RADIOTHERAPY FOR GLIOBLASTOMA MULTIFORME (GBM)

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INTRODUCTION

RADIOTHERAPY IN GBM

CONCLUSION

GBM

Multidisipline Approach :
Neurologist
Radiologist
Neurosurgery
patologist
Radiation Oncologist
Hemato Oncologist

TREATMENT :

- **Performance status**
- **Tumor location**
- **Histological grade**

Standard treatment for glioblastoma is surgery, followed by concomitant and adjuvant chemo-radiotherapy with temozolamid (TMZ).

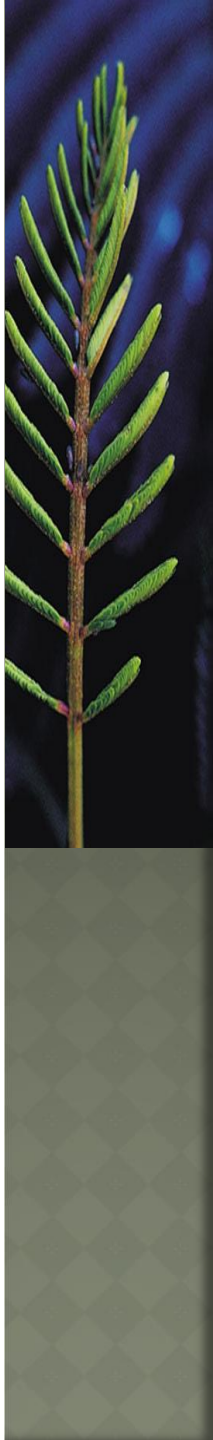
Radiotherapy is a part of the multidisciplinary management for malignant gliomas, with proven efficacy in randomized control trials.

The use of radiotherapy was based on two randomized trials conducted in the 1970 s that showed extension in survival.

Walkel et al (303 px): post S
with suportive, median survival 14 weeks
with Carmustine(BCNU), median survival 18,5 weeks
with RT , median survival 35 weeks
with RT + BCNU, median survival 34,5 weeks

Another trial of 118 patients also found a benefit in median survival with radiotherapy following surgery compared to no radiotherapy (10,8 vs 5,2 months)

Multi trials → adjuvat RT directed to residual microscopis and gross disease improving local control and survival after Surgery.



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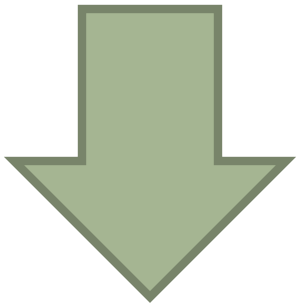
For radiation oncologists, GBM are very exciting topic, challenging but also a frustrating one. In order to improve local control, and survival

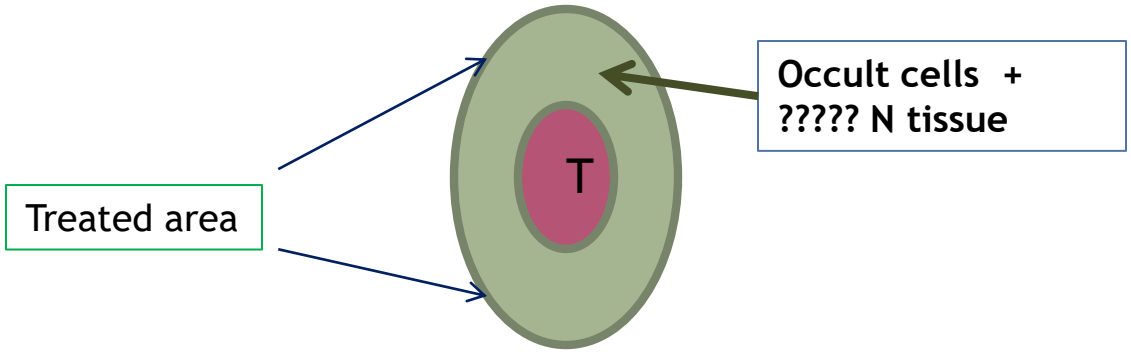


RADIATION GOAL :

- Determine what region of brain to be treated. Higher dose of RT - smaller chance of recurrent

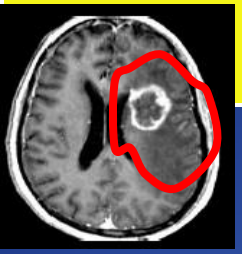
PROBLEMS :

- Just targeting visible tumor cell is NOT enough.....
- Must also kill " (radiologically) occult cancer cell surrounding tumor "
- Minimal number of normal cells ⟶ minimize loss of brain function.



Prof.P.K.Julka. Target delineation in Glioma. Perez and Brady. Principle and Practice of Radiation Oncology.2013.Yavas Guler.The role radiotherapy in the treatment of HGGs. 2017.

WHAT CAN WE DO TO ACHIEVE THE PRECISE TARGET AND TO REDUCE TOXICITY

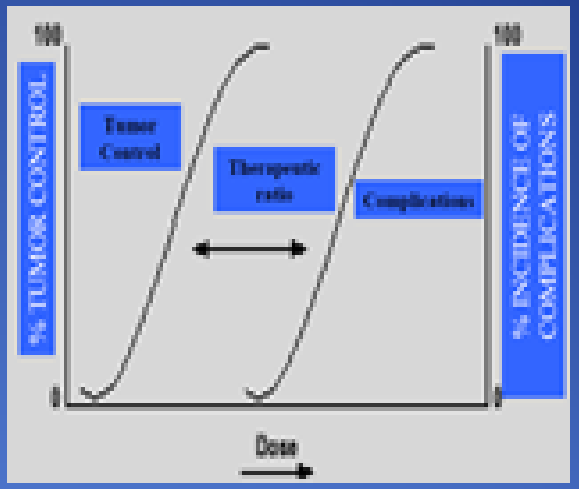


"High tech" imaging

HOW TO DETERMINE THE TARGET

HOW NOT TO MISS THE TARGET

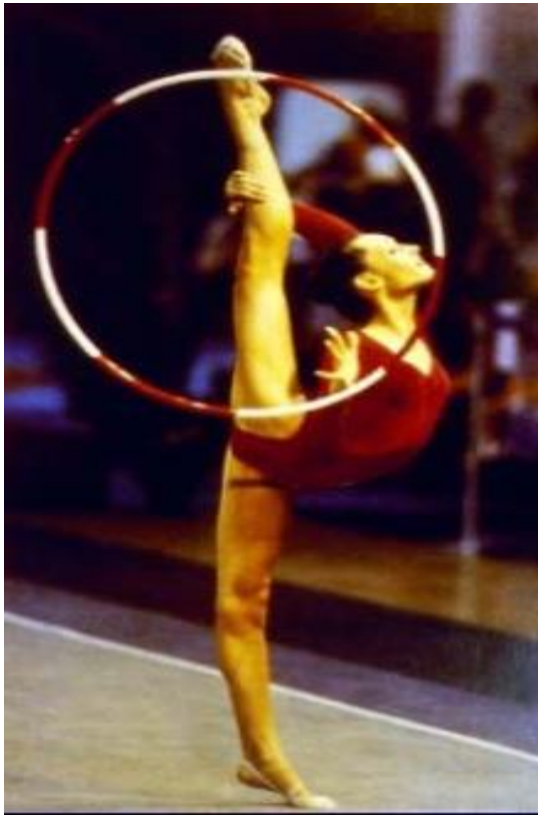
"High tech" delivery system



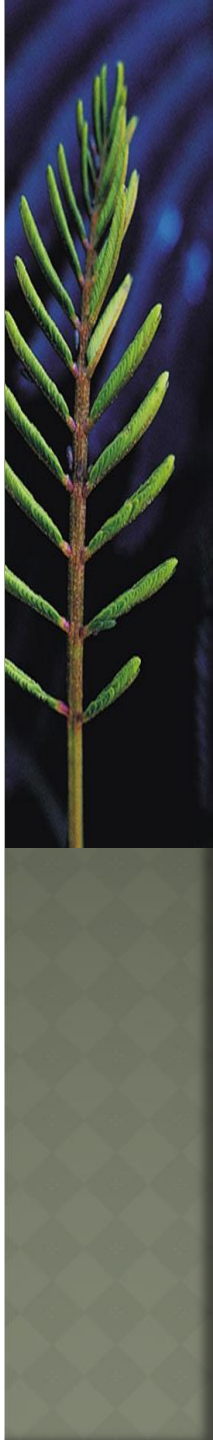
Improve therapeutic ratio

Management

Top skill



Perfect balance



STRATEGY TO IMPROVE RT

BIOLOGICAL APPROACH

DRUG COMBINATION
FRACTIONATION
HIGH LET

Improvement of radiosensitivity

PHYSICAL APPROACH

CT based RTPS
3 D, IMRT, IGRT/Rapid Arc
STEREOTACTIC

Improvement of dose distribution

ADVANCEMENT OF RT

LOCAL CONTROL → **SURVIVAL**

QOL

TARGET AND DOSIS

INCLUDE EDEMA ???

Little agreement..... Definition of CTV

Leibel and phillips

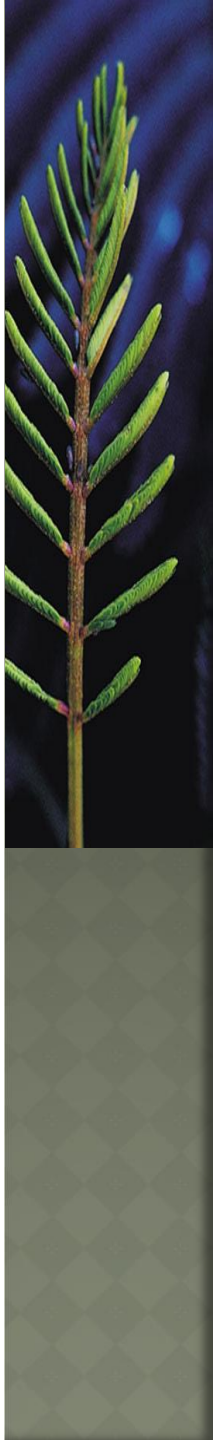
RTOG : post op peritumoral edema plus 2 cm

→ Shrinking Field Approach/ Cone down technique

I . Peritumoral edema plus 2 cm (defined from T2 or FLAIR MRI), prescribe to 46 Gy.
II. Boost , (T1 enhancing GTV) + 2,5 cm prescribe to 60 Gy

The rationale for including peritumoral edema is that such areas are believe to contain high concentrations of tumor cell

Yavas et al.J Radiol Radiat Ther 5(2): 1070 (2017)



EORTC : residual tumor and / resection cavity plus 2 cm without the intentional inclusion of peritumoral edema.

Single phase technique. Doses 60 Gy

Conventional fractionation...1,8-2 Gy/fr

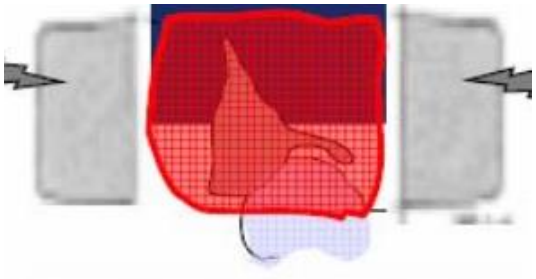
Yavas et al.J Radiol Radiat Ther 5(2): 1070 (2017)

Poor and Elderly patients ???

Hypofractionated RT : 34 Gy/10fr or 40,05 Gy/15 fr or 50 Gy/20fr , completing treatment in 2-4 week

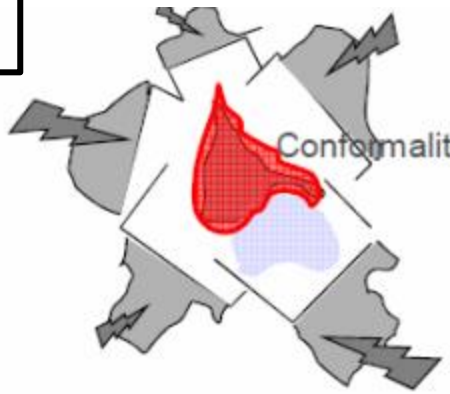
Hypofr has similar efficacy for survival as compare to conventional

RADIOTHERAPY TECHNIQUE



Conventional radiotherapy

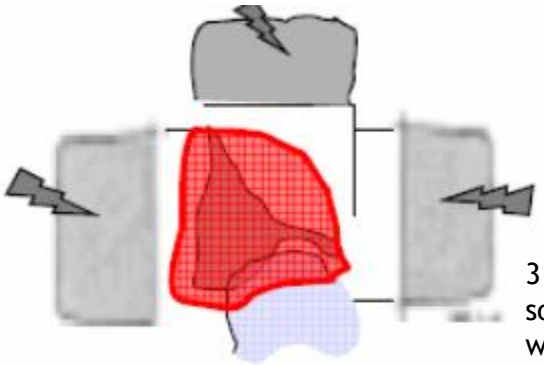
2 D Technique



Intensity modulated radiotherapy

Highly conformal radiation technique, such as IMRT offer the potential to reduce the spectrum side effects associated with RT by decreasing the volume of normal tissue receiving RT

- **Improves precision/accuracy**



3 DCRT utilizes CT-based treatment planning with dosimetric software to create composite treatment plans. Fusion of planning CT with MRI is extremely helpful in assisting with target definitio

GRO 3D-conformal radiotherapy

PK Julka. Dept of Radiotherapy and Oncology AIIMS . New Delhi

Advanced Techniques : SRS and SRT

- Delivery of high dose of radiation in a **single fraction** to small and precisely delineated intracranial lession → **S**tereotactic **R**adio**S**urgery (SRS) .

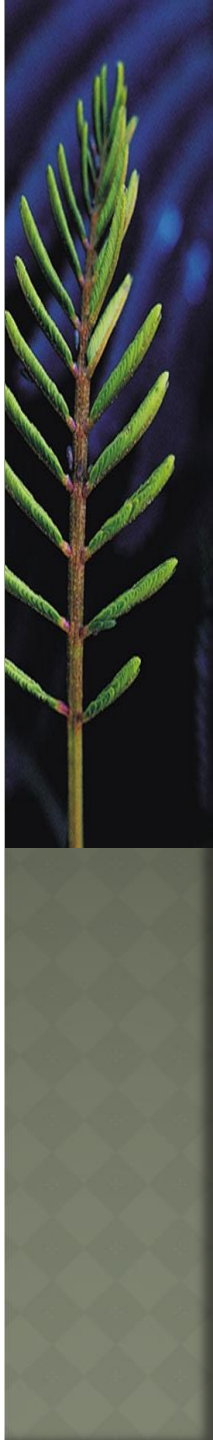
- Delivery of high dose of radiation in a **multiple fraction** to small and precisely delineated intracranial lession → **S**tereotactic **R**adio**T**herapy (SRT) .

RAPID ARC TECHNOLOGY → Form volumetric modulated arc therapy (VMAT)

Heavy particle RT

BRACHYTHERAPY

Yavas et al.J Radiol Radiat Ther 5(2): 1070 (2017)



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LOCAL CONTROL → **SURVIVAL**

QOL

Drug combination

TEMOZOLAMID (TMZ) + RT

Stupp Trial:
Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

Patients characteristic

- Newly diagnosed
- Histologically confirmed glioblastoma
- WHO PS 0-2

Radiotherapy alone
(Fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy)

RT+TMZ (TMZ 75 mg/m2 per day 7 days per week, during RT and continue with 6 cycles of TMZ 150-200mg/m2 for 5 days per 28 days)

- primary end point was overall survival
- secondary end points were progression-free survival, safety,
  and the quality of life

N Engl J Med 352;10 www.nejm.org march 10, 2005
The new england journal *of* medicine

SCHEDULE

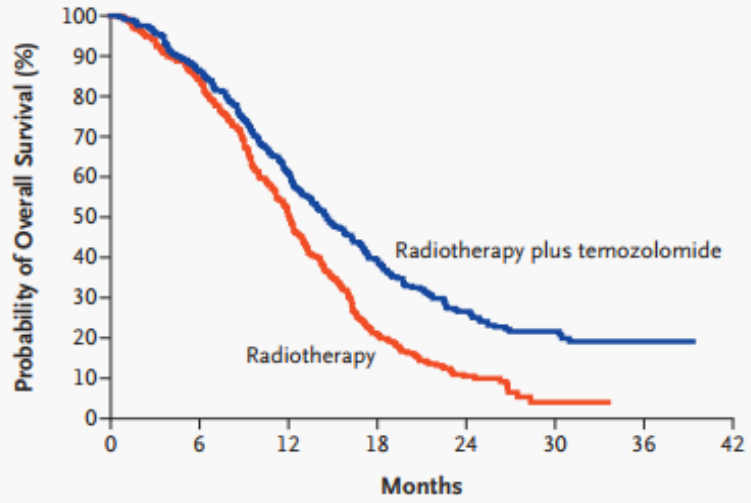
= RT

TMZ : 75 mg/m2

ADJ TMZ

Radiotherapy Plus Concomitant And Adjuvant Temozolomide For Glioblastoma Has The Survival Benefit

Overall Survival



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

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).

	Median OS	2 year survival rate
RT+TMZ	14.6 months	26.5%
RT alone	12.1 months	10.4%

P<0.001

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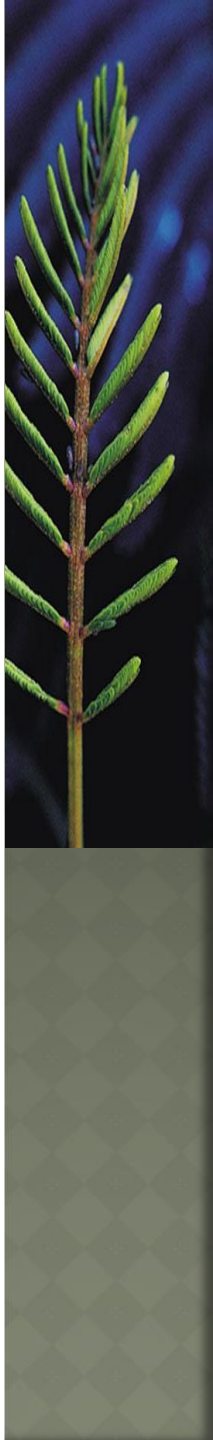


Radiotherapy Plus Concomitant And Adjuvant Temozolomide For Glioblastoma Also Prolonged The Progression Free Survival

PFS

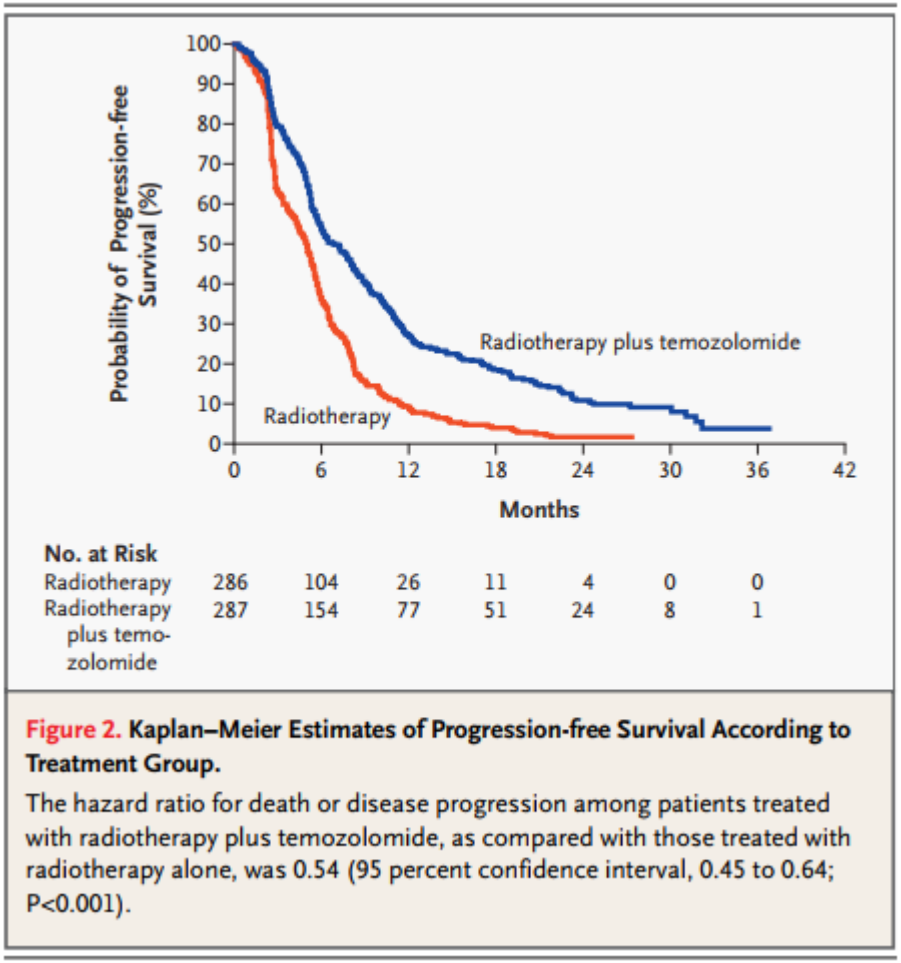


Figure 2. Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.

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).

Median PFS:
RT+TMZ: 6.9 months
RT alone: 5.0 months
HR: 0.54 [95 percent confidenc
interval, 0.45 to 0.64]

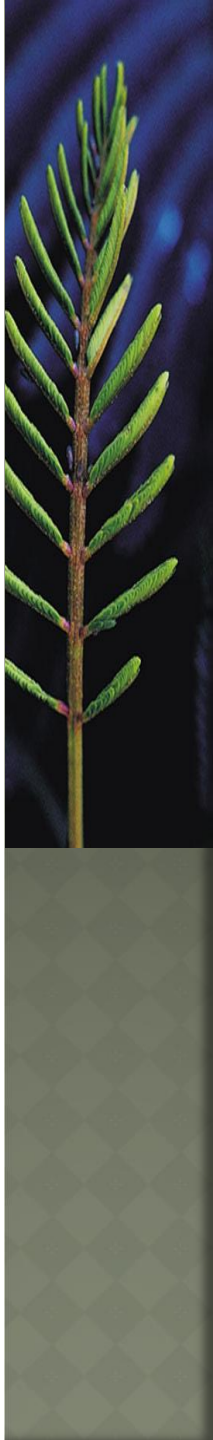
P<0.001

N Engl J Med 352;10 www.nejm.org march 10, 2005
The new england journal *of* medicine

Grade 3 – 4 Hematologic Toxic Effects[1]

Toxic Effect	Concomitant Temozolomide	Adjuvant Temozolomide	Entire Study Period
Leukopenia	7 (2)	11 (5)	20 (7)
Neutropenia	12 (4)	9 (4)	21 (7)
Thrombocytopenia	9 (3)	24 (11)	33 (12)
Anemia	19 (7)	2 (1)	4 (1)
Any	19 (7)	32 (14)	46 (16)

References: **1.** Stupp R et al. *N Engl J Med*. 2005;352:987–996

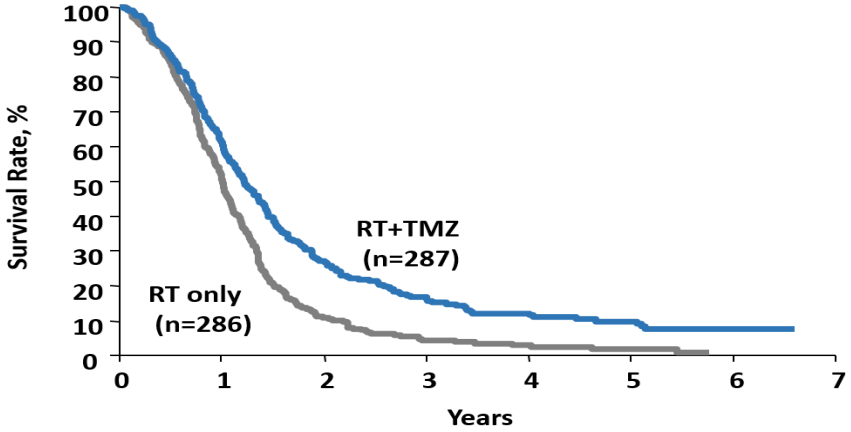


Temozolomide: consistent long-term survival benefit with RT + Temozolomide in GBM

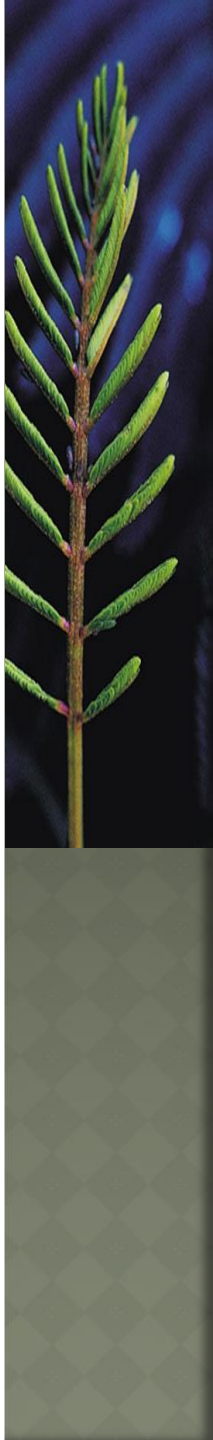
5 Year Analysis of RT + concomitant and adjuvant Temozolomide vs RT alone

Survival Outcomes[1]

Risk of death reduced by 37% in 5Y analysis of RT + temozolomide

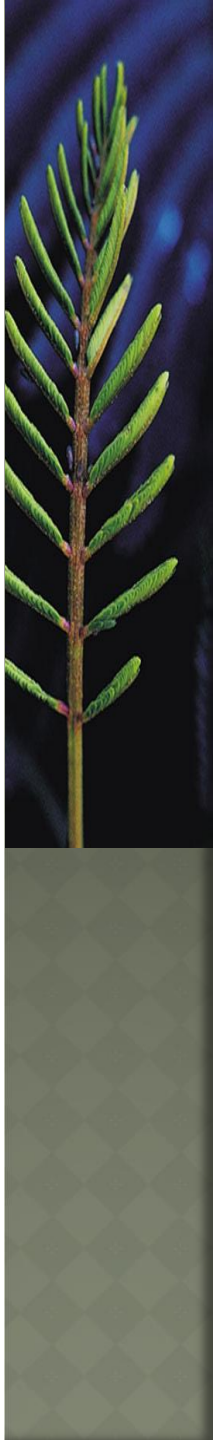


Overall Survival, %		
	RT (n=286)	RT+TMZ (n=287)
2 years	10.9	27.2
3 years	4.4	16.0
4 years	3.0	12.1
5 years	1.9	9.8
Hazard ratio	0.63 [95% CI.,0.53−0.75] *P*<0.0001	



Overall survival	TMZ + RT	VS	RT alone
1 year	27%		11%
5 years	10%		2%
MGMT Methylation (+) 2 years	49%		24%
MGMT Methylation (-) 2 years	15%		2%

- Altwairgi et al. Management & Treatment Recommendations for WHO gr. III & IV Glioma. IJHS II, July-August; 2017



Toxicities of radiation therapy

Related :

1. Radiation volume.

2. Total doses.

3. Dose perfraction

4. Combination with Chemotherapy

Nausea, vomiting, Hairloss, fatique, alopecia, erythema, headaches, seizure, weakness, radiation necrosis, endocrine dysfunction, and radiation induced neoplasma.

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Faculty of Medicine Airlangga University/ Dr. Soetomo General Academic Hospital. SURABAYA

EBRT :

3 LINAC

1 COBALT-60

BRACHYTHERAPY

High Dose Rate
Ir192 (IGBT/3-D)

Radiation Treatment Planning System (RTPS

simulator:
Conventional
CT-SIM

dosimetri

Mould immobilization

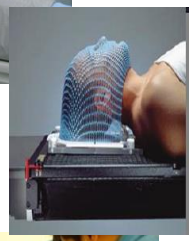
2 D/ 3 D - CRT

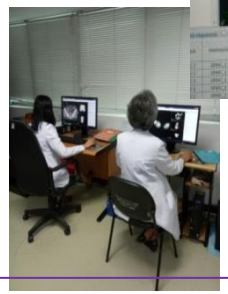
IMRT

As a referral hospital for East Indonesia and national

RT PROCESS

Immobilization + CT-Plan



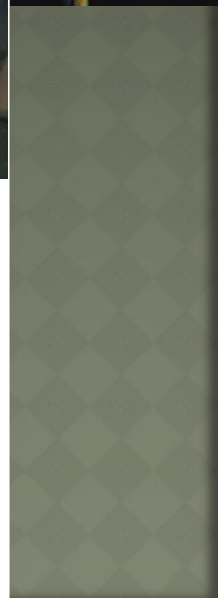


Radiation Treatment Planning

Verification

Treatment

CONSULTATION/follow up



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GBM is challenging for multidisciplinary team to obtain better prognosis and prolong survival.

The combination of development of neuro-imaging, surgical technique, radiation technique, newer cytotoxic for better tomorrow as clinical trials of various modalities of treatment continous.

TEAM WORK

RT TEAM

- **RADIATION ONCOLOGIST (RO)**
- **MEDICAL PHYCISIST (MP)**
- **DOSIMETRIST**
- **RADIOTHERAPY TECHNOLOGIST (RTT)**
- **NURSE ONCOLOGIST**

And

- **OTHER ONCOLOGIST (neurologist, neurosurgeon, radiologist, hemato-oncologist, ect)**
- **NUTRITION**
- **REHABILITATION**
- **SOCIAL WORKER**

THANK YOU