東葛肺癌治療セミナー
2015.11.20. Fri.
聖徳大学10号館

Brain metastasis

～多様性疾患に対する治療戦略を理解するうえでの基本的コンセプト～

東京慈恵会医科大学附属柏病院
脳神経外科
田中俊英

転移性脳腫瘍のPrinciple

“Seed & Soil”: 微小環境と解剖学的特性

画像で捉えられている転移巣が1個もしくは数個であっても脳全体に微小腫瘍が散布された状態である。

太田富雄：脳神経外科学（改訂11版）p.603

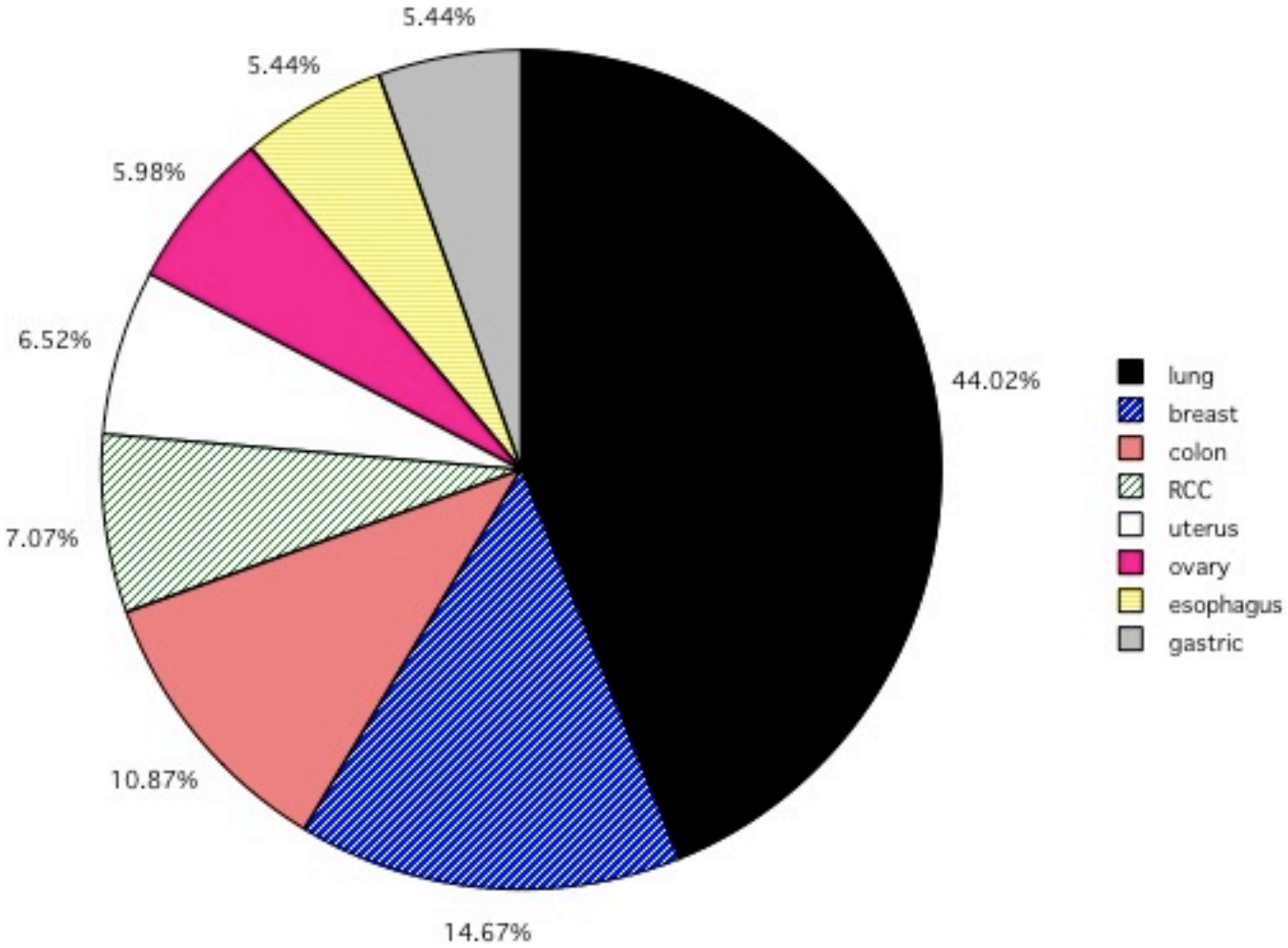
脳神経外科医がめざす転移性脳腫瘍治療のゴールは「中枢神経死を防ぐ」こと。

Pitfall of brain metastasis

- Most of neurosurgeons reluctant to dedicate in treatment
  - Rely on radiologist
- Systemic disease
  - Cumbersome of evaluation for clinical outcome
  - OS, PFS, QOL, … etc.
- Contribution of local control : significance is questionable
  - CNS vs. non-CNS
- Distribution of intracranial lesions : diversity
  - Number of lesions vs. total tumor volume
- Limitation of repeated/salvage therapy
  - Drug delivery
  - Sanctuary for irradiation & immunology
- Discordance in genetic profiles between primary & metastatic tumors

Br J Cancer 99:923-929, 2008
Ann Oncol 20:696-702, 2009

Frequency of Primary Cancer of Brain Metastasis

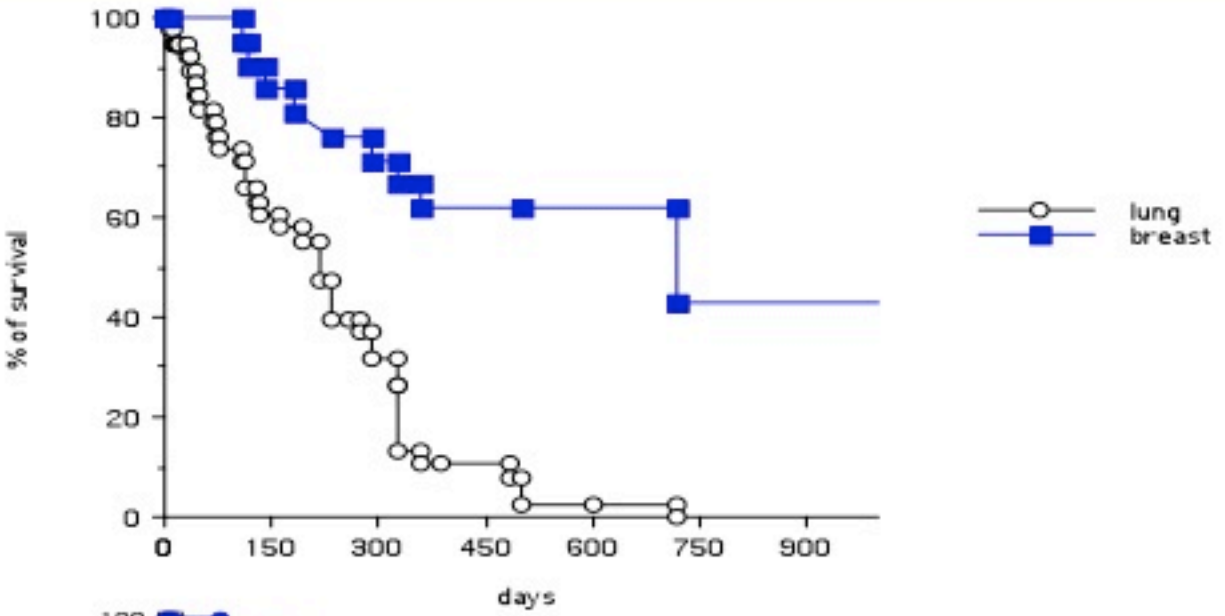


Brain Tumor Registry of Japan
13th Edition
(2001-2004)

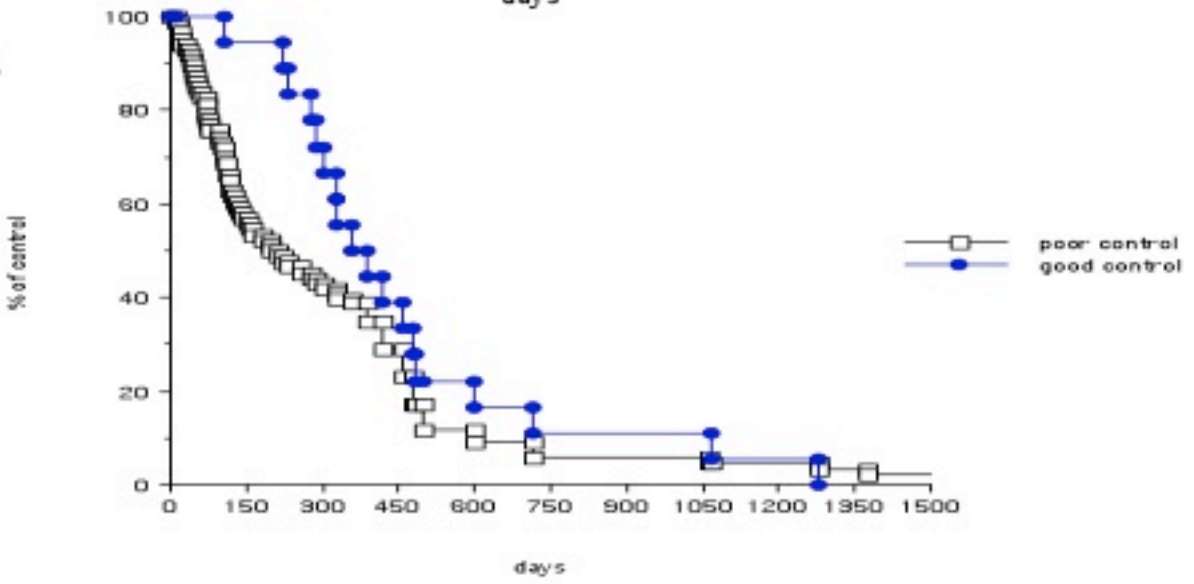
Origin	Total
Lung	1326 (45.6%)
Breast	373 (12.8%)
Colon	166 (5.7%)
Kidney	152 (5.2%)
Unknown	138 (4.7%)
Rectum, anus	113 (3.9%)
Stomach	96 (3.3%)
Head and neck	62 (2.1%)
Esophagus	60 (2.1%)

OS is dependent on primary site & disease control

OS for lung cancer vs. breast cancer with Brain metastases

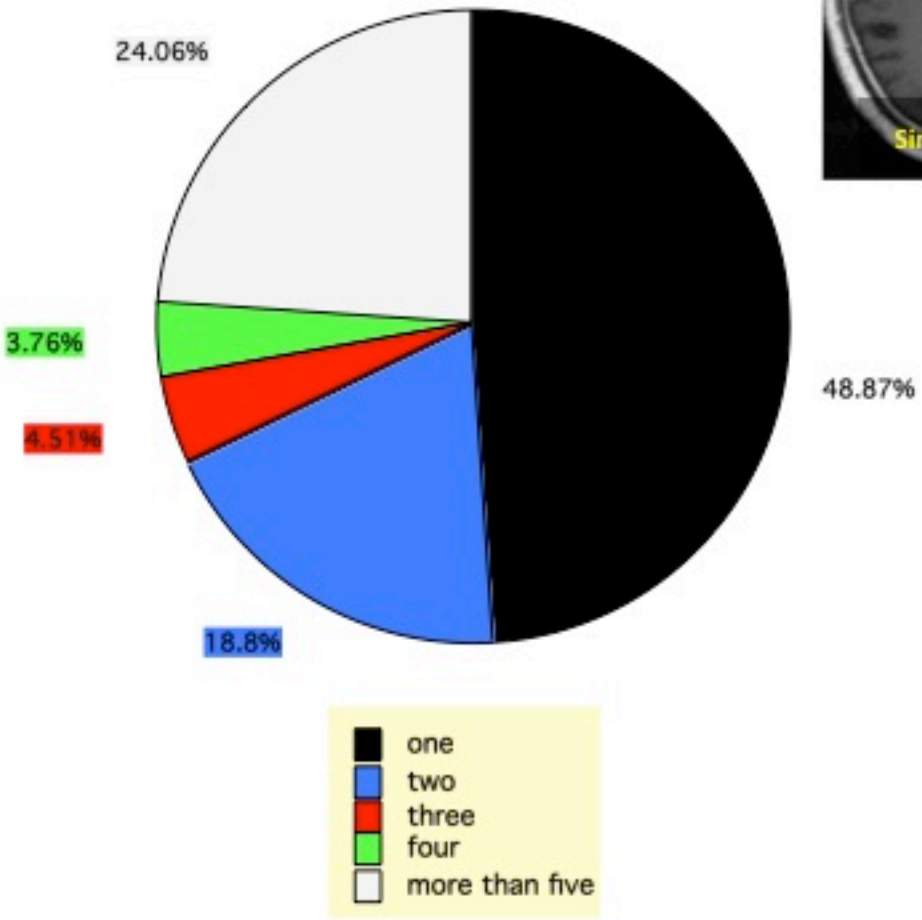


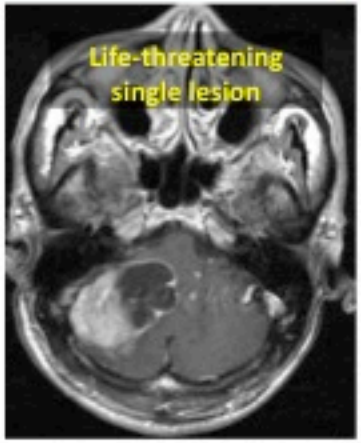
OS of brain metastases with/without extracranial metastases

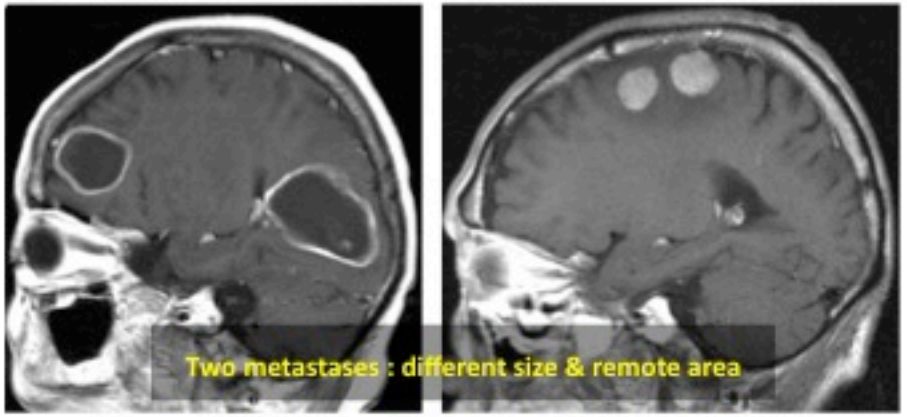


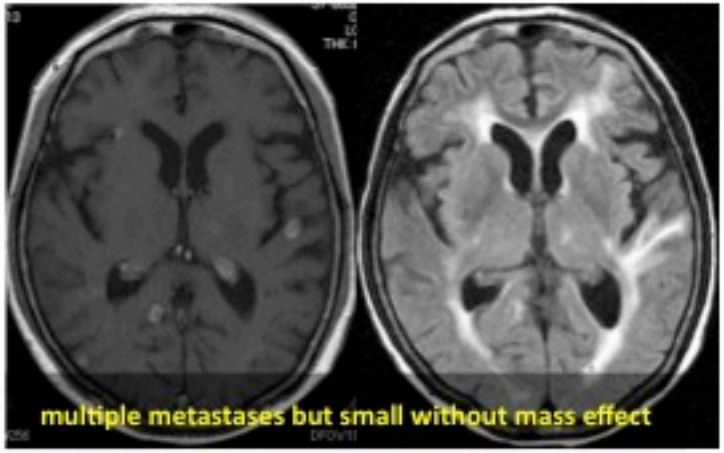
※ OS : overall survival from diagnosis of brain metastases

Number of brain metastases







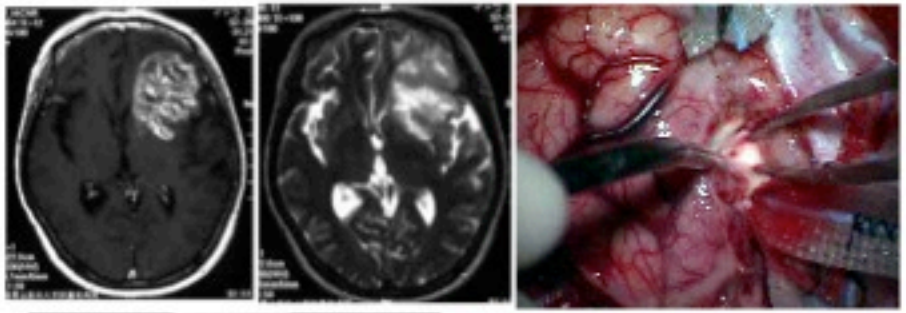


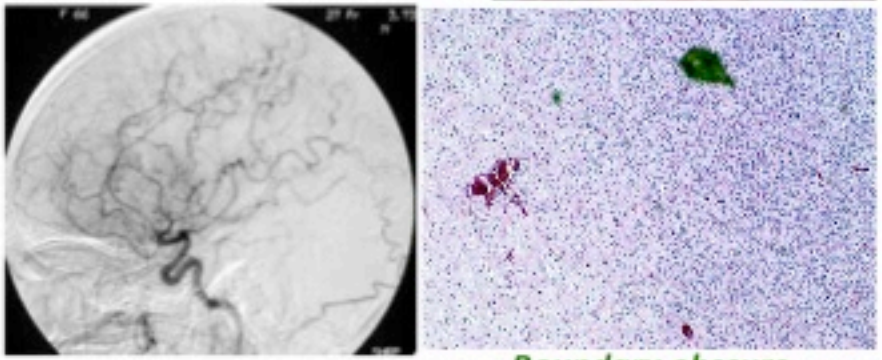
Role of surgery in brain metastasis

- Rapid reduction of tumor volume
- Release of mass effect leading to improvement of QOL
- Confirmation of histology (esp. unknown origin/ simultaneous discovery of cancer lesions)
- Rescue of life-threatening status as brain herniation caused by tumors especially in the posterior fossa

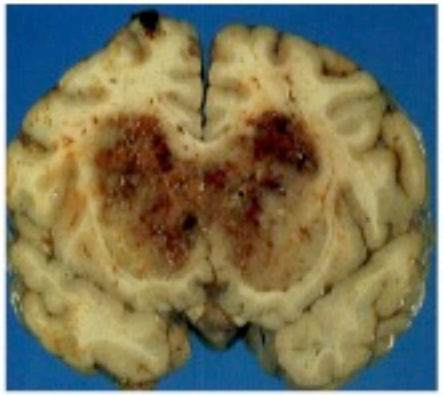
Difference between GBM vs. metastasis

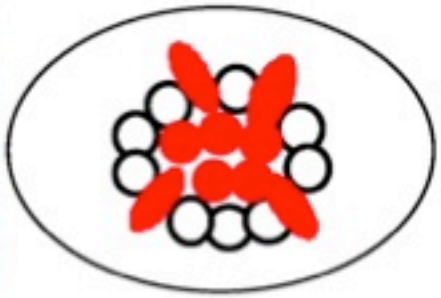
GBM





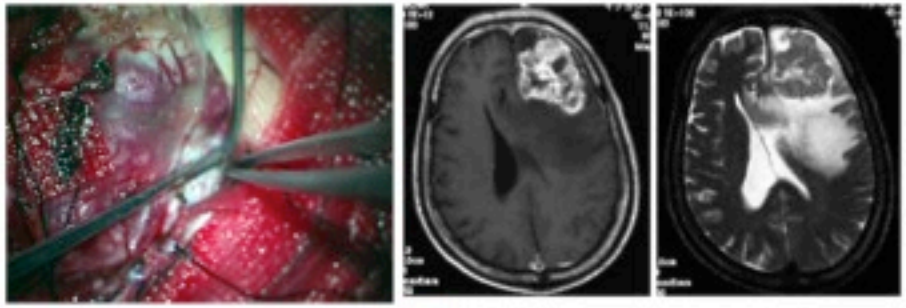
Boundary obscure

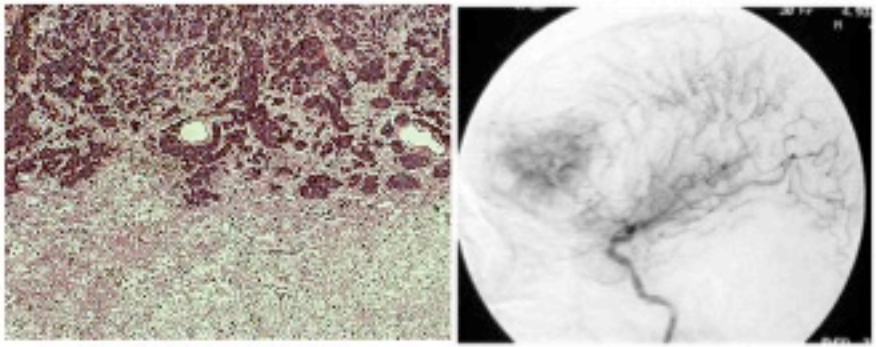




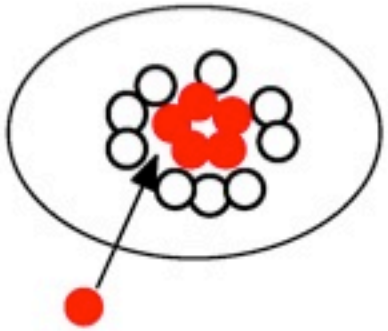
endogenous

metastasis

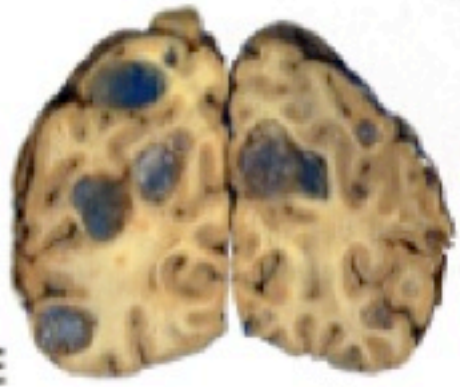




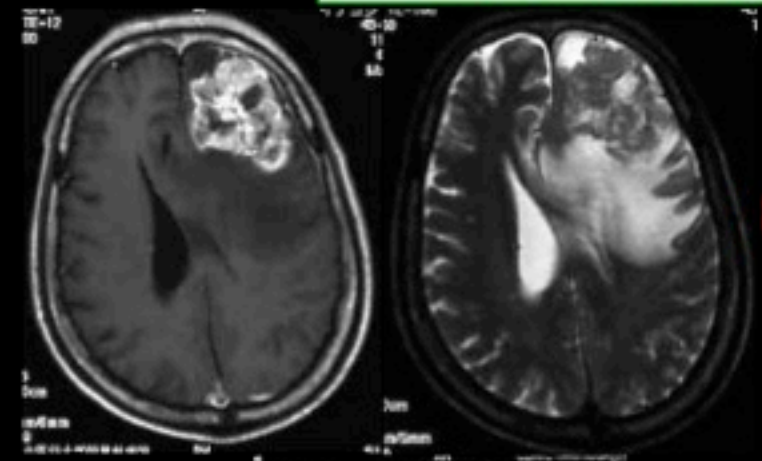
Boundary distinct



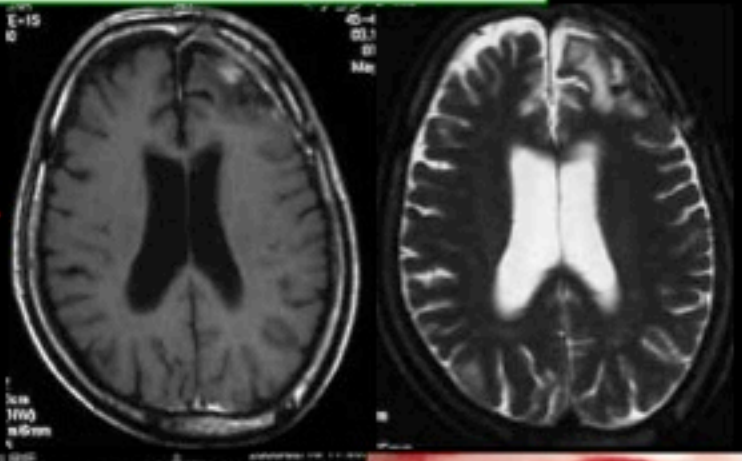
exogenous

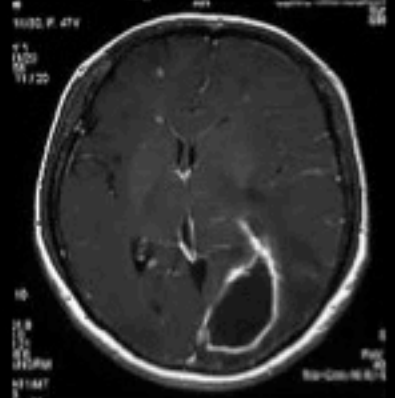


Role of surgery in brain metastasis

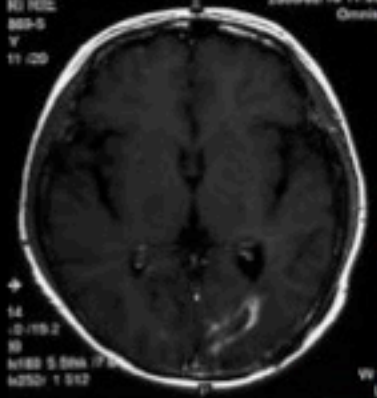


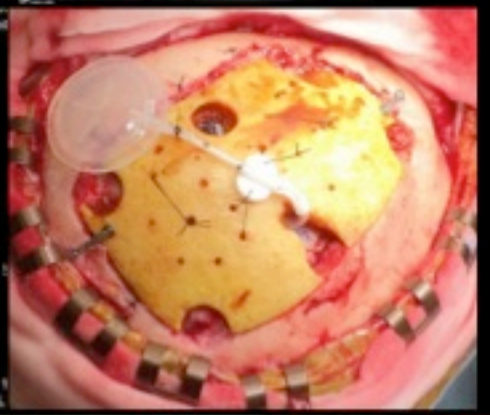
Craniotomy
&
Gross total resection

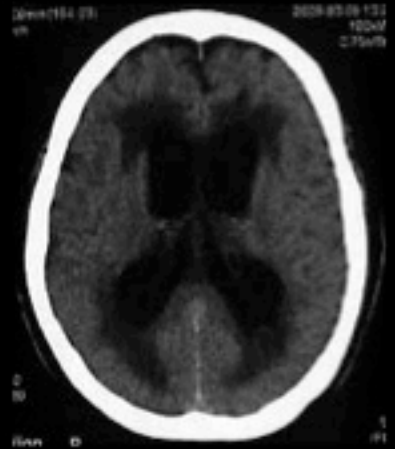




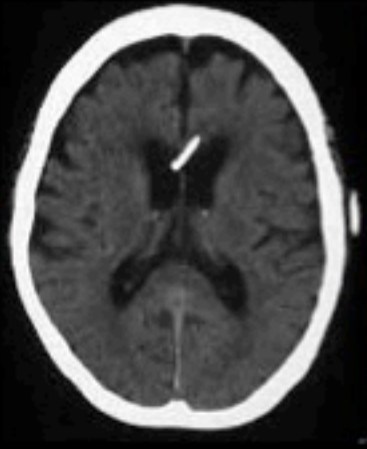
Setting of
Ommaya resevoir

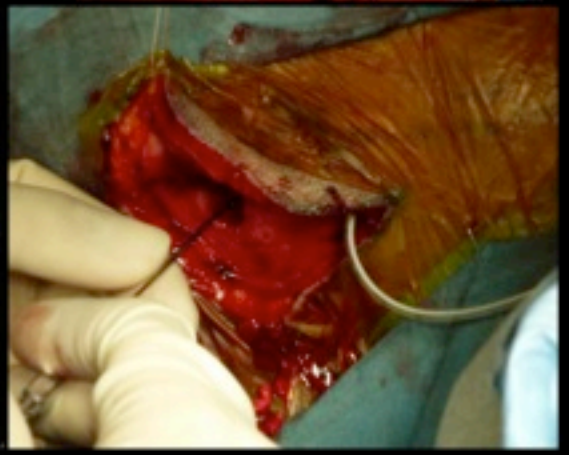






V-P shunt
for
hydrocephalus





Pattern of brain metastasis

At first diagnosis

	Primary tumor	Metastases	Recurrence of metastases
I	+	0	months
II	+	+	
III	0	+	
IV	+	0	years
V*	+	+	

Nat Med 1 (1) ; 27, 1995

* Metastases regress when primary tumor removed : Renal carcinoma, rare

Primary Site	I	II	III	IV	Total
Breast	6	0	1	20	27
Colon	1	0	4	15	20
Esophagus	4	1	0	5	10
Gastric	2	2	2	4	10
Lung	10	32	18	21	81
Ovary	3	0	0	8	11
RCC	1	2	3	7	13
Uterus	2	0	0	10	12
Total	29	37	28	90	184

Interval and Overall Survival for Brain Metastasis

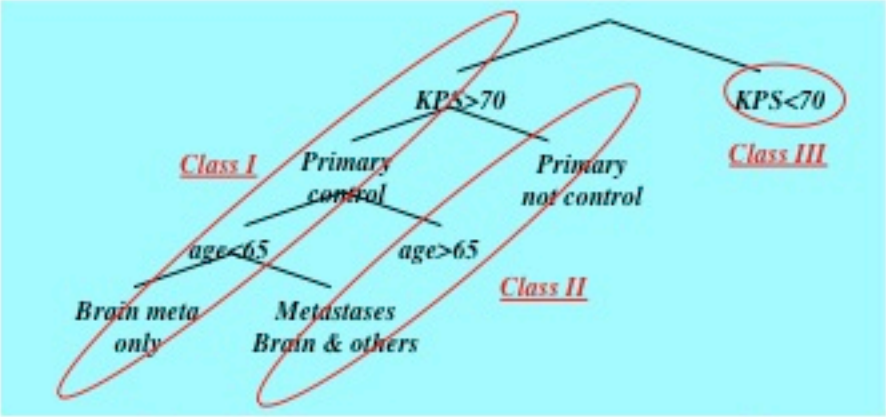
Primary site	Interval between diagnosis of primary cancer and brain metastases (months)	Overall survial after brain metastases (months)
Breast	57.2 ± 67.8	20.0 ± 13.6
Colon	40.5 ± 38.7	4.1 ± 4.5
Esophagus	7.8 ± 5.3	3.9 ± 1.9
Gastric	40.4 ± 58.3	3.8 ± 1.2
Lung	10.7 ± 23.9	7.6 ± 7.0
Ovary	40.3 ± 24.6	18.8 ± 7.6
RCC	46.2 ± 55.2	21.6 ± 14.1
Uterus	53.2 ± 38.4	9.9 ± 2.2
Total	28.9 ± 43.6	8.1 ± 9.3

Lethal for Brain Metastasis?

Primary Site	Yes (%)	No (%)	Total
Breast	12 (44.4)	17 (55.6)	29
Colon	12 (60.0)	8 (40.0)	20
Esophagus	3 (30.0)	7 (70.0)	10
Gastric	4 (40.0)	6 (60.0)	10
Lung	41 (50.6)	40 (49.4)	81
Ovary	2 (15.4)	11 (84.6)	13
RCC	2 (15.4)	11 (84.6)	13
Uterus	5 (41.7)	7 (58.3)	12
Total	81 (43.1)	107 (56.9)	188

転移性脳腫瘍の各種グレードと治療成績

RPA Classification (recursive partitioning analysis)



Median Survival : class I ; 20.4 months
class II ; 7.2 months
class III; 2.2 months
Int J Radiat Oncol Biol Phys 83 : 1399, 2012

GPA Classification (graded prognostic assessment)

	0 point	0.5 point	1 point
Age	60<	50-59	50>
KPS	<60	70-80	90-100
No. of Brain Meta	4<	2~3	1
Metastases Others	present	—	none

Median Survival : 3.5~4.0 points ; 17.7 months
3.0 points ; 12.6 months
1.5~2.5 points ; 7.4 months
0~1.0 point ; 4.0 months
Int J Radiat Oncol Biol Phys 83 : 1399, 2012

SIR Classification (score index for radiosurgery)

	0 point	1 point	2 points
Age	60<	50-59	50>
KPS	<50	60-70	80-100
No. of Brain Meta	3<	2	1
Metastases Others	Progressive	Stable	Complete response or no evidence of disease
Volume of largest lesion (ml)	13<	5-13	<5

Median Survival : 8~10 points ; 21.0 months
4~7 points ; 8.1 months
1~3 points ; 3.6 months
Int J Radiat Oncol Biol Phys 83 : 1399, 2012

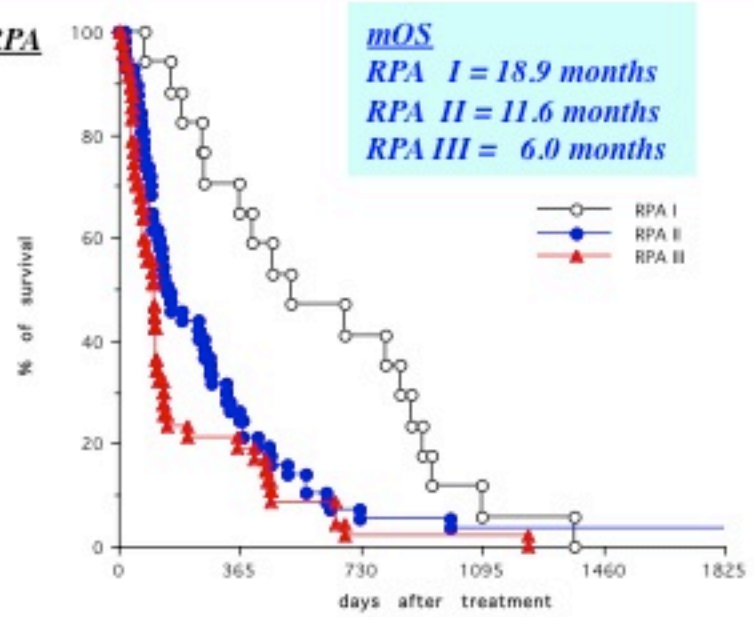
BSBM Classification (basic core for brain metastases)

	0 point	1 point
KPS	70>	80-100
No. of Brain Meta	—	—
Metastases Others	present	none
Controlled primary	no	yes

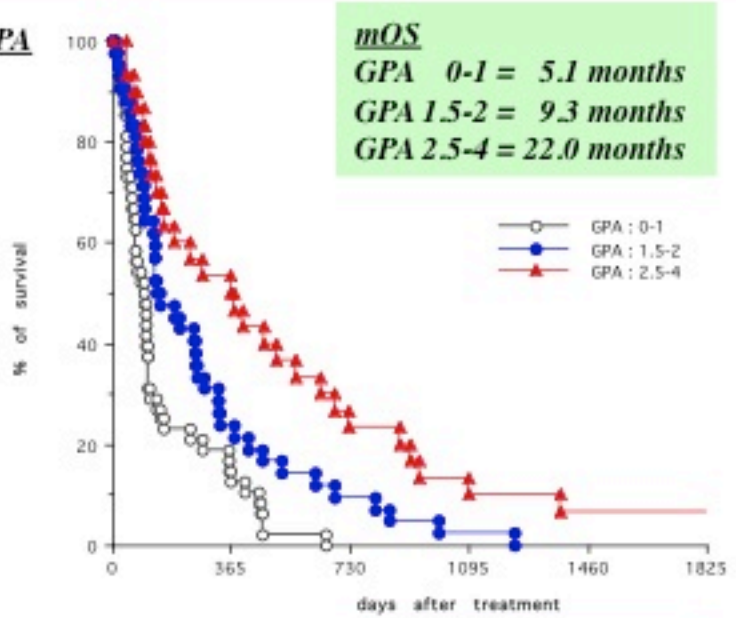
Median Survival : 3 points ; 19.0 months
2 points ; 8.4 months
1 point ; 5.1 months
0 point ; 2.2 months
Int J Radiat Oncol Biol Phys 83 : 1399, 2012

当科での転移性脳腫瘍の各種グレード別治療成績

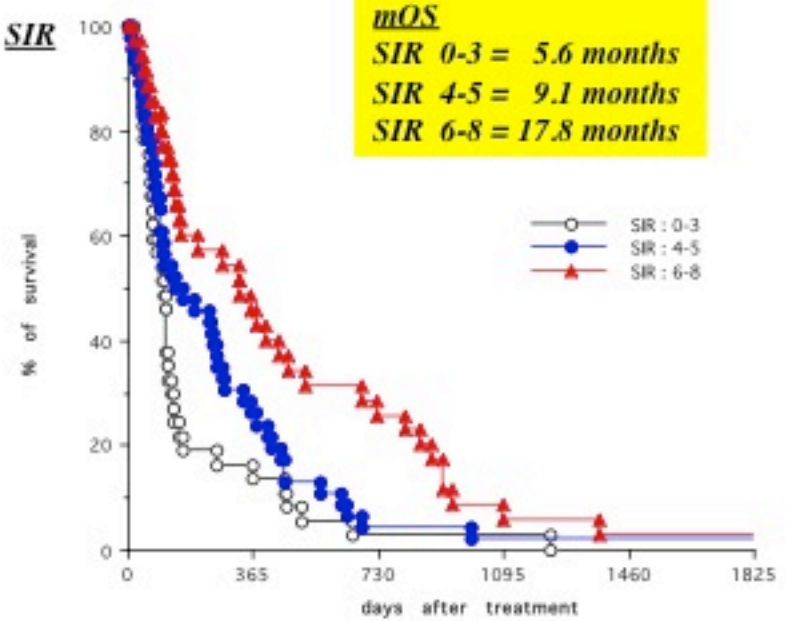
RPA



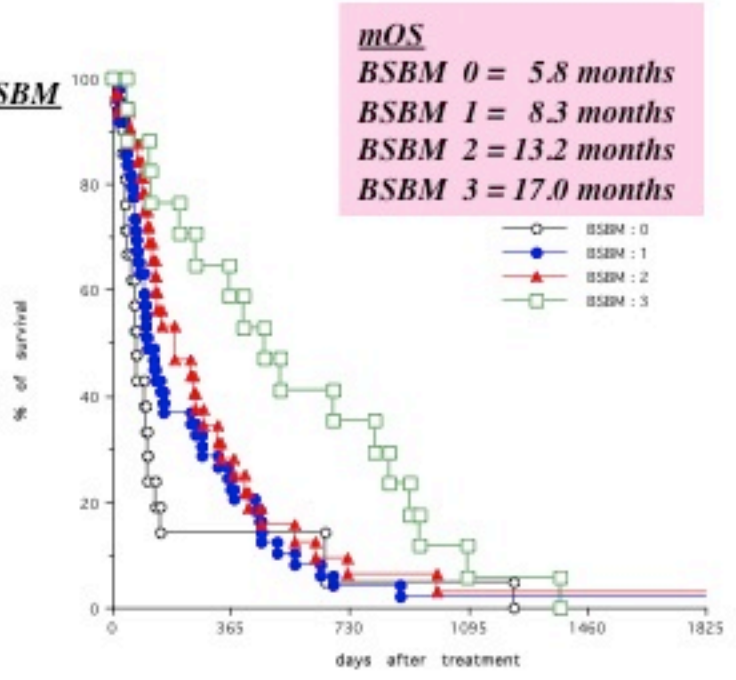
GPA



SIR



BSBM

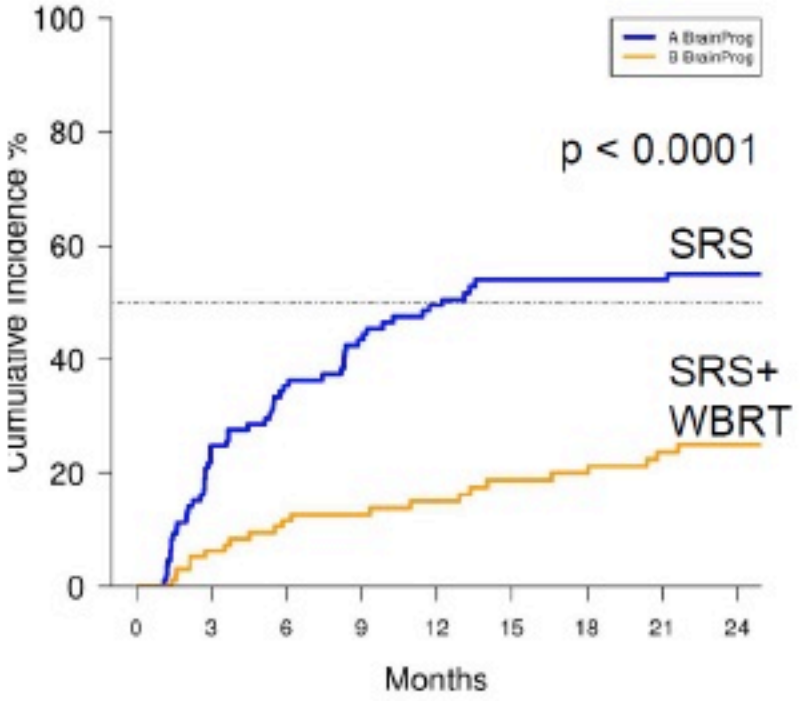


転移性脳腫瘍に対する SRS vs. SRS & WBRT

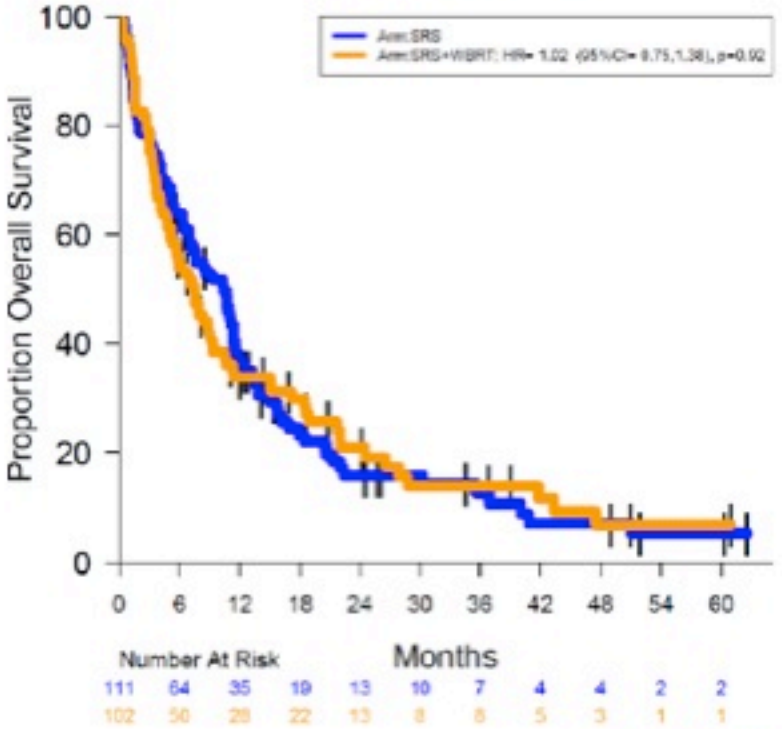
Primary Endpoint: Cognitive Progression at 3 mos

	SRS	SRS+WBRT	P-value
Cognitive Progression at 3 months (95% CI)	63.5% (50.5, 75.3)	91.7% (80.0, 97.7)	0.0007

N0574 Brain Control vs. ARM



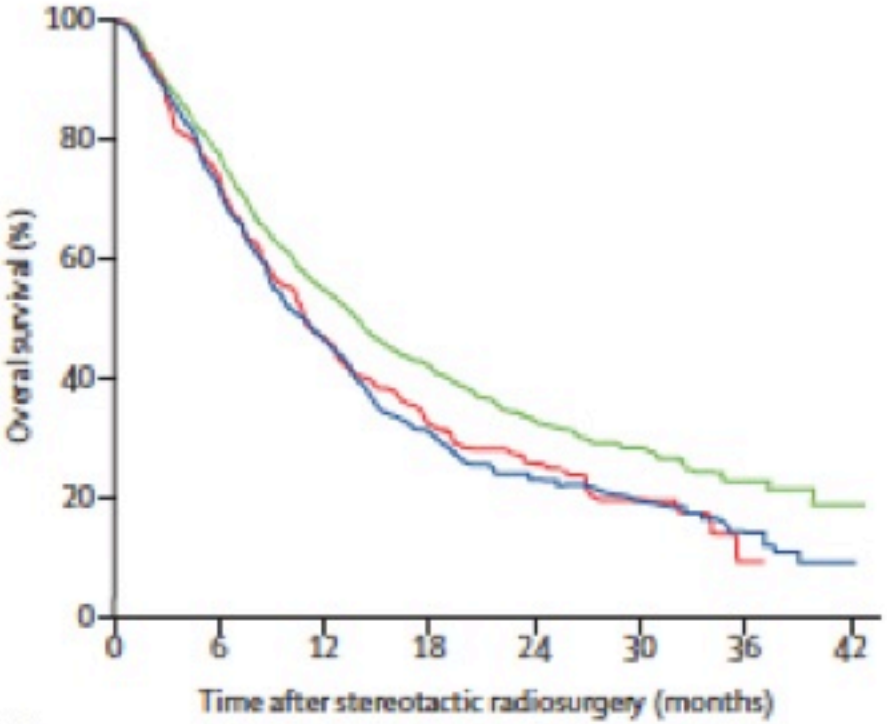
N0574 OS vs. ARM



ASCO Direct 2015

転移性脳腫瘍に対する SRS : 2-4 lesions vs. 5-10 lesions

Group	Median overall survival, months (95% CI)	HR (95% CI)	p value
1 tumour	13·9 (12·0–15·6)	0·76 (0·66–0·88)	0·0004
2–4 tumours	10·8 (9·4–12·4)	Reference	
5–10 tumours	10·8 (9·1–12·7)	0·97 (0·81–1·18)	0·78

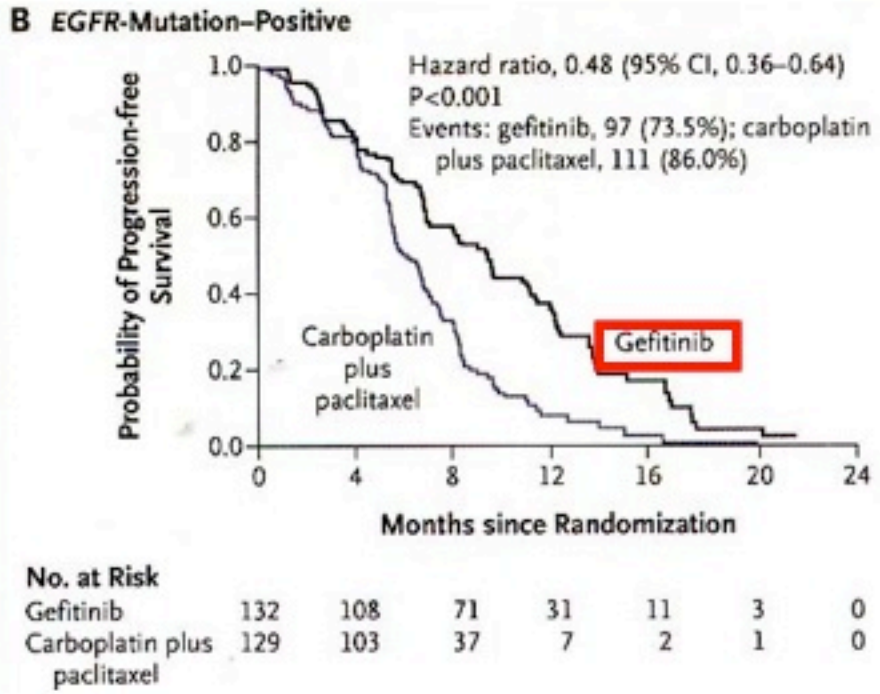


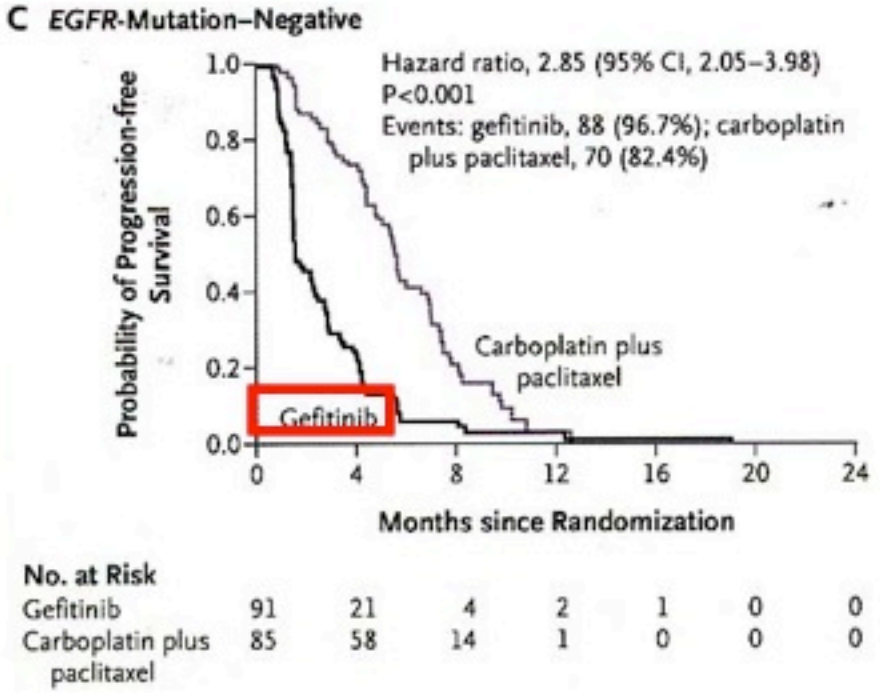
Number at risk				
1 tumour	455	234	97	22
2–4 tumours	531	215	61	16
5–10 tumours	208	84	31	1

	Total (n=1194)	1 tumour (n=455)	2–4 tumours (n=531)	5–10 tumours (n=208)	p value
Tumour number					
Median (IQR)	2 (1–4)	1 (1–1)	2 (2–3)	6 (5–8)	–
Mean (SD)	3 (2)	1 (0)	3 (1)	7 (2)	–
Age, years					
Mean (SD)	65·8 (10·2)	65·9 (10·7)	65·8 (9·9)	65·4 (9·9)	0·55
Range	30–91	30–91	36–91	37–89	–
≥65	693 (58%)	270 (59%)	310 (58%)	113 (54%)	0·46
Primary cancer					0·35
Lung	912 (76%)	348 (76%)	400 (75%)	164 (79%)	–
Breast	123 (10%)	42 (9%)	57 (11%)	24 (12%)	–
GI tract	85 (7%)	35 (8%)	41 (8%)	9 (4%)	–
Kidney	36 (3%)	15 (3%)	19 (4%)	2 (1%)	–
Other	38 (3%)	15 (3%)	14 (3%)	9 (4%)	–
Extracerebral diseases					0·075
Controlled	811 (68%)	325 (71%)	355 (67%)	131 (63%)	–
Not controlled	383 (32%)	130 (29%)	176 (33%)	77 (37%)	–
KPS					0·92
≥80 points	1036 (87%)	395 (87%)	459 (86%)	182 (88%)	–
≤70 points	158 (13%)	60 (13%)	72 (14%)	26 (13%)	–
RPA class					0·76
1	334 (28%)	134 (29%)	141 (27%)	59 (28%)	–
2	819 (69%)	304 (67%)	371 (70%)	144 (69%)	–
3	41 (3%)	17 (4%)	19 (4%)	5 (2%)	–
Neurological symptoms					0·085
No	835 (70%)	335 (74%)	357 (67%)	143 (69%)	–
Yes	359 (30%)	120 (26%)	174 (33%)	65 (31%)	–

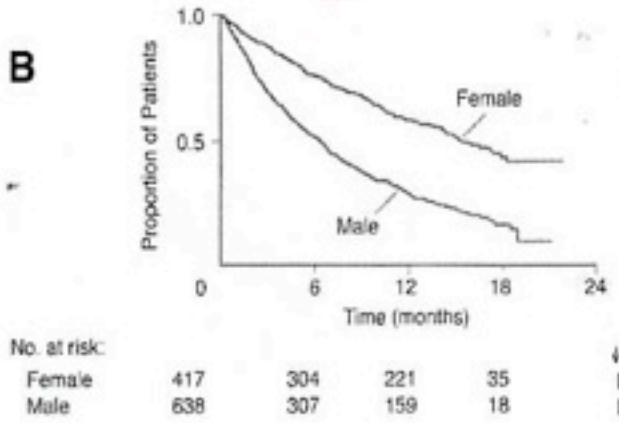
Lancet Oncol 15:387-395, 2014

Effect of Gefatinib on lung cancer

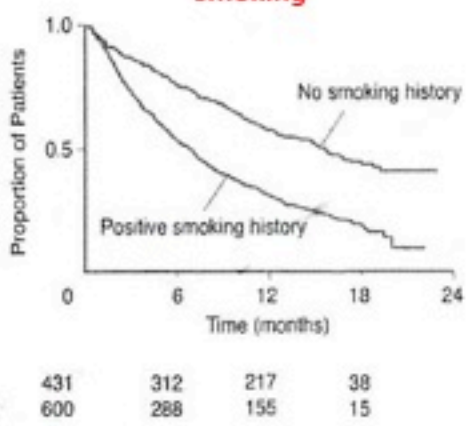




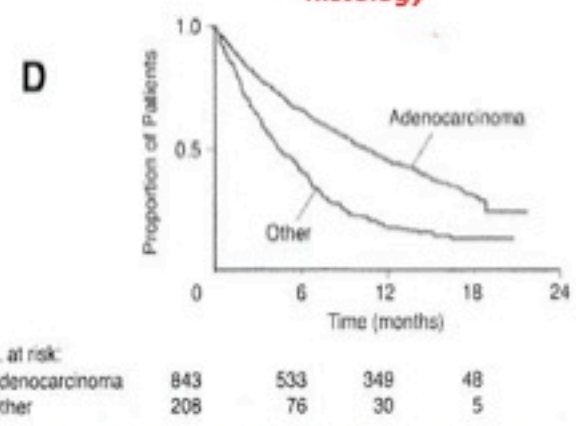
sex



smoking



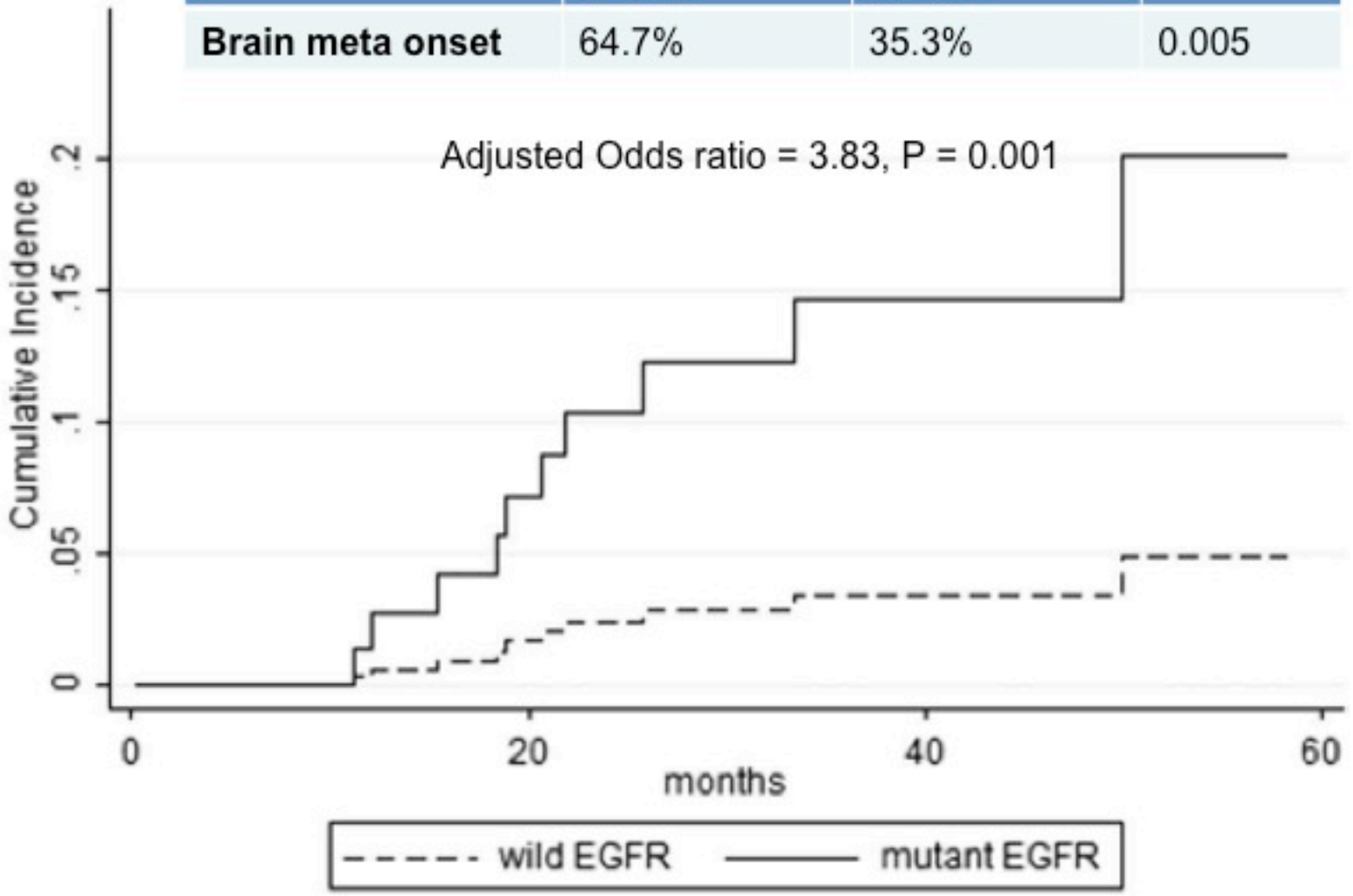
histology



J Clin Oncol 24 ; 2549-2556, 2006

EGFR mutation brain meta incidence

	EGFR (+) N=138	EGFR (-) N=176	P
Brain meta onset	64.7%	35.3%	0.005



Shin DY, et al. J Thorac Oncol;9:195-199, 2014

Effect of Gefatinib on metastatic brain tumors from lung cancer

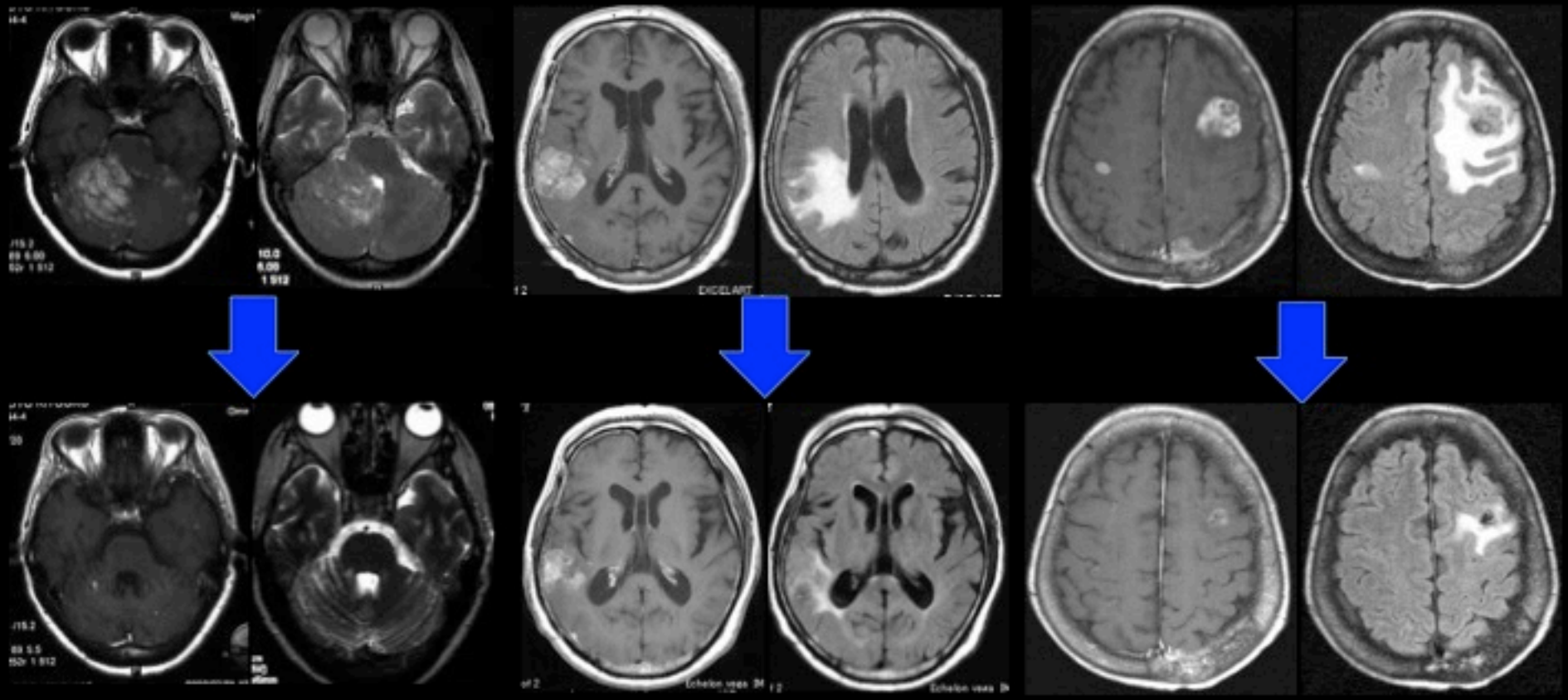
Gefatinib (Iressa) ; EGFRを標的
肺癌（腺癌）の脳転移に有効。
若年女性、腺癌、
$EGFR_{vIII}$の変異
exon 19 base pair deletion (del746-A750)
exon 21 point mutation (L858R)
（副作用）肺線維症

Brain metastases

Clinical Lung Cancer 6 (2) ; 123-128, 2004
Lung Cancer 47 ; 129-138, 2005
Neurol Med Chir (Tokyo) 46 ; 504-507, 2006
Lung Cancer 82 ; 282-287, 2013

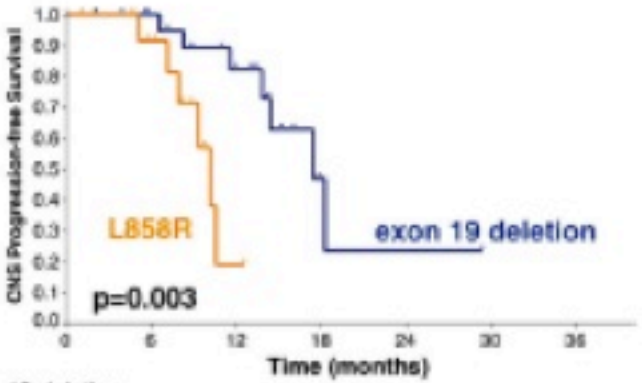
Glioblastoma

J Clin Oncol 22 ; 133-142, 2004



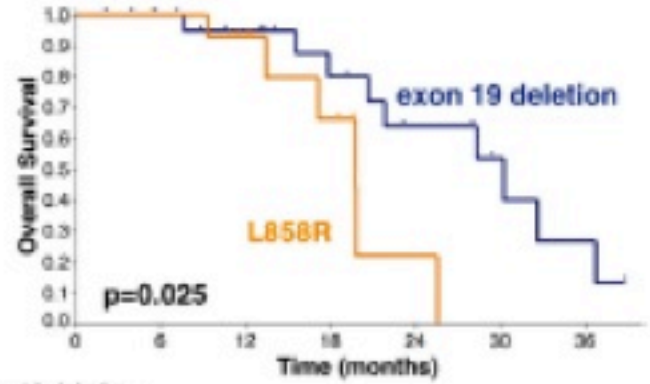
Effect of Gefatinib on metastatic brain tumors from lung cancer

B



exon 19 deletion							
n	23	20	12	3	1	0	0
Events	0	0	3	2	1	0	0
L858R							
n	15	11	2	1	0	0	0
Evnets	0	1	5	0	0	0	0

F

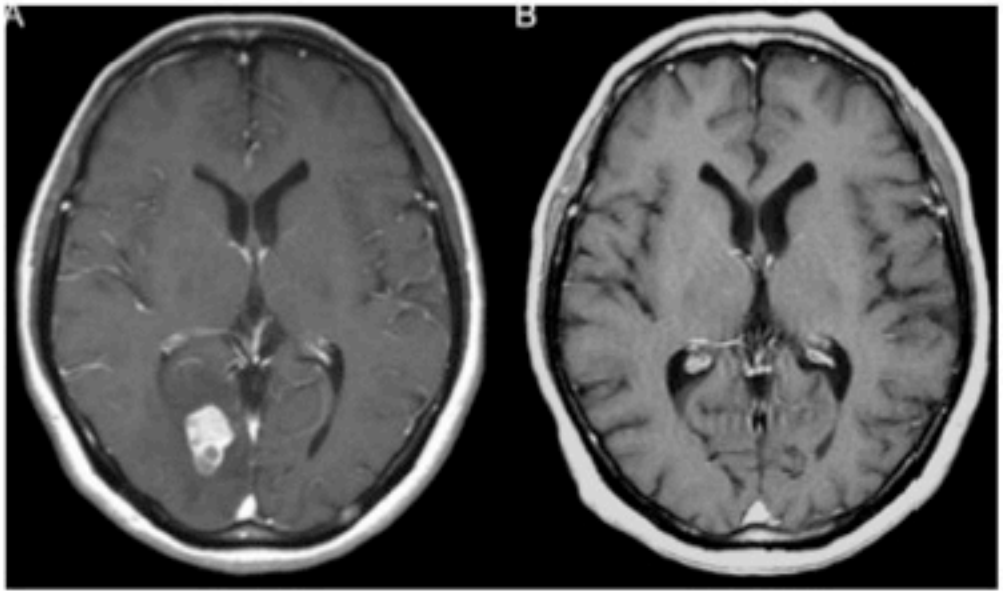


exon 19 deletion							
n	23	21	17	12	8	5	3
Events	0	0	1	2	2	1	2
L858R							
n	15	15	11	6	2	0	0
Evnets	0	0	1	2	2	1	0

Response of brain metastases to gefitinib.

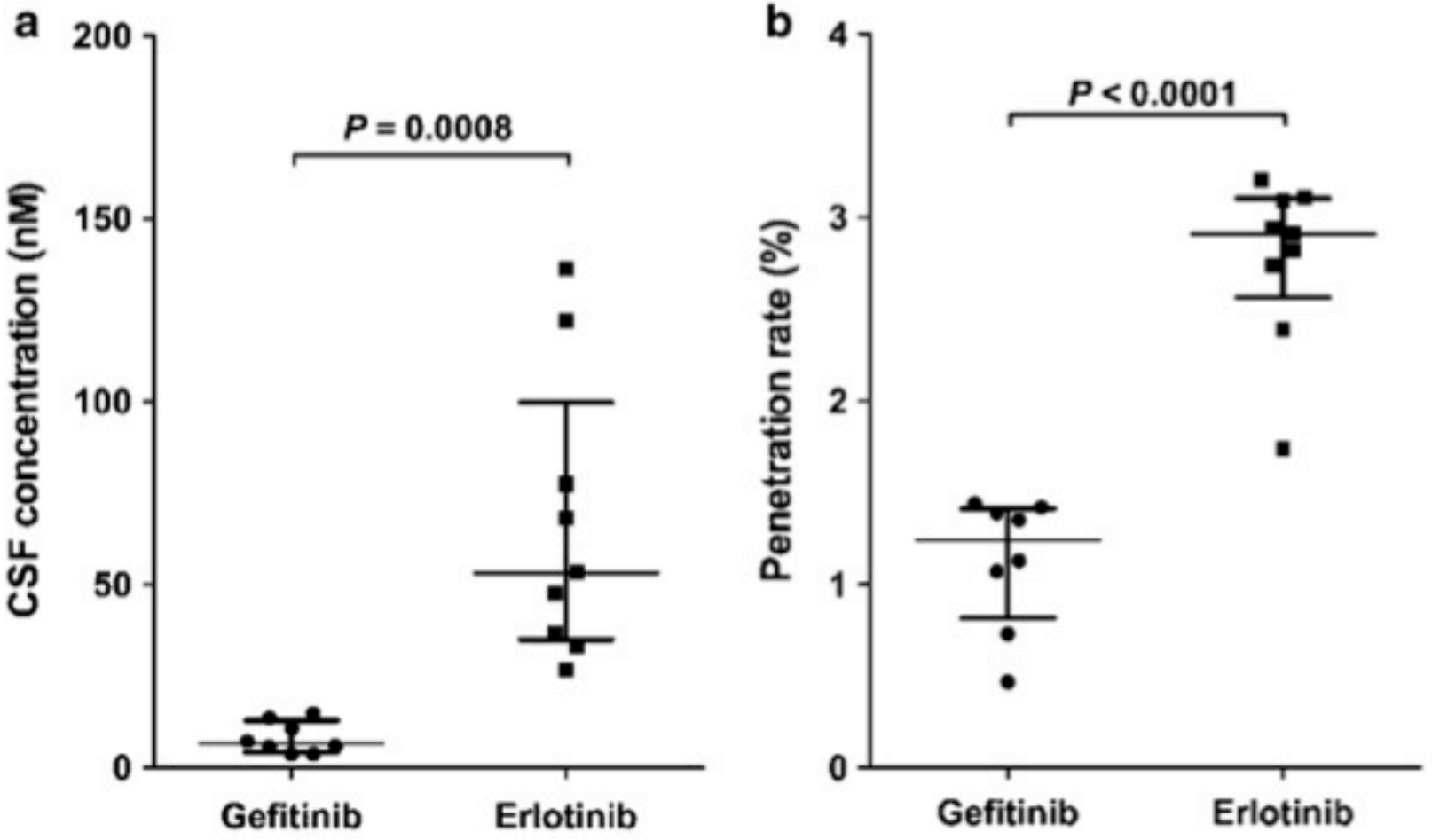
	All patients	Ex19 deletion	Ex21 L858R
Patients number	41	23	15
CR	13 (31.7%)	10 (43.5%)	3 (20.0%)
PR	23 (56.1%)	13 (56.5%)	9 (60.0%)
CR + PR	36 (87.8%)	23 (100.0%)	12 (80.0%)
SD	4 (9.8%)	0 (0.0%)	3 (20.0%)
PD	1 (2.4%)	0 (0.0%)	0 (0.0%)

Ex, exon; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.



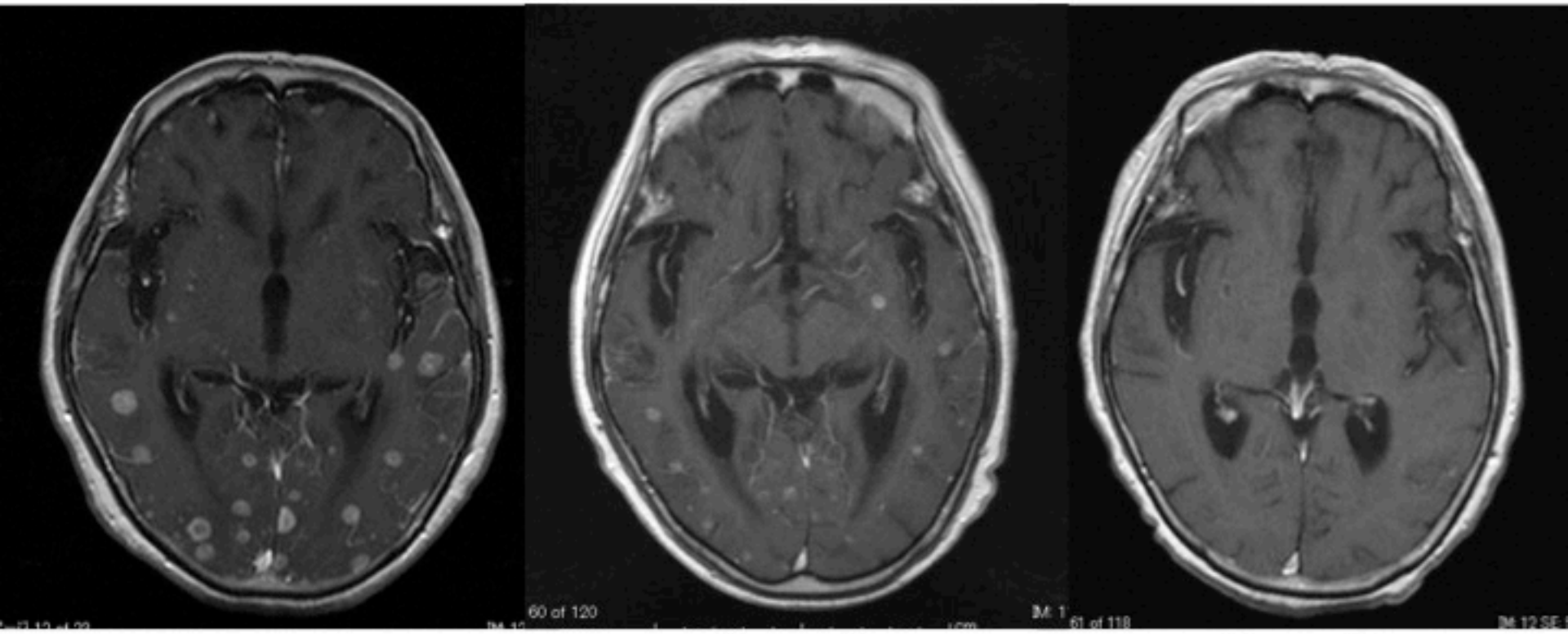
Lung Cancer 82 ; 282-287, 2013

Comparison of CSF concentrateion between Erlotinib and Gefitinib



Togashi Y et al. Cancer Chemother Pharmacol. 2012

Effect of Erlotinib for meningeal dissemination



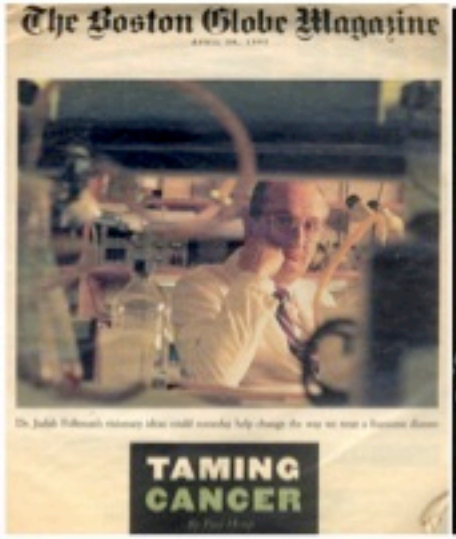
before treatment

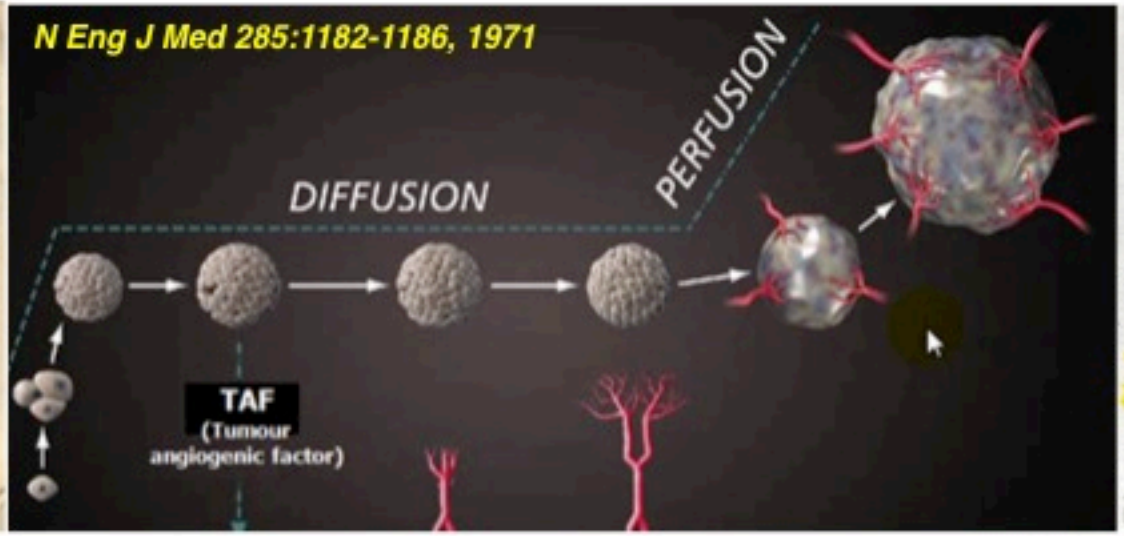
2 months
after treatment

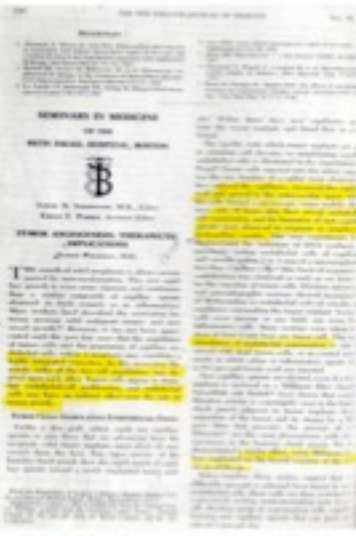
6 months
after treatment

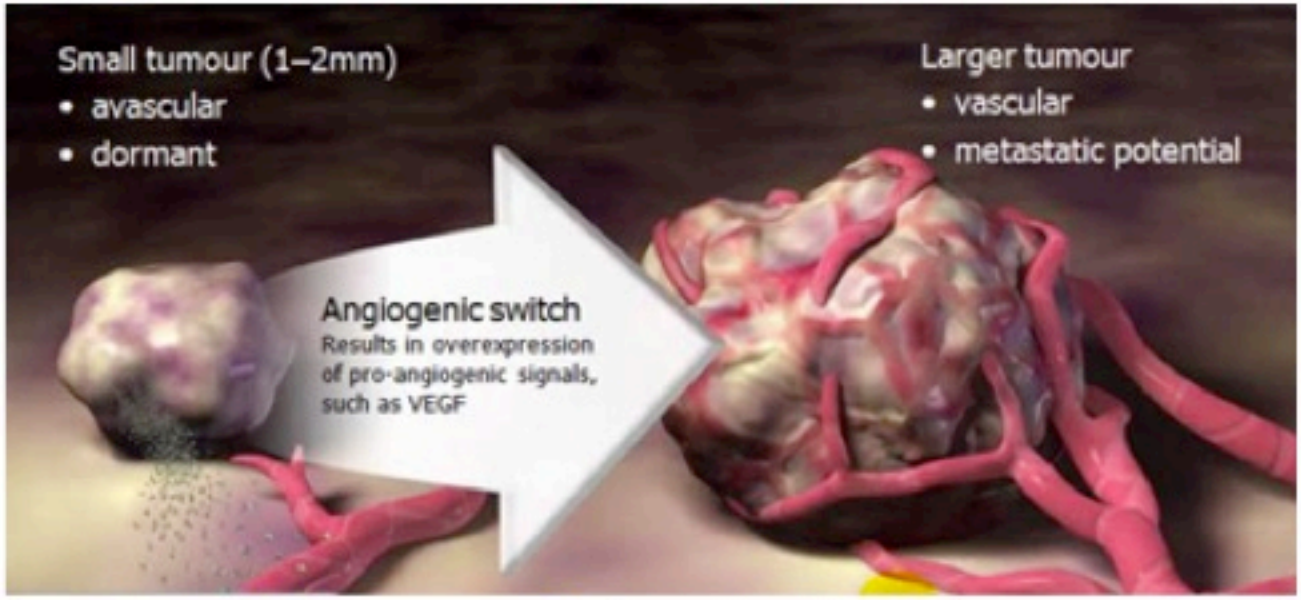
Erlotinib 150mg /day

WBRT(30Gy/10回)



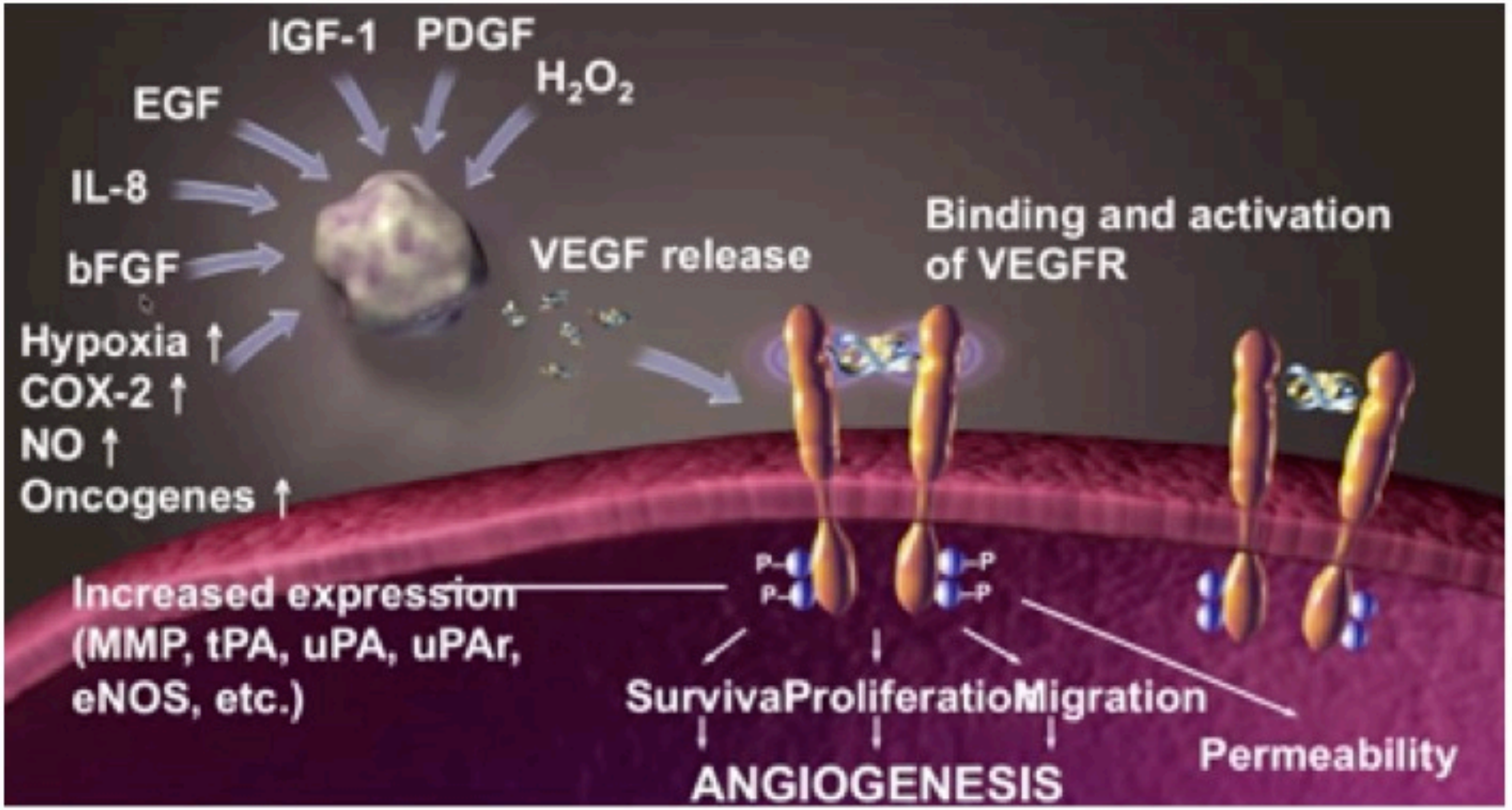






Premalignant Stage	→	Malignant Tumor	→	Tumor Growth	→	Vascular Invasion	→	Dormant Micrometastasis	→	Overt Metastasis
avascular tumor		*angiogenic switch*		*vascularized tumor*		*tumor cell intravasation*		*seeding in distant organ*		*secondary angiogenesis*

Role of VEGF and its receptor in metastatic brain tumors



[CANCER RESEARCH 55, 360–368, January 15, 1995]

Pathogenesis of Ascites Tumor Growth: Vascular Permeability Factor, Vascular Hyperpermeability, and Ascites Fluid Accumulation[1]

Janice A. Nagy[2], Elizabeth M. Masse, Kemp T. Herzberg, Michelle S. Meyers, Kiang-Teck Yeo, Tet-Kin Yeo, Tracy M. Sioussat, and Harold F. Dvorak

Departments of Pathology, Beth Israel Hospital and Harvard Medical School, Boston, Massachusetts 02215

[CANCER RESEARCH 55, 369–375, January 15, 1995]

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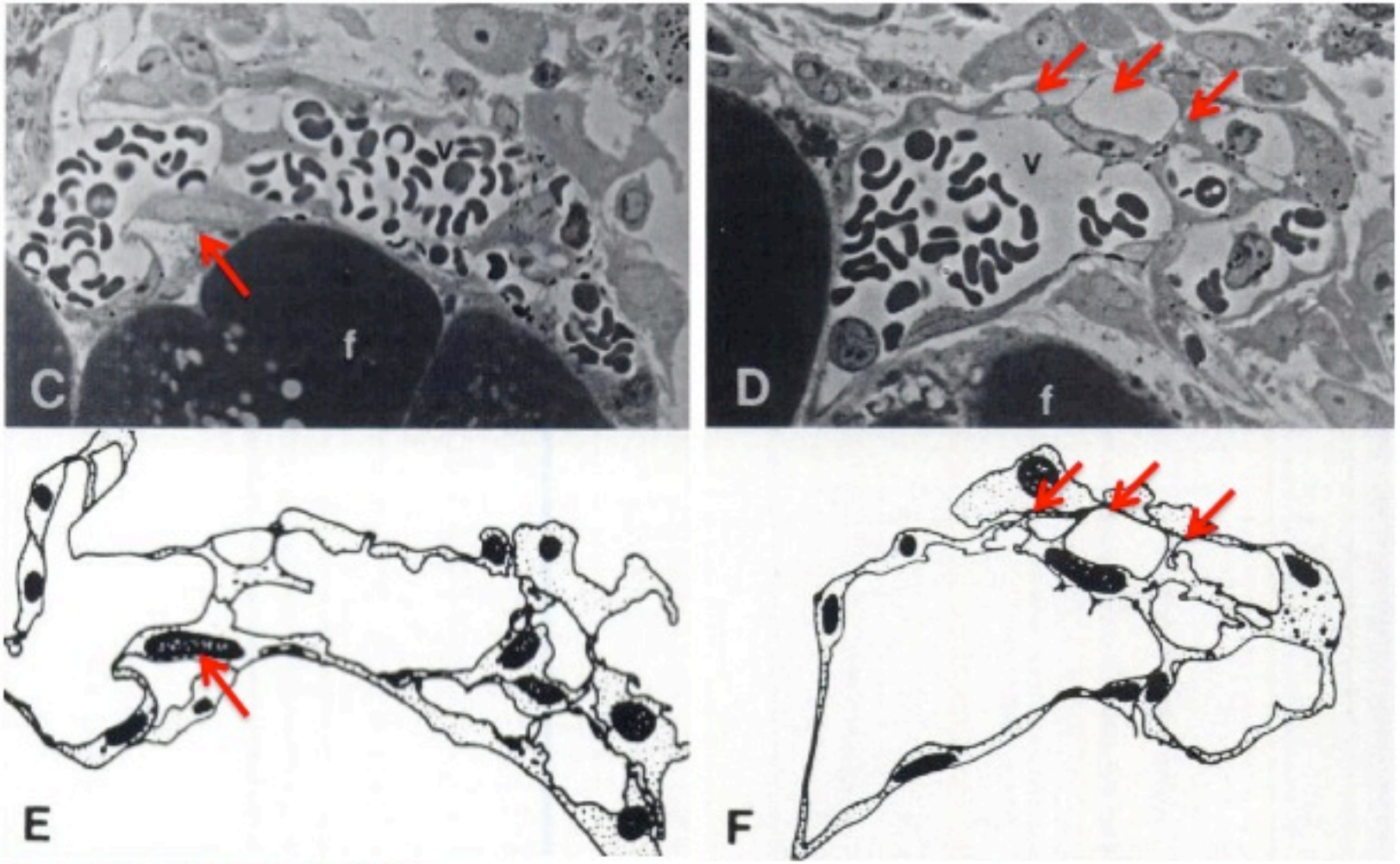
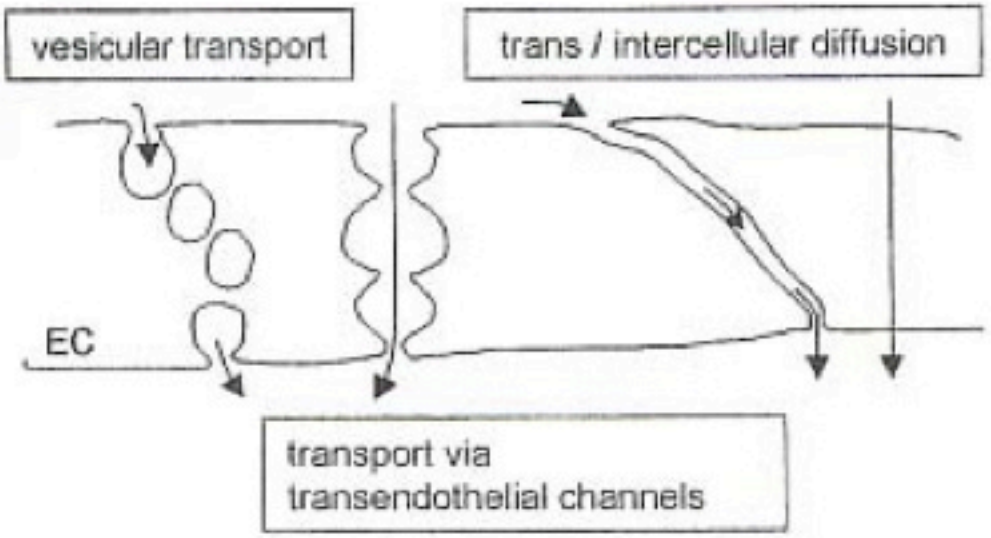
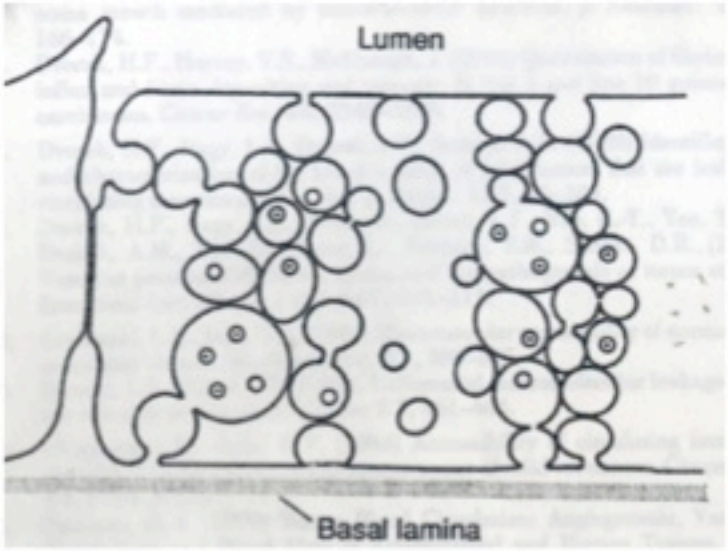
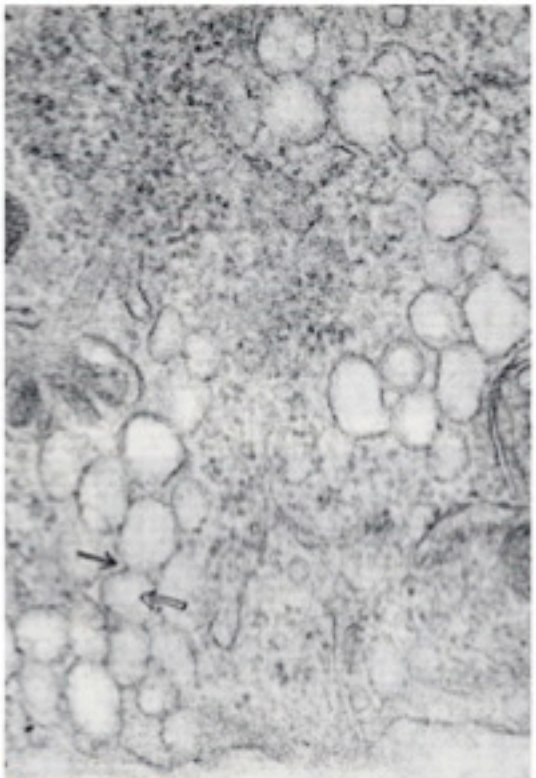


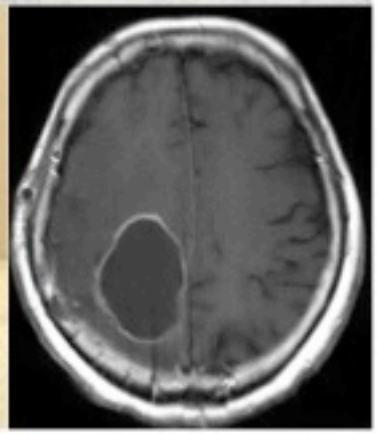
Cancer Res 55:360-368, 1995

Vesiculo Vacuolar Organella (VVO) formation by VEGF/VPF



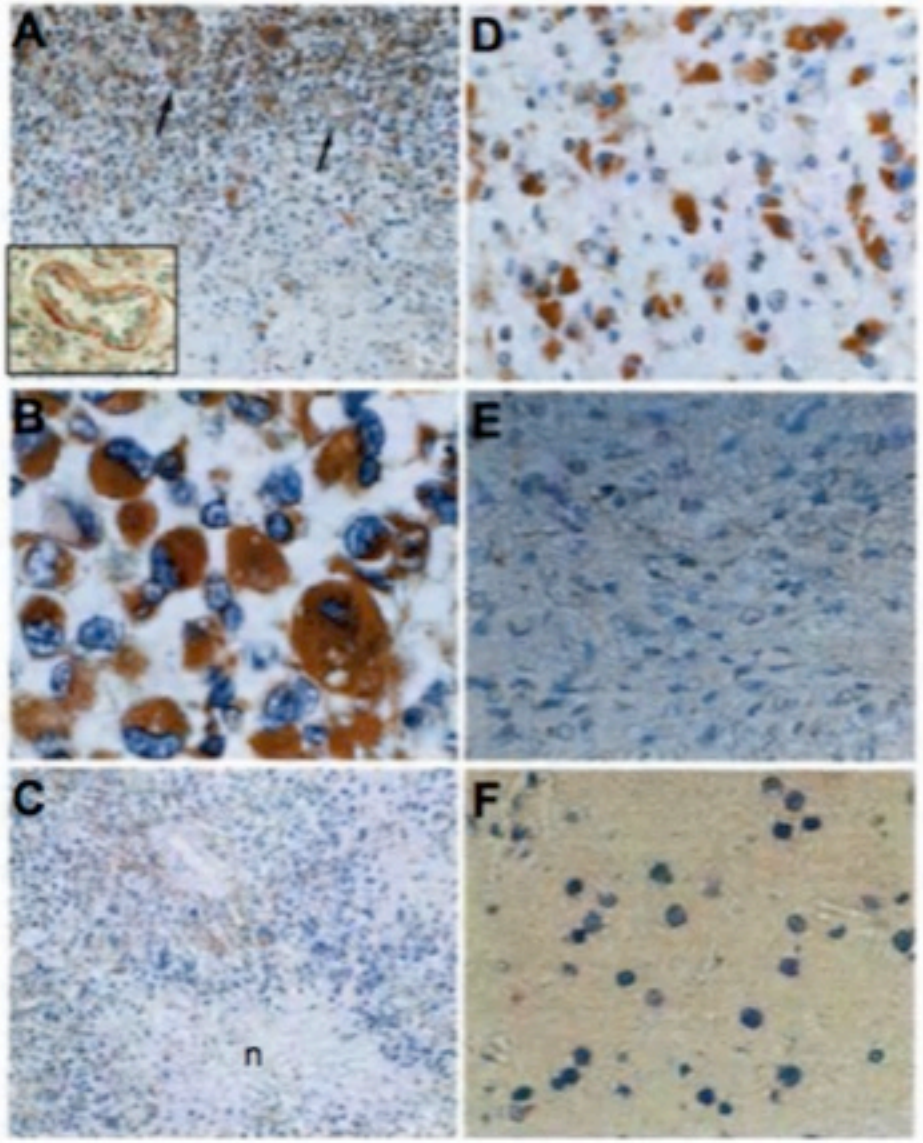


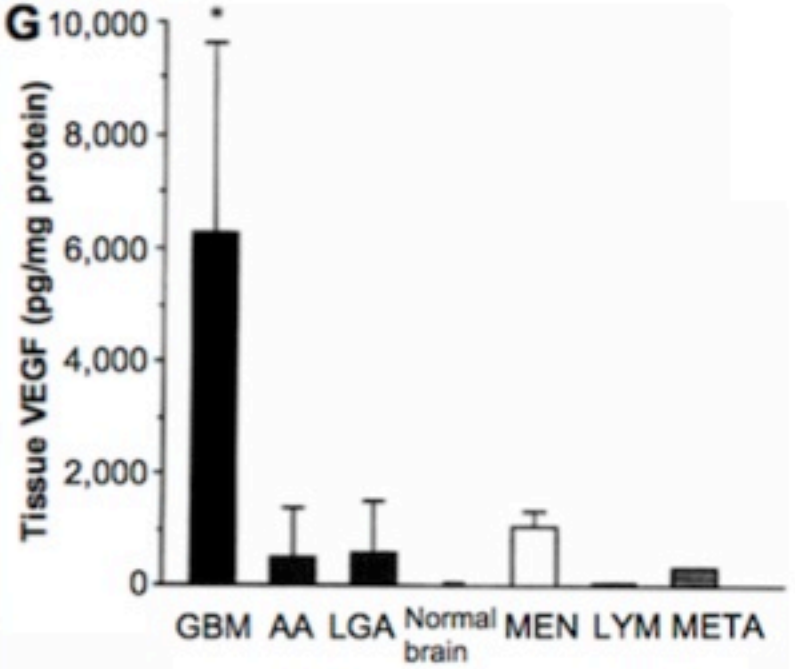


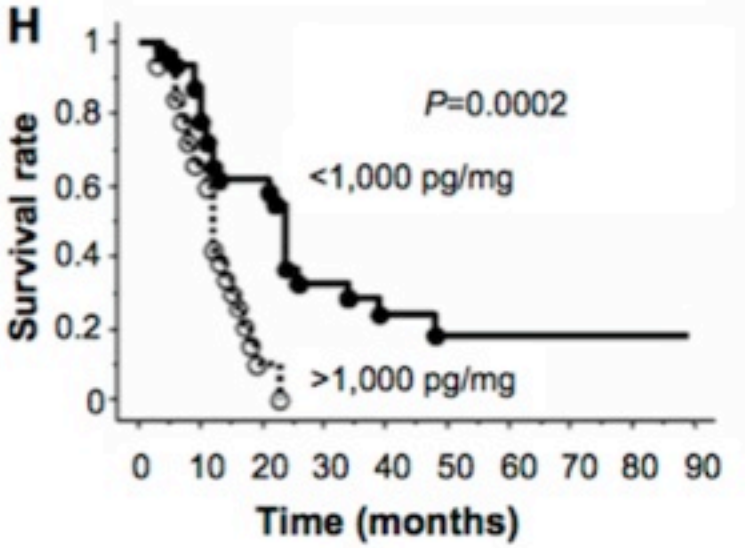


J Leukoc Biol 59:100-115, 1996

VEGF concentration in brain tumor & brain tissue





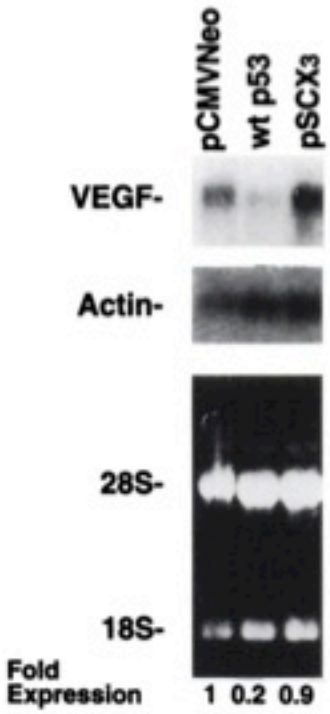


Onco Target Therapy 7:1551-1562, 2014

p53 & VEGF expression

Wild-type p53 and v-SRc exert opposing influences on human VEGF gene expression

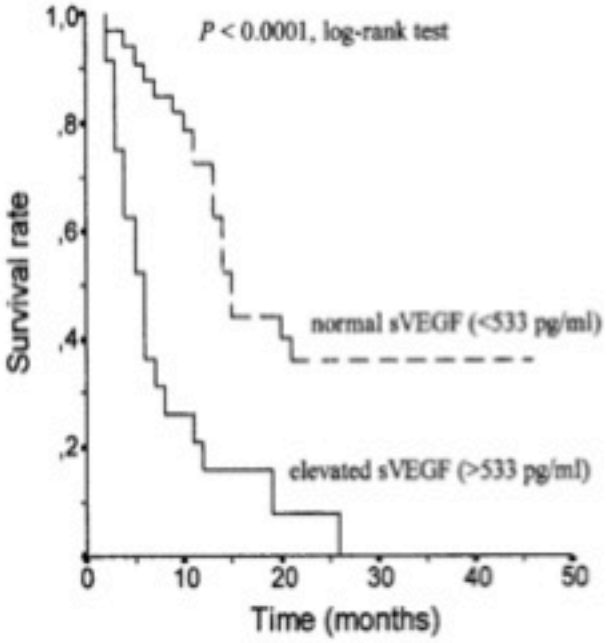
Cancer Res 1995;55:6161-6165



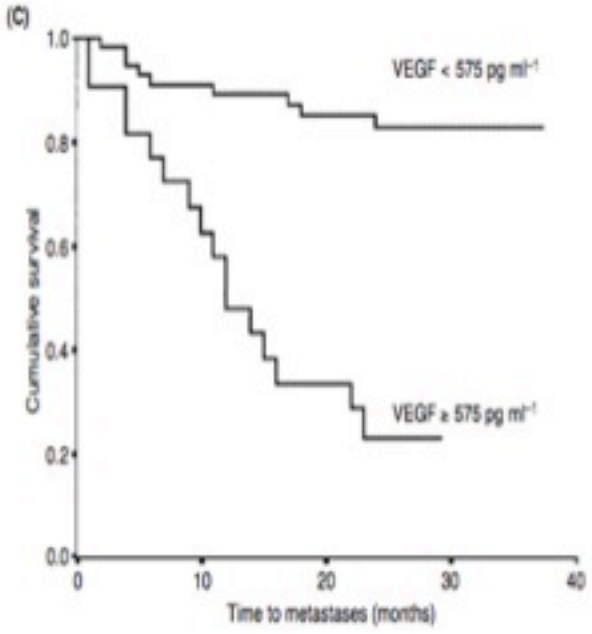
•	Colorectal cancer	; Int J Cancer	1997;74(5):502-507
•	Malignant glioma	; Brain Tumor Pathol	1998;15(2):95-100
•	Gastric cancer	; Oncology	1998;55(6):594-599
•	Lung cancer (NSCLC)	; Clin Cancer Res	1998;4(12):3017-3024
•	Breast cacner	; Int J Cancer	2000;89(1):51-62
•	Prostate cancer	; Prostate	2000;45(3):216-224
•	Esophagus cancer	; Am J Gastroenterol	2001;96(6):1733-1740
•	Renal cell carcinoma	; J Surg Oncol	2001;77(1):55-60
•	Uterus cancer	; Gynecol Oncol	2002;85(3):469-475
•	Ovary cancer	; Int J Gynecol Pathol	2011;30(6):521-526

Prognostic value of serum level of VEGF

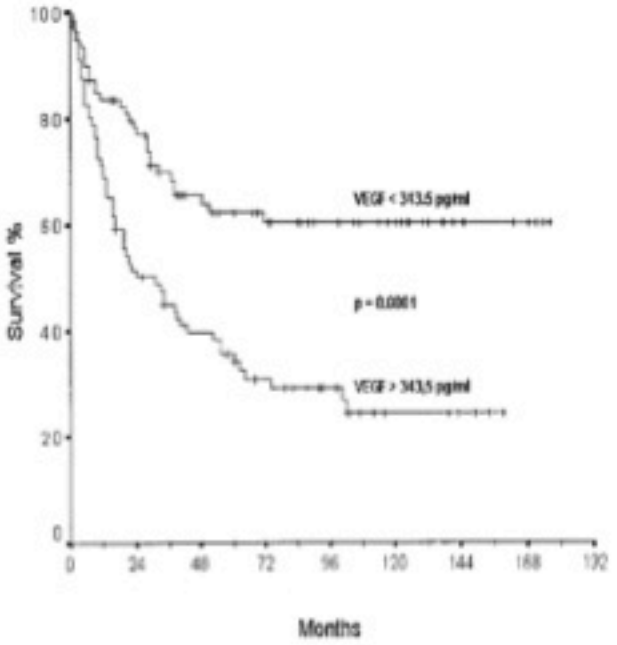
gastric cancer
(Ann Surg 2002)



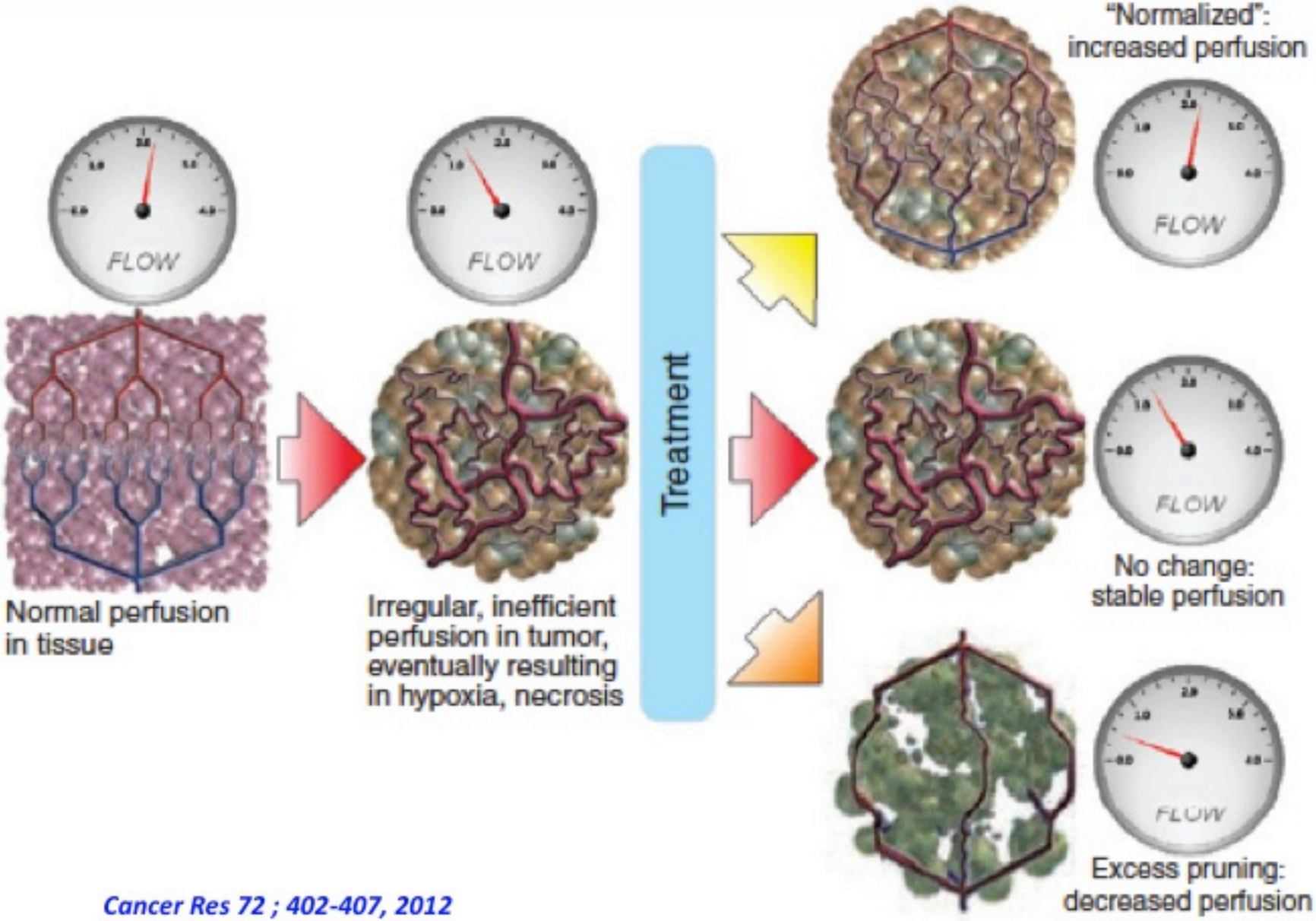
colorectal cancer
(Br J Cancer 83:1425-1431, 2000)



renal cell carcinoma
(J Urol 163:343-347, 2000)

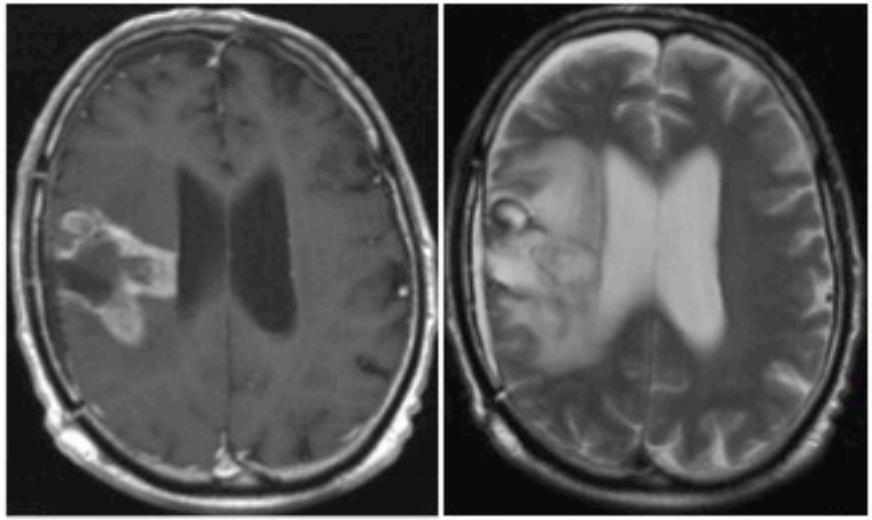


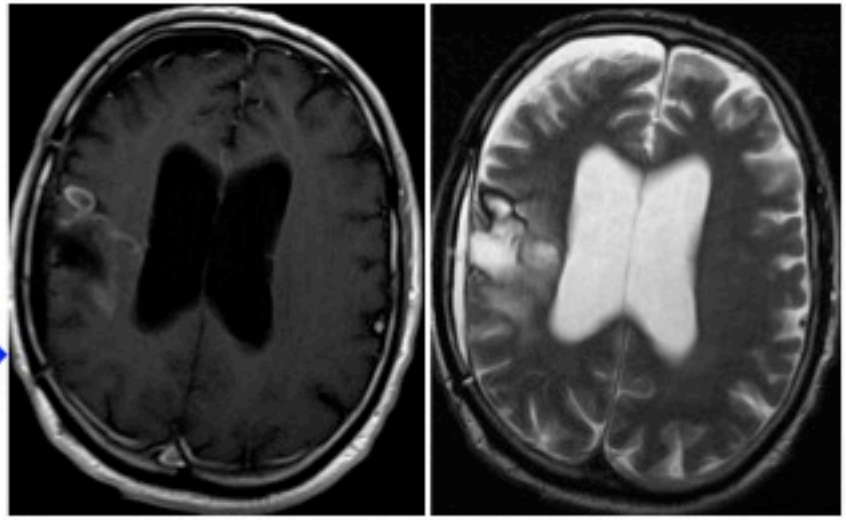
Vascular normalization



Cancer Res 72 ; 402-407, 2012

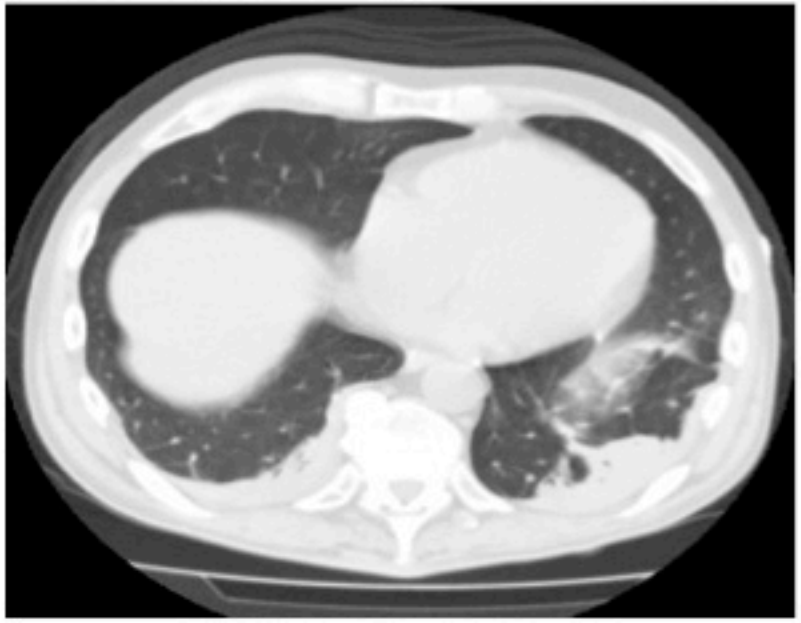
Effect of Bevacizumab on malignant brain tumor with lung cancer

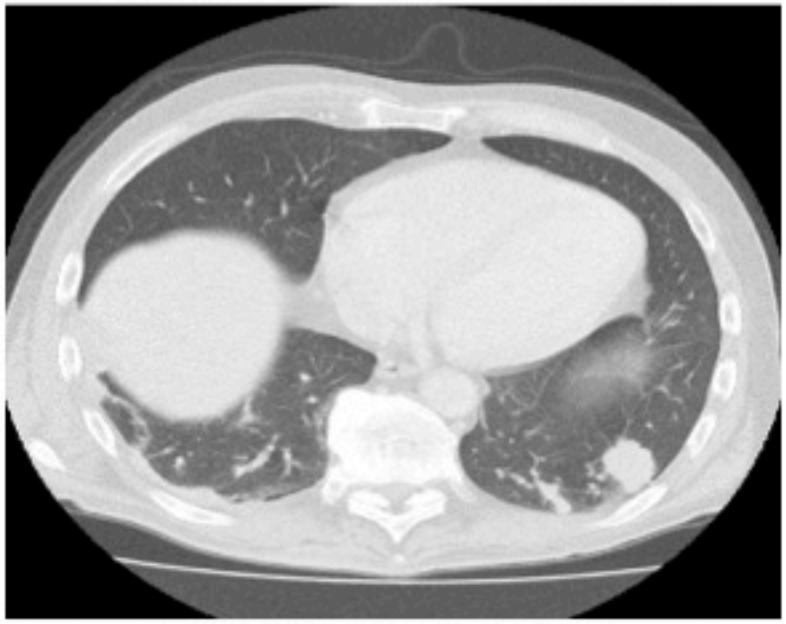




LBRT
+
TMZ
+
Bev

10mg/kg
q2wk
4 cycles





東京女子医科大学脳神経外科　丸山隆志先生より

Effect of Bevacizumab on malignant brain tumor with lung cancer

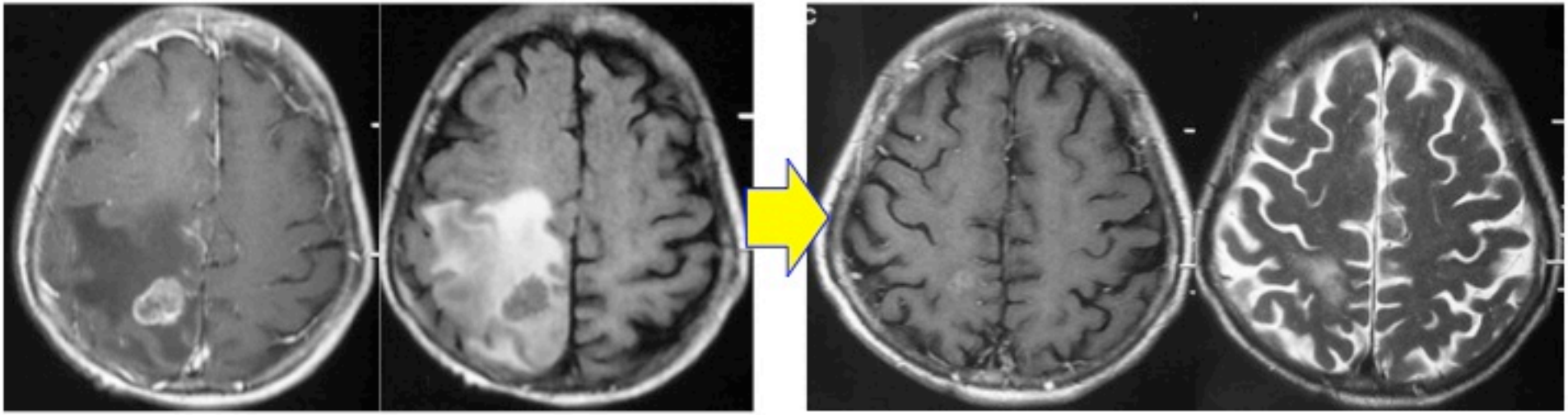
BEV+weeklyPTX

Intern Med 53: 1813-1818, 2014

A new strategy of cyberknife treatment system based radiosurgery followed by early use of adjuvant bevacizumab treatment for brain metastasis with extensive cerebral edema

Primary endpoint : response rate of tumor volume and edema volume

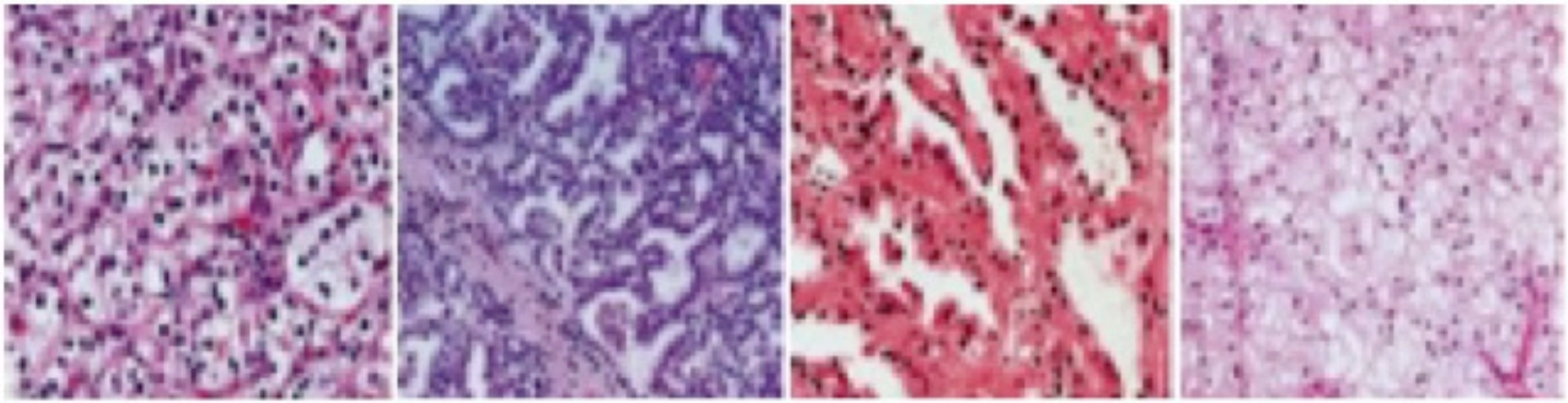
Start within two weeks Post SRS
BEV 5mg/kg/2wks



J Neurooncol 119:369–376, 2014

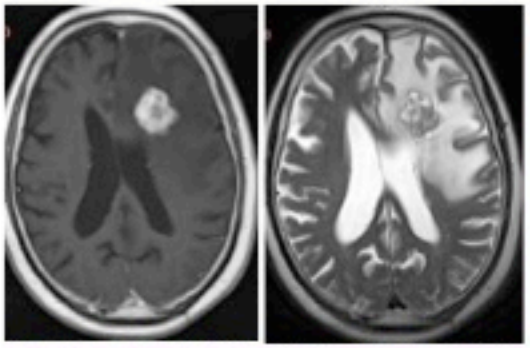
Histological classification of human renal epithelial neoplasms

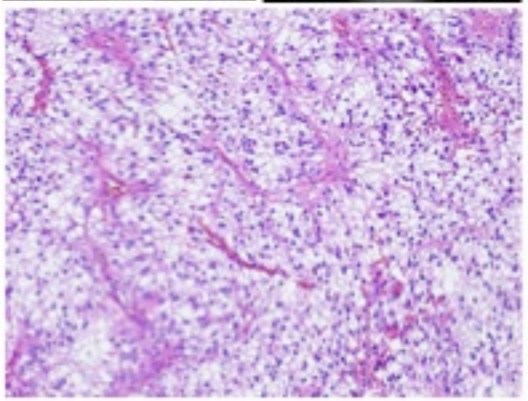
RCC

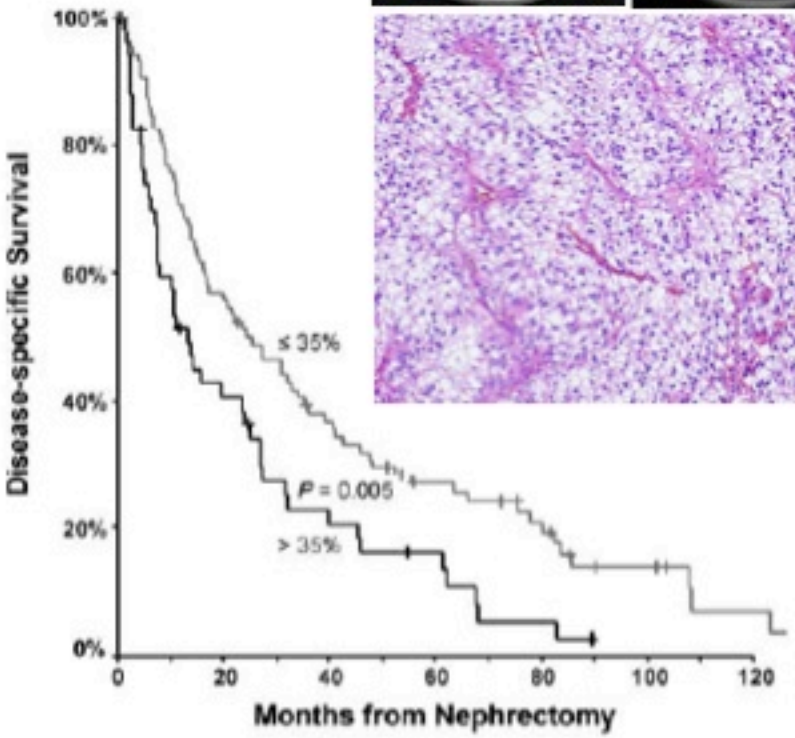


Type	Clear cell	Papillary type I	Papillary type II	chromophobe
Incidence (%)	75 %	5 %	5 %	5 %
Associated mutation	VHL	C-Met	C-Met	BHD

Interaction of VHL & HIF with/without oxygen

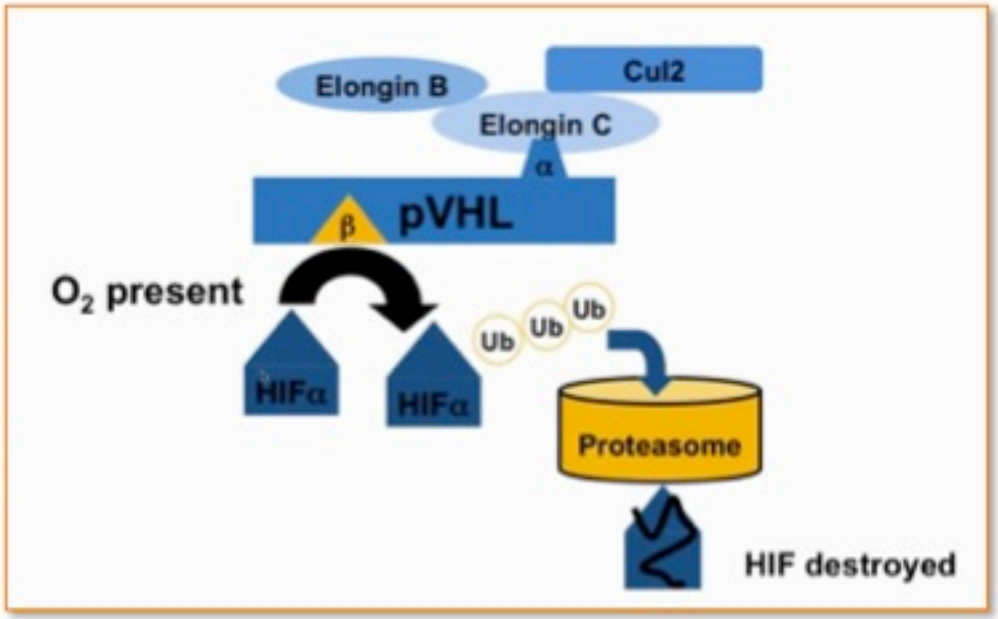


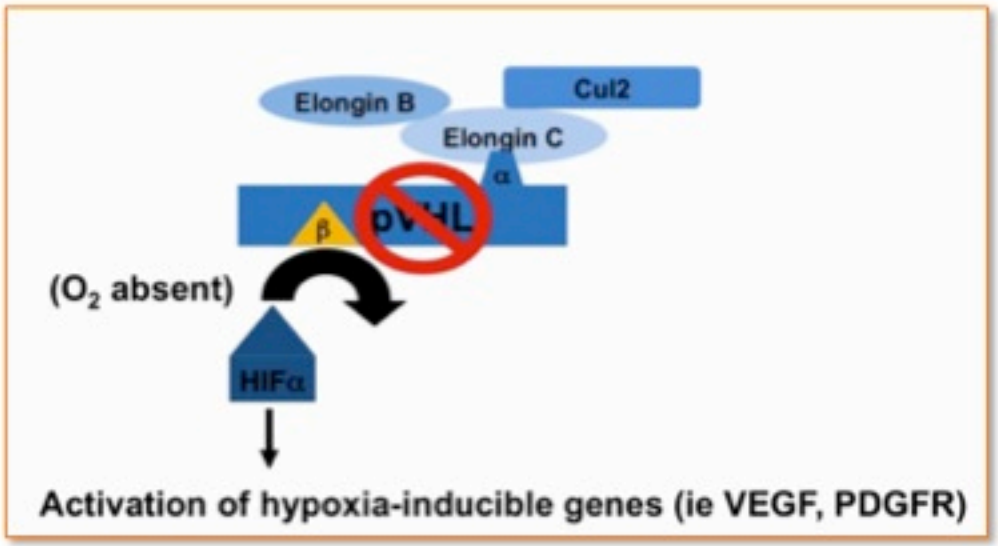




Kaplan-Meier survival estimates for patients with metastatic clear cell RCC substratified in high (>35%) and low (≤35%) HIF-1 α expression

Clin Cancer Res 13 ; 7388-7393, 2007





Does anti-angiogenesis therapy for brain tumors induce intracranial hemorrahge?

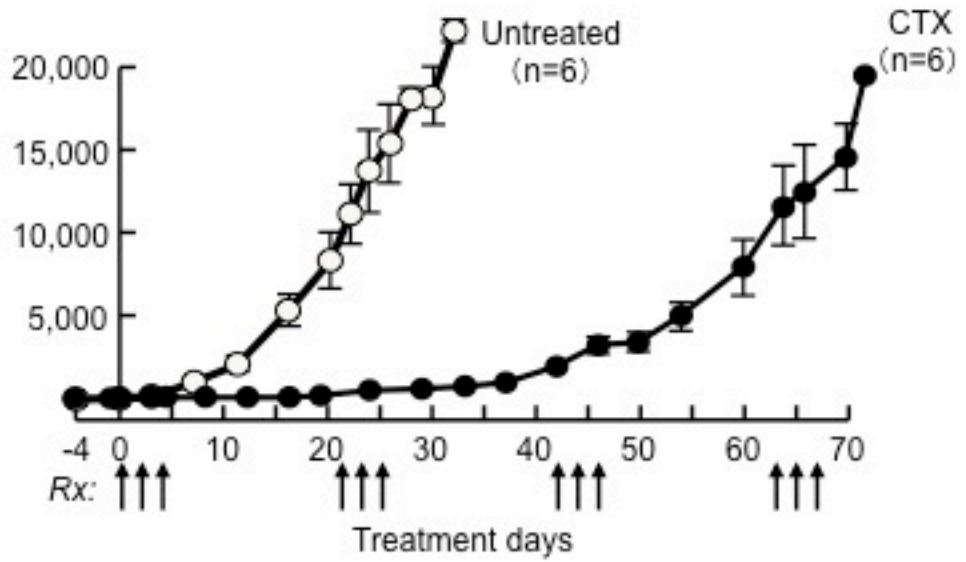
Incidence of intracranial hemorrhage in brain tumors

tumor	brain tumor with intracranial hemorrhage	
	without bevacizumab	with bevacizumab
Ovarian	4.3% (6 / 141)	0.0% (0 / 0)
NSCLC	3.6% (28 / 789)	3.9% (3 / 77)
Colon	2.9% (1 / 35)	7.0% (1 / 14)
Angiosarcoma	28.6% (4 / 14)	100.0% (1 / 1)
GBM	3.4% (61/1781)	2.8% (4 / 145)
Total for above tumors	3.6% (100/2760)	3.8% (9 / 237)

Ann Oncol 23 ; 458-463, 2012

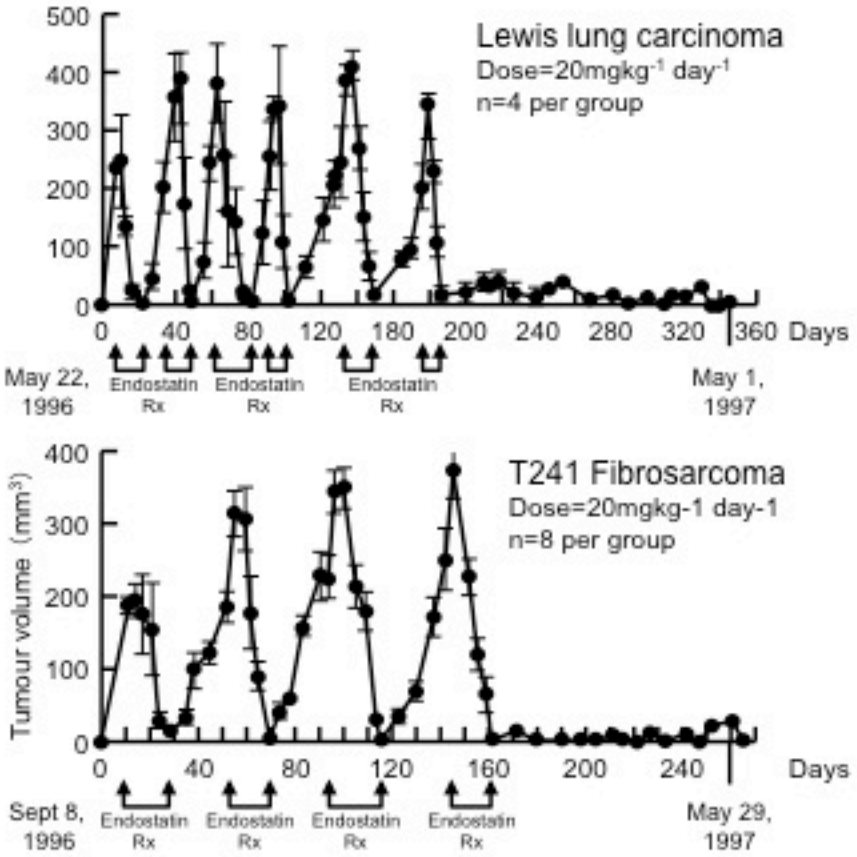
Does anti-angiogenesis therapy induce drug resistance ?

Expereimental therapeutics by cyclophosphamide



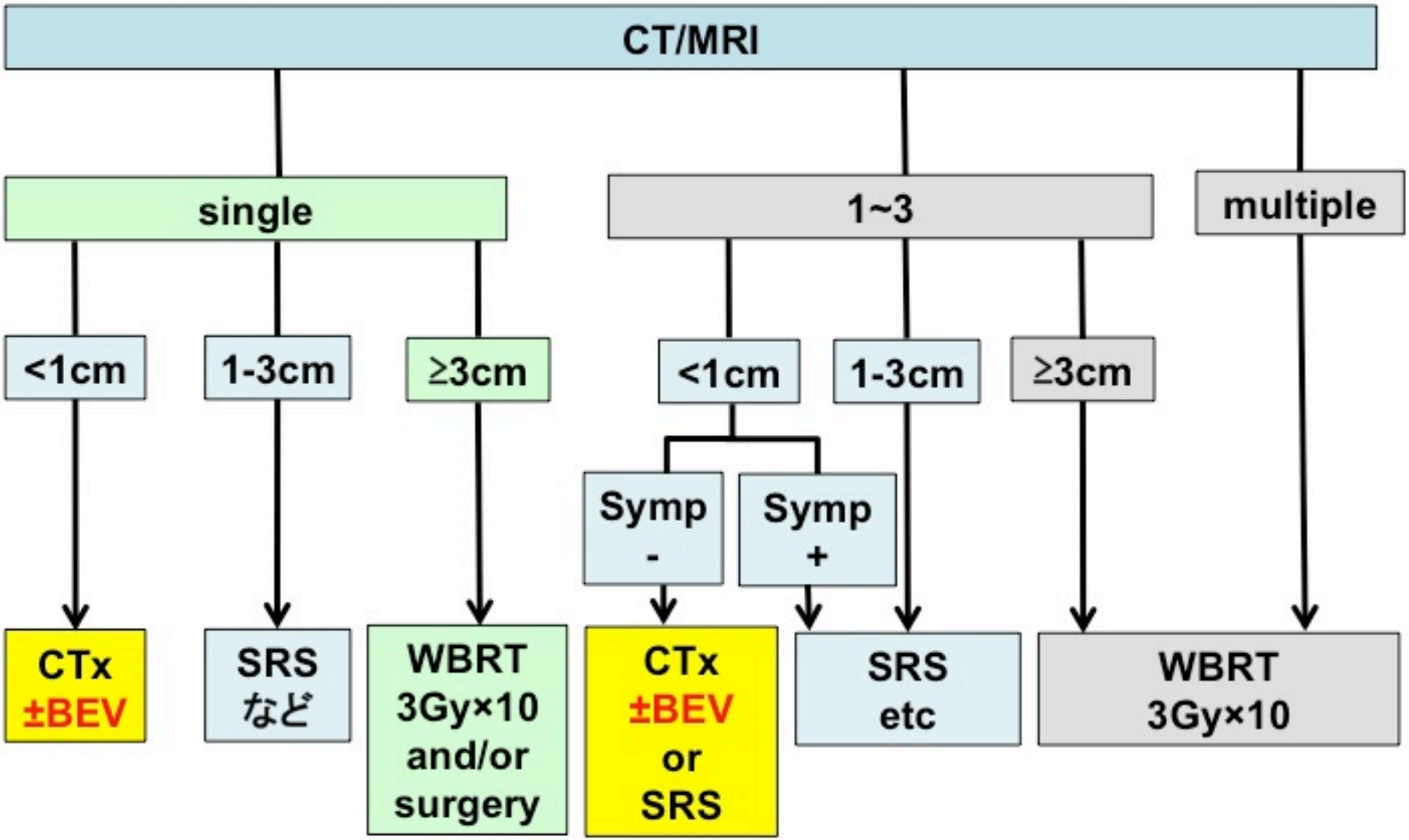
Cycled dormancy therapy

Expereimental therapeutics by endostatin



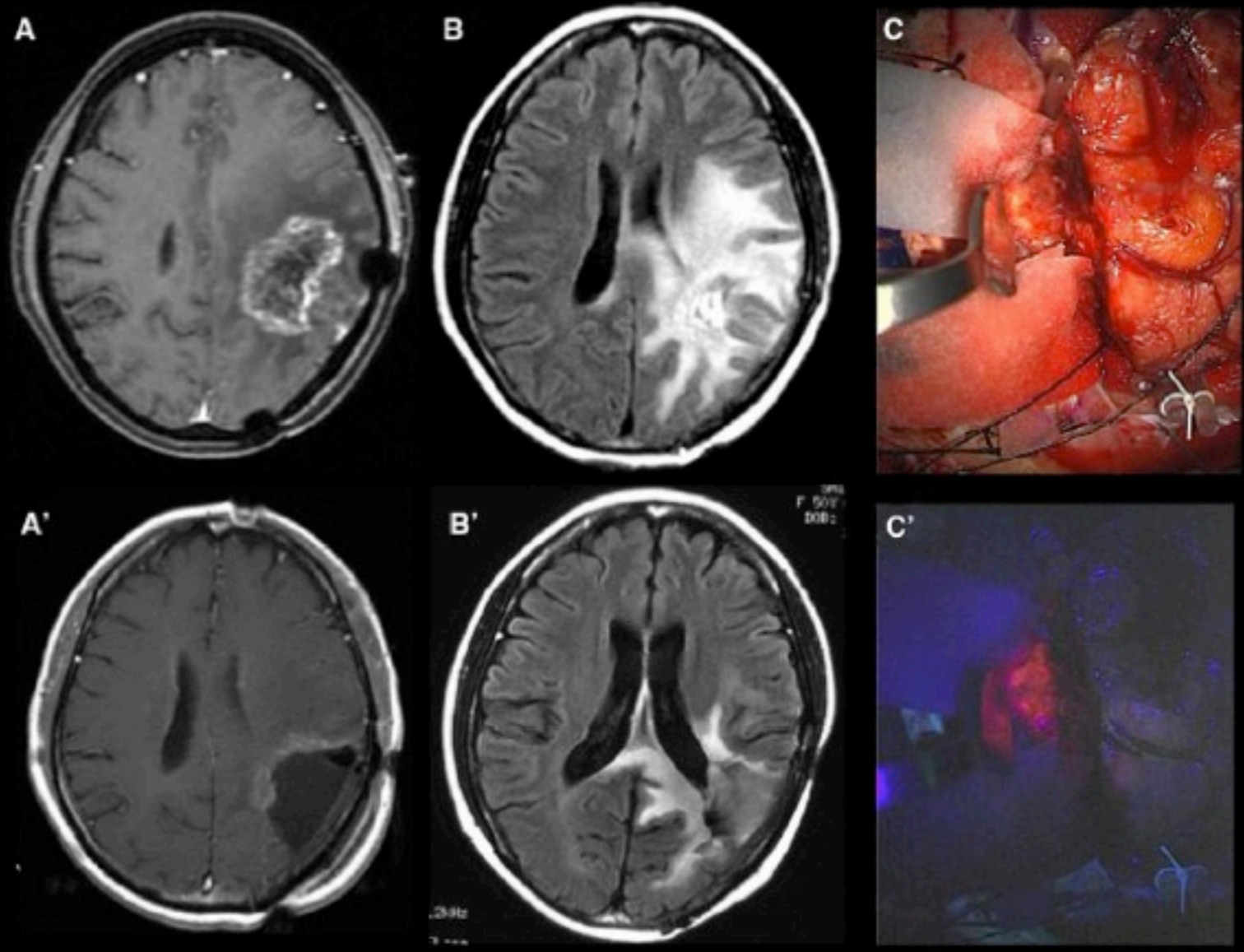
Thomas Boehm et al.Nature 390:404-407, 1998

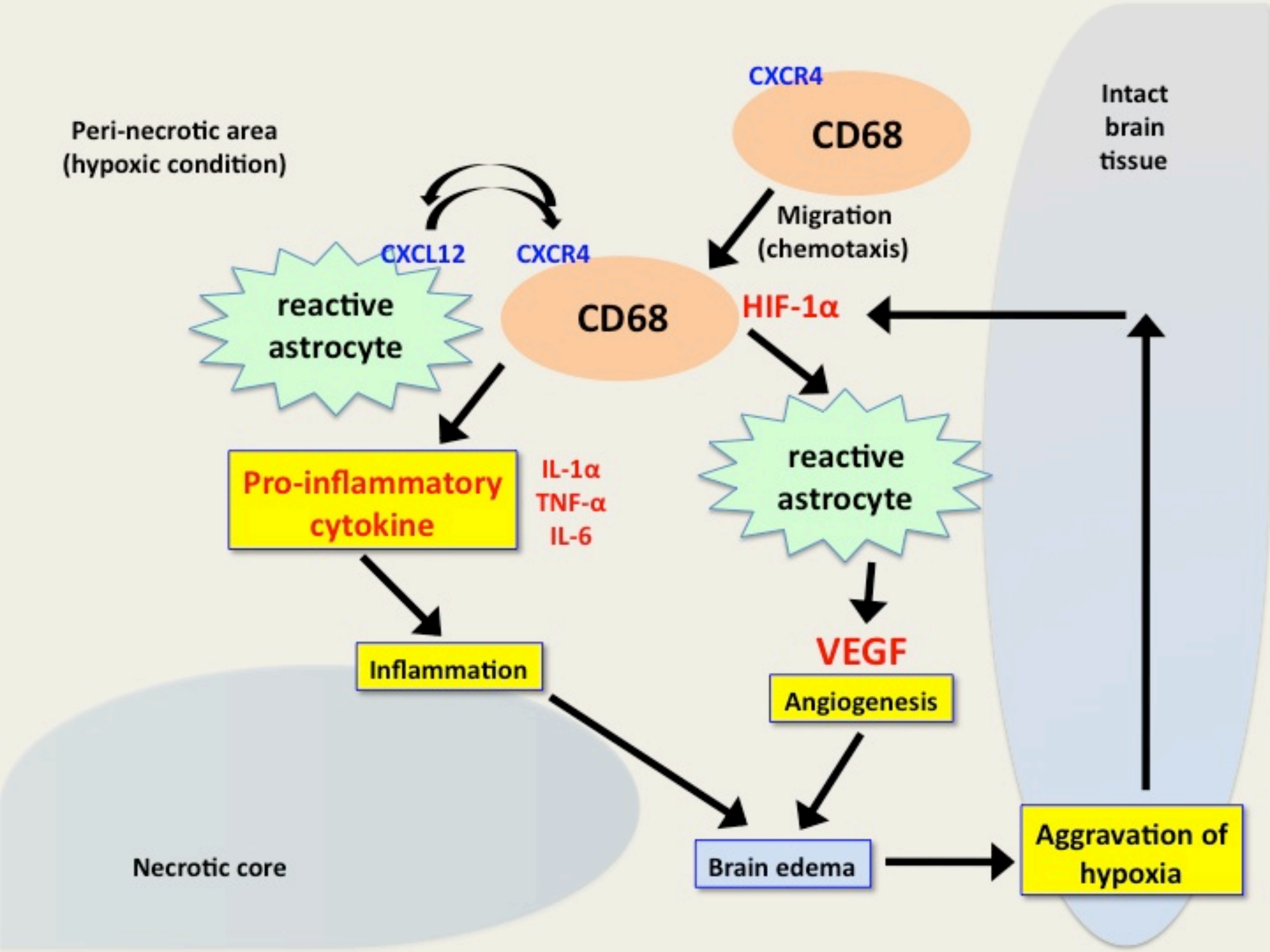
Algorithm for brain metastasis



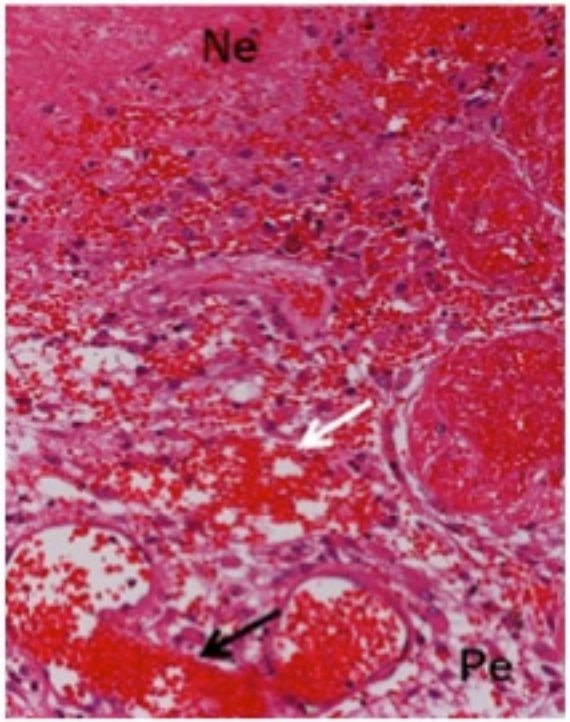
ガイドラインには載っていない 肺がん Practical Treatment,2014 改変

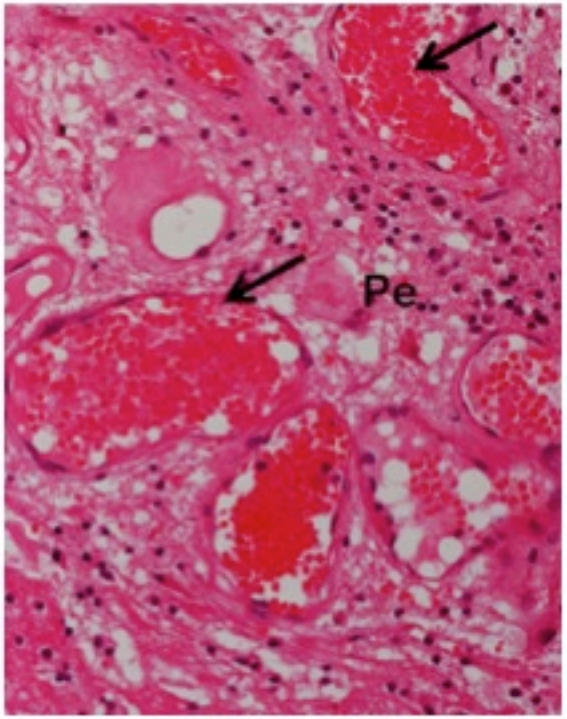
Radiation necrosis

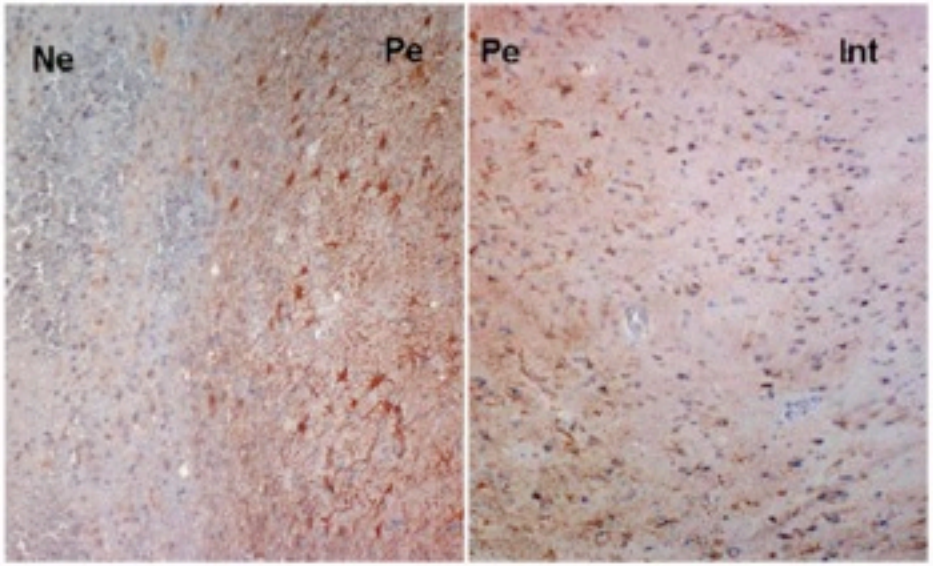


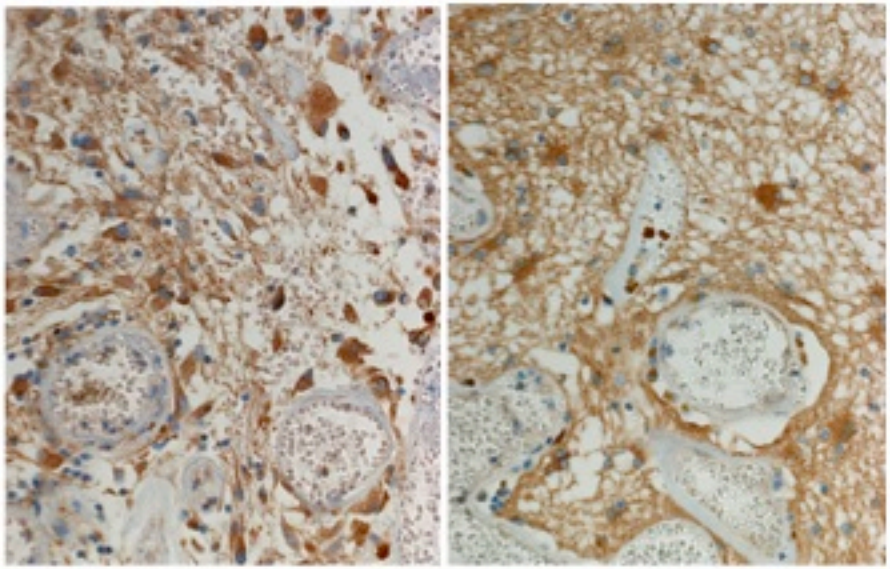

Peri-necrotic area
(hypoxic condition)
CXCR4
CD68
Intact
brain
tissue
Migration
(chemotaxis)
CXCL12
CXCR4
reactive
astrocyte
CD68
HIF-1α
Pro-inflammatory
cytokine
IL-1α
TNF-α
IL-6
reactive
astrocyte
VEGF
Inflammation
Angiogenesis
Necrotic core
Brain edema
Aggravation of
hypoxia

Radiation necrosis

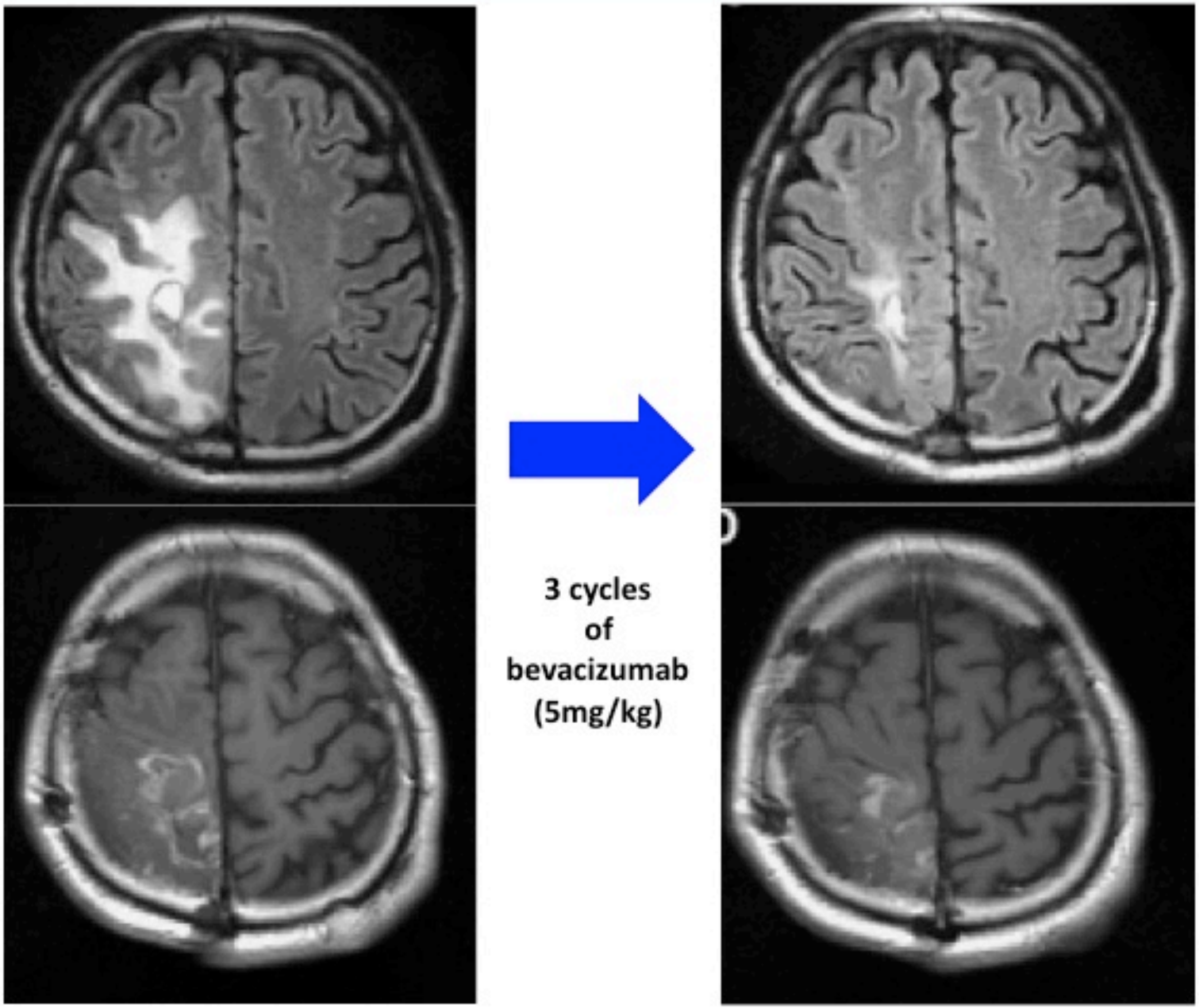








Bevacizumab for radiation necrosis



Summary

- Brain metastasis is a systemic disease.
- Combination therapy is inevitable including surgical operation.
  - Gamma knife is essential.
  - Surgery occasionally contribute to control larger volume of the tumor
- Molecular targeting agents is expected to improve clinical outcome of brain metastasis.
- Anti-angiogenesis therapy may be effective.
- "Vascular normalization" theory should be investigated.
  - Comprehension of BBB (blood brain barrier)