



## **DICHIARAZIONE**

**Relatore: Dr.ssa LORENA DRAGHINI**

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarità di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

XXV CONGRESSO NAZIONALE

**AIRO 2015**

PALACONGRESSI - Rimini, 7-10 novembre



## **RE-IRRADIAZIONE : STANDARD CLINICO O RICERCA?**

### **RE-IRRADIAZIONE DELLE NEOPLASIE CEREBRALI** **RE-IRRADIATION IN BRAIN TUMORS**

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## Review Article

# Increasing frequency of reirradiation studies in radiation oncology: systematic review of highly cited articles

Carsten Nieder<sup>1,2</sup>, Nicolaus H Andratschke<sup>3</sup>, Anca L Grosu<sup>4</sup>

Am J Cancer Res 2013;3(2):152-158

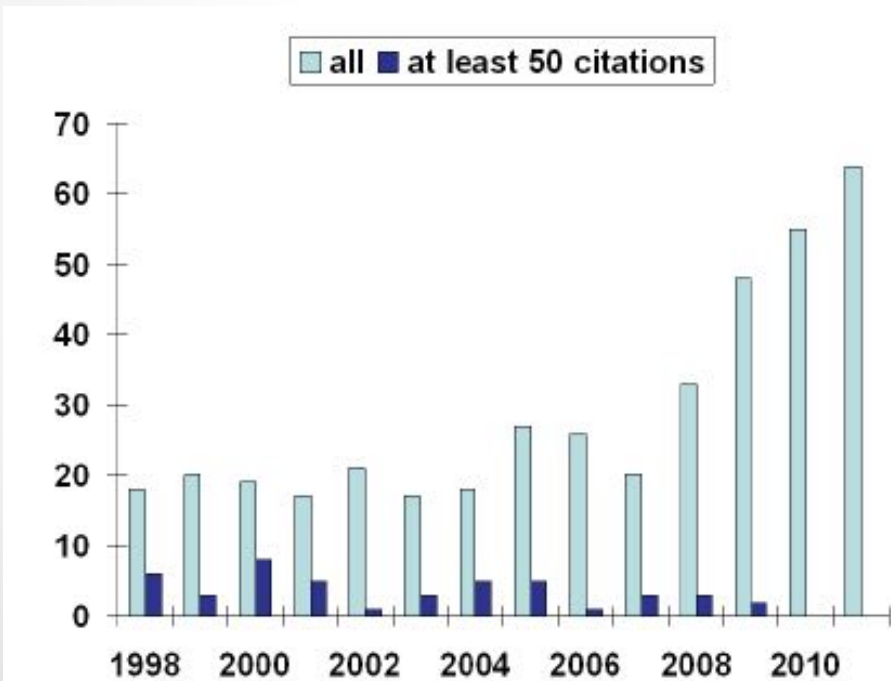


Figure 1. Number of articles and highly cited articles published per year.

- Highly conformal and precise radiotherapy
- Combined modality treatment
- **BRAIN** and head and neck tumors

# GENERAL CONSIDERATIONS 1

- Increased risk of **late toxicity** limits re-irradiation → depends on the cumulative dose, re-irradiation brain volume, interval between treatments

## **CNS CHANGES are irreversible:**

- White matter necrosis
- Demyelination
- Leukoencephalopathy
- Alterations in cerebrovascular permeability
- Focal hemorrhage in white and grey matter

## **CLINICAL CONSEQUENCES:**

- Focal neurological symptoms (motor and sensory deficits, seizures)
- Neuropsychological impairment (learning deficit, intellectual decline, personality changes)
- Cerebrovascular effects (stroke, dementia)

*Maranzano et al. 2005 Re-irradiation of brain metastases and metastatic spinal cord compression: clinical practice suggestions*

*Tumori*

*Trippa et al. 2015 Radiation-induced neurocognitive deficits in patients with brain metastases*

*Reviews in Oncology* 4



# GENERAL CONSIDERATIONS 2

- Increased risk of **late toxicity** limits re-irradiation → depends on the cumulative dose, re-irradiation brain volume, interval between treatments



- 14% incidence of **radionecrosis** → cumulative EQD2 > 86 Gy

*Nieder et al. 2000 Tissue tolerance to reirradiation  
Seminars in Radiation Oncology*

# GENERAL CONSIDERATIONS 3

- Low repair capacity →  $\alpha/\beta = 2$  considered BED rather than “physical” dose
- $BED_{\text{initial}} + BED_{\text{re-irradiation}} = BED_{\text{cumulative}}$
- Linear quadratic model



*Review 21 studies FSRT, SRS, or 3DCRT*

$$NTD_{\text{initial}} + NTD_{\text{re-irradiation}} = NTD_{\text{cumulative}} > 100 \text{ Gy}$$

The applied re-irradiation dose and  $NTD_{\text{cumulative}}$  **increase** with a change irradiation technique from conventional to **FSRT –SRS re-treatment**, without increasing the probability of normal brain necrosis.

*Mayer et al.2008 Reirradiation tolerance in human brain*

*Int J Radiat Oncol Biol.Phys*

# GENERAL CONSIDERATIONS 4

➤ Recurrent tumor or radionecrosis?

Metabolic and vascular imaging techniques (MRI Spectroscopy, SPECT, PET)

➤ Risk of **late vascular insufficiency** (7,5% increase in relative risk per Gy from a zero dose, data from breast RT)

*Maranzano et al. 2010 Tumor relapse or radionecrosis after radiosurgery: single-photon emission computed tomography for differential diagnosis.*

*Int J Radiat Oncol Biol Phys*

*Jones et al. 2014 Retreatment of Central Nervous System tumours*

**OVERVIEW**

*Clinical Oncology*

# GENERAL CONSIDERATIONS 5

- **Concurrent chemotherapy** can influence risk of **late toxicity**
- **Drugs such as Temozolomide** seems to sensitize  $\beta$  more than  $\alpha$  tumor cells → lowering  $\alpha/\beta$  ratio for normal tissue → **fractionation sensitivity**
- The role of supportive drugs and antivasular agents during reirradiation remains to be defined → **appropriate steroid - anticonvulsant drug support**

*Jones et al. 2014 Retreatment of Central Nervous System tumours*

*Clinical Oncology*

**OVERVIEW**



# **RE-IRRADIATION IN BRAIN TUMORS**

***BRAIN METASTASES***

***GLIOBLASTOMA***

# **RE-IRRADIATION IN BRAIN TUMORS**

***BRAIN METASTASES***

***GLIOBLASTOMA***

# Re-irradiation of central nervous system tumors

Muhammad B. Tariq • Ehsan H. Balagamwala •  
Samuel T. Chao

J Radiat Oncol (2015) 4:105–115  
DOI 10.1007/s13566-015-0189-4

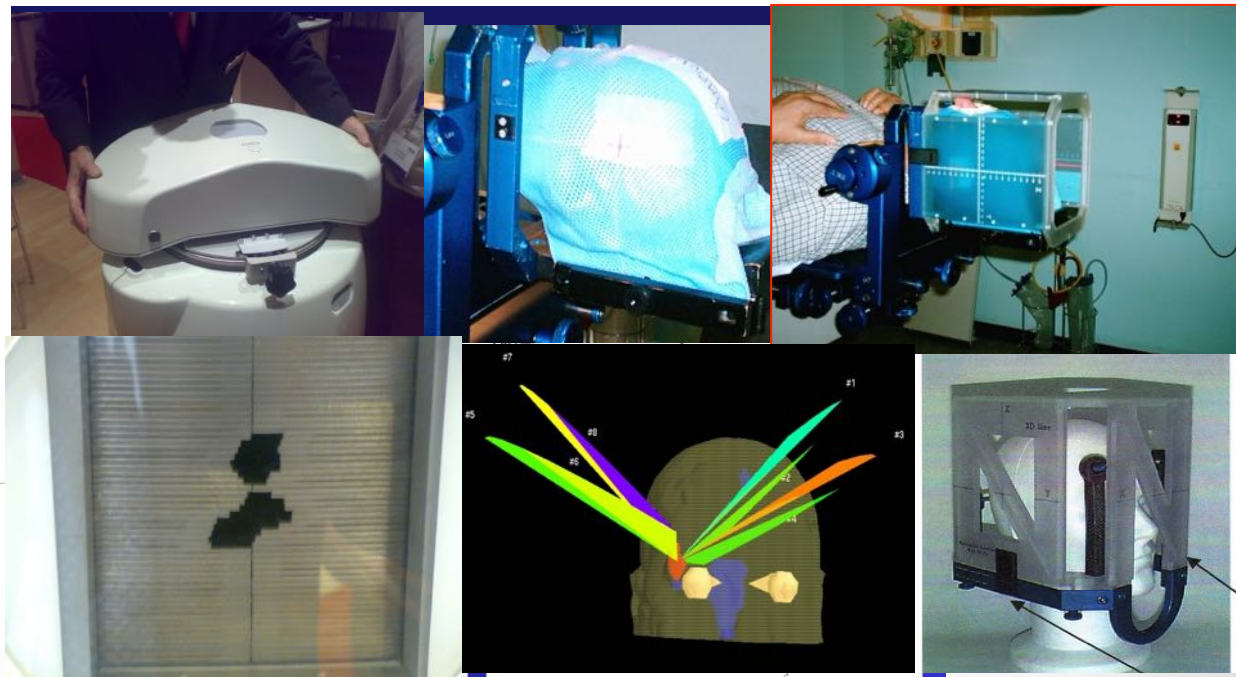
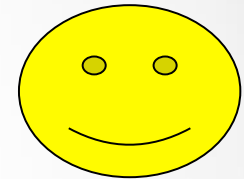
REVIEW

- **20-40%** of all cancer patients will develop brain metastases during the course of their disease
- Survival ranges from 2-19 months (RPA e GPA classes)
- WBRT → multiple metastases
- SRS → 1-3 metastases
- **50%** of patients eventually relapse or have disease progression
- Increasing % of long-term survivors

# RE-IRRADIATION TECHNIQUES

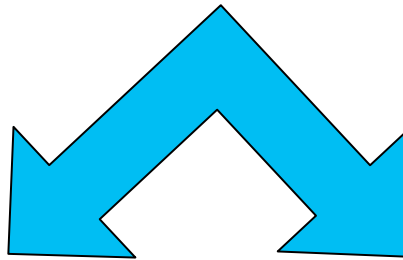
**WBRT**

**STEREOTACTIC RADIOTHERAPY  
SRS-FSRT**



# **RTOG 90-05**

## **PHASE I DOSE ESCALATION**



**Safety of SRS salvage** after  
primary WBRT or partial brain  
Radiotherapy (**primary brain  
tumors and brain metastases**)

**Dose limits for SRS:**  
**24 Gy** for tumor  $\leq 20\text{mm}$   
**18 Gy** for tumor  $\leq 21\text{-}30\text{ mm}$   
**15 Gy** for tumor  $\leq 31\text{-}40\text{ mm}$

**Maximum tumor diameter** is associated with a significant **increased risk** of unacceptable acute and/or chronic **neurotoxicity** at multivariate analysis

Original article

## Reirradiation of brain metastases with radiosurgery

**2012**

Ernesto Maranzano <sup>a,\*</sup>, Fabio Trippa <sup>a</sup>, Michelina Casale <sup>a</sup>, Sara Costantini <sup>a</sup>, Paola Anselmo <sup>a</sup>, Sandro Carletti <sup>b</sup>, Massimo Principi <sup>c</sup>, Claudia Caserta <sup>d</sup>, Fabio Loreti <sup>e</sup>, Cesare Giorgi <sup>b</sup>

<sup>a</sup> Radiotherapy Oncology Center; <sup>b</sup> Neurosurgery Center; <sup>c</sup> Neuroradiology Service; <sup>d</sup> Medical Oncology Center; and <sup>e</sup> Nuclear Medicine Service, S. Maria Hospital, Terni, Italy



- ✓ **91 %** achieved **LC**, 1 year LC rate was 74%
- ✓ **≥ 23 Gy** and **responders** had a longer duration of response
- ✓ Median **OS** was **10 months** after SRS and **12 months** for patients with **KPS ≥70%**
- ✓ Good **NFS** improved outcome

**SAFE and GOOD RESULTS**

## **The role of retreatment in the management of recurrent/ progressive brain metastases: a systematic review and evidence-based clinical practice guideline**

**Mario Ammirati • Charles S. Cobbs • Mark E. Linskey • Nina A. Paleologos •  
Timothy C. Ryken • Stuart H. Burri • Anthony L. Asher • Jay S. Loeffler •  
Paula D. Robinson • David W. Andrews • Laurie E. Gaspar • Douglas Kondziolka •  
Michael McDermott • Minesh P. Mehta • Tom Mikkelsen • Jeffrey J. Olson •  
Roy A. Patchell • Steven N. Kalkanis**

## **Re-irradiation of central nervous system tumors**

**Muhammad B. Tariq • Ehsan H. Balagamwala •  
Samuel T. Chao**

J Radiat Oncol (2015) 4:105–115

DOI 10.1007/s13566-015-0189-4

REVIEW

**13 studies** : role of *SRS* for recurrent/progressive brain metastases

**9 studies** evaluated *SRS* after *WBRT*

**4 studies** evaluated *SRS* after *SRS*

**1 study** prospective, case series level evidence III

**1-year LC 40-90%**

**Median survival: 6-19 months, from first RT 22 months**

**Acceptable toxicity**



LITERATURE DATA	PROGNOSTIC FACTORS
<p>Alexander et al.1995 Hoffman et al. 2001</p>	<p>Sopratentorial tumors, homogeneous enhancement, fewer metastases, no active systemic disease, age &lt;60 years, RPA</p>
<p>Maranzano et al. 2012 RTOG 90-05</p>	<p>KPS, NFS, RPA, dose ≥23 Gy, complete/partial response NFS</p>
<p>Noel et al 2001 Chao et al. 2008</p>	<p>KPS, higher interval between treatments</p>
<p>Bahl et al. 2009</p>	<p>Breast histology, responded to primary WBRT, KPS, age &lt; 60 years, no active systemic disease</p>

# **Brain metastases re-irradiation: REVIEW POINTS**

- ❖ **RE-IRRADIATION** for brain metastases can achieve reasonable local tumor control and improves neurological outcome with low toxicity (median OS, 6-19 months)
  
- ❖ **THE BEST PATIENT SELECTION FOR RE-IRRADIATION**
  - **KPS  $\geq$  70**
  - **age < 60**
  - **higher interval between first and second RT treatments**
  - **no active systemic disease**
  - **life expectancy of at least 12 months**
  - **small treatment volume**
  - **cancer histology**

# **RE-IRRADIATION IN BRAIN TUMORS**

*BRAIN METASTASES*

*GLIOBLASTOMA*

# PROGNOSTIC FACTORS

CLASS		MEDIAN SURVIVAL
I	Age <50 yy, AA , no neurologic deficits	58,6
II	Age ≥50 yy, AA , symptoms ≥ 3 months duration	34,7
III	Age <50, AA, abnormal mental status	
	Age <50, <b>Glioblastoma</b> , KPS 90-100%	17,9
IV	<b>Age</b> <50, Glioblastoma, KPS <90%	
	Age ≥50, KPS 70-100%, AA, symptoms ≤ 3 months duration	11,1
	Age ≥50, Glioblastoma, <b>surgery</b> , no neurologic deficits	
V	Age ≥50, <b>KPS 70-100%</b> , Glioblastoma, surgery with neurologic deficits or biopsy	8,9
	Age ≥50, KPS <70%, no <b>neurologic deficits</b>	
VI	Age ≥50, KPS 70-100%, Glioblastoma, biopsy	4,6
	Age ≥50, KPS <70%, neurologic deficits	

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Validation and predictive power of Radiation Therapy Oncology Group (RTOG) **Recursive Partitioning Analysis** classes for malignant glioma patients: A report using **RTOG 90-06. IJROBP 40:51, 1998**

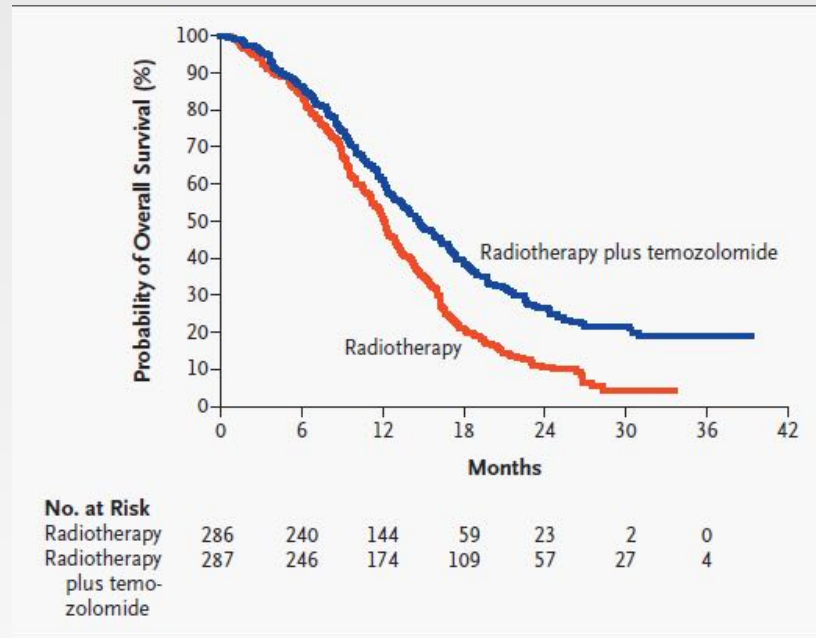
# **GLIOBLASTOMA**

- ***STANDARD TREATMENT: surgery + Rt/Ct (Stupp)***
- *Within 24 months from surgery ~95% of patients had a relapse*
- *95 % of which had “in field relapse”*

**THE AMERICAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY  
(ASTRO) EVIDENCE BASED REVIEW OF THE ROLE OF RADIOSURGERY FOR  
MALIGNANT GLIOMA,  
IJROBP 2005**

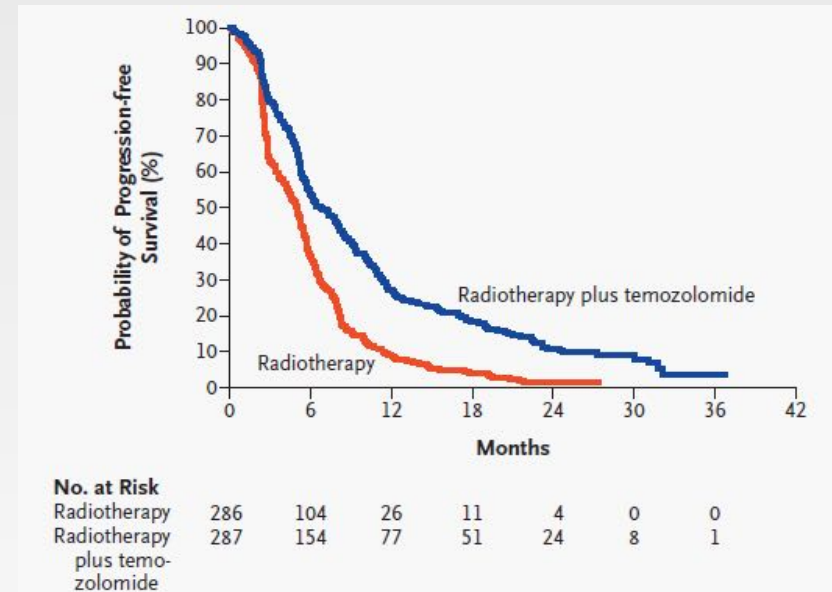
↑ Median OS 2.5 months  
(from 12,1 to 14.6 months)

↑ Median DFS of 1.9 months  
(from 5 to 6.9 months)



**Figure 1.** Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75;  $P < 0.001$ ).



**Figure 2.** Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.

The hazard ratio for death or disease progression among patients treated with radiotherapy plus temozolomide, as compared with those treated with radiotherapy alone, was 0.54 (95 percent confidence interval, 0.45 to 0.64;  $P < 0.001$ ).

G3-G4 hematological  
toxicities: 7% of patients

# ***GLIOBLASTOMA***

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- ***Within 24 months from surgery ~95% of patients had a relapse***
- ***95 % of which had “in field relapse”***

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IJROBP 2005***

# ***GLIOBLASTOMA***

- ***Surgery (+/- chemotherapy)***
- ***RE-IRRADIATION (+/- chemotherapy)***
- ***Second line chemotherapy***
- ***Best supportive care***





*Neuro-Oncology* 15(1):4–27, 2013.  
doi:10.1093/neuonc/nos273  
Advance Access publication November 7, 2012

2013

NEURO-ONCOLOGY

# Standards of care for treatment of recurrent glioblastoma— are we there yet?

Michael Weller, Timothy Cloughesy, James R. Perry, and Wolfgang Wick

## Treatment options for recurrent gliomas

Claudia Scaringi<sup>1</sup>  
Paola Caporello<sup>2</sup>  
Giuseppe Minniti<sup>1,3</sup>

2014

Reviews in Oncology 2014; 2(2):33-45

*J Radiat Oncol* (2015) 4:105–115  
DOI 10.1007/s13566-015-0189-4

2015

REVIEW

## Re-irradiation of central nervous system tumors

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## Summary of main published studies on radiotherapy for recurrent gliomas

Authors	Patients No	Diagnosis	Type of RT	Median dose Gy	OS from re-RT months	PFS from re-RT months
Combs et al. [69]	32	Recurrent GBM	SRS	15	10	7
Kong et al. [70]	114	Recurrent gliomas	SRS	16	13 (GBM)	4.6 (GBM)
Biswas et al. [71]	18	Recurrent GBM	SRS	14	5.3	3.4
Patel et al. [72]	26	Recurrent GBM	SRS	18	8.4	NA
Maranzano et al. [73]	13	Recurrent GBM	SRS	17	11	4

Authors	Patients No	Diagnosis	Type of RT	Median dose Gy	OS from re-RT months	PFS from re-RT months
Sirin et al. [74]	19	Recurrent GBM	SRS	16	9.3	5.7
Torok et al. [75]	14	Recurrent GBM	SRS	24	10	5
Villavicencio et al. [76]	26	Recurrent GBM	CK SRS	20	7	NA
Elliott et al. [77]	26	Recurrent gliomas	GK SRS	15	13.5	NA
Skeie et al. [78]	51	Recurrent GBM	GK SRS	12.2	12	6
Ernst-Stecken et al. [79]	15	Recurrent gliomas	HSRT	35	12-OS: 43%	15
Fokas et al. [80]	53	Recurrent GBM	HSRT	30	9	22% at 1 year
Henke et al. [81]	31	Recurrent gliomas	HSRT	20	10.2	NA
McKenzie et al. [84]	35	Recurrent gliomas	HSRT	30	8.6	NA
Ogura et al. [85]	30	Recurrent gliomas	HSRT	35	10.4	3
Anand et al. [86]	16	Recurrent gliomas	HSRT	30	9.3	6.4
Miwa et al. [87]	21	Recurrent GBM	HSRT IMRT	25-35	11	6
Yazici et al. [88]	37	Recurrent GBM	CK HSRT	30	10.6	7.9
Combs et al. [89]	53	Recurrent GBM	FSRT	36	8	5
Combs et al. [90]	172	Recurrent gliomas	FSRT	36	8 (GBM)	10 (GBM)
Patel et al. [72]	10	Recurrent GBM	FSRT	36	7.4	NA
Maranzano et al. [73]	9	Recurrent GBM	FSRT	30	11	4

## *RE-IRRADIATION with SRS or FSRT:*

- *safe and feasible option with no severe toxicity*
- *may improve patient neurological status and reduce steroid dependency*
- *Tumor control: ranged from 20-80%*
- *Median survival: ranged from 5.3 to 13.5 months*
- *Pay attention to CONCURRENT CHEMORADIOTHERAPY:  
It did not improve outcome  
But can increase **toxicity**: necrosis in up 13% of patients,  
intratumoral bleeding, wound dehiscence, bowel perforation*

# GBM: how to select patients for re-irradiation?

To be eligible, patients must have received:

- Partial brain fractionated external beam radiotherapy  $\geq 5$  months before re-irradiation for GBM.
- MRI with contrast evidence of a recurrence and/or progression of disease
- KPS  $\geq 70\%$
- life expectancy  $\geq 3$  months
- No concomitant chemotherapy was admitted during re-irradiation.
- Diameter  $\leq 3$  cm  $\rightarrow$  SRS,  $\geq 3$  cm or near OAR  $\rightarrow$  FSRT

**Maranzano et al.** *Treatment of recurrent glioblastoma with stereotactic radiotherapy: long-term results of a mono-institutional trial*

**Tumori 2011**

2011

## Molecular Subclassification of Diffuse Gliomas: Seeing Order in the Chaos

JASON T. HUSE,<sup>1</sup> HEIDI S. PHILLIPS,<sup>2</sup> AND CAMERON W. BRENNAN<sup>3\*</sup>

<sup>1</sup>Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York

<sup>2</sup>Department of Tumor Biology and Angiogenesis, Genentech, Inc., South San Francisco, California

<sup>3</sup>Human Oncology and Pathogenesis Program and Department Neurosurgery, Memorial Sloan-Kettering Cancer Center, New York, New York

CLASSIFICATION	PRIMARY GBM	SECONDARY GBM
PHILLIPS et al.	NF1mt/-	IDH1/2 mt
VERHAAK et al./The Cancer Genome Atlas (TCGA)	EGFR+++	MGMT methylation
	-10 chromosome	-1p/19q chromosome
	VEGFR+++	p53 mt VEGFR+
TRANSCRIPTIONAL SUBTYPES	MESENCHYMAL	PRONEURAL

**The future of high-grade glioma: Where we are and where are we going**  
*Neuro-Oncology, a supplement to Surgical Neurology International*

2015

Emilie Le Rhun, Sophie Taillibert<sup>1</sup>, Marc C. Chamberlain<sup>2</sup>

**RE-IRRADIAZIONE :**  
**STANDARD CLINICO O RICERCA?**  
**RE-IRRADIAZIONE DEI TUMORI CEREBRALI**



**“IL VERO VIAGGIO DI SCOPERTA  
NON CONSISTE NEL CERCARE  
NUOVE TERRE, MA NELL'AVERE  
NUOVI OCCHI.”**

*Marcel Proust*

**GRAZIE PER L'ATTENZIONE**