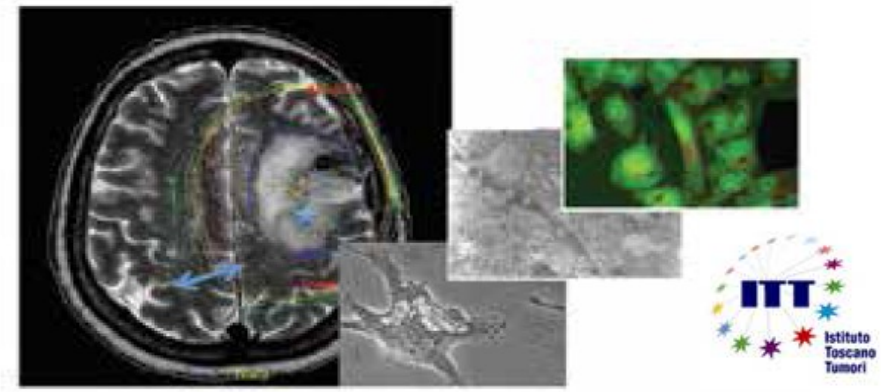


Correlazione tra espressione di Epidermal Growth Factor Receptor (*EGFR*) e Patterns di recidiva/progressione di malattia dopo trattamento radio-chemioterapico in pazienti affetti da Glioblastoma (GB).

Paolo Tini [1,3] **M.D.** :

in collaborazione con:

Silvia Palumbo, PhD [2], **Noemi Palla, MD** [1,3] , **Marzia Toscano, PhD** [1,3], **Giovanni Rubino, MD** [1,2], **Clelia Miracco, MD** [1,4], **and Luigi Pirtoli, MD** [1,3]

[1] *Istituto Toscano Tumori, Florence, Italy*

[2] *Department of Biotechnology, University of Pavia, Italy*

[3] *Department of Radiation Oncology, University Hospital of Siena, Italy.*

[4] *Department of Human Pathology, University Hospital of Siena, Italy.*

Azienda Ospedaliera Universitaria Senese
Complesso Ospedaliero di Rilievo Nazionale e di Alta Specializzazione
Ospedale Santa Maria alle Scotte

Background

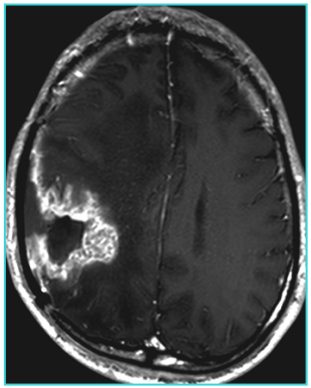
✓ Glioblastoma has an unfavorable prognosis mainly due to its high propensity for ***tumor recurrence***.

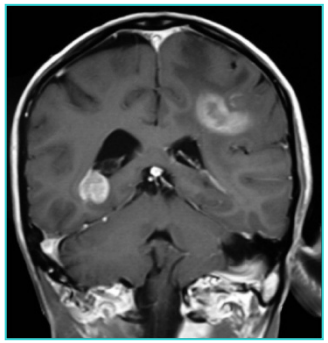
✓ It has been suggested that GBM recurrence is unavoidable after a median survival time of 32 to 36 weeks.

Ammirati et al. 1987 NeuroSurg.

Choucair AK. 1986 J NeuroSurg

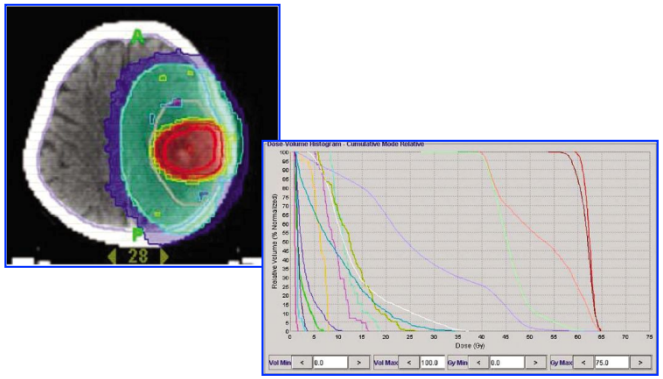
✓ GBM recurrence after treatment most often occurs as a local continuous growth within 2 to 3 cm from the border of the original lesion (90 %) but sometimes is represented by multiple and /or distant lesions (5%)





Background

✓ Treatment modality and type of recurrence in GB were often correlated with technical and dosimetric factors, in the related literature:



Sherriff J, Br J Radiol. 2013

Dobelbower MC,. J Med Imaging Radiat Oncol. 2011

Lee SW, Int J Radiat Oncol Biol Phys. 1999.

Sneed PK,. Int J Radiat Oncol Biol Phys. 1994

Minniti G, Radiother Oncol. 2010

✓ Some authors investigated the relationship beetween type of recurrence and biological factors (e.g.: MGMT methylation status and MIB-1 %)

Brandes AA, JCO 2009

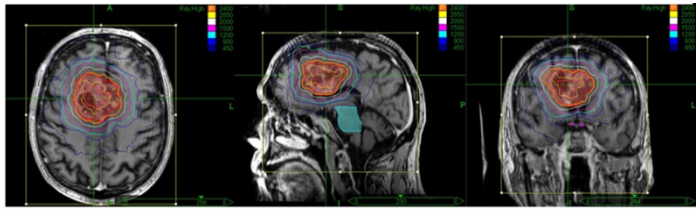
Uehara , Radiat. Oncol. 2012

Background

Our experience…

Three-dimensional conformal radiotherapy, temozolomide chemotherapy, and high-dose fractionated stereotactic boost in a protocol-driven, postoperative treatment schedule for high-grade gliomas

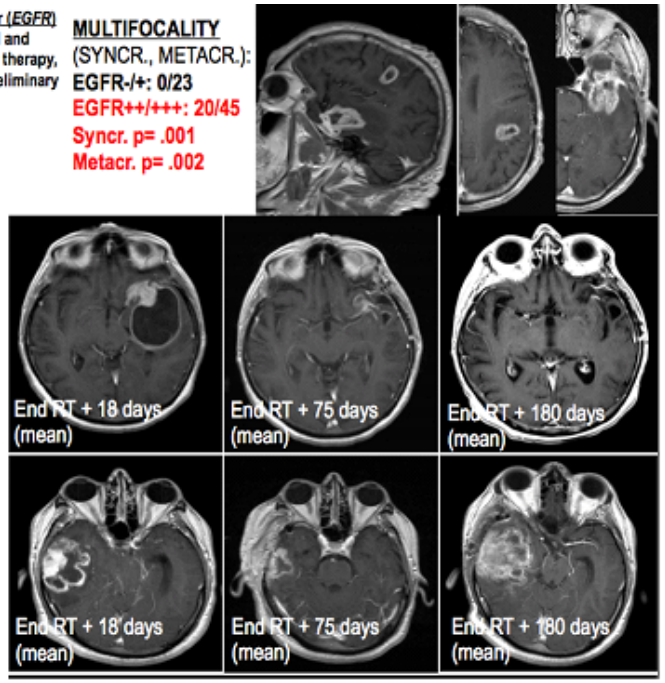
Luigi Pirtoli[1], Giovanni Rubino[2], Stefania Marsili[3], Giuseppe Oliveri[4], Marta Vannini[2], Paolo Tini[1], Clelia Miracco[5], and Riccardo Santoni[6]



Epidermal Growth Factor Receptor (*EGFR*) Expression correlates with clinical and pathological features, response to therapy, and survival in Glioblastoma. A preliminary report based on a patient series. (P. Tini, G. Rubino, S. Palumbo, A. Cerase, L. Pirtoli, C. Miracco, 2013, unpublished data).

68 pts, 2007➔ 2011;
IHC EGFR -/+: 23/68;
EGFR ++/+++: 45/68

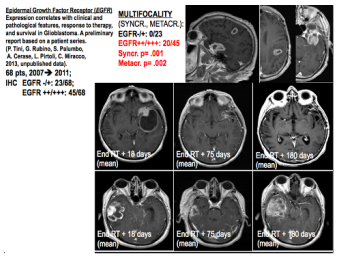
MULTIFOCALITY
(SYNCR., METACR.):
EGFR-/+: 0/23
EGFR++/+++: 20/45
Syncr. p= .001
Metacr. p= .002

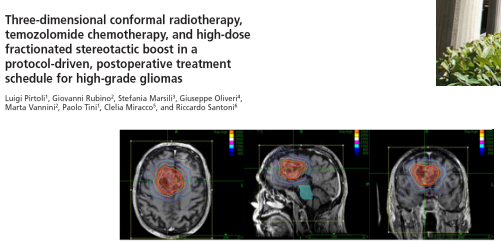


A subset of patients with less invasive disease could benefit by more aggressive treatment (dose >60 Gy)

EGFR expression levels seems to correlate with Uni/multifocality and peritumoral edema in GB patients

Aim



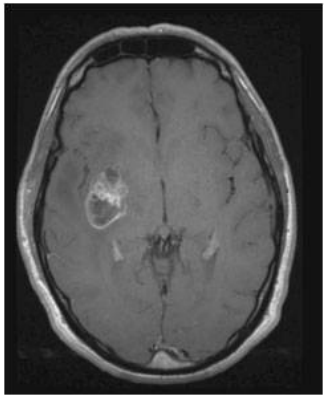


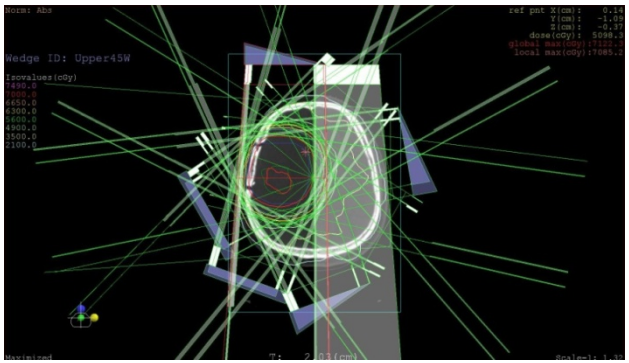
The aim of this study is **to find correlations between the type of recurrences after TMZ-RT** in patients treated at our institution and *EGFR expression*

Method and Materials

Retrospective and prospective analysis: *Patients with unifocal presentation were treated with radiotherapy plus temozolomide in the adjuvant setting between June '08 and October '12 and experienced recurrence disease during follow-up.*

Brain MRI (T1-weighted with gadolinum) *showing recurrence was co-registrated with original CT scan of RT planning:*





RT was delivered with ***3D-CRT technique or IMRT tecnique****: total dose (54-70Gy) with standard fractionation (1.8 -2Gy).*

Target delination*:* ***GTV : residual disease or surgical cavity (post.op T1-weighted MRI)***

CTV*: GTV plus 1,5-2 cm in cases >60 Gy* ***CTVboost*** *: GTV +0,5-1 cm*

Method and Materials

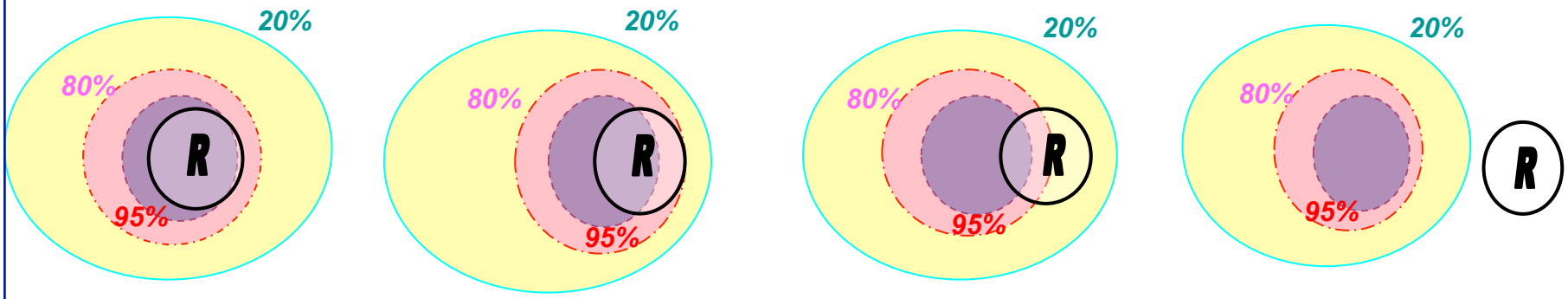
Classification Patterns of recurrence:

Central — *> 95% recurrence volume inside isodose 95% of prescription dose*

In-field — *> 95% recurrence volume inside isodose 80 % of prescription dose*

Marginal — *> 95% recurrence volume inside isodose 20% of prescription dose*

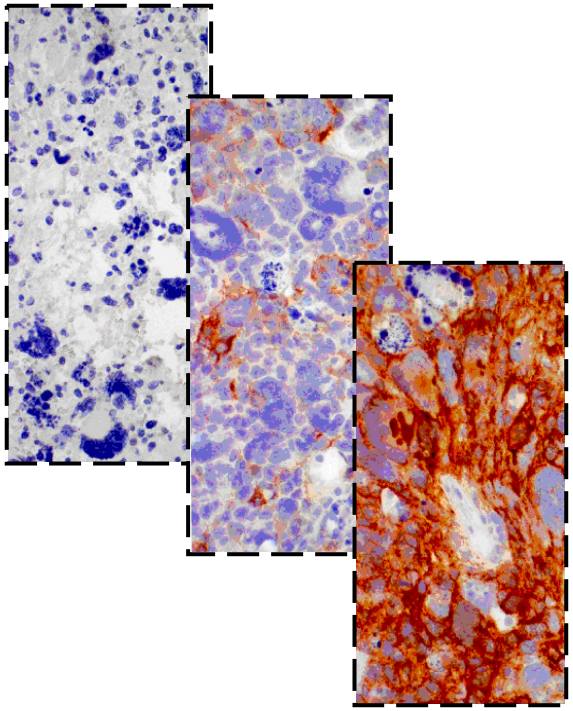
Distant — *Recurrence outside isodose 20% of prescription dose*



Method and Materials

EGFR espression score

✓ *A Neuropathologist evaluated EGFR expression on surgical samples by IHC :*



IHC Intensity + **% positive cells**

EGFR espression score

Low EGFR expression

High EGFR expression

Results

Clinical and pathological characteristics

Patients n°: 51

Follow-up (mean) : **11.2 months**

Age at diagnosis: **63 yrs** *(range 35-77)*

Extent of Surgery: **GRT** *in 20 patients vs* **SRT-biopsy** *in 31 patients*

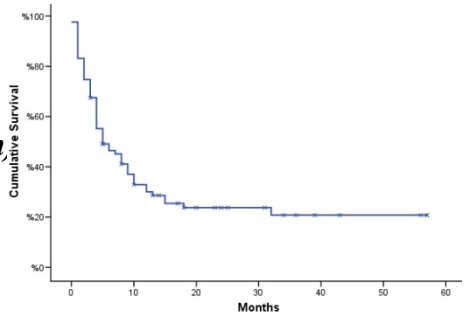
Pre-op Performance Status: **KPS 100-80** *in 32 pts vs* **KPS <70** *in 19 pts*

RT dose: *mean* **58,75 Gy** *(range 54 -70Gy)*

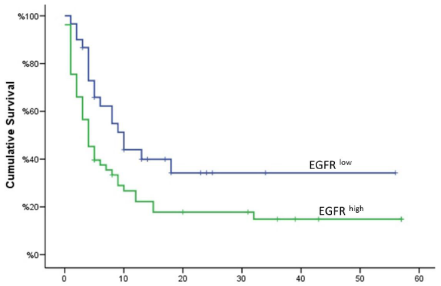
EGFR expression (in surgical samples): **Low EGFR** *in 18 pts vs* **High EGFR** *in 33 pts*

Overall Survival: **11 months** *(median)*

Time to progression: **6 months** *(median)*



Time to progression (EGFR subgroups):



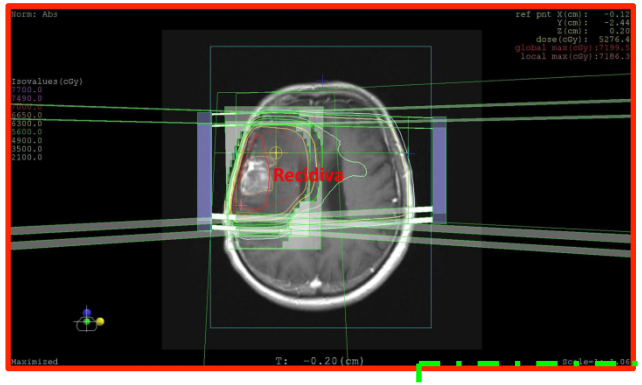
4 months *in HighEGFR vs* **17 months** *in LowEGFR*

p=0.01

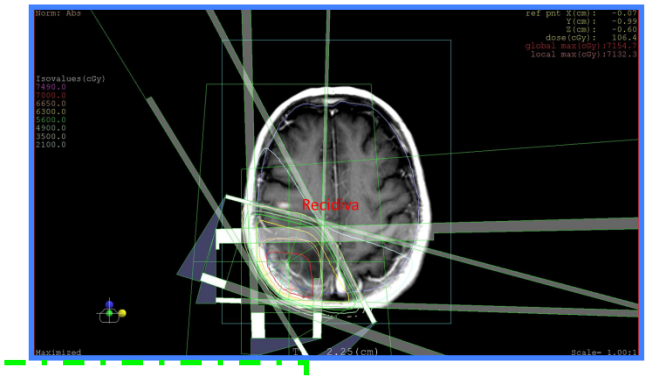
Results

Correlation EGFR - Patterns of recurrence

Type of recurrence	EGFR expression: Low	EGFR expression: High	Total
Central	11	5	16
In-field	4	12	16
Marginal	2	7	9
Distant	1	9	10
Total	18	33	51

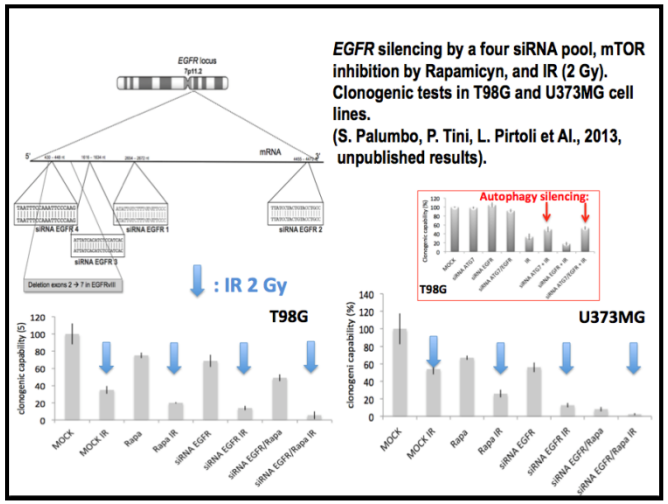


≠

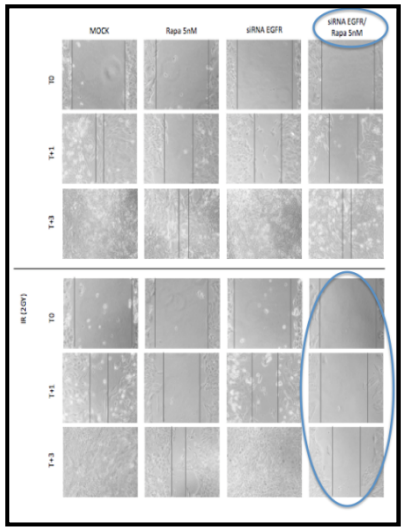


Fischer exact's test p=0.016

Discussion



EGFR silencing by a four siRNA pool, mTOR inhibition by Rapamicyn, and IR (2 Gy). Clonogenic tests in T98G and U373MG cell lines.
(S. Palumbo, P. Tini, L. Pirtoli et Al., 2013, unpublished results).

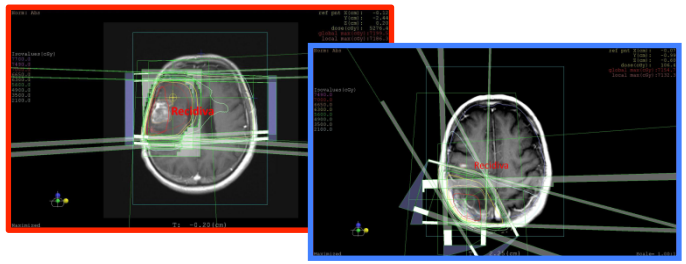


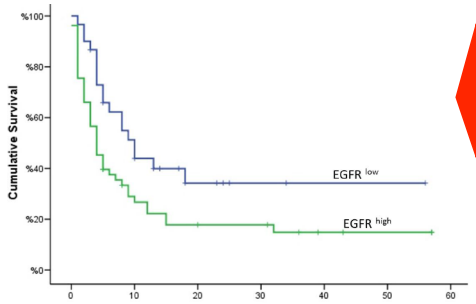
In vitro

Modulating EGFR espression

affects IR response and cell motility in cell lines

In vivo





Azienda Ospedaliera Universitaria Senese
Complesso Ospedaliero di Rilievo Nazionale e di Alta Specializzazione
Ospedale Santa Maria alle Scotte

Istituto Toscano Tumori

Conclusion

✓*Our results, if confirmed on a larger number of patients, seem to demonstrate that an overexpression of EGFR in GB patients could be a contra-indication to too narrow margins in delineating the clinical target volume around the tumor mass. On the other hand, dose escalation beyond 60 Gy in suitable cases coud be a reasonable choice, when there is a low EGFR expression.*

✓*Therefore, issues of total dose (and of fractionation) and of GTV-PTV volume expansion might be re-considered on the grounds of the biological characterization of glioblastoma.*

✓*Further biomolecular markers predictive of aggressiveness must be investigated in GB.*

Grazie per l'attenzione!!!

"L'ironia e l'intelligenza sono sorelle di sangue. "