, and the Executive Committee of the Gliadel Study Group. Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial. *Acta Neurochir (Wien)* 2006; **148**: 269–75.
20. Weller M, Van den Bent M, Hopkins K, et al. EANO guideline for the diagnosis and treatment of anaplastic gliomas and glioblastomas. *Lancet Oncology* 2014; **15**: 395-403
21. Brem H, Piantadosi S, Burger PC et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group. *Lancet* 1995; **345**(8956); 1008-12.
22. Fogh SE, Andrews DW, Glass J et al. Hypofractionated stereotactic radiation therapy: an effective therapy for recurrent high-grade gliomas. *J Clin Oncol* 2010; **28**: 3048-3053.
23. Perry JR, Bélanger K, Mason WP, et al. Phase II trial of continuous dose-intense temozolomide in recurrent

- malignant glioma: RESCUE study. *J Clin Oncol* 2010; **28**: 2051–57.
24. Wick W, Puduvalli VK, Chamberlain MC, et al. Phase III study of enzastaurin compared with lomustine in the treatment of recurrent intracranial glioblastoma. *J Clin Oncol* 2010; **28**: 1168–74.
 25. Brandes AA, Tosoni A, Franceschi E et al. Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Grupo Italiano Cooperativo di Neuro-Oncologia (GICNO). *Cancer Chemother Pharmacol* 2009; **64**: 769-775
 26. Brada M, Stenning S, Gabe R et al. Temozolomide vs procarbazine, lomustine and vincristine in recurrent high-grade glioma. *J Clin Oncol* 2010; **13**: 4601-4608.
 27. Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. *J Clin Oncol* 2009; **27**: 4733–40.
 28. Taal W, Oosterkamp HM, Walenkamp AME, et al. Single-agent bevacizumab or lomustine versus a combination of bevacizumab plus lomustine in patients with recurrent glioblastoma (BELOB study): a randomised controlled phase 2 trial. *Lancet Oncol* 2014; **15**: 943–53.
 29. W K Yung, WK, Mechtler L and Gleason MJ. Intravenous carboplatin for recurrent malignant glioma: a phase II study. *J Clin Oncol* 1991; **9**:860-844
 30. Stupp R, Wong Et, Kanner AA e al. Novo TTF-100^a versus physician’s choice chemotherapy in recurrent glioblastoma: a randomized phase III trial of a novel treatment modality. *Eur J cáncer* 2012; **48**: 2192-2202.
 31. Yung WK, Prados MD, Yaya-Tur R et al. Multicenter phase II trial of temozolomide in patients with anaplastic astrocytoma or anaplastic oligoastrocytoma at first relapse. Temodal Brain Tumor Group. *J Clin Oncol* 1999; **17**: 2762–2771.
 32. Gilbert MR, Wang M, Aldape KD et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol* 2013; **31**: 4085–4091.
 33. Levin VA, Wara WM, Davis RL, et al Phase III comparison of BCNU and the combination of procarbazine, CCNU, and vincristine administered after radiotherapy with hydroxyurea for malignant gliomas. *J of Neurosurgery* 1985; **63**: 218-223
 34. Addeo R et al. A new schedule of fotemustine in temozolomide-pretreated patients with relapsing glioblastoma. *J Neurooncol.* 2011 May;102(3):417-24. Epub 2010 Aug 10. PubMed PMID: 20694830.
 35. Brandes AA et al. Fotemustine as second-line treatment for recurrent or progressive glioblastoma after concomitant and/or adjuvant temozolomide: a phase II trial of Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). *Cancer Chemother Pharmacol.* 2009 Sep;64(4):769-75. Epub 2009 Jan 24. PubMed PMID:19169684.
 36. Fabrini MG et al. A multi-institutional phase II study on secondline Fotemustine chemotherapy in recurrent glioblastoma. *J Neurooncol.* 2009 Mar;92(1):79-86. Epub 2008 Nov 19. PubMed PMID: 19018476.
 37. Cloughesy TF, Filka E,, Nelson G, et al. Irinotecan Treatment for Recurrent Malignant Glioma Using an Every-3-Week Regimen. *Am J Clin Oncol (CCT)* **25** (2): 204–208, 2002.
 38. Soffietti R, Trevisan E, Bertero L, et al Bevacizumab and fotemustine for recurrent glioblastoma: a phase II study of AINO (Italian Association of Neuro-Oncology) *J Neurooncol* 2014; **116**(3): 533–541.