PTCOG 47
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Hyperfractionated concomitant boost proton radiotherapy for supratentorial glioblastoma multiforme

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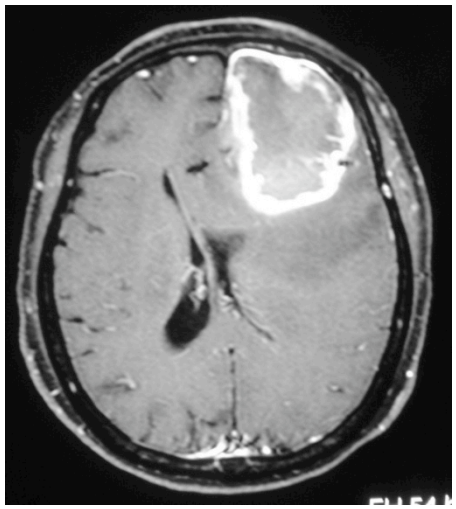
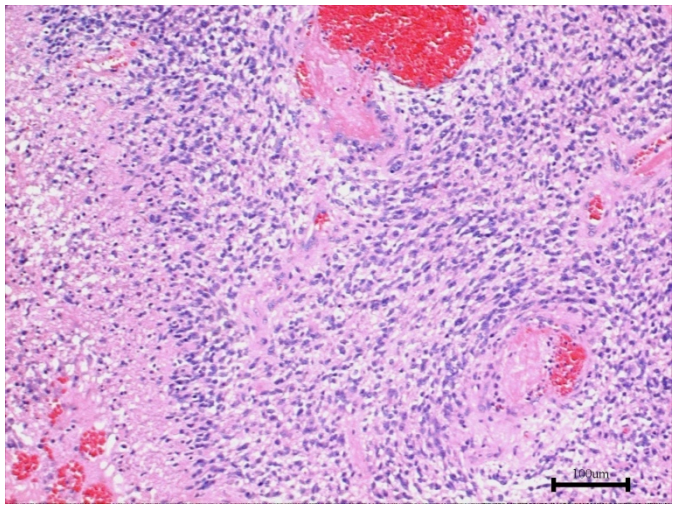
Glioblastoma Multiforme





Poorly differentiated neoplastic tumor with vascular proliferation and necrosis. Prominent proliferation with a MIB-1 positive index of 15-20 % or more.

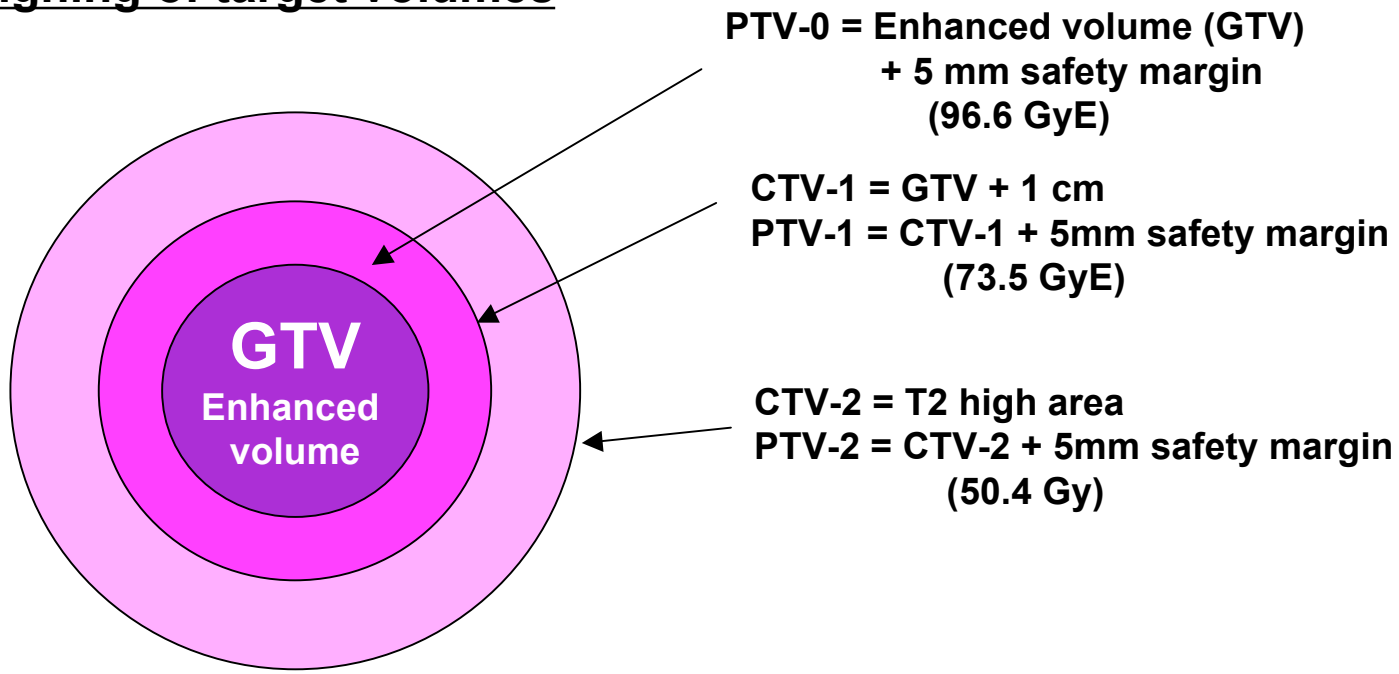
		2-year S/So	MST
Fitzek (*J Neurosurg, 1999*)	90 GyE	34.0%	20.0 m
Stupp (*New Eng J Med, 2005*)	60 Gy + TMZ	26.5%	14.6 m
Tanaka (*Lancet Oncol, 2005*)	80 - 90 Gy	38.4 %	16.2 m
JBTR (*2000-2003*)	60 Gy	21.2 %	12.4 m

Protocol-1

Eligible criteria

- Newly diagnosed supratentorial GBM.
- Age between 20 and 80.
- Visible enhanced residual tumor on MRI taken within 72 hours after surgery.
- Diameter of the enhanced area before radiotherapy is 4 cm or less.
- KPS is 70 % or more.
- Enhanced area does not reach to the brain stem, hypothalamus or thalamus.

Designing of target volumes

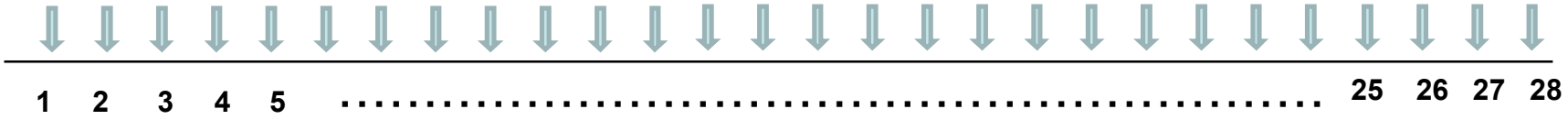


Protocol-2

In the morning:

PTV-2 : X-ray: 50.4 Gy / 28 fractions

1.8 Gy/frac



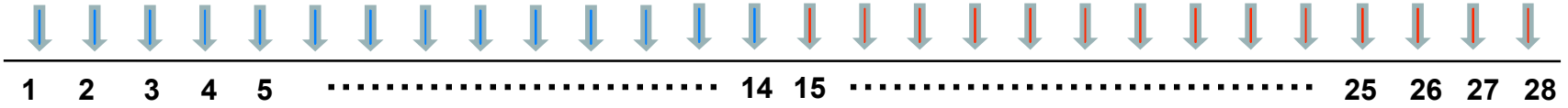
More than 6 hours later:

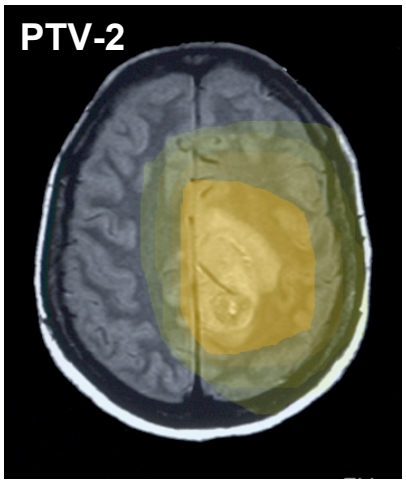
PTV-1 : Proton: 23.1 GyE / 14 frac

PTV-0 : Proton: 23.1 GyE / 14 frac

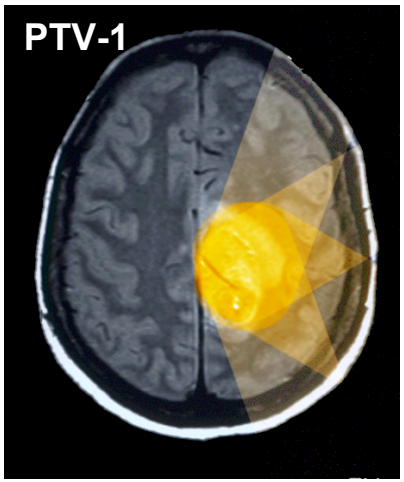
1.65 GyE/frac

1.65 GyE/frac

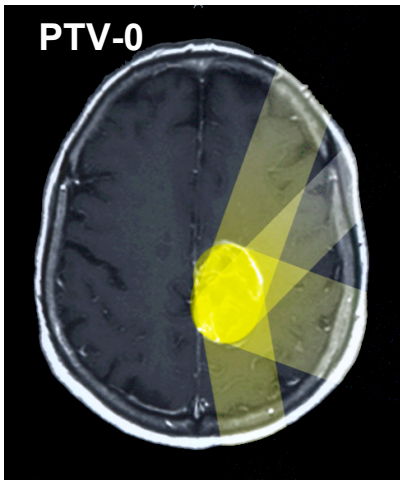




50.4 Gy (x-ray)



73.5 GyE



96.6 GyE

List of Patients

No	Age/Sex	KPS	Location	Surgery	Preope T.V.	MIB-1(%)	p53(%)
1	71/M	80%	Lt. Temporal	Subtotal	18×28×20	30.8	38.9
2	55/M	80%	Rt. Parietal	Partial	40×30×25	23.0	3.0
3	54/M	70%	Lt. Parietal	Partial	50×50×45	34.0	0.4
4	55/M	90%	Rt. Temporal	Partial	40×30×25	23.7	10.5
5	31/M	80%	Lt. Frontal	Partial	60×50×45	32.4	0
6	61/M	80%			×35	17.2	59.0
7	45/M	80%			×27	29.6	52.5
8	63/F	70%			×45	26.2	2
9	46/F	70%			×45	20.2	4.6
10	62/F	90%			6×58	45.5	0
11	56/M	80%	Rt. Occipital	Partial	50×50×53	---	---
12	76/M	70%	Rt. Temporal	Subtotal	41×46×58	15.9	11.6
13	76/F	70%	Lt. Temporal	Subtotal	70×50×60	27.6	2.1
14	49/F	90%	Lt. Parietal	Subtotal	52×50×50	3.8	41.2
15	65/F	70%	Rt. Frontal	Subtotal	33×33×25	7.4	19.5
16	59/M	80%	Rt. Temporal	Partial	60×48×48	15.4	2.6
17	31/M	80%	Rt. Frontal	Partial	52×50×50	36.7	3.7
18	46/F	90%	Rt. Frontal	Subtotal	52×50×50	7.9	0

Age: 55.6 (31-76)

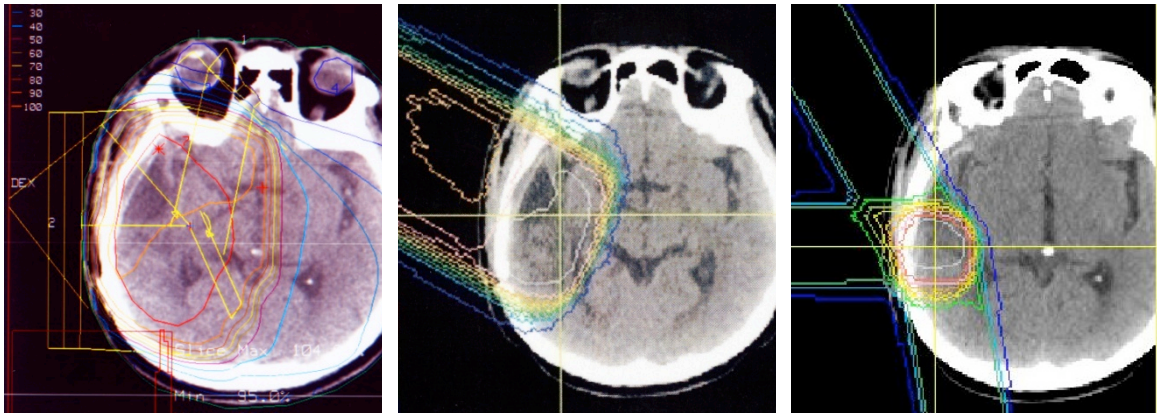
M / F: 11 / 7

KPS: 78% (60-90)

MIB-1: 23.2 % (3.8 – 45.5)

No. 6: 61/M
Rt. Temporal GBM

PTV-2 (x-ray) PTV-1 PTV-0



Surgery
(2004.04.25)

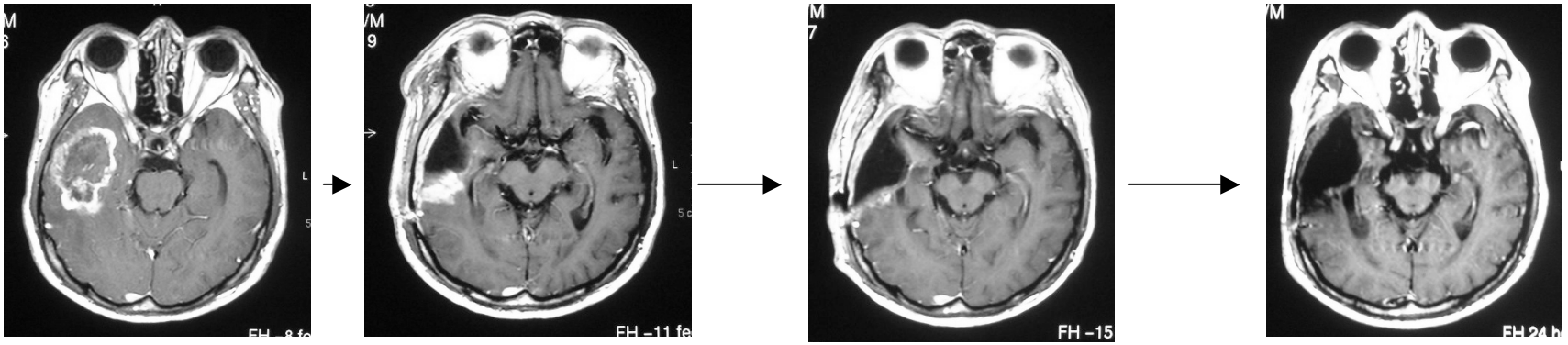
Proton + x-ray
(96.6 GyE)

32 months after surgery

KPS 80%

ACNU **ACNU**

KPS 100%



2004.04 **2004.05** **2004.07** **2007.01**

Toxicity in 18 cases

Skin: In one patient (55/M), local infection occurred after this treatment where an Ommaya reservoir was implanted. Skin graft was placed after debridement.

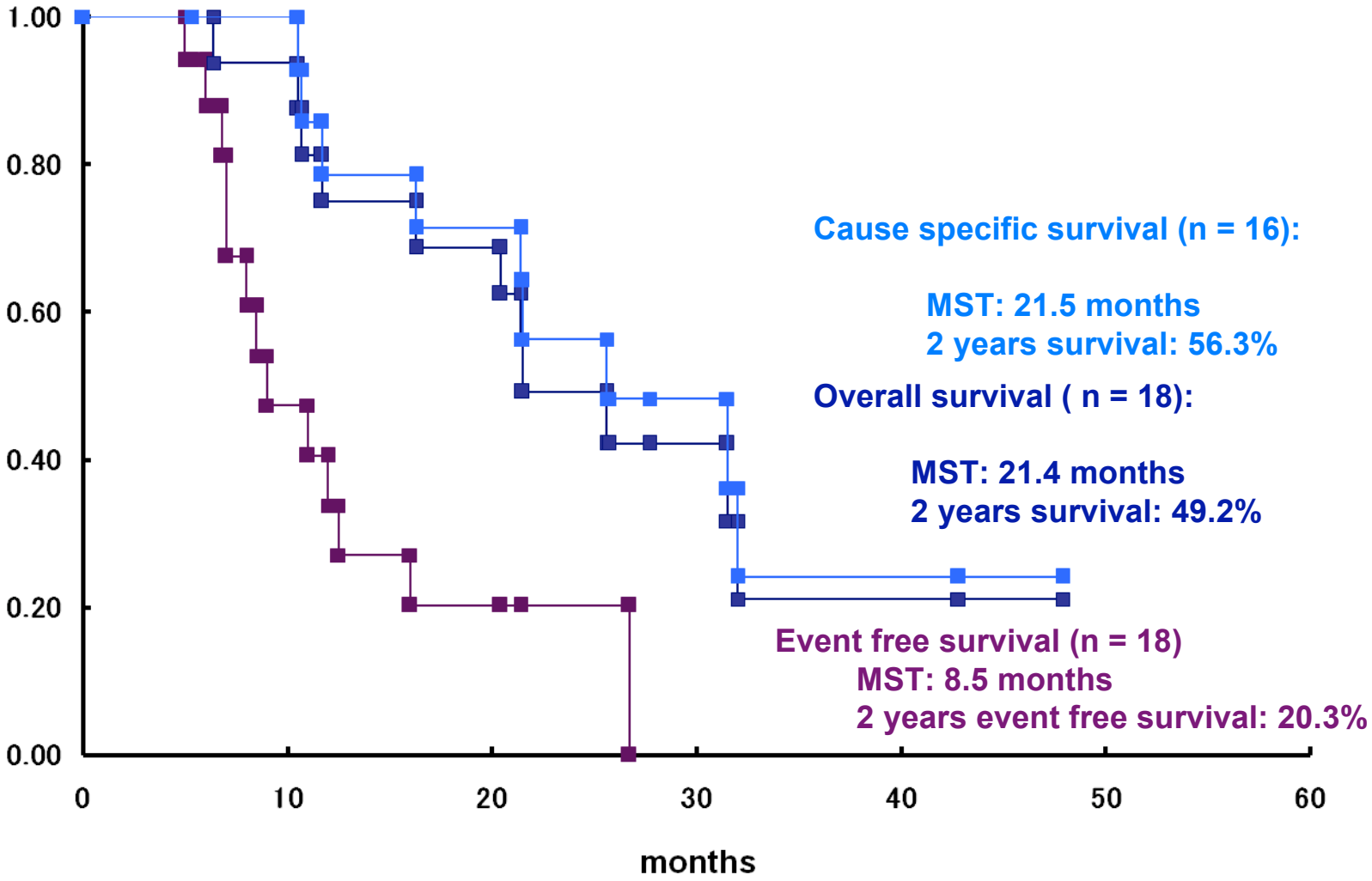
CNS: Only one case was diagnosed as radiation necrosis on MRI and SPECT

Two patients died of diseases that were not related to tumor recurrence.

One patient (76/M) died of respiratory insufficiency and consciousness disturbance 20.4 months after initial surgery. Pulmonary embolism was strongly suspected. His KPS before RT was 70 %. There was no evidence of tumor recurrence on the last MRI.

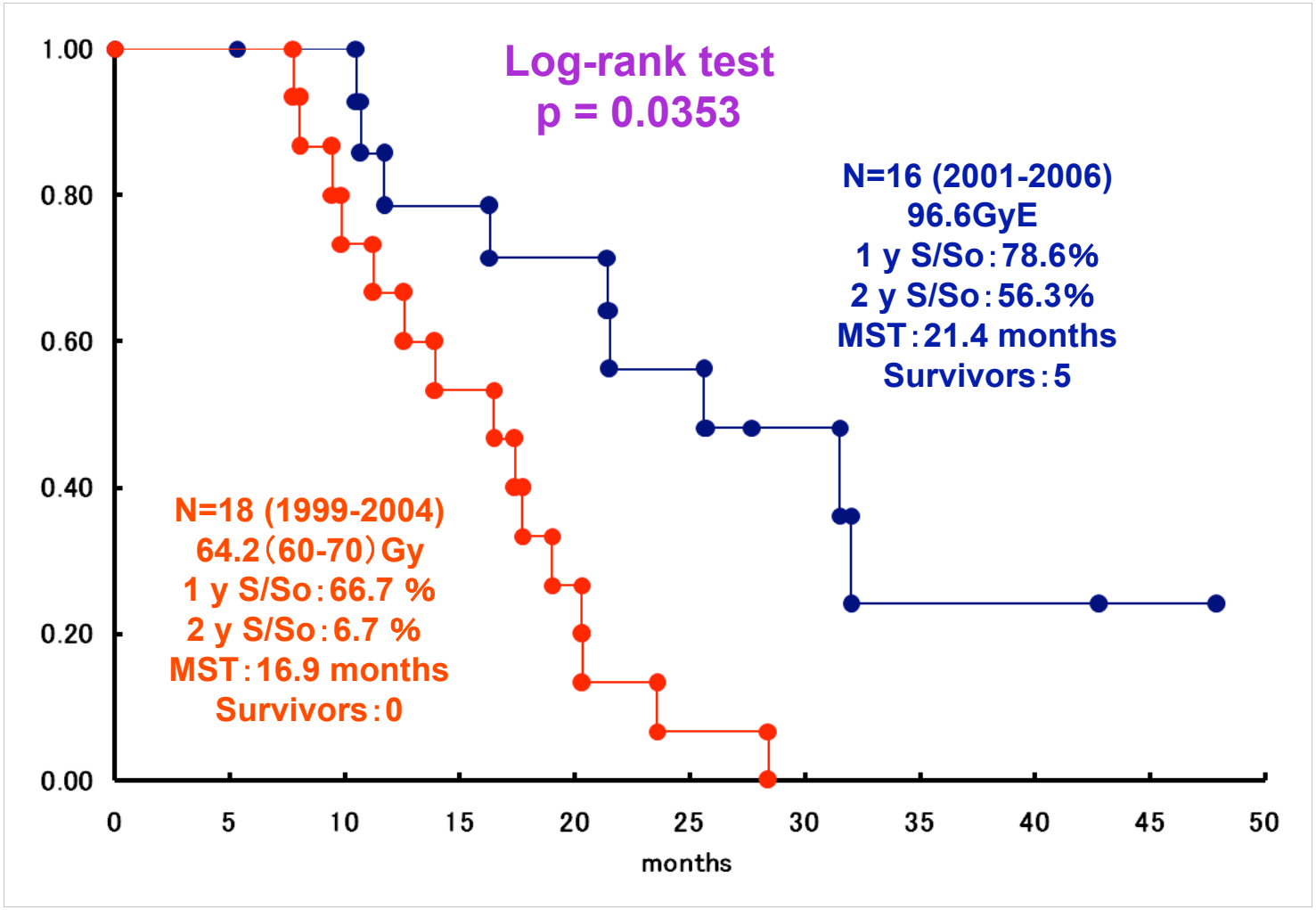
The other patient (59/M) died of sepsis following cholelithiasis with cholelcystitis and panperitonitis 6.4 months after initial surgery. He had moderate diabetes. His KPS before RT was 70 %. There was no evidence of tumor recurrence on the last MRI.

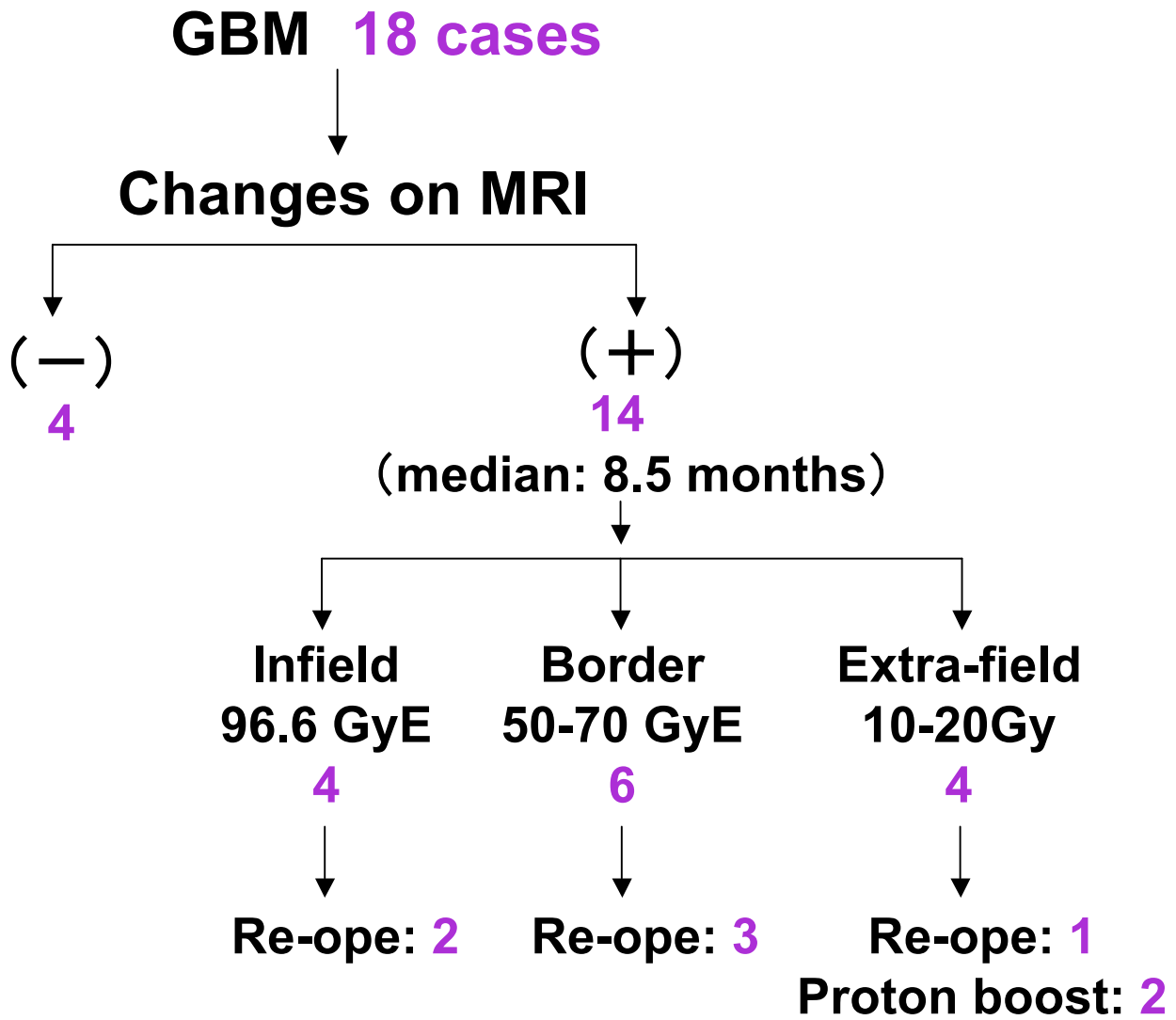
Survival curves



Cause specific survival

historical comparison

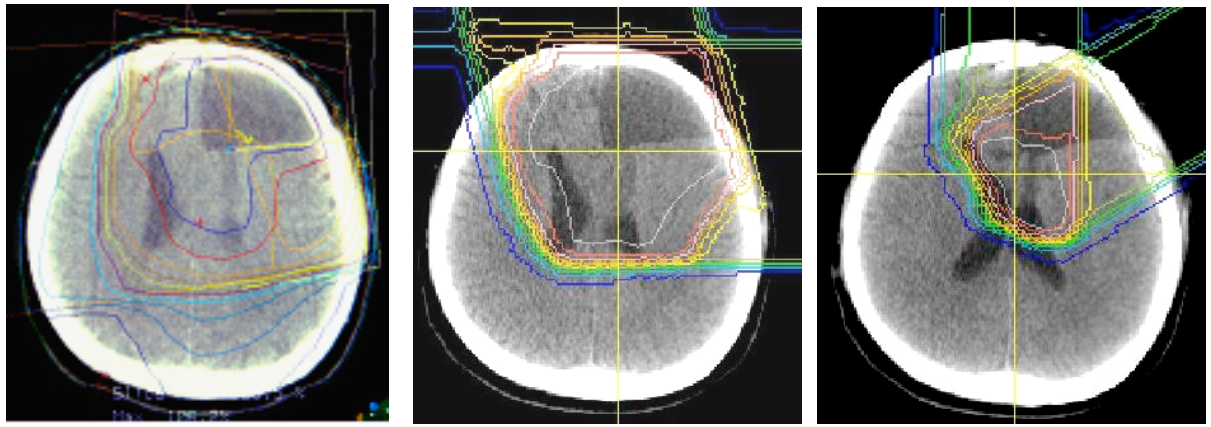




6 cases underwent reoperation or biopsy 14 to 210 days after this protocol is finished due to MRI changes.

Case 5: 31/M
Lt. frontal GBM

PTV-2 (X-ray) PTV-1 PTV-0



Surgery
(2003.10.31)

X-ray and Proton
(96.6 GyE)

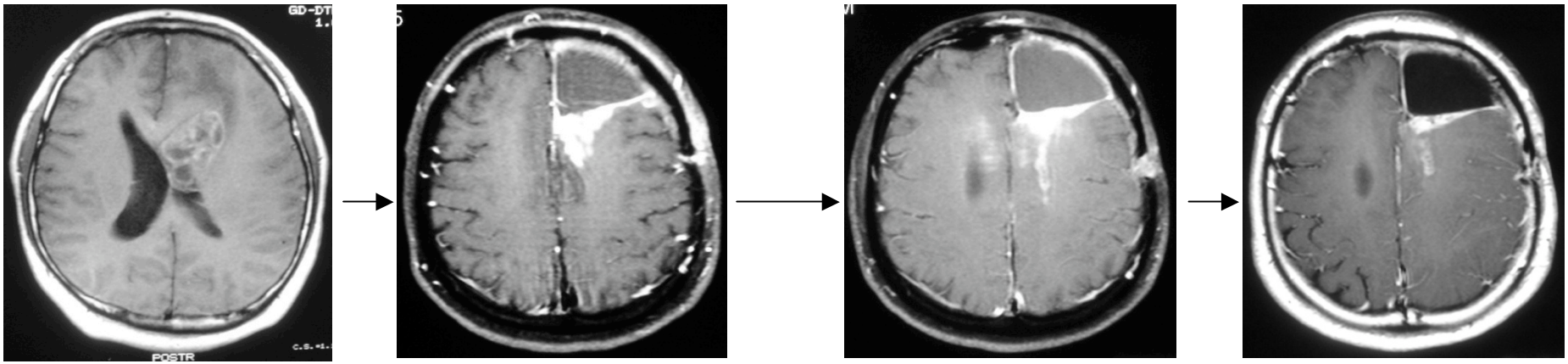
Biopsy
(2004.02.03)

12/2 — 1/20

KPS 90%

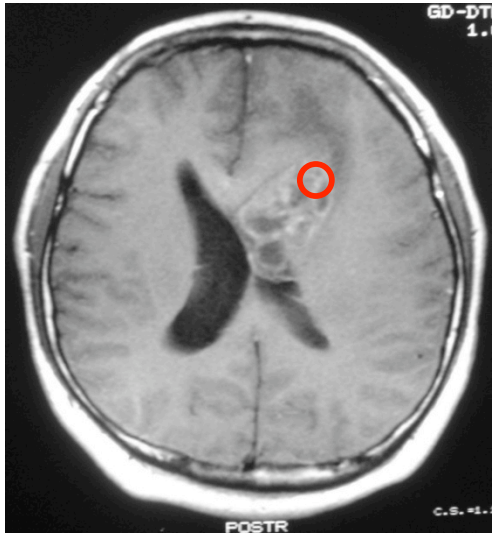
ACNU **ACNU**

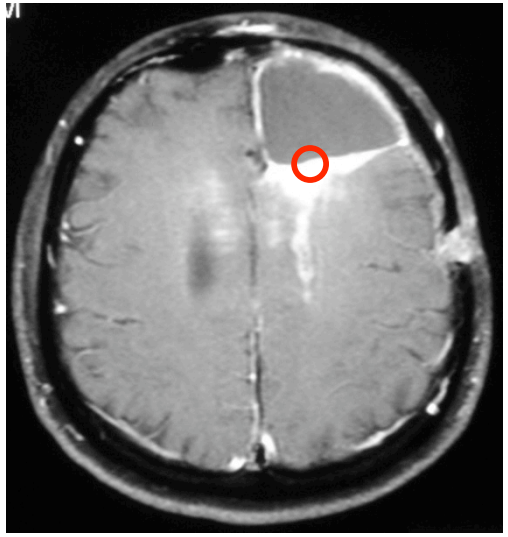
KPS 90%



2003.10 **2003.11** **2004.02** **2004.06**

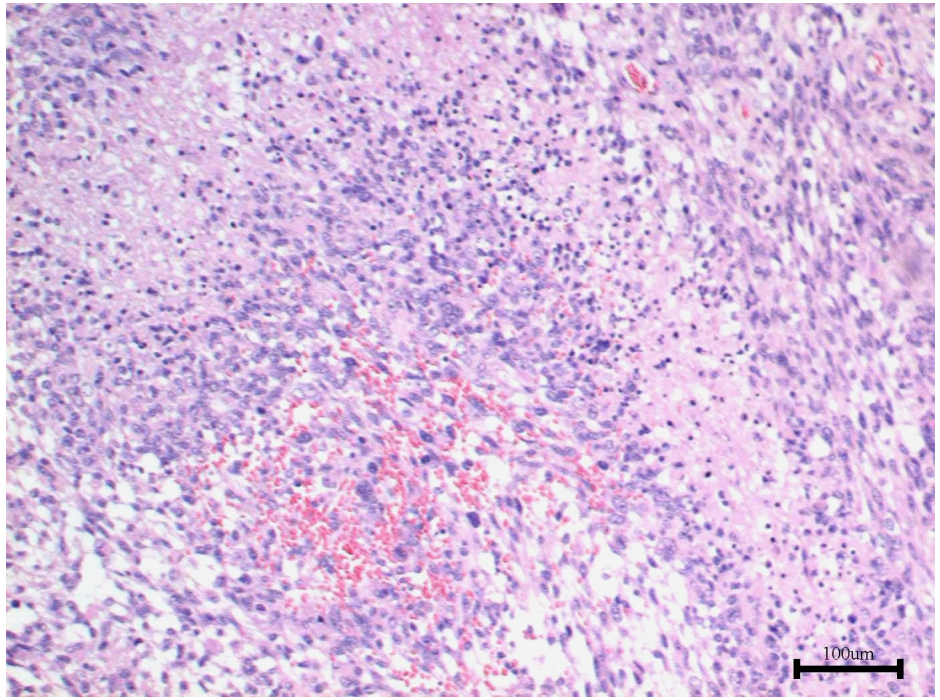
HE x100

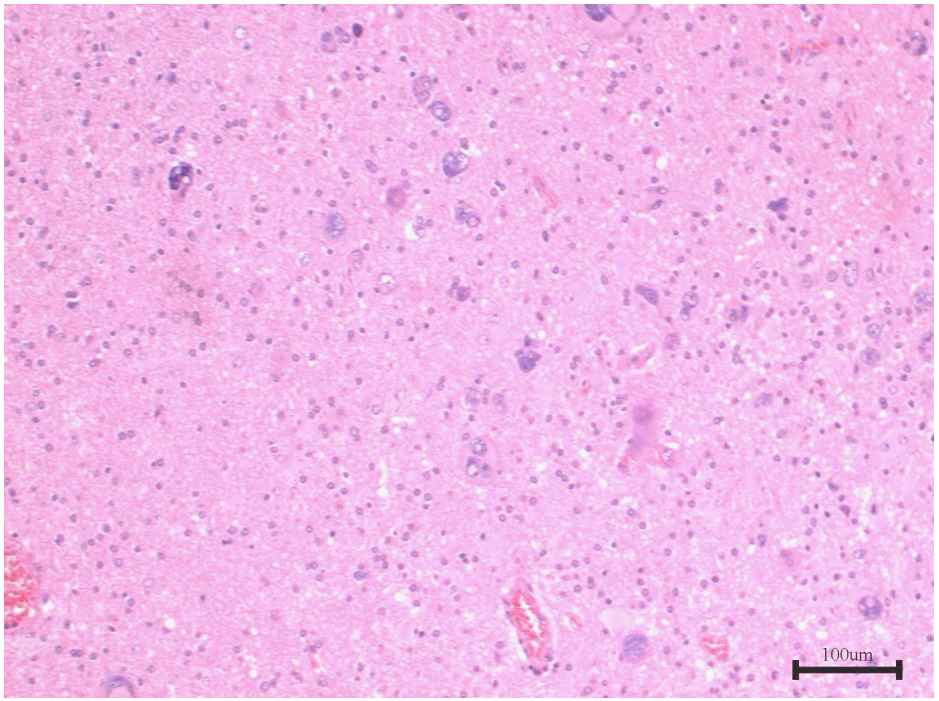




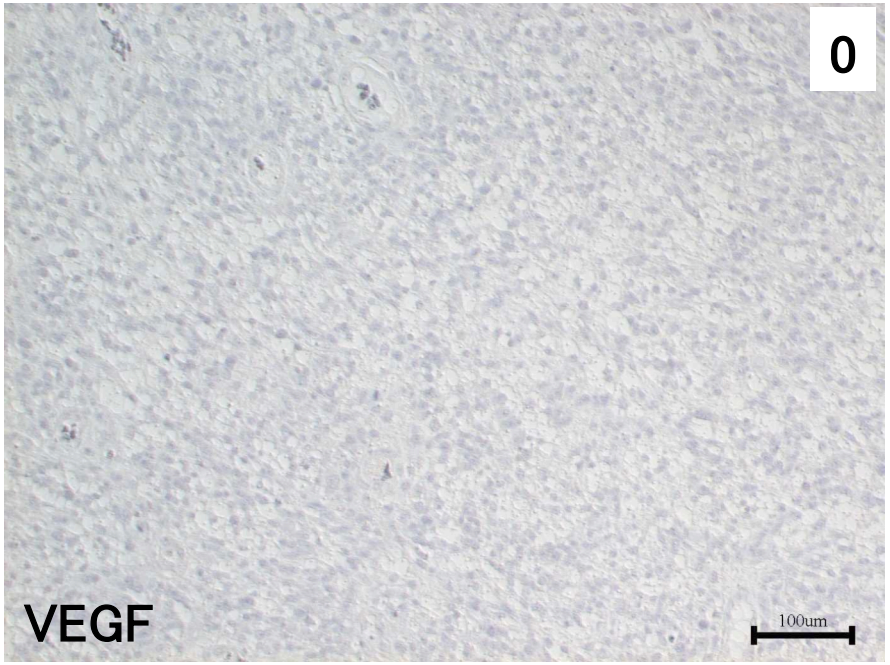
2003.10

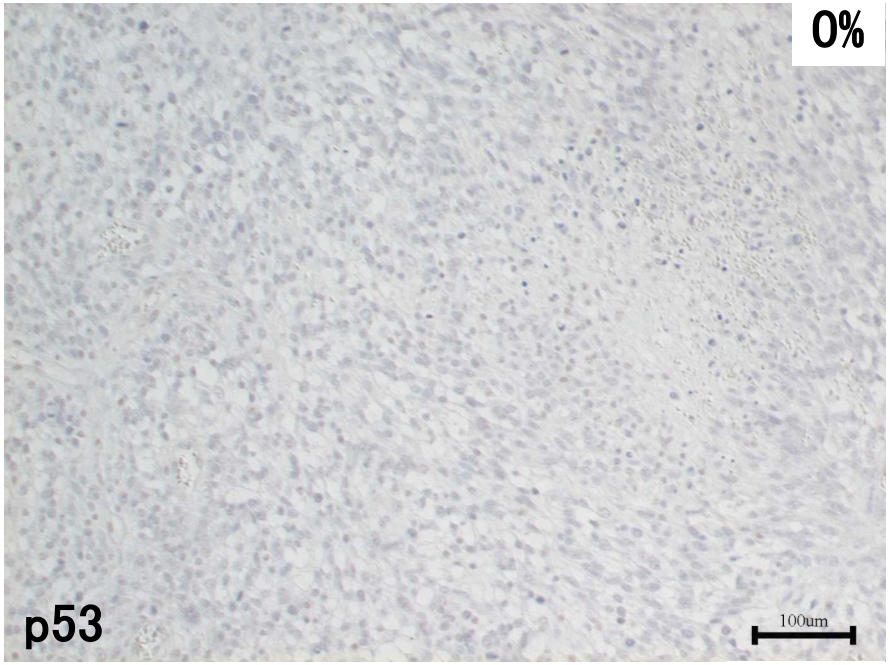
14 days after the end of RT 2004.02

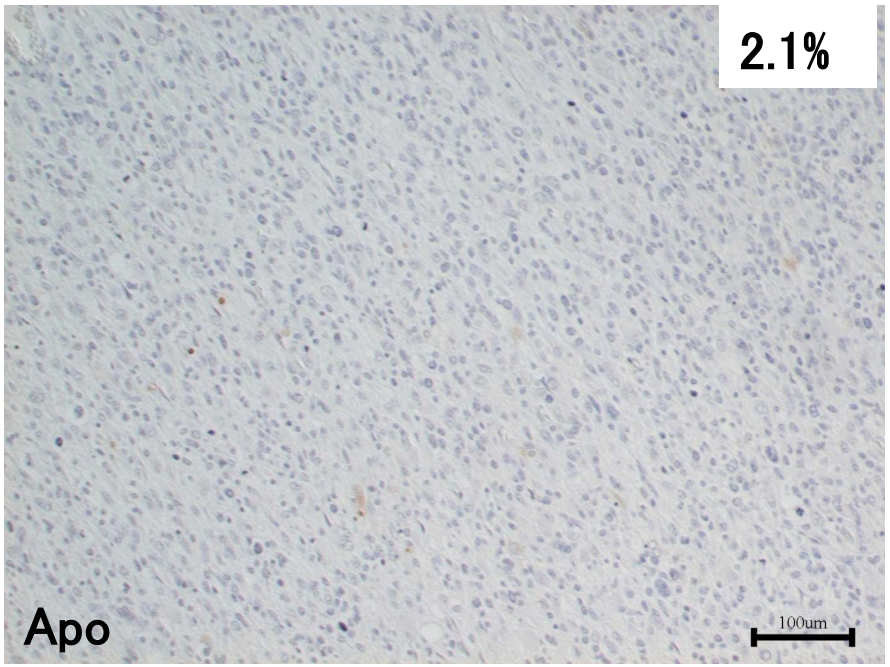


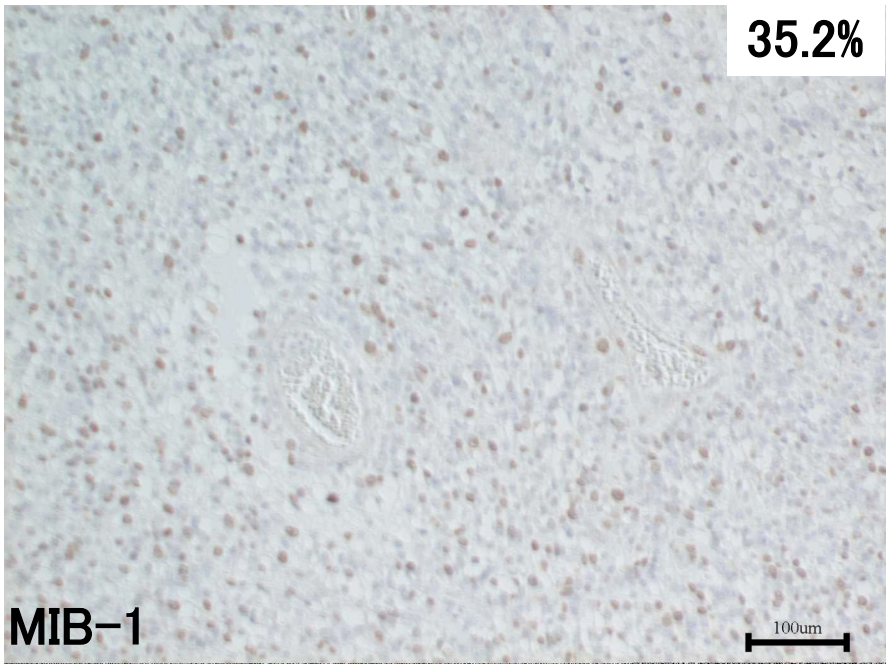


Pre-Radiation

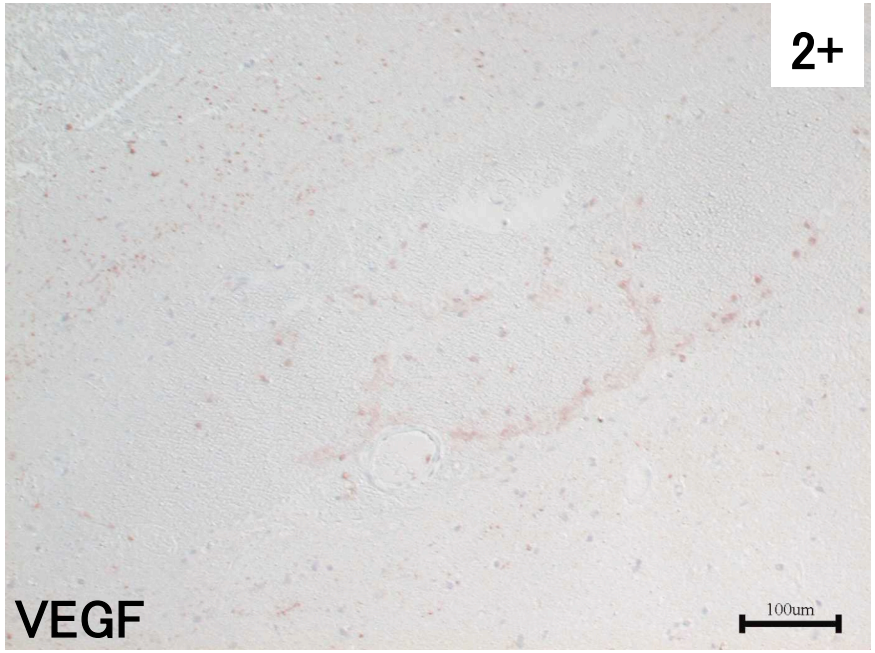


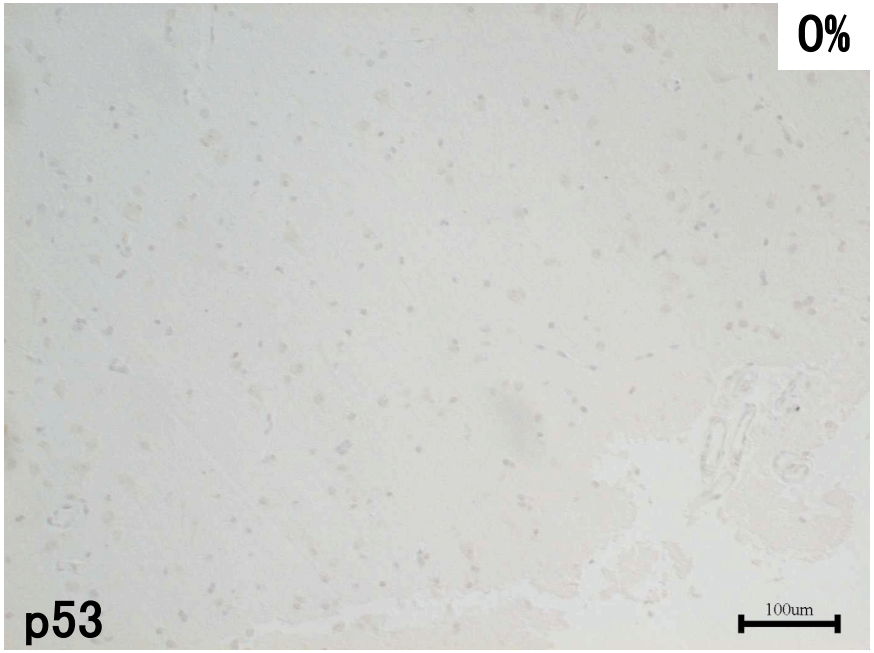


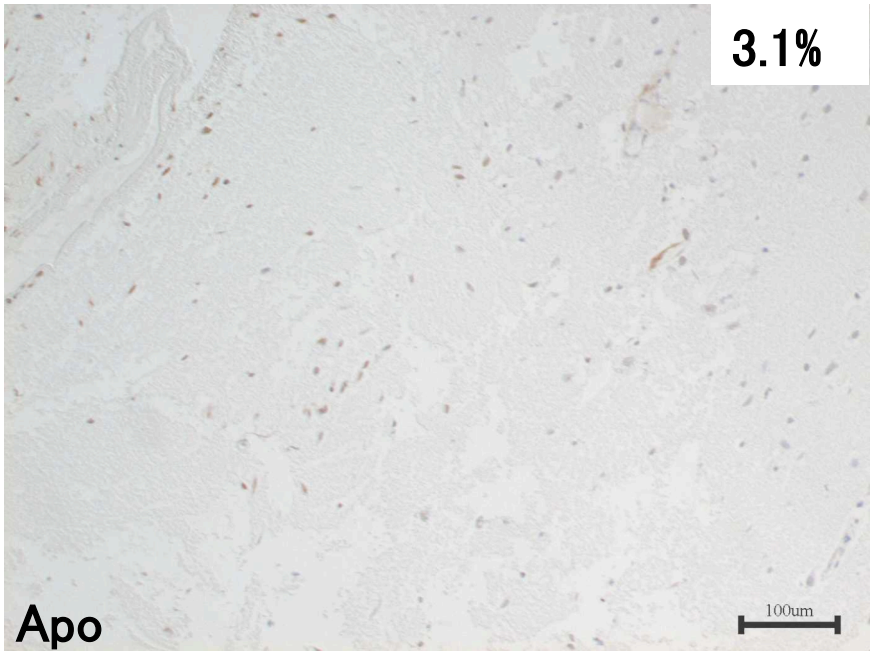


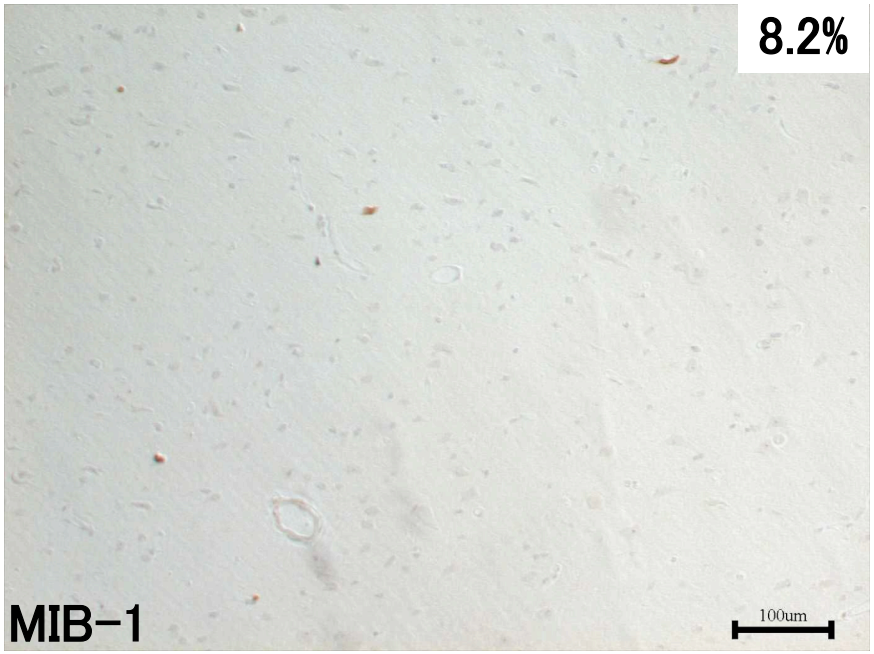


Post-Radiation（14 days）









Histopathological findings by HE staining

Common histological features in 6 cases

1) Sparse cell density with interstitial edema.
2) Necrotic foci with myxoid change
3) Capillary angiogenesis
4) Infiltration of macrophages phagocyting hemosiderine

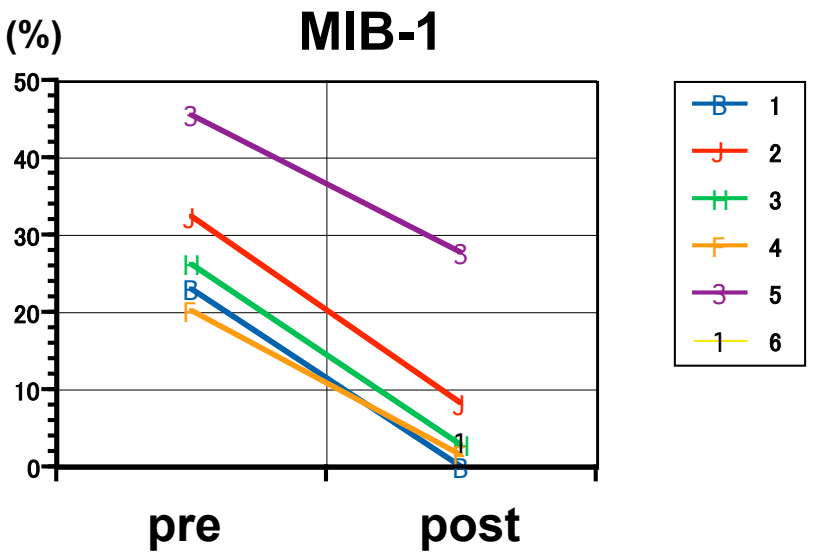
Tumor cells

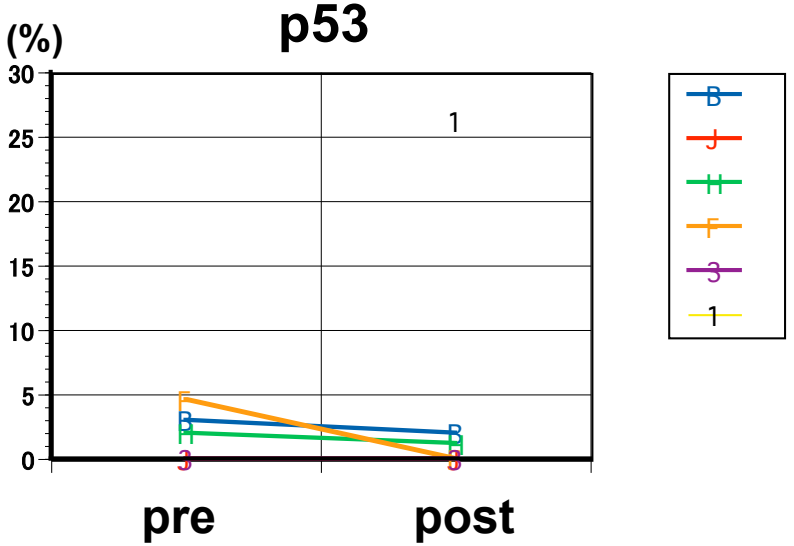
1) Multinuclear or giant nuclear cells
2) Gemistocytic cells

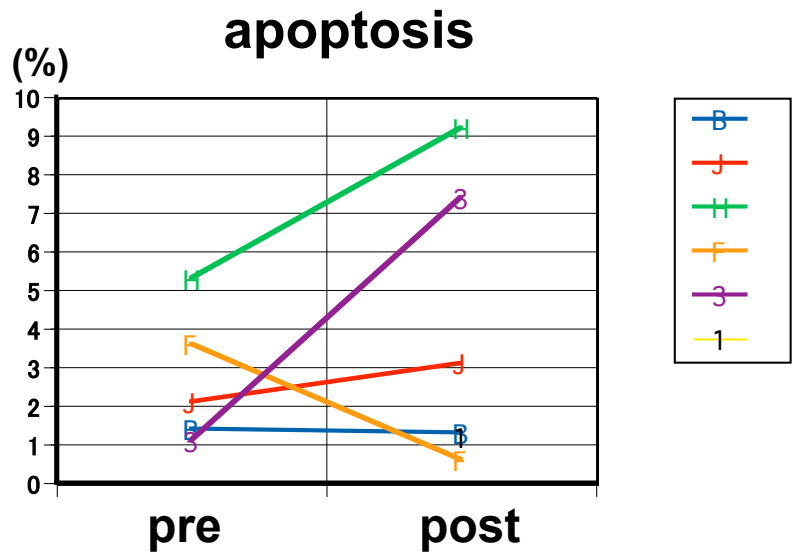
→ G2/M arrested or degenerated tumor cells

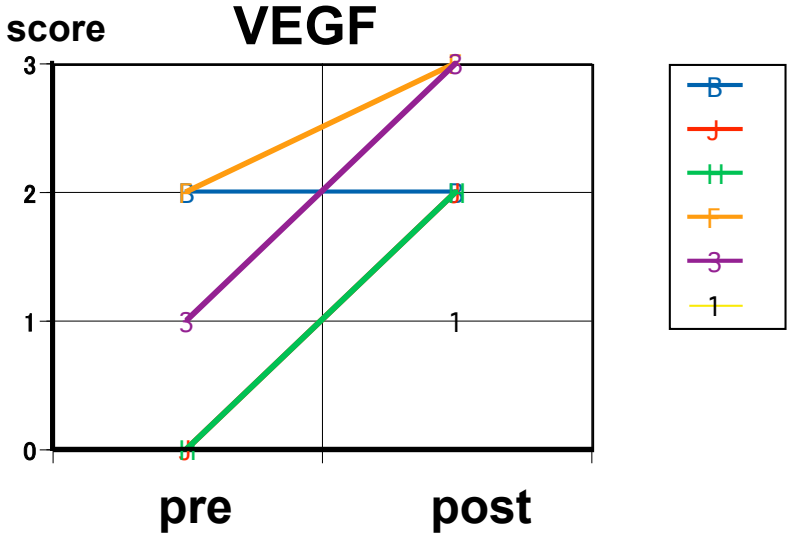
3) Small high chromatin density cells → Viable tumor cells
4) Very low incidence of mitotic figures → Low proliferative activity

Immunohistochemical findings









Summary

1. 18 cases of supratentorial GBM were treated with hyperfractionated concomitant boost proton radiotherapy.
2. In this protocol, the GTV plus 5 mm margin was irradiated to 96.6 GyE.
3. Toxicity was within a tolerable range.
4. The overall survival rate at 2 years was 49.2 %, and the median survival time was 21.4 months, which were significantly longer than the historical control in the same institution.
5. Histopathological examination of specimens taken after this treatment demonstrated a mixture of various degree of necrosis, interstitial edema and myxoid change containing degenerated but still alive tumor cells. MIB-1 index decreased significantly while expression of VEGF increased.
6. Modification of the eligible criteria, such as higher KPS and smaller residual tumor size may improve the outcome.

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