TUMORI PRIMITIVI DEL SISTEMA NERVOSO CENTRALE

Sessione 5_ Radiochirurgia Encefalica: quale standard nel 2023

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ASU FC Azienda sanitaria universitaria Friuli Centrale

Sessione 5_ Radiochirurgia Encefalica: quale standard nel 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Central Nervous System Cancers

NCCN Guidelines Index
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Discussion

PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

RT Dosing Information

- The recommended dose is 60 Gy in 2.0 Gy fractions or 59.4 Gy in 1.8 Gy fractions.
- A slightly lower dose, such as 54–55.8 Gy in 1.8 Gy or 57 Gy in 1.9 Gy fractions, can be applied when the tumor volume is very large there is brainstem/spinal cord involvement, or for grade 3 astrocytoma.
- If a boost volume is used, the initial phase of the RT plan will receive 46 Gy in 2 Gy fractions or 45–50.4 Gy in 1.8 Gy fractions. The boost plan will typically then receive 14 Gy in 2 Gy fractions or 9–14.4 Gy in 1.8 Gy fractions.[4]
- In poorly performing patients or elderly patients, a hypofractionated accelerated course should be considered with the goal of completing the treatment in 2–4 weeks. Typical fractionation schedules are 34 Gy/10 fx or 40.05 Gy/15 fx.[7,8] Alternatively, a shorter fractionation schedule of 25 Gy/5 fx may be considered for elderly and/or frail patients with smaller tumors for whom a longer course of treatment would not be tolerable.[9]

PRINCIPLES OF RADIATION THERAPY FOR BRAIN AND SPINAL CORD

Reirradiation for Gliomas

- Reirradiation of tumors of the CNS can be done safely in select circumstances, but requires careful attention to treatment technique and taking into account such patient-specific factors such as size of intended target volume, prior and cumulative doses to critical structures, and interval from the preceding radiotherapy course. While improved tumor control can be seen in appropriately selected patients, the impact on quality of life and overall survival can vary by histology and patient PS.
- Highly focal techniques like intensity-modulated RT (IMRT), proton therapy, or SRS may be required in these reirradiation settings in order to improve dose distribution to critical structures, and reduce overlap with prior radiation fields.
- Recurrence of glioma can be managed with reirradiation in select scenarios when clinical trial options and new systemic therapy options are limited. Target volumes will be defined using contrast-enhanced CT and/or MRI images. Normal tissues should include the brain, brainstem, optic nerves, and chiasm. Radiation dose should be optimized and conformed to the target volume, while diminishing dose to critical structures. Treatment may be performed with highly focused modern SRS techniques for lower volume disease[10]; fractionated IMRT, including doses of 35 Gy in 10 fractions for recurrent glioblastoma[11], and proton therapy to help spare previously irradiated normal brain. For recurrence of lower grade gliomas, more extended fractionation schedules may be considered, especially if there is a longer interval between the first and second course of radiotherapy. Image-guided radiotherapy (IGRT) using imaging techniques may be used during treatment to ensure accuracy.

1. ELDERLY / FRAGILE PATIENTS

Glioblastoma (GBM) is the most common malignant brain tumor in adults. The standard treatment includes Gross total resection (GTR) followed by external beam RT with concomitant and maintenance temozolomide, with a reported median survival time of 14.6 months and 2-year survival rate of 26.5%, respectively. (*Stupp R 2005)*

However, the Stupp trial design only included patients younger than 70 years of age with an Eastern Cooperative Oncology Group performance status of 0 to 2, and a subgroup analysis illustrated a decreased benefit with increasing age. Elderly and/or frail individuals fare worse than younger and healthier patients, with a median survival time of approximately 6 months.

The National Comprehensive Cancer Network (NCCN) guidelines (Version 2.2021) define elderly patients as age > 70 years and encourage active treatments in patients with KPS scores ≥ 60. While, in elderly patients with poor performance status, KPS<60, NCCN recommend hypofractionated radiotherapy alone, temozolomide alone on palliative/ best supportive care.

VOLUME 22 · NUMBER 9 · MAY 1 2004

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

2004

Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial

W. Roa, P.M.A. Brasher, G. Bauman, M. Anthes, E. Bruera, A. Chan, B. Fisher, D. Fulton, S. Gulavita, C. Hao, S. Husain, A. Murtha, K. Petruk, D. Stewart, P. Tai, R. Urtasun, J.G. Cairncross, and P. Forsyth

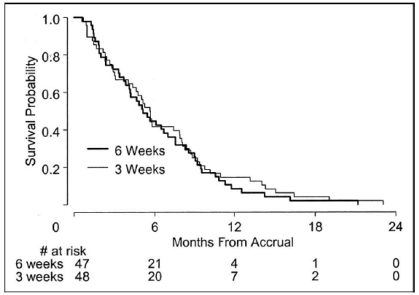
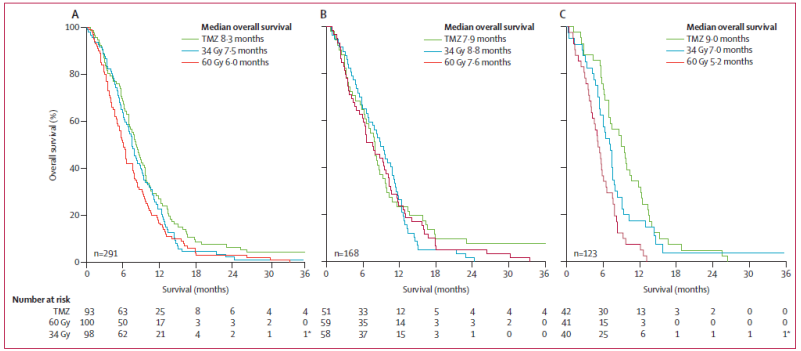


Fig 1. Overall survival from randomization by treatment group. There was no difference in the overall survival between the standard 6-week (thick line) versus abbreviated 3-week (thin line) course of radiation therapy (Log-rank test, $P = .57$).

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Bjørn Henning Grønberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)

2012



ELDERLY/FRAGILE PATIENTS

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

2015

International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients With Newly Diagnosed Glioblastoma Multiforme

Wilson Roa, Lucyna Kepka, Narendra Kumar, Valery Sinaika, Juliana Matiello, Darejan Lomidze, Dalenda Hentati, Douglas Guedes de Castro, Katarzyna Dyttus-Cebulok, Suzanne Drodge, Sunita Ghosh, Branislav Jeremić, Eduardo Rosenblatt, and Elena Fidarova

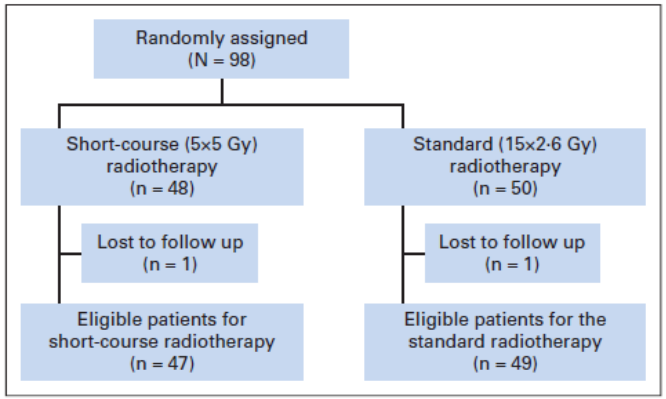


Fig 1. CONSORT diagram.

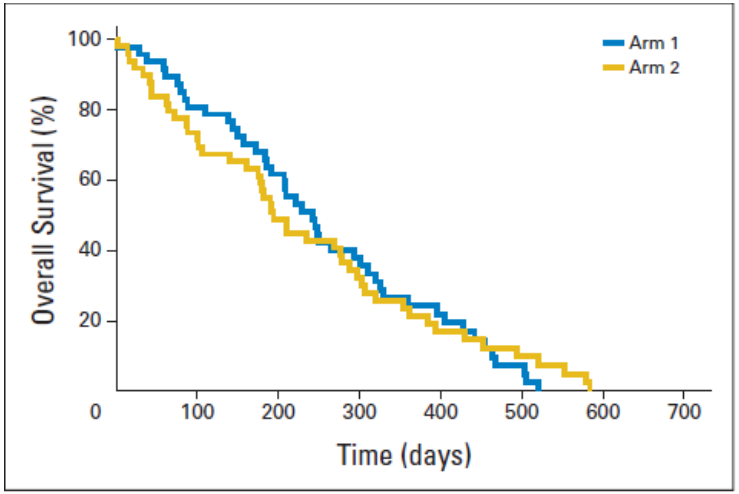


Fig 2. Overall survival (OS). Kaplan-Meier plots of OS according to the treatment arm (arm 1 = short-course radiotherapy: 25 Gy in five daily fractions; arm 2 = commonly used radiotherapy: 40 Gy in 15 daily fractions). Comparison of median OS showed no statistically significant difference between arms (7.9 *v* 6.4 months in arms 1 and 2, respectively; $P = .988$).

ELDERLY/FRAGILE PATIENTS

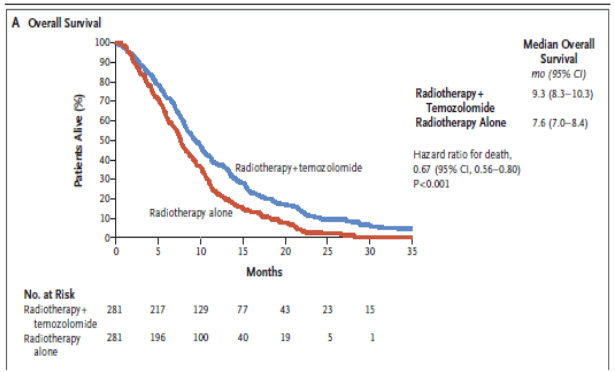
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

2017
CE.6 trial

Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma

James R. Perry, M.D., Normand Laperriere, M.D.,
Christopher J. O'Callaghan, D.V.M., Alba A. Brandes, M.D., Johan Menten, M.D.,



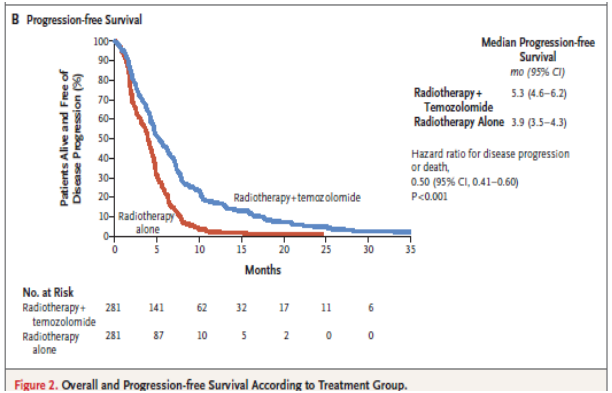


Figure 2. Overall and Progression-free Survival According to Treatment Group.

ELDERLY/FRAGILE PATIENTS

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Meisner, Jörg Felsberg, Ghazaleh Tabatabai, Matthias Simon, Guido Nikkhah, Kirsten Papsdorf, Joachim P Steinbach, Michael Sabel, Stephanie E Combs, Jan Vesper, Christian Braun, Jürgen Meixensberger, Ralf Ketter, Regine Mayer-Steinacker, Guido Reifenberger, Michael Weller, for the NOA-08 Study Group of the Neuro-oncology Working Group (NOA) of the German Cancer Society*

2012

The NOA-08 trial demonstrated that the regimen of dose-dense temozolomide (100 mg/m2, given on days 1–7 of 1 week on, 1 week off cycle) alone is **non-inferior** to radiotherapy at 54–60 Gy in 30 fractions among elderly patients with anaplastic astrocytoma or glioblastoma and age > 65 years.

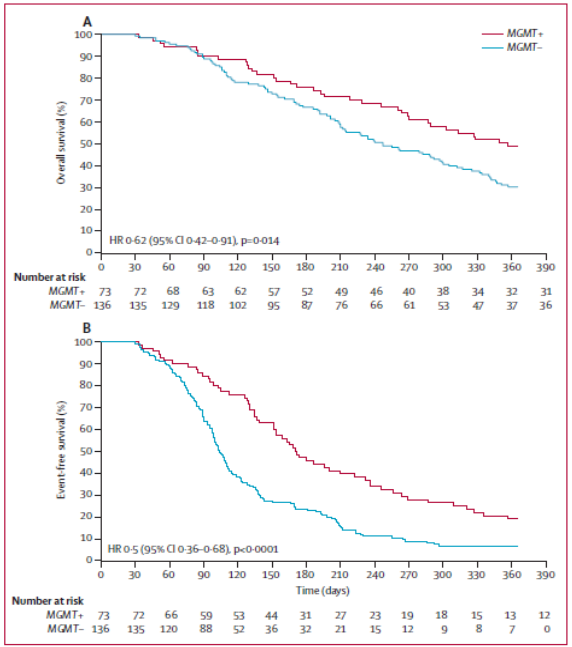


Figure 3: **Kaplan-Meier analysis of overall and event-free survival in relation to *MGMT* promoter methylation status**
(A) Overall survival. (B) Event-free survival. HR=hazard ratio.

ELDERLY/FRAGILE PATIENTS

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 29: 1423–1430, 2018
doi:10.1093/annonc/mdy120
Published online 10 April 2018

ORIGINAL ARTICLE

2018
ARTE Trial

Bevacizumab plus hypofractionated radiotherapy versus radiotherapy alone in elderly patients with glioblastoma: the randomized, open-label, phase II ARTE trial

H.-G. Wirsching[1,2†], G. Tabatabai[1,2], U. Roelcke[3], A. F. Hottinger[4,5], F. Jörger[6], A. Schmid[7], L. Plasswilm[8], D. Schrimpf[9,10], C. Mancao[11], D. Capper[9,10], K. Conen[12], T. Hundsberger[13], F. Caparrotti[14], R. von Moos[15], C. Riklin[16], J. Felsberg[17], P. Roth[1,2], D. T. W. Jones[10,18], S. Pfister[10,18], E. J. Rushing[1,19], L. Abrey[20], G. Reifenberger[17,21], L. Held[22], A. von Deimling[9,10], A. Ochsenbein[7] & M. Weller[1,2*]

The Oncologist®

Clinical Trial Results

2018
ANOCEF Trial

Temozolomide Plus Bevacizumab in Elderly Patients with Newly Diagnosed Glioblastoma and Poor Performance Status: An ANOCEF Phase II Trial (ATAG)

Germán Reyes-Botero,[a] Stéphanie Cartalat-Carel,[b,c] Olivier L. Chinot,[d] Maryline Barrie,[d] Luc Taillandier,[e] Patrick Beauchesne,[e] Isabelle Catry-Thomas,[f] Jérôme Barrière,[g] Jean-Sebastien Guillamo,[h] Michel Fabbro,[i] Didier Frappaz,[j]

STUDY PROTOCOL Open Access

A randomized phase III study of short-course radiotherapy combined with Temozolomide in elderly patients with newly diagnosed glioblastoma; Japan clinical oncology group study JCOG1910 (AgedGlio-PIII)

Yoshiki Arakawa[1*], Keita Sasaki[2], Yohei Mineharu[1], Megumi Uto[3], Takashi Mizowaki[3*], Junki Mizusawa[2], Yuta Sekino[2], Tomohiro Ono[3], Hidefumi Aoyama[4], Kaishi Satomi[5], Koichi Ichimura[6], Manabu Kinoshita[7], Makoto Ohno[8], Yoshinori Ito[9], Ryo Nishikawa[10], Haruhiko Fukuda[2], Yasumasa Nishimura[11], Yoshitaka Narita[8] and Brain Tumor Study Group and Radiation Therapy Study Group of the Japan Clinical Oncology Group

Interventions

Arm A:

(1) 40 Gy in 15 daily fractions with temozolomide.
(i) Concomitant phase, temozolomide (75 mg/m^2, daily from first to last day of radiation), radiation (2.67 Gy/day, 5 days/week, 15 times and 40 Gy in total)
(ii) Maintenance phase, temozolomide (150–200 mg/m^2, days 1–5, every 4 weeks) 12 cycles.

Arm B:

(1) 25 Gy in 5 daily fractions with temozolomide.
(i) Concomitant phase, temozolomide (150 mg/m^2, 5 days from first day), radiation (5 Gy/day, 5 days/week, 5 times and 25 Gy in total)
(ii) Maintenance phase, temozolomide (150–200 mg/m^2, days 1–5, every 4 weeks) 12 cycles.

2021

Inclusion criteria

First registration criteria:

(1) Tumor diagnosed as glioblastoma or Grade III glioma (WHO 2016 criteria) in pathological diagnosis during surgery, or histologically proven glioblastoma diagnosed according to WHO 2016 criteria.
(2) Tumor specimen available for analysis of MGMT promoter methylation status.
(3) No history of treatments for glioma except for resection including biopsy; in that case, second resection within 21 days after first resection.
(4) First registration within 21 days after surgery.
(5) Tumor present in the supratentorial region on preoperative contrast-enhanced MRI of the brain.
(6) Preoperative contrast-enhanced MRI of the brain reveals no dissemination.
(7) Presence of a measurable lesion is not mandatory.
(8) Patient 71 years old or older at registration; 71 to 75 years old with resection of less than 90% of contrast-enhanced region.
(9) ECOG performance status (PS) of 0, 1, 2, or 3 due to neurological symptoms caused by the tumor.
(10) No prior chemotherapy or radiation therapy to the brain for any intracranial tumors.
(11) Sufficient organ function.

ELDERLY/FRAGILE PATIENTS

Statistical analysis

This study is designed as a multi-institutional, randomized controlled trial to confirm the non-inferiority of radiotherapy of 25 Gy in 5 fractions with concomitant and adjuvant temozolomide over 40 Gy in 15 fractions with concomitant and adjuvant temozolomide in terms of OS in elderly patients with newly diagnosed glioblastoma. The required sample size for randomization is cal-

Procedures of radiotherapy

Contouring was performed using computed tomography (CT) with a maximum slice thickness of 5 mm. Gross tumor volume (GTV) was defined as residual tumor according to pre- and postoperative contrast-enhanced MRI. Clinical target volume (CTV) was created by adding 1.5-cm margins to the GTV and resection cavity. In addition, CTV included surrounding edema (high-

Actually ongoing..

2. RECURRENT DISEASE

In case of tumor relapse or progression, treatment options include surgery, chemotherapy or reirradiation, alone or in combination, as potentially salvage strategies. Due to its complexity, all treatment decisions require a multidisciplinary approach and should consider patients specific characteristics.

Normal brain tissue dose tolerance is the limiting factor when giving reirradiation.

In recent update of the literature (Minniti G. et Al. 2021) on reirradiation of GBM, a risk of radionecrosis of

- of 0 to 3% has been shown after conventional fractionation with cumulative *EQD2 doses < 101 Gy,*
- **of** 7 to 13% after hypofractionated SRT with cumulative EQD2 doses of *102 to 130 Gy,* and
- up to 24.4% after SRS with cumulative EQD2 doses of *120 to 150 Gy* .

Niyazi et al. 2013 found no relevant long-term toxicity in a series of 58 patients who received reirradiation for a malignant glioma using maximum EQD2 values of 80.3 Gy, 79.4 and 95.2 Gy to the optic chiasm, optic nerves and brainstem, respectively, considering an α/β ratio of 2 Gy for these structures.

RECURRENT DISEASE

GLIOBLASTOMA

Median survival times from 7 to 13 months and 1-year OS rates of 30–55% have been observed following either SRS or fractionated SRT, with 1-year incidence of neurological toxicities ranging from 5 to 20%.

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-018-03064-0

CLINICAL STUDY

Re-irradiation for recurrent glioblastoma (GBM): a systematic review and meta-analysis

Farasat Kazmi[1] · Yu Yang Soon[1] · Yiat Horng Leong[1] · Wee Yao Koh[1] · Balamurugan Vellayappan[1,2]

Received: 8 October 2018 / Accepted: 24 November 2018

In a recent systematic review of reirradiation with different SRS modalities for recurrent glioblastoma including 50 studies (2096 patients), Kazmi et al. observed similar **12-month** OS and PFS rates of **34%** and 16%, respectively.

RECURRENT DISEASE

Hypofractionated SRT, given as moderate hypofractionation (35-37.5 Gy in 10–15 fractions of 2.5–3.5 Gy each) or as high-dose hypofractionation (27–35 Gy in 3–5 fractions of 5–9 Gy each) is increasingly used in the setting of reirradiation as an alternative to single-fraction SRS.

VOLUME 28 · NUMBER 18 · JUNE 20 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Hypofractionated Stereotactic Radiation Therapy: An Effective Therapy for Recurrent High-Grade Gliomas

Shannon E. Fogh, David W. Andrews, Jon Glass, Walter Curran, Charles Glass, Colin Champ, James J. Evans, Terry Hyslop, Edward Pequignot, Beverly Downes, Eileen Comber, Mitchell Maltenfort, Adam P. Dicker, and Maria Werner-Wasik

Fogh et al. observed a **median OS of 11 months** in 105 patients with relapsed glioblastoma who received a total dose of 35 Gy in 10 fractions.

RECURRENT DISEASE

A similar OS of 7 to 10 months has been observed using conventionally fractionated SRT in 2 Gy fractions.

In 172 patients with recurrent low- and high grade gliomas who were treated with 36 Gy delivered in 2-Gy fractions, Combs et al. observed **median OS** and PFS times of **8** and 5 months, respectively.

Superior survival benefit of reirradiation in combination with systemic therapy remains a matter of debate.

In a few retrospective studies, the combination of RT with alkylating agents offered longer OS and PFS times compared with RT alone, but this benefit seems to be limited to MGMT methylated tumors. In contrast, other few series failed to show significant survival benefit with the addition of chemotherapy to RT. Retrospective studies observed significantly longer OS with the addition of bevacizumab to SRS and SRT compared to reirradiation alone.

J Neurooncol (2011) 103:683–691
DOI 10.1007/s11060-010-0446-8

CLINICAL STUDY – PATIENT STUDY

Fractionated stereotactic reirradiation and concurrent temozolomide in patients with recurrent glioblastoma

G. Minniti · V. Armosini · M. Salvati · G. Lanzetta · P. Caporello · M. Mei · M. F. Osti · R. Enrici Maurizi

International Journal of Radiation Oncology • biology • physics
www.redjournal.org

Clinical Trial · J Clin Oncol. 2023 Feb 20;41(6):1285-1295. doi: 10.1200/JCO.22.00164. Epub 2022 Oct 19.

NRG Oncology/RTOG1205: A Randomized Phase II Trial of Concurrent Bevacizumab and Reirradiation Versus Bevacizumab Alone as Treatment for Recurrent Glioblastoma

Christina I Tsien [1], Stephanie L Pugh [2], Adam P Dicker [3], Jeffrey J Raizer [4], Martha M Matuszak [5],

Investigating the Effect of Reirradiation or Systemic Therapy in Patients With Glioblastoma After Tumor Progression: A Secondary Analysis of NRG Oncology/ Radiation Therapy Oncology Group Trial 0525

Wenyin Shi, MD, PhD,* Molly Scannell Bryan, PhD,† Mark R. Gilbert, MD,‡ Minesh P. Mehta, MD,§

RECURRENT DISEASE

EPENDYMOMAS

Recurrent disease may occur in 30–50% of patients and it is treated by local excision plus reirradiation as systemic therapies have proven to be of a little benefit. Reirradiation given as focal treatment or CSI RT have been associated with survival benefit.

101 patients with recurrent ependymoma were treated with a second course of fractionated RT after prior focal RT given to a dose of 54 Gy in 1.8 Gy daily fractions. Recurrent tumors received a median dose of 39.6 Gy delivered in 1.8 Gy daily fractions to sites of gross or resected recurrent tumor using either photons (n = 88) or protons (n = 13); 55 patients with recurrent ependymoma were treated with CSI.

RECURRENT DISEASE

Neuro-Oncology Advances
1
3(1), 1–10, 2021 | https://doi.org/10.1093/noajnl/vdab158 | Advance Access date 08 November 2021

Reevaluating surgery and re-irradiation for locally recurrent pediatric ependymoma—a multi-institutional study

David Y. Mak, Normand Laperriere, Vijay Ramaswamy, Eric Bouffet, Jeffrey C. Murray, Rene Y. McNall-Knapp, Kevin Bielamowicz, Arnold C. Paulino, Wafik Zaky, Susan L. McGovern, M. Fatih Okcu, Uri Tabori, Doaa Atwi, Peter B. Dirks, Michael D. Taylor, Derek S. Tsang, and Abhishek Bavle

Among 22 patients with local failure after the first course of RT, the use of CSI as reirradiation was associated with significant improvement in time to recurrence; median time and 5-year rate of time to recurrence were: 26.7 months and 15.2% in those who did not receive CSI, respectively, versus not reached and 83.3% for those who received CSI ($p = 0.03$).

Diffuse Midline Gliomas

Few studies investigated clinical outcomes of patients with recurrent/progressive diffuse midline glioma treated with reirradiation. Using median doses for reirradiation of 18–24 Gy in 1.8-2.0 Gy daily fractions, median OS reported in six published studies ranges from 4 to 8.3 months and median PFS from 3 to 4.5 months from the time of reirradiation.

RECURRENT DISEASE


European Journal of Cancer 73 (2017) 38–47

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

ELSEVIER

EJC

Original Research

Survival benefit for patients with diffuse intrinsic pontine glioma (DIPG) undergoing re-irradiation at first progression: A matched-cohort analysis on behalf of the SIOP-E-HGG/DIPG working group☆

CrossMark

Geert O. Janssens [a,*], Lorenza Gandola [b], Stephanie Bolle [c], Henry Mandeville [d], Monica Ramos-Albiac [e], Karen van Beek [f].

Most patients were treated with a conventionally fractionated regimen up to a total dose of 20 Gy in 1.8-2.0 Gy daily fractions, given alone or in combination with systemic therapy. Following reirradiation, the reported median survival time was 6.4 months compared to 3 months.

In addition, a clinical improvement was noted in nearly 80% of the patients with no life-threatening or fatal toxicities observed during the follow-up.

RECURRENT DISEASE

Received: 22 October 2017 | Accepted: 18 December 2017
DOI: 10.1002/pbc.26988

RESEARCH ARTICLE

WILEY Pediatric Blood & Cancer

Reirradiation in patients with diffuse intrinsic pontine gliomas: The Canadian experience

Alvaro Lassaletta[1] | Douglas Strother[2] | Normand Laperriere[3] | Juliette Hukin[4] | Magimairajan Issai Vanan[5] | Karen Goddard[4] | Lucie Lafay-Cousin[2] | Donna L. Johnston[6] | Shayna Zelcer[7] | Michal Zapotocky[1] | Revathi Rajagopal[1] | Vijay Ramaswamy[1] | Cynthia Hawkins[1] | Uri Tabori[1] | Annie Huang[1] | Ute Bartels[1] | Eric Bouffet[1]

In another Canadian retrospective study including 14 patients with diffuse midline glioma who received focal reirradiation using doses of 21.6 to 36 Gy given in 1.8 Gy daily fractions, median OS from reirradiation was **6.5 months.**

Clinical benefit can be observed in up to 80% of patients and this has been associated with an improvement in quality of life.

TAKE HOME MESSAGES

Patients selection.

In **elderly/fragile** with GBM: to encourage the consideration of hypofractionated radiotherapy for elderly patients with glioblastoma, adding chemotherapy for patients with good performance. The optimal dose and number of fractions remain unclear.

According to international recommendations and prognostic score indexes, **reirradiation** should be considered in young patients with good performance status, and at least 6 months interval from the first course of RT.