XXV CONGRESSO NAZIONALE
AIRO 2015
PALACONGRESSI - Rimini, 7-10 novembre

Gliomi di terzo grado: radioterapia, chemioterapia o radio-chemioterapia?

Dr Silvia Chiesa

Policlinico Agostino Gemelli
Università Cattolica del Sacro Cuore

Gemelli ART
Advanced Radiation Therapy

Relatore: Silvia Chiesa

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.

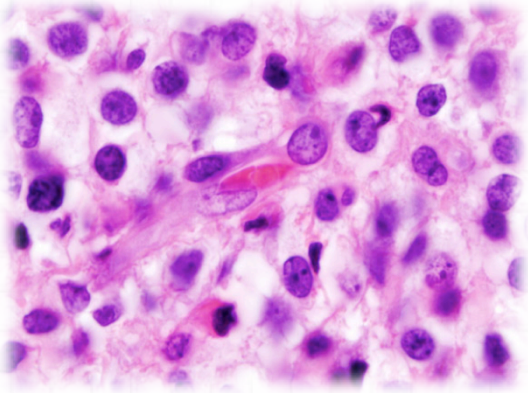
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà 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)**

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

Epidemiology

- **6-10%** of all newly diagnosed **primary brain tumours** in adults

- Three major types:
  - anaplastic astrocytoma (**AA**)
  - anaplastic oligoastrocytoma (**OA**)
  - anaplastic oligodendroglioma (**OD**)



Ohgaki H, *Methods in Molecular Biology*, 2009

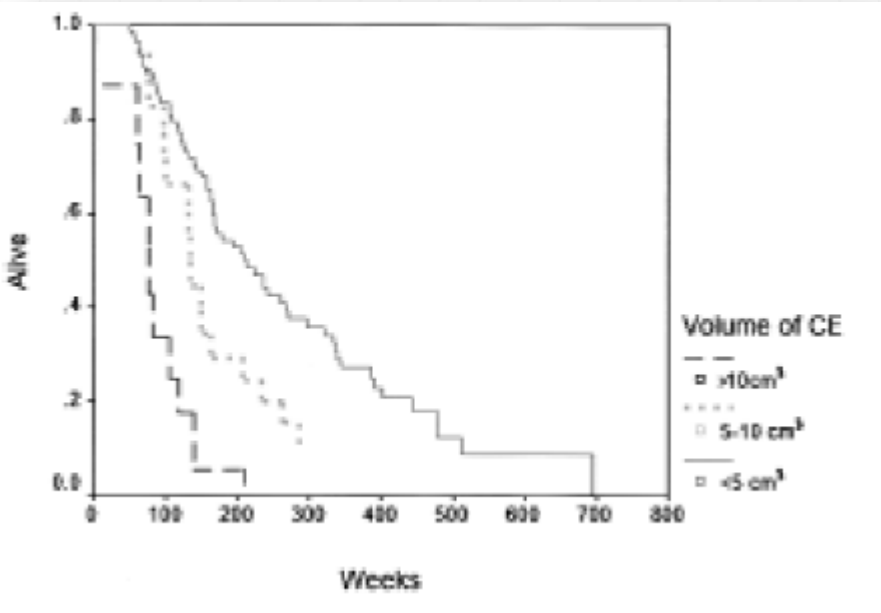
Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

Surgery

Volumetric extent of resection and residual contrast enhancement on initial surgery as predictors of outcome in adult patients with hemispheric anaplastic astrocytoma

G. Evren Keles, M.D., Edward F. Chang, M.D., Kathleen R. Lamborn, Ph.D., Tarik Tihan, M.D., Chih-Ju Chang, M.D., Susan M. Chang, M.D., and Mitchel S. Berger, M.D.

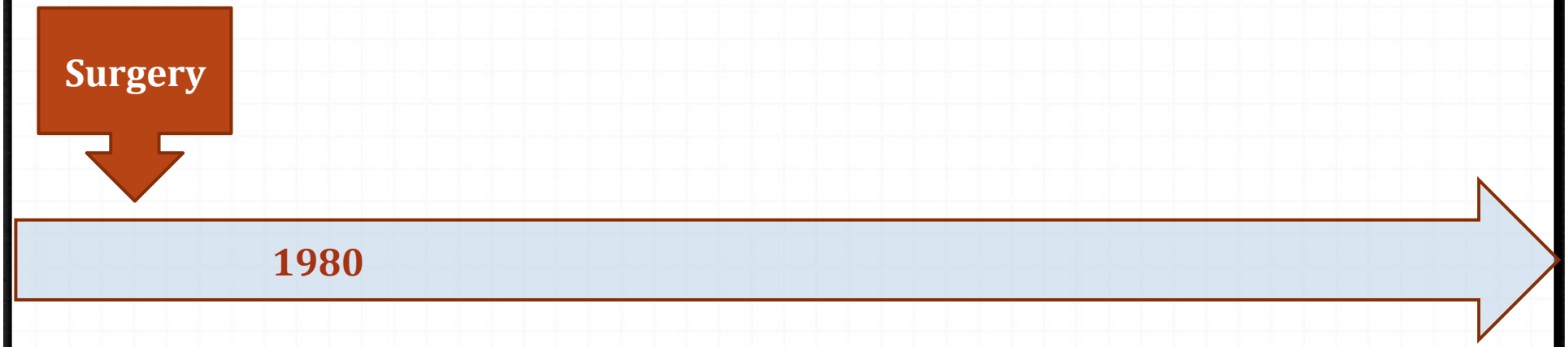
Department of Neurological Surgery, and Brain Tumor Research Center, University of California, San Francisco, California



p=0.03

J Neurosurg 105:34–40, 2006

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?



Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

A cooperative clinical trial

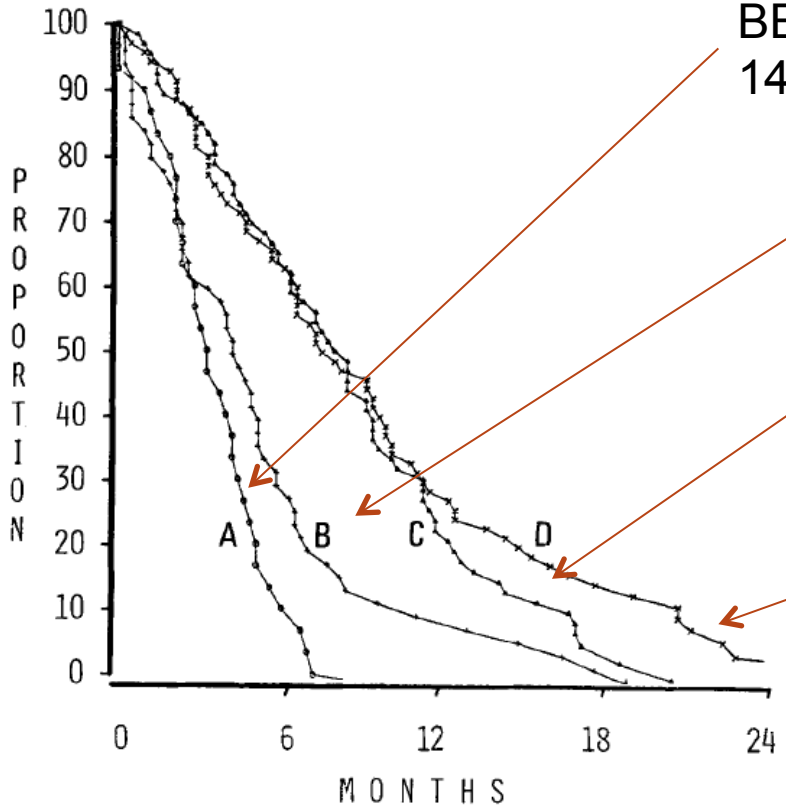


FIG. 1. Survival curves of patients who received: A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.

BEST CONVENTIONAL CARE: 14 weeks

BCNU: 18.5 weeks

RT + BCNU: 34.5 weeks

RT: 36 weeks

The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland

J Neurosurg 49:333–343, 1978

Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas

A cooperative clinical trial

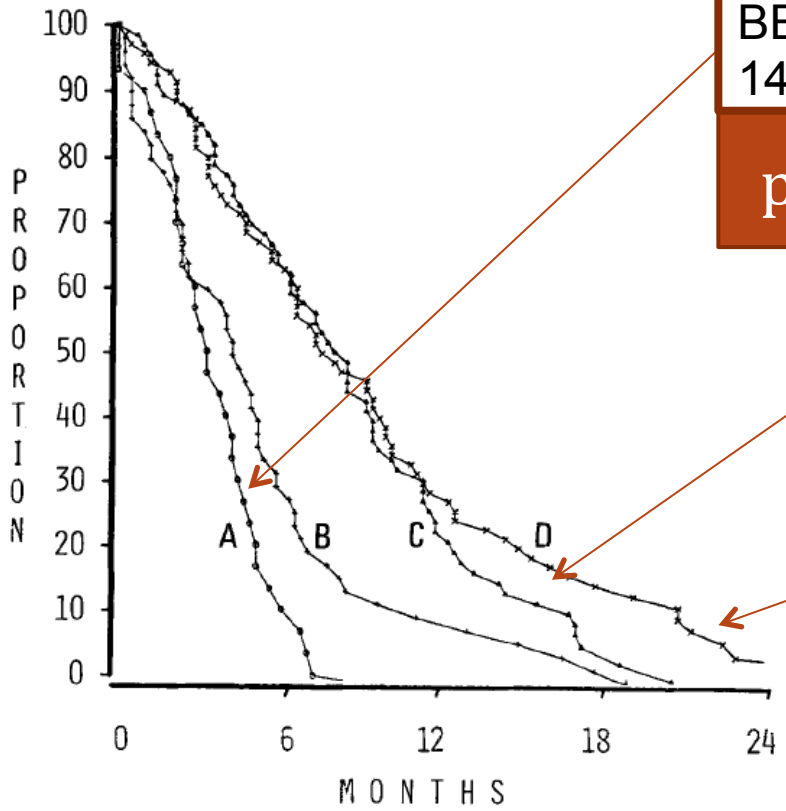


FIG. 1. Survival curves of patients who received: A) best conventional care but no radiotherapy or chemotherapy, B) BCNU, C) radiotherapy, or D) BCNU and radiotherapy.

BEST CONVENTIONAL CARE:
14 weeks

p= .001

RT + BCNU:
34.5 weeks

RT: 36 weeks

The Brain Tumor Study Group and the National Cancer Institute, National Institutes of Health, Bethesda, Maryland

J Neurosurg 49:333–343, 1978

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

RT Adj
Walker 1978,
Walker 1980,
Andersen 1978

1980

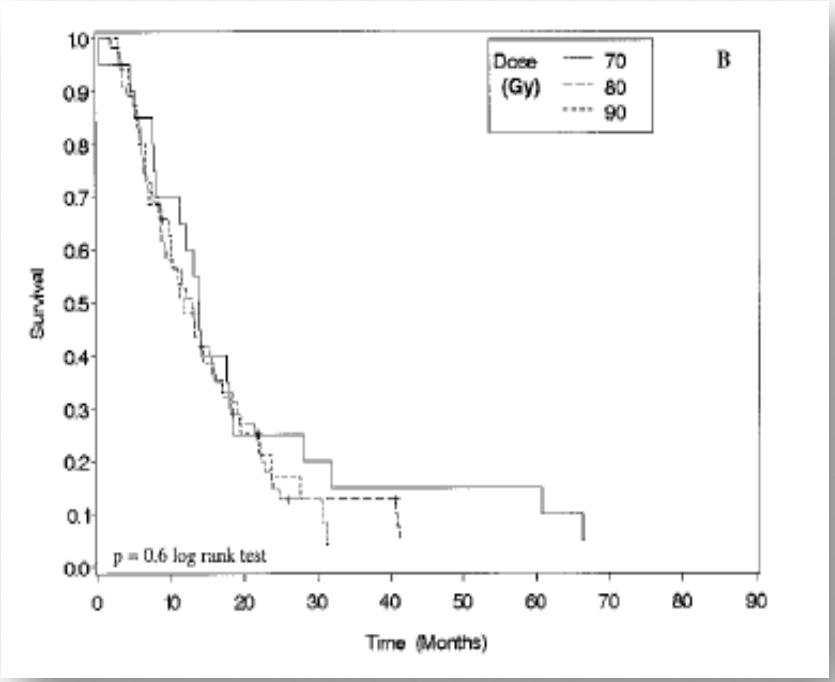
Journal of Clinical Oncology, Vol 20, No 6 (March 15), 2002

Survival and Failure Patterns of High-Grade Gliomas After Three-Dimensional Conformal Radiotherapy

By June L. Chan, Susan W. Lee, Benedick A. Fraass, Daniel P. Normolle, Harry S. Greenberg, Larry R. Junck, Stephen S. Gebarski, and Howard M. Sandler

>60 Gy
No advantage
in Median OS

60 Gy



Br. J. Cancer (1991), 64, 769–774

A Medical Research Council trial of two radiotherapy doses in the treatment of grades 3 and 4 astrocytoma

N.M. Bleehen & S.P. Stenning on behalf of the Medical Research Council Brain Tumour Working Party*

<60 Gy
Median OS
↓3 months
p=0.04

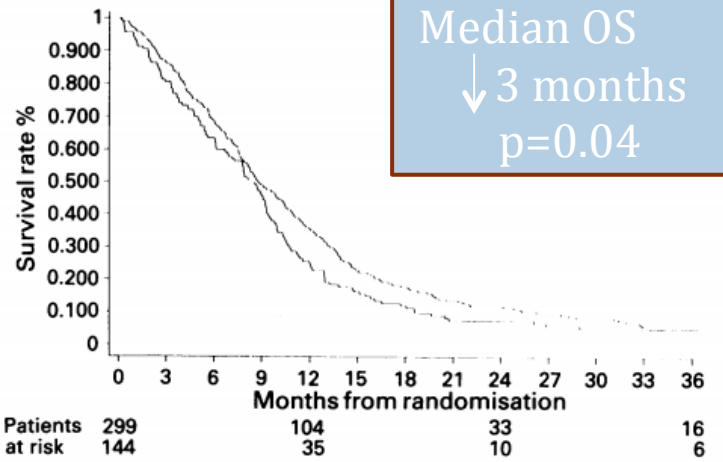


Figure 1 Survival by allocated treatment. —— Group 1 (45 Gy), – – – Group 2 (60 Gy).

Table V Survival rates %

Months	*Allocated treatment* 45 Gy	60 Gy
0	100	100
6	69	74
12	29	39
18	11	18
24	8	12
30	5	8
36	5	6
No. patients	144	299

Journal of Clinical Oncology, Vol 20, No 6 (March 15), 2002

Survival and Failure Patterns of High-Grade Gliomas After Three-Dimensional Conformal Radiotherapy

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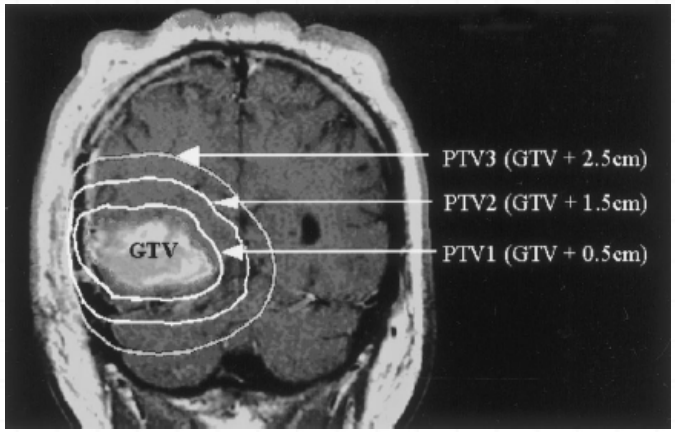
>60 Gy
No advantage
in Median OS

60 Gy
Focal
RT



Recurrence: 67,6 % -23/36)

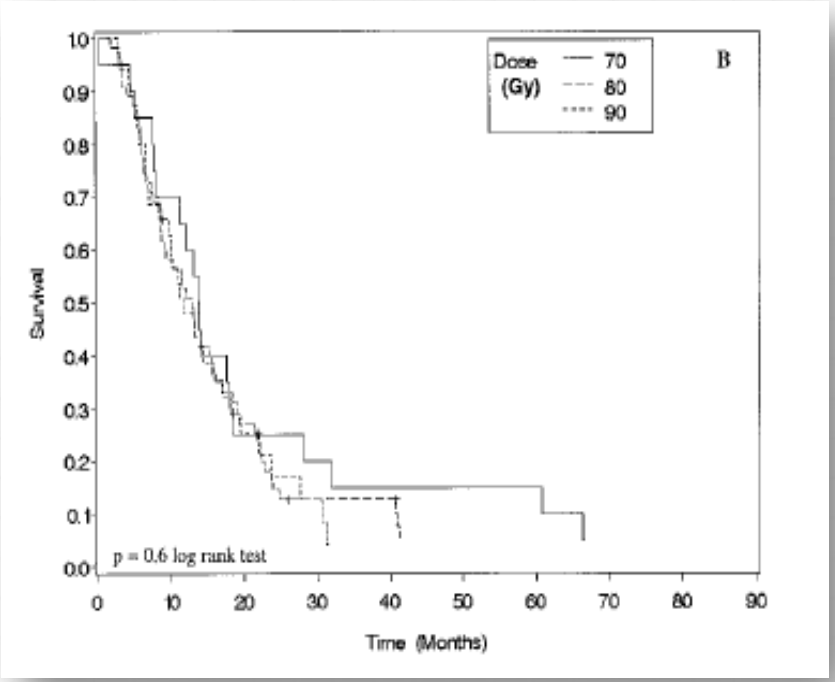


Table 5. Recurrence Location Characteristics

	Frequency	
	No. of Patients	%
Recurrence location		
Central	18/23	78
In-field	3/23	13
Marginal	2/23	9
Distant	0	
Reclassified location		
Inside	21/23	91
Marginal	2/23	9
Distant	0	

IMRT?

for OAR

Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 3, pp. 892–897, 2006

0360-3016/06/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2005.05.067

CLINICAL INVESTIGATION **Brain**

INTENSITY-MODULATED RADIOTHERAPY IN HIGH-GRADE GLIOMAS: CLINICAL AND DOSIMETRIC RESULTS

Ashwatha Narayana, M.D.,* Josh Yamada, M.D.,* Sean Berry, M.S.,† Priti Shah, B.S.,* Margie Hunt, M.S.,† Philip H. Gutin, M.D.,‡§ and Steven A. Leibel, M.D.‖

Departments of *Radiation Oncology, †Medical Physics, and ‡Surgery, Memorial Sloan-Kettering Cancer Center; §Department of Neurological Surgery, Weill Medical School and Cornell Medical Center, New York, NY; and ‖Stanford University Cancer Center, Stanford, CA

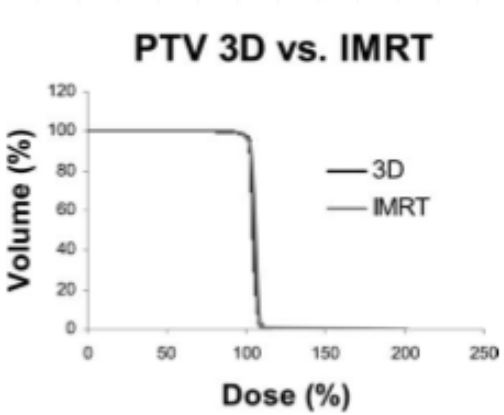


Fig. 5. Dose–volume histogram of planning target volume with three-dimensional (3D) and intensity-modulated radiot (IMRT) treatment.

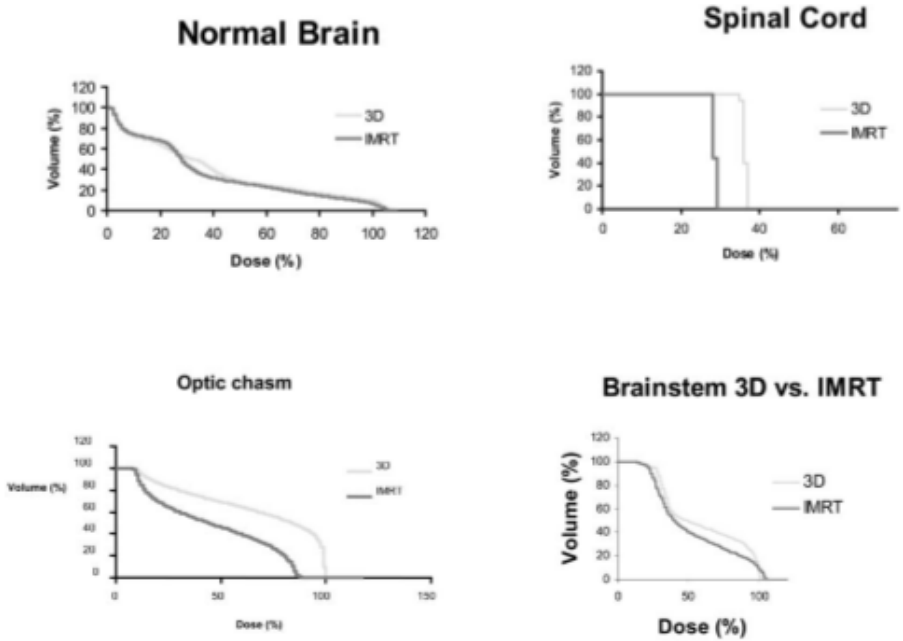


Fig. 6. Dose–volume histogram of critical structures and normal brain tissue with three-dimensional (3D) and intensity-modulated radiotherapy (IMRT) treatment volume (%).

IMRT?

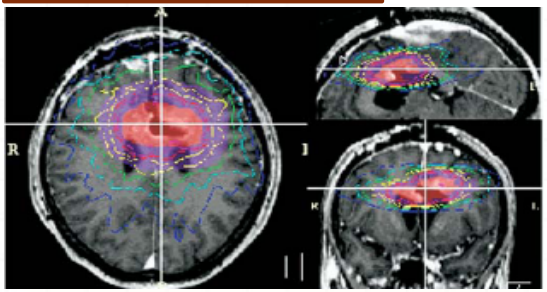
for OAR

Improving outcomes?

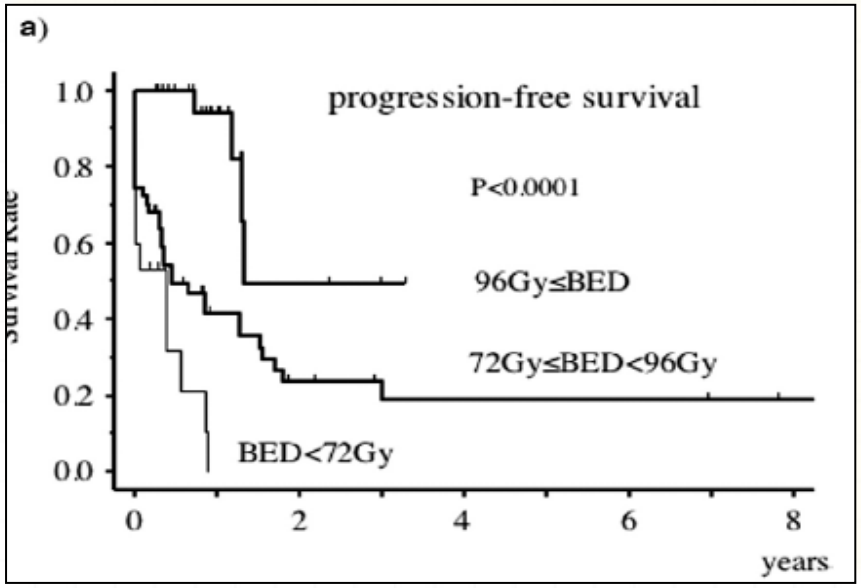
HYPOFRACTIONATED HIGH-DOSE IRRADIATION FOR THE TREATMENT OF MALIGNANT ASTROCYTOMAS USING SIMULTANEOUS INTEGRATED BOOST TECHNIQUE BY IMRT

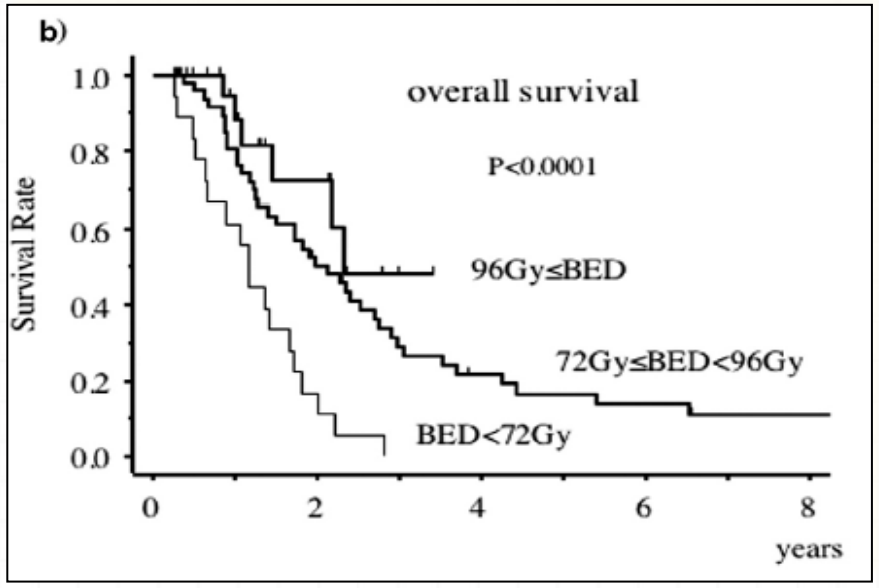
Toshihiko Iuchi, M.D.,* Kazuo Hatano, M.D.,† Yuichiro Narita, Ph.D.,† Takashi Kodama, Ph.D.,† Tomohiro Yamaki, M.D.,* and Katsunobu Osato, M.D.*

*Division of Neurological Surgery and †Radiation Oncology, Chiba Cancer Center, Chiba, Japan



- PTV-1 : area di enhanced con 5 mm di margine (48 - 68 Gy)
- PTV-2 : area con 15 mm di margine attorno al PTV-1 (40 Gy)
- PTV-3 : area di edema perilesionale (32 Gy)





Int J Radiat Oncol Biol Phys. 2006

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

RT Adj
Walker 1978,
Walker 1980,
Andersen 1978

1980

Clinical practice

Neuro-Oncology 14(6):761–767, 2012.
doi:10.1093/neuonc/nos065

NEURO-ONCOLOGY

Initial treatment patterns over time for anaplastic oligodendroglial tumors

Katherine S. Panageas, Fabio M. Iwamoto, Timothy F. Cloughesy, Kenneth D. Aldape, Andreana L. Rivera, April F. Eichler, David N. Louis, Nina A. Paleologos, Barbara J. Fisher, Lynn S. Ashby, J. Gregory Cairncross, Gloria B. Roldán Urgoiti, Patrick Y. Wen, Keith L. Ligon, David Schiff, H. Ian Robins, Brandon G. Rocque, Marc C. Chamberlain, Warren P. Mason, Susan A. Weaver, Richard M. Green, Francois G. Kamar, Lauren E. Abrey, Lisa M. DeAngelis, Suresh C. Jhanwar, Marc K. Rosenblum, and Andrew B. Lassman

Initial Treatment	1980–1984 (*n* = 6%)	1985–1989 (*n* = 28%)	1990–1994[a] (*n* = 101%)	1995–1999[a] (*n* = 294%)	2000–2004[a] (*n* = 469%)	2005–2007 (*n* = 115%)
CT alone, *n* (%)	0 (0)	1 (4)	10 (10)	43 (15)	103 (22)	44 (38)
RT alone	4 (67)	15 (54)	30 (30)	65 (22)	80 (17)	6 (5)
CT + RT	1 (17)	11 (39)	51 (51)	144 (49)	262 (56)	59 (51)
Observation	1 (17)	1 (4)	7 (7)	32 (11)	17 (4)	6 (5)

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

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Observation	1 (17)	1 (4)

Clinical practice

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

RT Adj
Walker 1978,
Walker 1980,
Andersen 1978

Chemio sensitivity
Cairncross 1988
Fine, 1993,
Stewart 2002

1980 **1990**

Initial Treatment	1980–1984 (n = 6%)	1985–1989 (n = 28%)
CT alone, n (%)	0 (0)	1 (4)
RT alone	4 (67)	15 (54)
CT + RT	1 (17)	11 (39)
Observation	1 (17)	1 (4)

Clinical practice

Chemiosensitivity

Ann Neurol. 1988 Apr;23(4):360-4.

Successful chemotherapy for recurrent malignant oligodendroglioma.

Cairncross JG[1], Macdonald DR.

Author information

Abstract

Eight consecutive patients with recurrent malignant oligodendroglioma were treated with systemic chemotherapy. Six patients received a combination of procarbazine, lomustine (CCNU), and vincristine; 1 received carmustine (BCNU), and 1 diaziquone. All responded by clinical and computed tomographic scan criteria. One patient had a complete response for 78 weeks, and 7 patients had unequivocal partial responses lasting 30+ to 68+ weeks. Two partial responders had complete control of systemic metastases. Malignant oligodendroglioma is a uniquely chemosensitive glial tumor.

Author	Treatment arm
Reagan[39]	XRT
	XRT + CCNU
Garrett[40]	XRT
	XRT + CCNU
Walker[10]	XRT
	XRT + BCNU
Eagan[41]	XRT
	XRT + dianhydrogalactitol
Solero[42]	XRT
	XRT + BCNU
	XRT + CCNU
Walker[11]	XRT
	XRT + BCNU
	XRT + Me-CCNU
Cianfriglia[43]	XRT
	XRT + CCNU
EORTC[44]	XRT
	XRT + VM-26 + CCNU
Chin[45]	XRT
	XRT + BCNU
	XRT + Me-CCNU
Kristiansen[46]	XRT
	XRT + bleomycin

Chang[47]	
Astrocytoma	XRT
	XRT + boost
	XRT + BCNU
	XRT + Me-CCNU + DTIC
Glioblastoma	XRT
	XRT + boost
	XRT + BCNU
	XRT + Me-CCNU + DTIC
Green[32]	XRT + methylprednisone
	XRT + BCNU
	XRT + procarbazine
	XRT + BCNU + methylprednisone
Afra[48]	XRT
	XRT + dibromodulcitol
	XRT + dibromodulcitol + CCNU
Ushio[49]	XRT
	XRT + bleomycin
	XRT + Me-CCNU
	XRT + Me-CCNU + bleomycin
Takakura[50]	
Astrocytoma	XRT
	XRT + ACNU
Glioblastoma	XRT
	XRT + ACNU
Trojanowski[15]	XRT
	XRT + CCNU

Chemiosensitivity

Meta-Analysis of Radiation Therapy with and without Adjuvant Chemotherapy for Malignant Gliomas in Adults

Howard A. Fine, M.D.,‖¶ Keith B. G. Dear, Ph.D.,†# Jay S. Loeffler, M.D.,§‖** Peter McL. Black, M.D., Ph.D.,‡‖ and George P. Canellos, M.D.**

CANCER *April 15, 1993,* Volume 71, No. 8

- **16** randomized **studies**
- **Anaplastic astrocitoma and GBM**
- **Increase in survival** of 23.4% at 1 year and 52.4% at 2 year.
- Survival advantage is conferred **by several** different **chemotherapeutic agents**
- Survival benefit from chemotherapy occurs **earlier in** patients with anaplastic astrocytoma (**AA**) than in patients with glioblastoma.

Table 2. Trials Included

Study no.	Author	Treatment arm	No. of patients	Median survival (mo)
1	Reagan[39]	XRT	22	11.6
		XRT + CCNU	19	12.0
2	Garrett[40]	XRT	35	8.0
		XRT + CCNU	34	13.0
3	Walker[10]	XRT	68	8.1
		XRT + BCNU	72	7.9
4	Eagan[41]	XRT	20	8.1
		XRT + dianhydrogalactitol	22	15.4
5	Solero[42]	XRT	32	10.5
		XRT + BCNU	34	12.0
		XRT + CCNU	36	16.0
6	Walker[11]	XRT	94	8.5
		XRT + BCNU	92	11.3
		XRT + Me-CCNU	91	9.9
7	Cianfriglia[43]	XRT	50	8.0
		XRT + CCNU	26	12.0
8	EORTC[44]	XRT	55	14.1
		XRT + VM-26 + CCNU	61	13.4
9	Chin[45]	XRT	25	10.8
		XRT + BCNU	26	15.9
		XRT + Me-CCNU	10	21.2
10	Kristiansen[46]	XRT	35	10.5
		XRT + bleomycin	45	10.3
11	Chang[47]			
	Astrocytoma	XRT	14	15.4
		XRT + boost	17	32.3
		XRT + BCNU	28	27.2
		XRT + Me-CCNU + DTIC	20	21.9
	Glioblastoma	XRT	102	8.7
		XRT + boost	75	7.7
		XRT + BCNU	108	8.1
		XRT + Me-CCNU + DTIC	90	8.9
12	Green[32]	XRT + methylprednisone	141	94
		XRT + BCNU	124	11.5
		XRT + procarbazine	128	9.9
		XRT + BCNU + methylprednisone	134	9.4
13	Afra[48]	XRT	32	9.4
		XRT + dibromodulcitol	28	13.1
		XRT + dibromodulcitol + CCNU	31	14.0
14	Ushio[49]	XRT	15	7.7
		XRT + bleomycin	16	9.8
		XRT + Me-CCNU	16	18.2
		XRT + Me-CCNU + bleomycin	13	26.5
15	Takakura[50]			
	Astrocytoma	XRT	18	34
		XRT + ACNU	14	46
	Glioblastoma	XRT	19	14
		XRT + ACNU	26	12.0
16	Trojanowski[15]	XRT	75	10.4
		XRT + CCNU	74	12.0

XRT: radiation therapy; VM-26: teniposide; Me-CCNU: methyl-CCNU.

Chemiosensitivity

Lancet 2002; **359:** 1011–18

Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials

- **12** randomized **studies**
- **3004 pazienti**

- prolongation of survival associated with CT with a HR of 0·85 (95% CI 0·78–0·91, **p<0·0001**).

- increase in 1-year survival of 6% (95% CI 3–9) from 40% to 46% and a **2-month increase in median survival time**

- **no difference according to age, sex, histology, performance status, or extent of resection**, or use of **single or combination** of drugs

Accrual dates	Treatment groups included	Eligible histology	Eligible surgery	Delay*	Radiotherapy details	Chemotherapy details	n†
1969–72	2/4‡	Anaplastic glioma	Definitive surgical resection	6	Whole brain; 50–60 Gy; 30–35 fractions; 6–7 weeks	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks	193
1971–73	2/3‡	High-grade astrocytoma	Resection, biopsy	2	Whole brain; 40–45 Gy; 25 fractions; 4–5 weeks; cobalt-60	Lomustine 130 mg/m² orally, every 6 weeks	20§
1972–76	All	Glioblastoma multiforme	Total or subtotal resection	2	Tumour and margin; 50 Gy; 25–30 fractions; 5 weeks	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; lomustine 130 mg/m² orally, every 6–8 weeks	105
1974–79	3/4‡	Astrocytoma, grade III/IV (Kernohan)	Resection, biopsy	4	Whole brain; 60 Gy; 35 fractions; 7 weeks; megavoltage	Carmustine 80 mg/m²×3 intravenously, every 6–8 weeks; methyl lomustine 125 mg/m² orally, every 8 weeks; dacarbazine 150 mg/m²×5 intravenously, every 4 weeks‖	511
1972–75	3/4‡	Malignant glioma	Definitive surgery	3	Whole brain; 60 Gy; 30–35 fractions; 6–7 weeks; megavoltage	Methyl lomustine 220 mg/m² orally, every 6–8 weeks; carmustine 80 mg/m²×3 intravenously, every 6–8 weeks	355
1974–78	2/4¶	Malignant glioma	Definitive surgery	3	Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks	Carmustine 80 mg/m²×3 intravenously, every 8 weeks: procarbazine 150 mg/m²×28 days, every 8 weeks	309
1975–78	**	Malignant glioma	Optimum resection	4	Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator	Lomustine 130 mg/m² orally; epipodophyllotoxin 60 mg/m² intravenously, every 6 weeks	116
1978–81	All	Glioblastoma; malignant astrocytoma grade III (WHO/Zulch)	At least subtotal resection	4	Tumour and margin; 51 Gy; 25–30 fractions; 5–6 weeks; cobalt-60	Mitolactol 400 mg/m², every 5 days during radiotherapy, with 1 month rest then repeat; mitolactol 400 mg/m², every 5 days during radiotherapy, with 6 weeks rest then (day 1) lomustine 100 mg/m² followed by dacarbazine 200 mg/m², every 5 days×7	91
NK	All	Glioma (high and low grade)††	Resection	3	Tumour and margin; 60 Gy; 30 fractions; 6 weeks; cobalt-60	Lomustine 100 mg/m² orally, every 6–8 weeks	125
1982–87	All	Malignant astrocytoma, glioblastoma, ependymo blastoma, oligondendroglioma	Optimum resection	3	Tumour and margin; 55–60 Gy; 30 fractions; 6 weeks; betatron, telecobalt, linear accelerator	Before radiotherapy: lomustine 130 mg/m² orally, plus epipodophyllotoxin 100 mg/m² intravenously, every 6 weeks 3 courses	235
1986–97	All	Astrocytoma grade III/IV (WHO/Zulch)	Resection, biopsy	6	Tumour and margin; 45 Gy; 20 fractions; 4 weeks; or 60 Gy; 30 fractions; 6 weeks; or 55 Gy; 34 twice-daily fractions‡‡	Lomustine 100 mg/m²; procarbazine 100 mg/m² orally×10; vincristine 1·5 mg/m², every 6 weeks	674
1989–91	All	Anaplastic astrocytoma, glioblastoma	Resection, stereotactic biopsy (stratified)	4	Tumour and margin; 60 Gy; 30–35 fractions; 6–7 weeks; cobalt-60 or megavoltage	Dacarbazine 700 mg/m²×6 orally during radiotherapy, then carmustine 150 mg/m² intravenously; dacarbazine 1000 mg/m² orally, every 6 weeks	270

Chemiosensitivity

Lancet 2002; **359:** 1011–18

Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials

- **12** randomized **studies**
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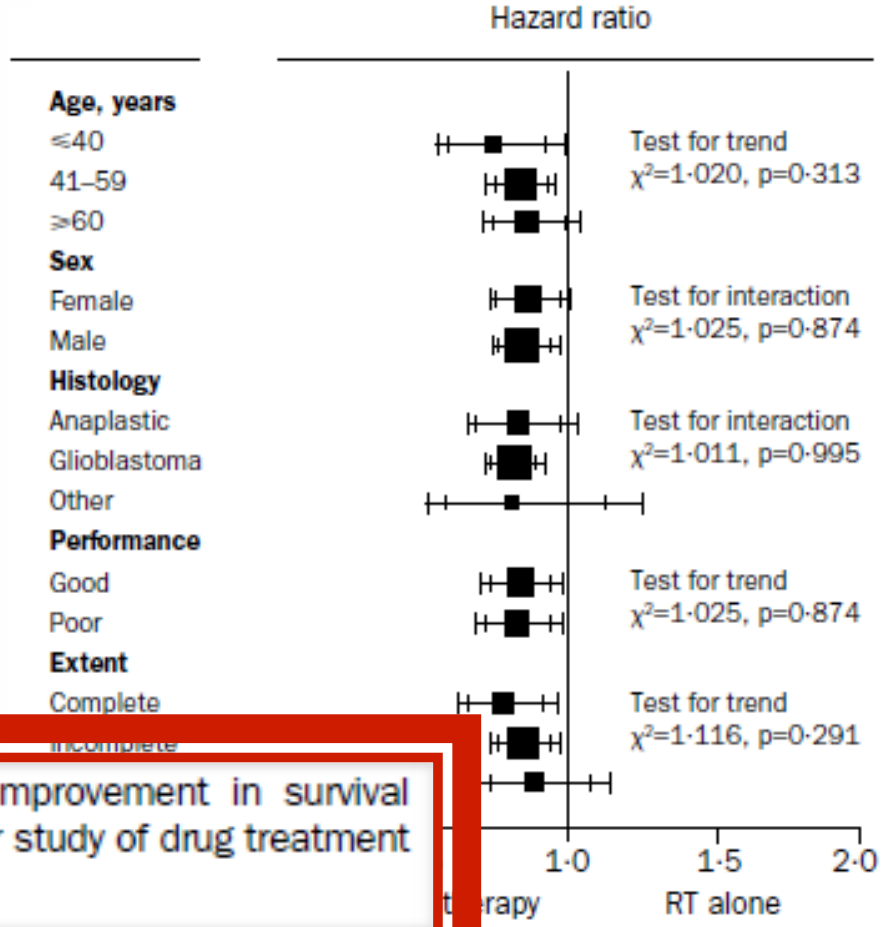
- prolongation of survival associated with CT with a HR of 0·85 (95% CI 0·78–0·91, **p<0·0001**).

- increase in 1-year survival of 6% (95% CI 3–9) from 40% to 46% and a **2-month increase in median survival time** (1–3).

- **no difference according to age, sex, histology, performance status or extent of resection**

or use f
of drug



Interpretation This small but clear improvement in survival from chemotherapy encourages further study of drug treatment of these tumours.

Chemiosensitivity: PVC

J Clin Oncol. 1994 Oct;12(10):2013-21.

Chemotherapy for anaplastic oligodendroglioma. National Cancer Institute of Canada Clinical Trials Group.

Cairncross G[1], Macdonald D, Ludwin S, Lee D, Cascino T, Buckner J, Fulton D, Dropcho E, Stewart D, Schold C Jr, et al.

⊕ Author information

Abstract

PURPOSE: To examine the rate and duration of response of anaplastic oligodendrogliomas to a dose-escalated combination chemotherapy regimen consisting of procarbazine, lomustine (CCNU), and vincristine (PCV) and to evaluate the side effects of this treatment.

METHODS: In this single-arm multicentered phase II study, patients with measurable, newly diagnosed or recurrent, contrast-enhancing anaplastic oligodendrogliomas were treated with up to six cycles of PCV. Central pathology and radiology review were mandatory, and rigorous response criteria based on imaging were used.

RESULTS: Thirty-three patients entered the trial; nine were excluded subsequently, seven due to ineligible pathology. Eighteen of 24 eligible patients (75%) responded, nine completely (38%), four had stable disease (SD), and two progressed during the first cycle of PCV. Responses were observed in nine of 10 patients (90%) with a preexisting low-grade oligodendroglioma and 10 of 15 (67%) with necrotic tumors, called glioblastoma multiforme by some. Previously irradiated patients were as likely to respond to PCV as those newly diagnosed (11 of 15 [73%] v seven of nine [78%]). The median time to progression will be at least 25.2 months for complete responders, and was 14.2 months for partial responders and 6.8 months for stable patients. Four ineligible patients also responded to PCV; all had gliomas with oligodendroglial differentiation. All responders, eligible or ineligible, were stable or improved neurologically, but nine of 22 (41%) experienced a decline in Eastern Cooperative Oncology Group (ECOG) performance status of one grade while on PCV. Adverse events on treatment included a death from Pneumocystis pneumonia, a severe reversible encephalopathy due to procarbazine, an intratumoral hemorrhage, and a subdural hematoma. All other acute toxicities were anticipated and manageable.

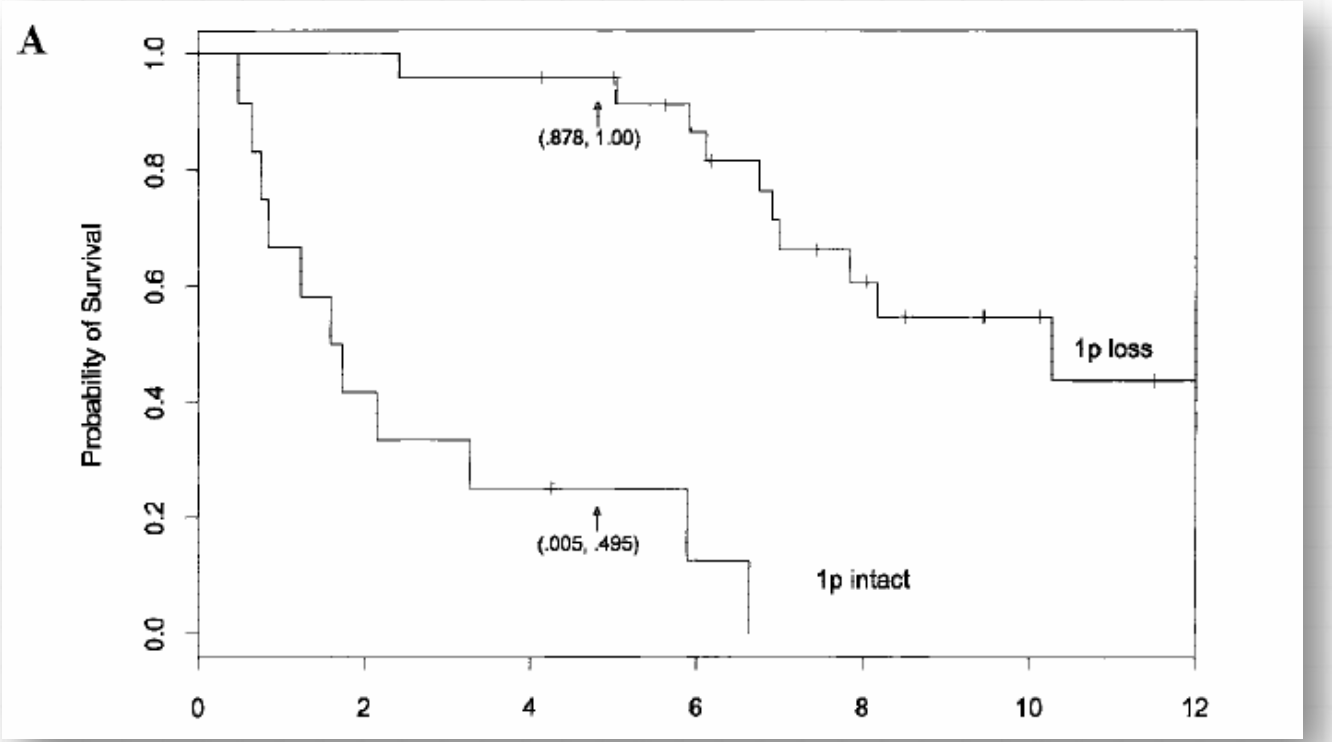
CONCLUSION: Anaplastic oligodendrogliomas are chemosensitive brain cancers. Patients with these tumors respond predictably, durably, and often completely to PCV, and many tolerate a dose-escalated formulation. Cooperative group and randomized trials will be necessary to explore fully the role of chemotherapy in the treatment of aggressive oligodendrogliomas.

Chemiosensitivity: PVC

Specific Genetic Predictors of Chemotherapeutic Response and Survival in Patients With Anaplastic Oligodendrogliomas

J. Gregory Cairncross, Keisuke Ueki, Magdelena C. Zlatescu, David K. Lisle, Dianne M. Finkelstein, Robert R. Hammond, Jonathan S. Silver, Paul C. Stark, David R. Macdonald, Yasushi Ino, David A. Ramsay, David N. Louis

Journal of the National Cancer Institute, Vol. 90, No. 19, October 7, 1998



1p/19q deletion

J Clin Oncol. 2000 Feb;18(3):636-45.

Alterations of chromosome arms 1p and 19q as predictors of survival in oligodendrogliomas, astrocytomas, and mixed oligoastrocytomas.

Smith JS[1], Perry A, Borell TJ, Lee HK, O'Fallon J, Hosek SM, Kimmel D, Yates A, Burger PC, Scheithauer BW, Jenkins RB.

Author information

Abstract

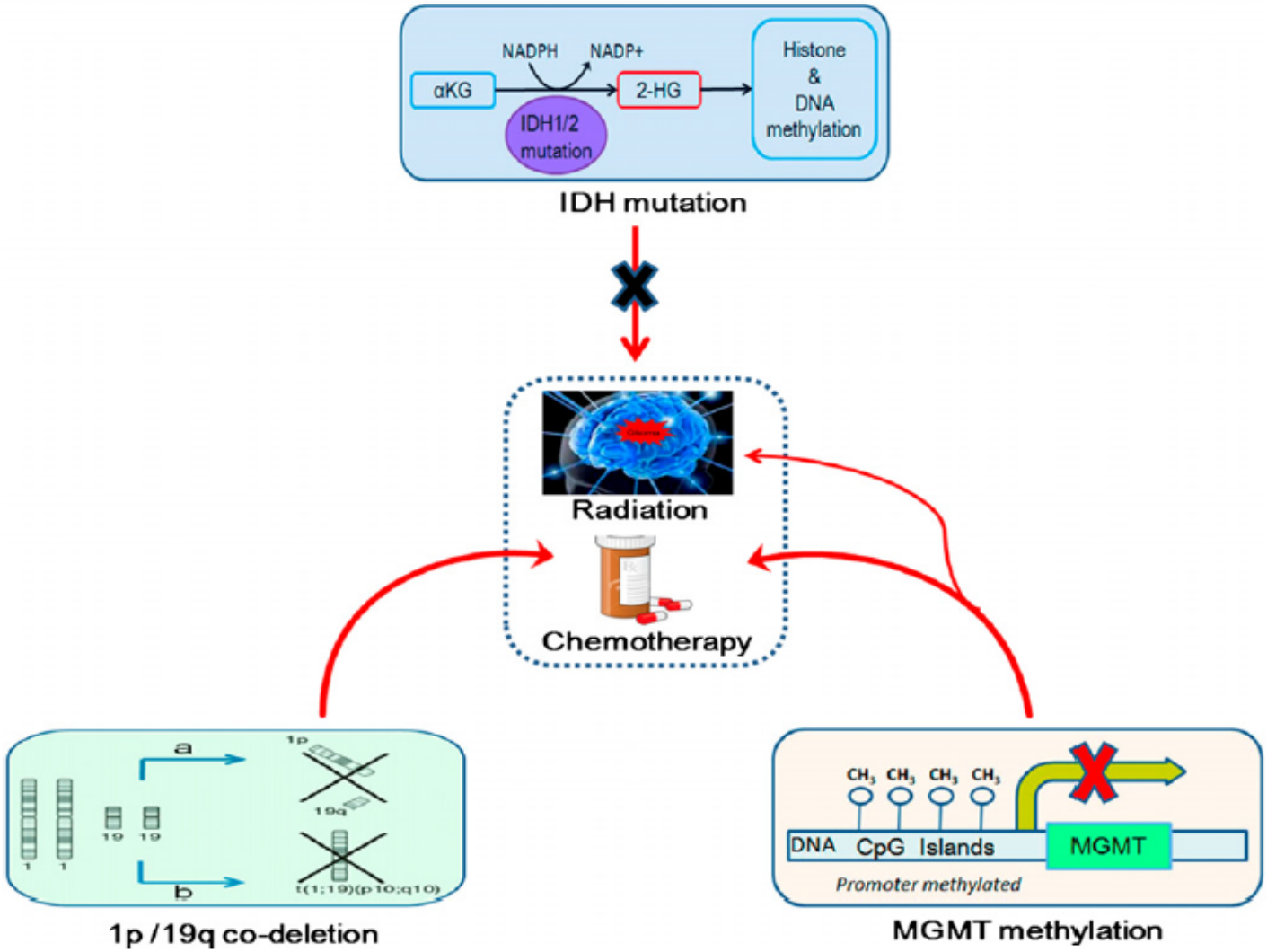
PURPOSE: A recent report suggests that alterations of chromosome arms 1p and 19q are associated with chemotherapeutic response and overall survival in anaplastic oligodendroglioma patients treated with procarbazine, lomustine, and vincristine chemotherapy. We set out to further clarify the diagnostic and prognostic implications of these alterations in a broader set of diffuse gliomas, including astrocytic neoplasms and low-grade oligodendrogliomas.

PATIENTS AND METHODS: Fluorescence in situ hybridization (FISH) signals from DNA probes mapping to 1p and 19q common deletion regions were enumerated in 162 diffuse gliomas (79 astrocytomas, 52 oligodendrogliomas, and 31 mixed oligoastrocytomas), collected as part of an ongoing prospective investigation of CNS tumors.

RESULTS: The oligodendroglial phenotype was highly associated with loss of 1p ($P = .0002$), loss of 19q ($P < .0001$), and combined loss of 1p and 19q ($P < .0001$). Combined loss of 1p and 19q was identified as a univariate predictor of prolonged overall survival among patients with pure oligodendroglioma (log-rank, $P = .03$) and remained a significant predictor after adjusting for the effects of patient age and tumor grade ($P < .01$). This favorable association was not evident in patients with astrocytoma or mixed oligoastrocytoma.

CONCLUSION: Combined loss of 1p and 19q is a statistically significant predictor of prolonged survival in patients with pure oligodendroglioma, independent of tumor grade. Given the lack of this association in patients with astrocytic neoplasms and the previously demonstrated chemosensitivity of oligodendrogliomas, a combined approach of histologic and genotypic assessment could potentially improve existing strategies for patient stratification and management.

Molecular era



Cancer Letters 331 (2013) 139–146

Molecular era

Table 1 WHO 2007 classification for diffuse gliomas

Type	Grade	Description	Median survival (years)
Astrocytoma	II	Found diffusely infiltrating into surrounding neural tissue; increased hypercellularity, no mitosis	6-8
Oligodendroglioma	II	Occur in the white matter and cortex of the cerebral hemispheres, low mitotic activity, no necrosis	12
Oligoastrocytoma	II	Diffuse mixed tumor with mixed glial background	3 to >10
Anaplastic-astrocytoma/ oligodendroglioma	III	Highly infiltrating tumors with increased mitotic activity; no necrosis or vascular proliferation	3
Glioblastoma	IV	Infiltrating glial neoplasm with necrosis and micro-vascular proliferation; high rate of mitosis	1 to 2

WHO, World Health Organization.

Table 2 Review of glioma markers that aid in diagnosis and prognosis of diffuse gliomas—utility of glioma markers and methods of assessment

Marker	Diagnosis	WHO Grade	Prognosis	IHC	FISH	PCR/SNP
IDH1/2	Glioma; 2^0 GBM	WHO > II	Progression free survival >5 years	Yes	No	Yes
1p19q	Oligodendroglioma	WHO > II	Progression free survival >5 years	No	Yes	Yes
MGMT	No diagnostic role	WHO III-IV	Improved response to TMZ	No	No	Yes
+7/+10	1^0 GBM; progression	WHO III-IV	Poor	No	No	Yes

WHO, World Health Organization; IHC, immunohistochemistry; PCR, polymerase chain reaction; MGMT, O^6-methyl-guanine-DNA methyltransferase; TMZ, temozolamide.

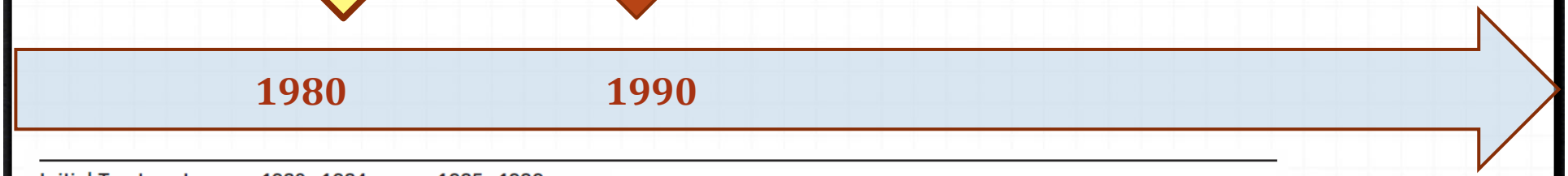
Vigneswaran et al. Molecular genetics of glioma classification *Ann Transl Med* 2015;3(7):95

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

RT Adj
Walker 1978,
Walker 1980,
Andersen 1978

Chemio sensitivity
Cairncross 1988
Fine, 1993,
Stewart 2002
Cairncross, 1994



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CT alone, n (%)	0 (0)	1 (4)
RT alone	4 (67)	15 (54)
CT + RT	1 (17)	11 (39)
Observation	1 (17)	1 (4)

Clinical practice

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1980 **1990**

Initial Treatment	1980–1984 (n = 6%)	1985–1989 (n = 28%)	1990–1994[a] (n = 101%)	1995–1999[a] (n = 294%)
CT alone, n (%)	0 (0)	1 (4)	10 (10)	43 (15)
RT alone	4 (67)	15 (54)	30 (30)	65 (22)
CT + RT	1 (17)	11 (39)	51 (51)	144 (49)
Observation	1 (17)	1 (4)	7 (7)	32 (11)

Clinical practice

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

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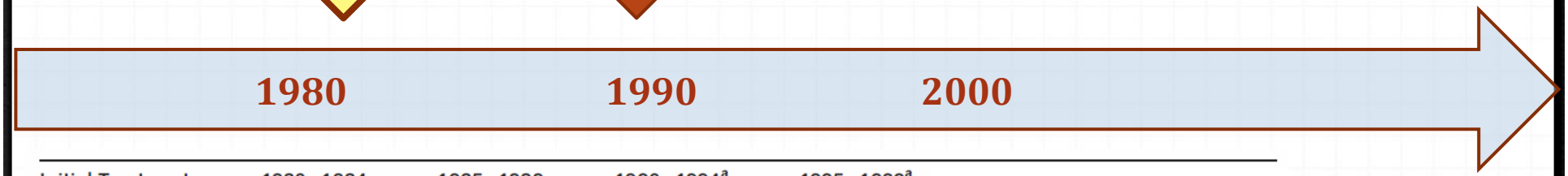

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Clinical practice

EORTC 26951

VOLUME 24 · NUMBER 18 · JUNE 20 2006
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Surgery

R

RT+PVC vs RT

RT: 59,4 Gy/33 fr + PVC x 6

RT: 59,4 Gy/33 fr

RTOG 9402

VOLUME 24 · NUMBER 18 · JUNE 20 2006
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Phase III Trial of Chemotherapy Plus Radiotherapy Compared With Radiotherapy Alone for Pure and Mixed Anaplastic Oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402

Gregory Cairncross, Brian Berkey, Edward Shaw, Robert Jenkins, Bernd Scheithauer, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperierre, Minesh Mehta, and Walter Curran

Surgery

R

PVC + RT vs RT

PVC x 4 + RT: 59,4 Gy/33 fr

RT: 59,4 Gy/33 fr

Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas

EORTC 26951

Median FUP: 60 months (2006)

VOLUME 24 · NUMBER 18 · JUNE 20 2006

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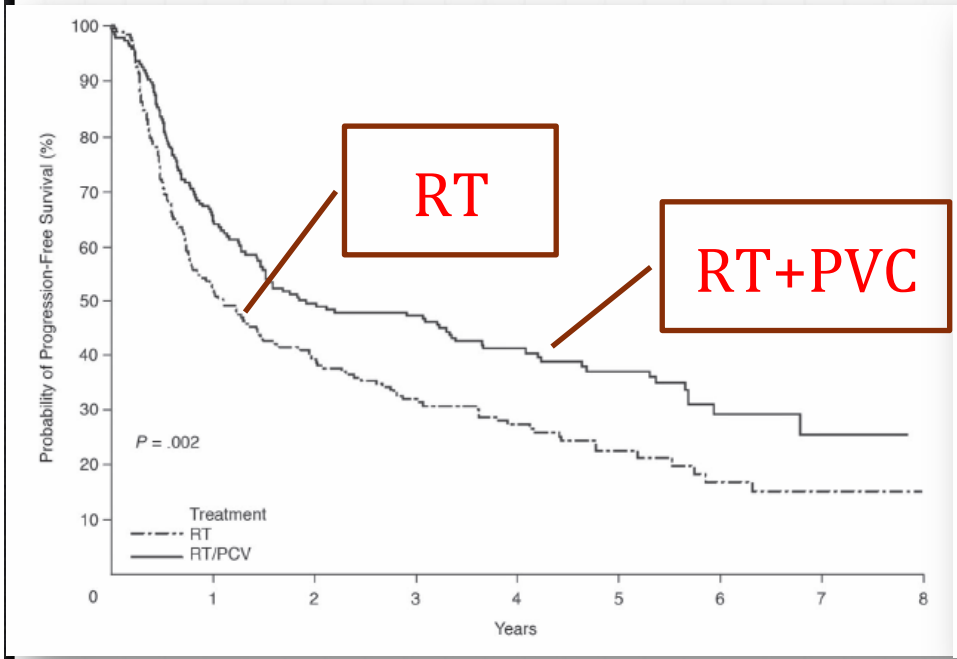
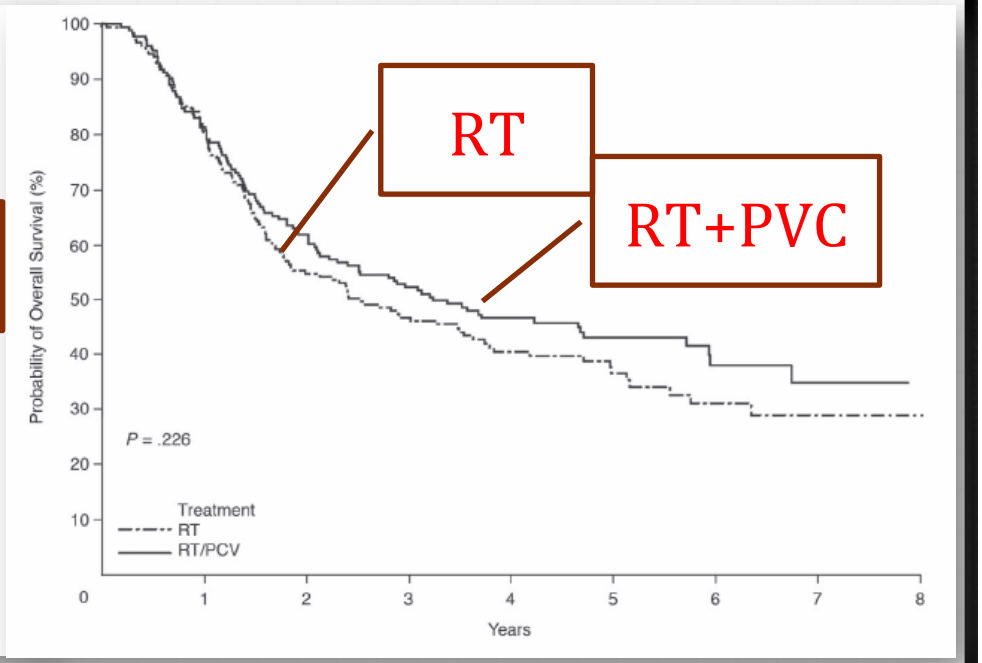
	PFS (p=.002)	OS
RT+PVC	23 months	40.3 months
RT alone	13.2 months	30.6 months





RTOG 9402

Median FUP: 3 years(2006)

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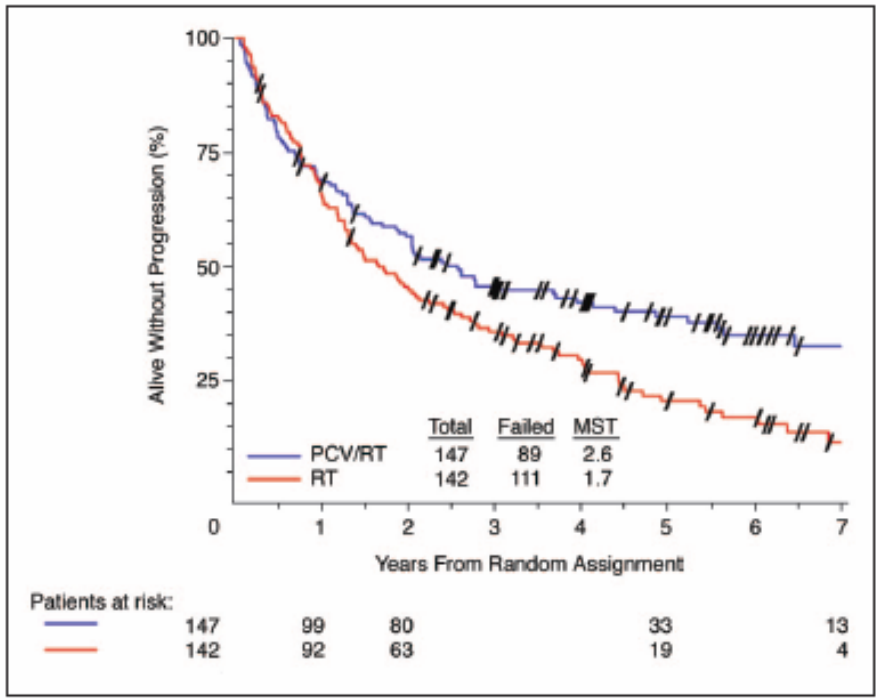
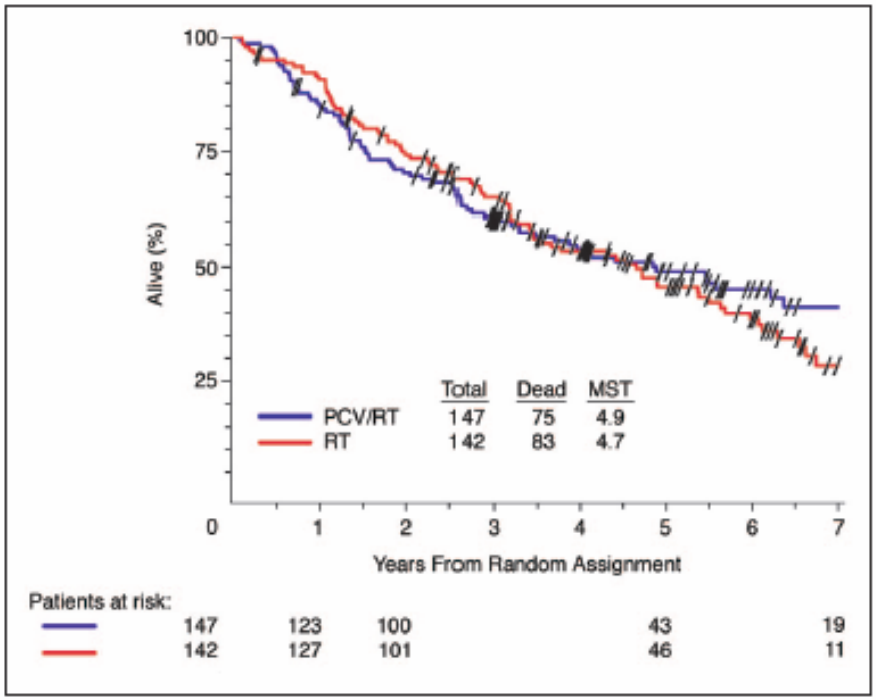
	PFS (p=.004)	Median OS
RT+PVC	30 months	57 months
RT alone	19 months	55 months





RTOG 9402

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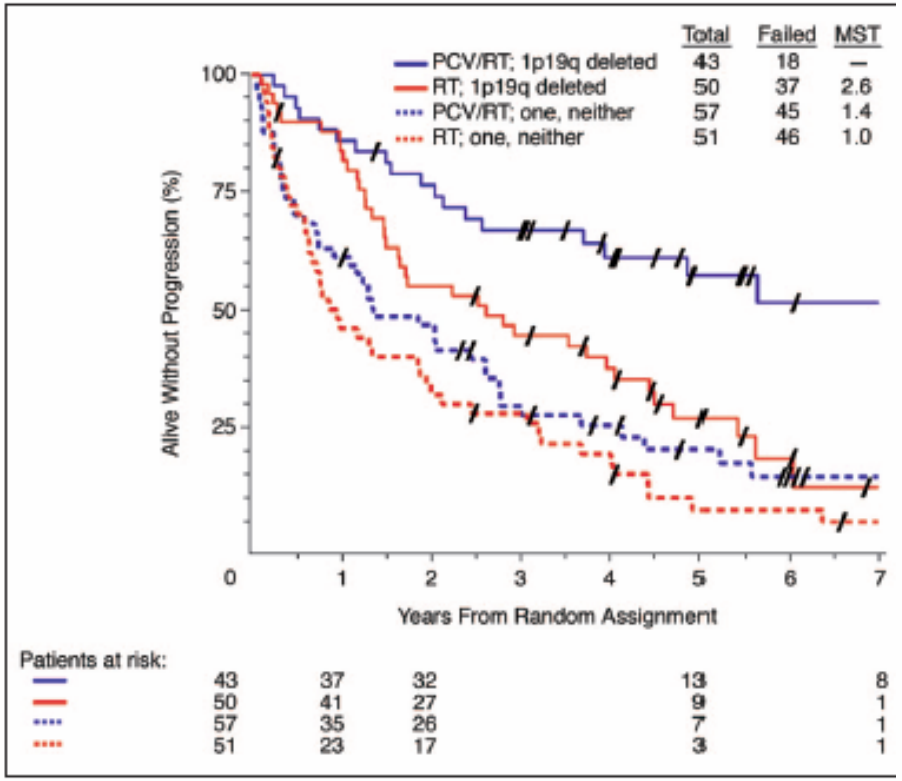

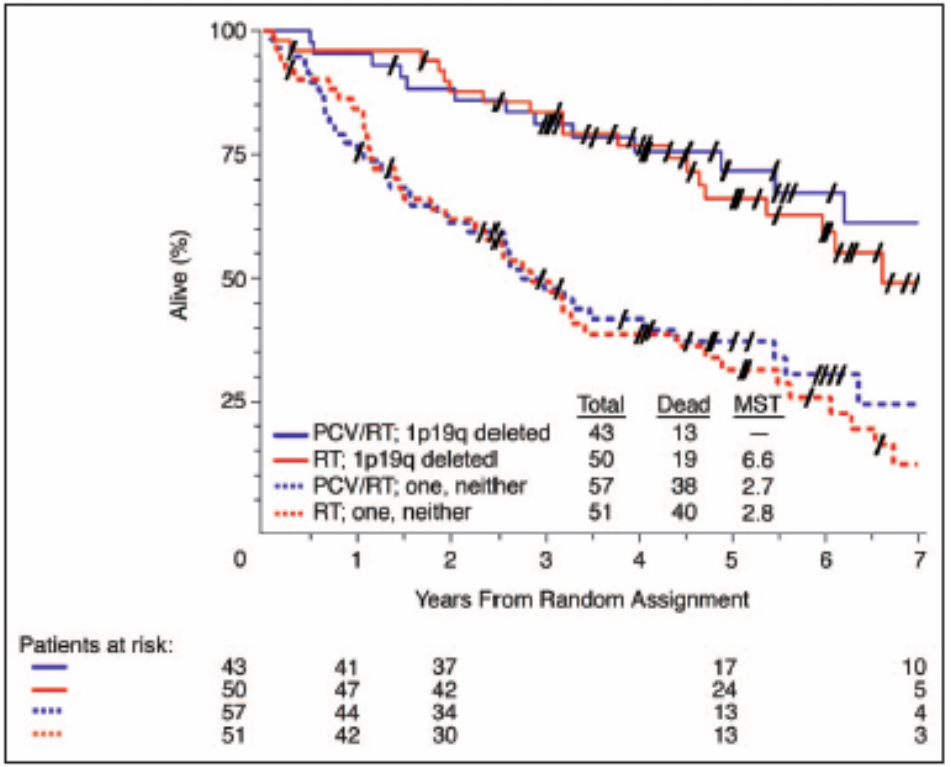

EORTC 26951

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Table 3. Grade 3 and 4 Toxicity in the Patients Who Started PCV Chemotherapy (N = 161)

Toxicity	Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%
WBC count	43	27	5	3
Neutrophils	39	24	13	8
Platelets	23	14	11	7
Hemoglobin	10	6	1	1
Any hematologic toxicity	51	32	23	14
Nausea	9	6	—	—
Vomiting	10	6	—	—
Polyneuropathy	3	2	—	—
Allergic skin reactions	2	1	—	—

Abbreviation: PCV, procarbazine, lomustine, and vincristine.

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Table 4. Grade 3 or 4 Toxicities During Treatment

Toxicity	During PCV (n = 146)		RT* After PCV (n = 131)		RT* Only (n = 141)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Hematologic, any	80	56	6	4	0	0
Neutropenia	62	42	4	3	0	0
Thrombocytopenia	54	37	3	2	0	0
Anemia	7	5	0	0	0	0
Neurologic, any	19	13	3	2	2	1
Cognitive change	1	1	1	1	0	0
Affective disturbance	1	1	0	0	2	1
Peripheral neuropathy	12	8	0	0	0	0
Autonomic neuropathy	3	2	0	0	0	0
Other neurologic	7	5	2	1	1	1
GI, any	13	9	0	0	0	0
Nausea or vomiting	12	8	0	0	0	0
Other GI	3	2	0	0	0	0
Hepatic	6	4	0	0	0	0
Dermatologic	6	4	0	0	3	2
Pulmonary	6	4	2	1	0	0
Ototoxicity	1	1	1	1	2	1
Fever	2†	1	0	0	0	0

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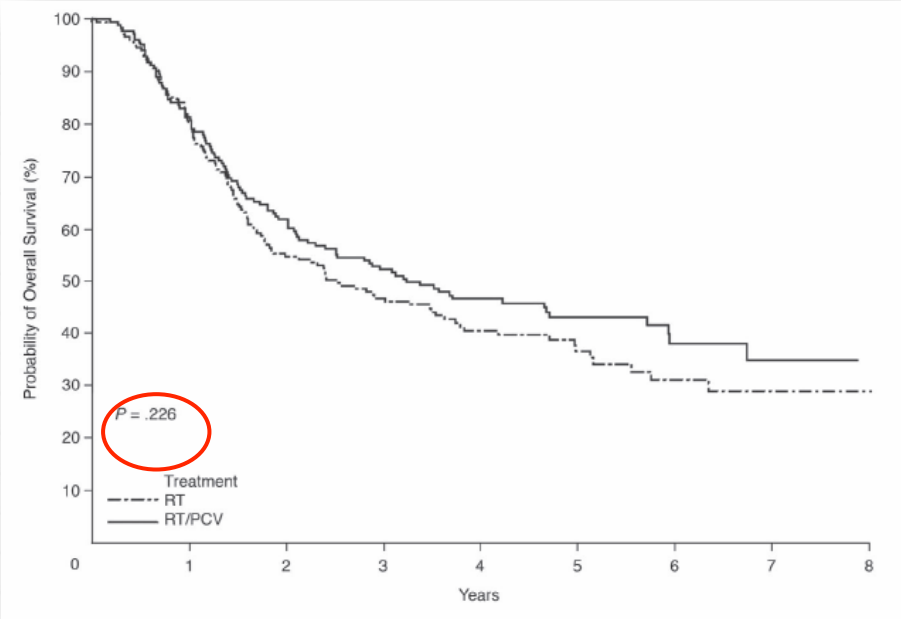

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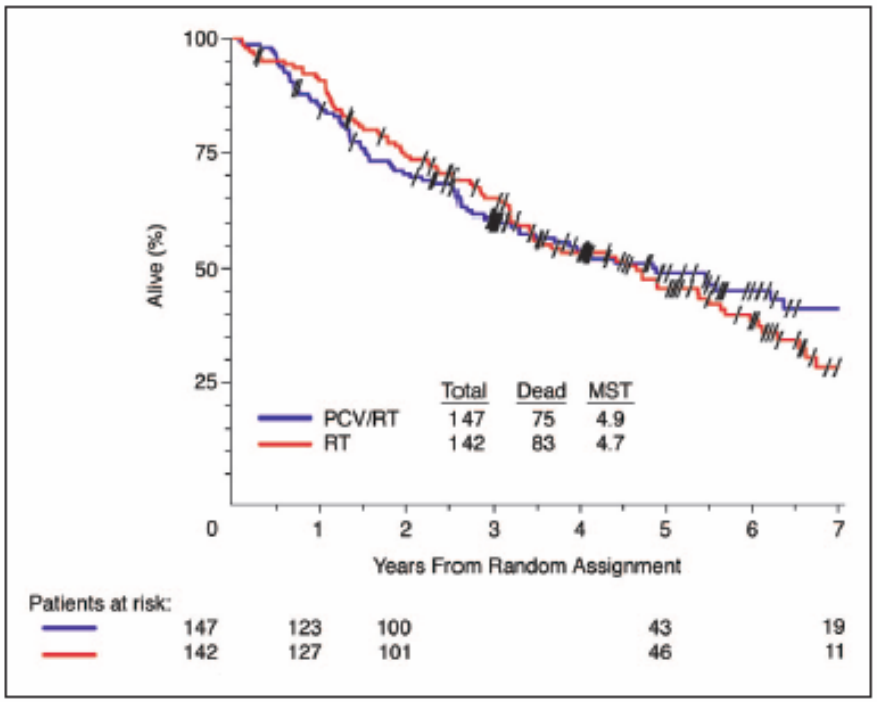

Adiuvant **PVC does not prolong OS** but does **increase PFS** in AO.
Combined loss of 1p/19q identifies a favorable subgroup of oligodendroglial tumors.

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

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EORTC 26951

RTOG 9402

1980 **1990** **2000** **TMZ**

Initial Treatment	1980–1984 (n = 6%)	1985–1989 (n = 28%)	1990–1994[a] (n = 101%)	1995–1999[a] (n = 294%)
CT alone, n (%)	0 (0)	1 (4)	10 (10)	43 (15)
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Clinical practice

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RTOG 9402

1980 **1990** **2000** **TMZ**

All Patients	1980–1984 (*n* = 6)	1985–1989 (*n* = 28)	1990–1994 (*n* = 101)	1995–1999 (*n* = 294)	2000–2004 (*n* = 469)	2005–2007 (*n* = 115)
RT alone, *n* (%)	4 (67)	15 (54)	30 (30)	65 (22)	80 (17)	6 (5)
CT alone						
TMZ	0 (0)	0 (0)	0 (0)	0 (0)	64 (14)	43 (37)
PCV	0 (0)	1 (4)	10 (10)	37 (13)	34 (7)	1 (1)
CT + RT						
TMZ + RT	0 (0)	0 (0)	0 (0)	10 (3)	169 (36)	57 (50)
PCV + RT	1 (17)	9 (32)	48 (48)	126 (43)	80 (17)	1 (1)

Clinical practice

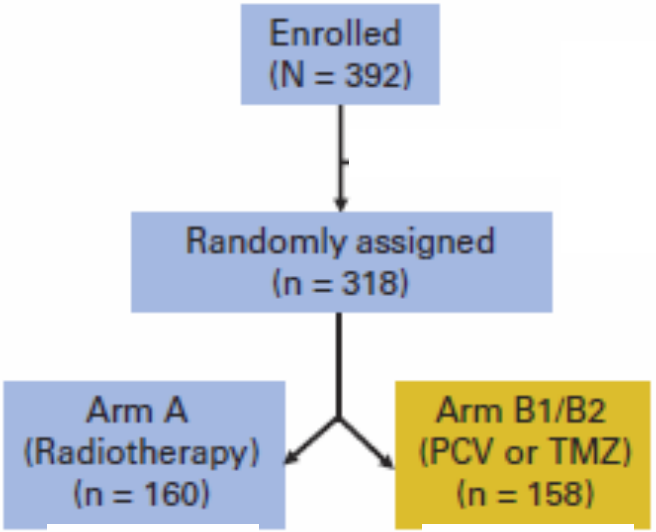
NOA-4 Phase III

VOLUME 27 · NUMBER 35 · DECEMBER 10 2009

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

NOA-04 Randomized Phase III Trial of Sequential Radiochemotherapy of Anaplastic Glioma With Procarbazine, Lomustine, and Vincristine or Temozolomide

Wolfgang Wick, Christian Hartmann, Corinna Engel, Mandy Stoffels, Jörg Felsberg, Florian Stockhammer, Michael C. Sabel, Susanne Koeppen, Ralf Ketter, Richard Meyermann, Marion Rapp, Christof Meisner, Rolf D. Kortmann, Torsten Pietsch, Otmar D. Wiestler, Ulrike Ernemann, Michael Bamberg, Guido Reifenberger, Andreas von Deimling, and Michael Weller



Conclusion

Initial radiotherapy or chemotherapy achieved comparable results in patients with anaplastic gliomas. *IDH1* mutations are a novel positive prognostic factor in anaplastic gliomas, with a favorable impact stronger than that of 1p/19q codeletion or *MGMT* promoter methylation.

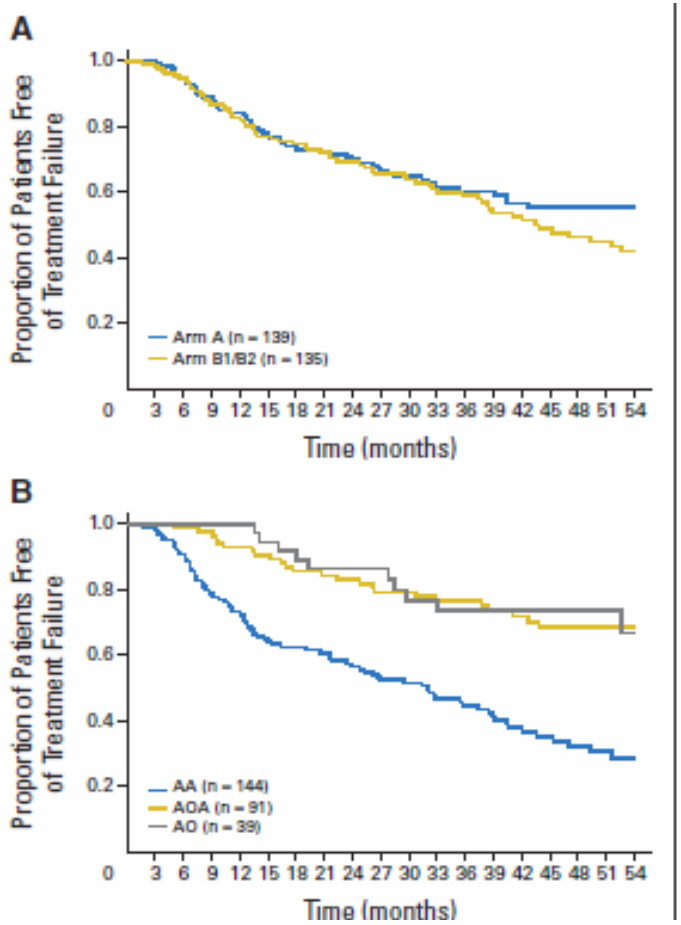


Table 4. Complete Model of Major Prognostic Factors As Determined in a Multivariate Cox Regression Analysis for the Primary End Point of Time to Treatment Failure

Variable	Hazard Ratio	95% CI	*P*
Anaplastic astrocytoma *v* anaplastic oligoastrocytoma/ anaplastic oligodendroglioma	1.95	1.1 to 3.5	.0237
IDH1, wild-type *v* mutated	2.0	1.2 to 3.3	.0128
1p/19q retained *v* 1p/19q deleted	1.8	0.9 to 3.4	.0718
MGMT promoter, unmethylated *v* methylated	1.9	1.1 to 3.4	.0172
Age, > 50 *v* ≤ 50 years	2.6	1.5 to 4.3	.0004
Extent of resection			
Incomplete *v* complete resection	1.6	0.9 to 3.0	
Biopsy *v* incomplete resection	2.1	1.1 to 4.0	.0006
Biopsy *v* complete resection	3.5	1.8 to 7.0	

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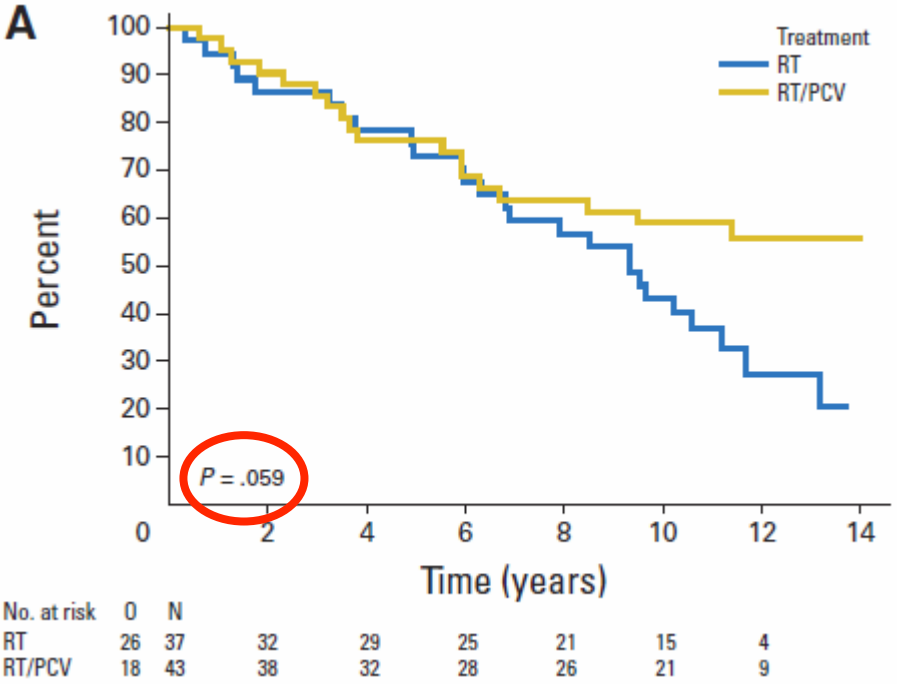
Long term FUP (2013)

RTOG 9402

VOLUME 31 · NUMBER 3 · JANUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951

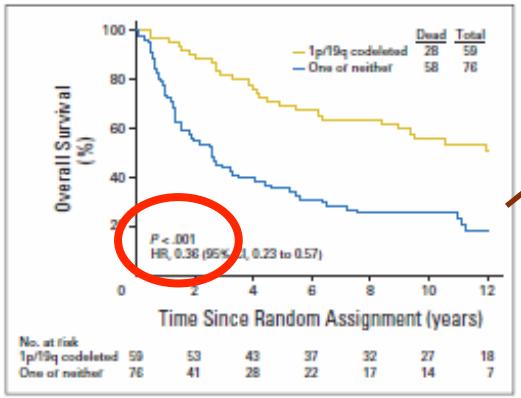


VOLUME 31 · NUMBER 3 · JANUARY 20 2013

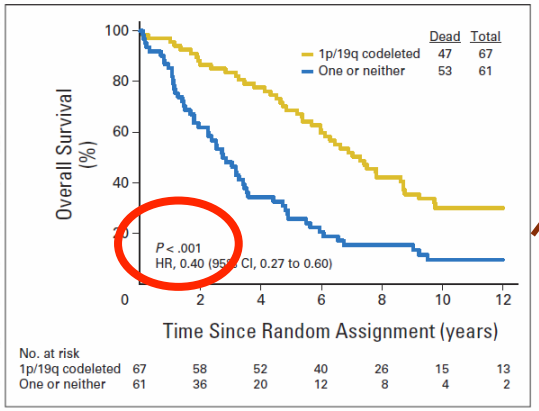
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

Gregory Cairncross, Meihua Wang, Edward Shaw, Robert Jenkins, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperriere, Walter Curran, and Minesh Mehta



RT+PVC



RT

	RT+PVC	RT
1p19q codel	nr	112 ms
1p19q intact	25 ms	21 ms

	PVC+RT	RT
1p19q codel	14,7 yrs	7,3 yrs
1p19q intact	2 yrs	2 yrs

EORTC 26951

Long term FUP (2013)

RTOG 9402

VOLUME 31 · NUMBER 3 · JANUARY 20 2013

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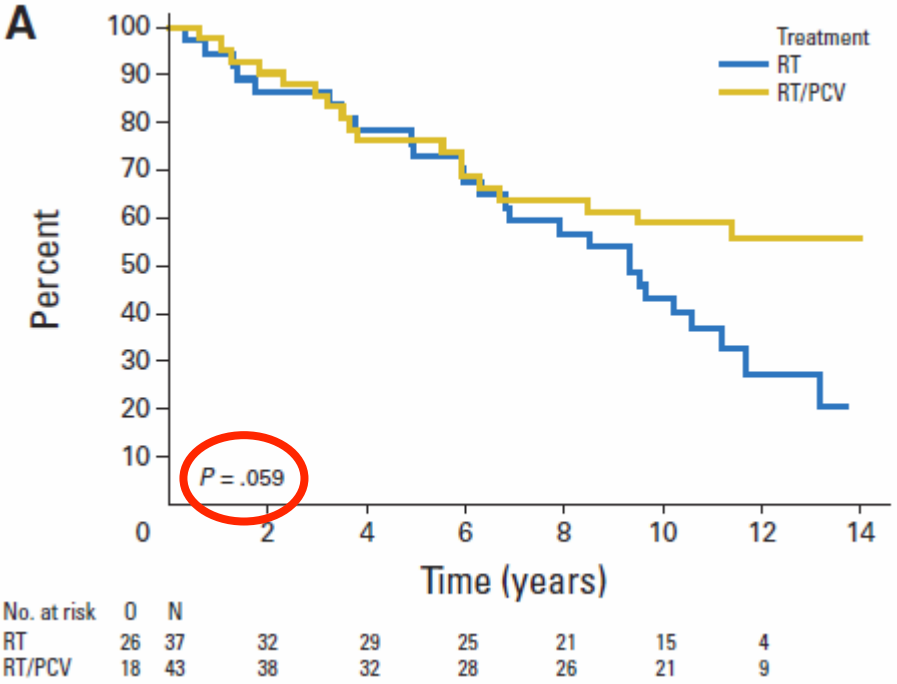
Adjuvant Procarbazine, Lomustine, and Vincristine Chemotherapy in Newly Diagnosed Anaplastic Oligodendroglioma: Long-Term Follow-Up of EORTC Brain Tumor Group Study 26951



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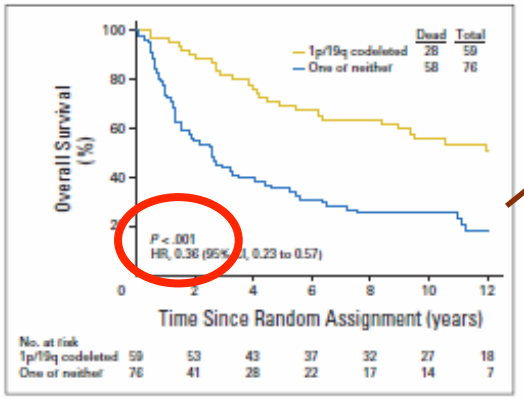
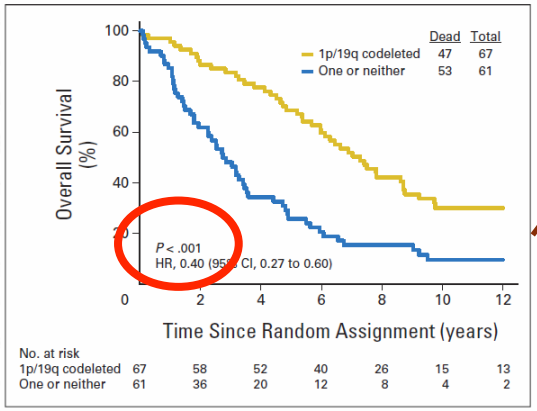


RT+PVC



RT

For subset of 1p/19q codeleted AO/AOA PVC plus RT or after may be an especially effective treatment.

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

RT Adj
Walker 1978,
Walker 1980,
Andersen 1978

Chemio sensitivity
Cairncross 1988
Fine, 1993,
Stewart 2002
Cairncross, 1994

EORTC 26951

RTOG 9402

COMBINED TREATMENT for 1p/19q loss
Long term EORTC 26951 and RTOG 9402

1980 — 1990 — 2000 — TMZ — > 2010

Initial Treatment	1980–1984 (*n* = 6%)	1985–1989 (*n* = 28%)	1990–1994[a] (*n* = 101%)	1995–1999[a] (*n* = 294%)	2000–2004[a] (*n* = 469%)	2005–2007 (*n* = 115%)
CT alone, *n* (%)	0 (0)	1 (4)	10 (10)	43 (15)	103 (22)	44 (38)
RT alone	4 (67)	15 (54)	30 (30)	65 (22)	80 (17)	6 (5)
CT + RT	1 (17)	11 (39)	51 (51)	144 (49)	262 (56)	59 (51)
Observation	1 (17)	1 (4)	7 (7)	32 (11)	17 (4)	6 (5)

Clinical practice

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

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EORTC 26951

RTOG 9402

COMBINED TREATMENT for 1p/19q loss
Long term EORTC 26951 and RTOG 9402

1980 — 1990 — 2000 — TMZ — > 2010

NCCN National Comprehensive Cancer Network®

1p/19q Codeleti

PATHOLOGY	ADJUVANT TREATMENT
1p19q codeleted: Anaplastic oligodendroglioma Anaplastic oligoastrocytoma	Fractionated external beam RT[j] and neoadjuvant or adjuvant[k] PCV chemotherapy (category 1)[l] or Fractionated external beam RT[j] and temozolomide chemotherapy[l] or PCV or temozolomide chemotherapy[l] (category 2B)

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

National Comprehensive Cancer Network®

1p/19q intact

1p19q uni- or non-deleted: **Anaplastic oligodendroglioma** **Anaplastic oligoastrocytoma** **Anaplastic astrocytoma**	→ **Fractionated external beam RT[j] (category 1)** **or** **Fractionated external beam RT[j]** **and temozolomide chemotherapy[l]** **or** **PCV or temozolomide chemotherapy[l]**

All Patients	1980–1984 (*n* = 6)	1985–1989 (*n* = 28)	1990–1994 (*n* = 101)	1995–1999 (*n* = 294)	2000–2004 (*n* = 469)	2005–2007 (*n* = 115)
No 1p19q deletion	(*N* = 0)	(*N* = 6)	(*N* = 25)	(*N* = 71)	(*N* = 112)	(*N* = 28)
RT alone, *n* (%)	0 (0)	2 (33)	11 (44)	15 (21)	20 (18)	2 (7)
CT alone						
TMZ	0 (0)	0 (0)	0 (0)	0 (0)	8 (7)	1 (4)
PCV	0 (0)	0 (0)	1 (4)	3 (4)	4 (4)	0 (0)
CT + RT						
TMZ + RT	0 (0)	0 (0)	0 (0)	1 (1)	49 (44)	22 (79)
PCV + RT	0 (0)	3 (50)	11 (44)	38 (54)	26 (23)	0 (0)

National Comprehensive Cancer Network®

1p19q uni- or non-deleted: Anaplastic oligodendroglioma Anaplastic oligoastrocytoma Anaplastic astrocytoma	→	Fractionated external beam RT[j] (category 1) or Fractionated external beam RT[j] and temozolomide chemotherapy[l] or PCV or temozolomide chemotherapy[l]

AA

Radiotherapy and temozolomide in anaplastic astrocytoma: a retrospective multicenter study by the Central Nervous System Study Group of AIRO (Italian Association of Radiation Oncology)

Silvia Scoccianti, Stefano Maria Magrini, Umberto Ricardi, Beatrice Detti, Marco Krengli, Salvatore Parisi, Filippo Bertoni, Guido Sotti, Samantha Cipressi, Vincenzo Tombolini, Stefano Dall'Oglio, Marco Lioce, Calogero Saieva, Michela Buglione, Cristina Mantovani, Giovanni Rubino, Paolo Muto, Vincenzo Fusco, Laura Fariselli, Costantino de Renzis, Laura Masini, Riccardo Santoni, Luigi Pirtoli, and Giampaolo Biti

- Data of 295 newly diagnosed AA
- RT vs RT+TMZ
- Chemotherapy with TMZ was confirmed not to be a significant factor

Neuro-Oncology 14(6):798–807, 2012.

National Comprehensive Cancer Network®

AA

1p19q uni- or non-deleted: Anaplastic oligodendroglioma Anaplastic oligoastrocytoma Anaplastic astrocytoma	→ Fractionated external beam RT[j] (category 1) or Fractionated external beam RT[j] and temozolomide chemotherapy[l] or PCV or temozolomide chemotherapy[l]

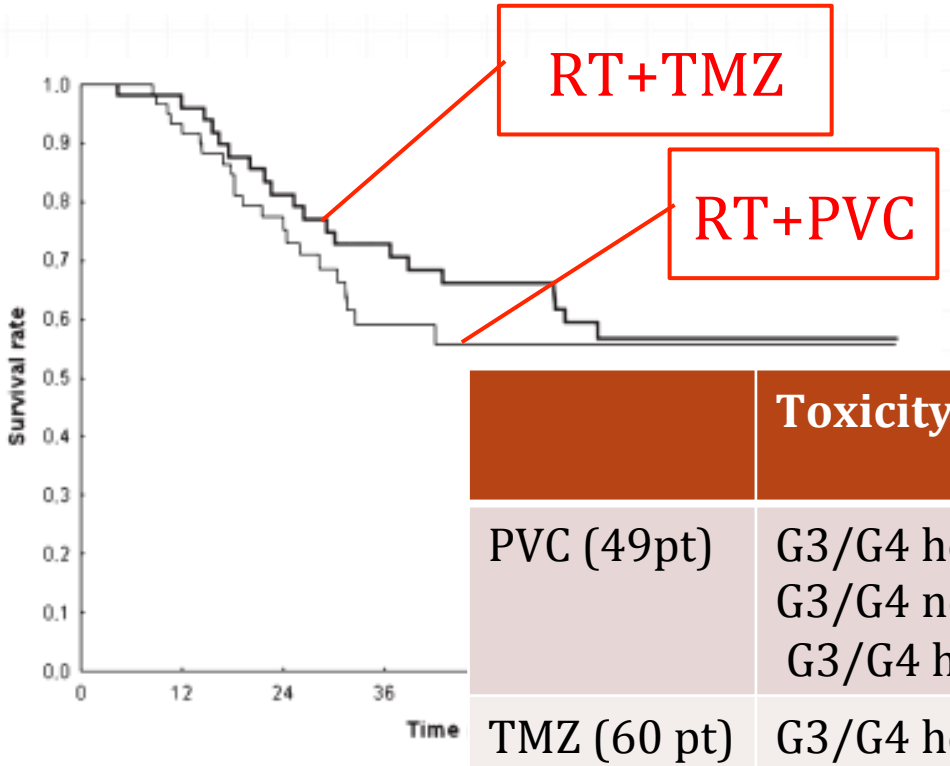
Radiotherapy and temozolomide in anaplastic astrocytoma: a retrospective multicenter study by the Central Nervous System Study Group of AIRO (Italian Association of Radiation Oncology)

Table 5. Studies that addressed the use of postoperative radiotherapy + temozolomide in anaplastic astrocytoma

Author	Study	Treatment arms	Histotypes	*n* Patients	Differences in OS	Differences in PFS	Survival Data Regarding OS in AA			
							Median Survival	Actuarial survival		
								@1y	@2y	@4y
Gilbert et al[11]	Ph II	Neoadj TMZ + RT	HGG	$n = 57$ (AA $n = 18$)	–	–	23.5 m	na	50%	na
Brada et al[12]	Ph II	Neoadj TMZ + RT	HGG	$n = 162$ (AA = 37)	–	–	14 m	56%	na	na
Chang et al[13]	Ph II	Neoadj TMZ + BCNU ± RT	WHO grade III gliomas	$n = 41$ (AA $n = 33$)	–	–	na	na		
Brandes et al[14]	Retrosp	RT + sTMZ vs RT + PCV	AA	$n = 109$ (RT + TMZ $n = 60$)	NS	NS	na	na na	75% 83%	na na
Combs et al[15]	Retrosp	RT vs RT + cTMZ	AA + AOA (AA $n = 54$)	$n = 60$ (RT + TMZ $n = 20$)	NS	NS	na	na		
Current study	Retrosp	RT vs RT + cTMZ + sTMZ	AA	$n = 295$ (RT + cTMZ + sTMZ $n = 166$)	NS	na	18.1 m 21.4 m	60.5% 75.0%	45.4% 48.1%	31.0% 27.1%

Survival following adjuvant PCV or temozolomide for anaplastic astrocytoma

Alba A. Brandes,[1,2] Linda Nicolardi, Alicia Tosoni, Marina Gardiman, Paolo Iuzzolino, Claudio Ghimenton, Michele Reni, Antonino Rotilio, Guido Sotti, and Mario Ermani



109 pt

	Toxicity (CTCAv3)	Interruption Adj CT
PVC (49pt)	G3/G4 hematological: 9% G3/G4 neurological:3% G3/G4 hepatic	37%
TMZ (60 pt)	G3/G4 hematological: 4-5%	None

National Comprehensive Cancer Network®

AA

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Acta Neuropathol (2010) 120:707–718
DOI 10.1007/s00401-010-0781-z

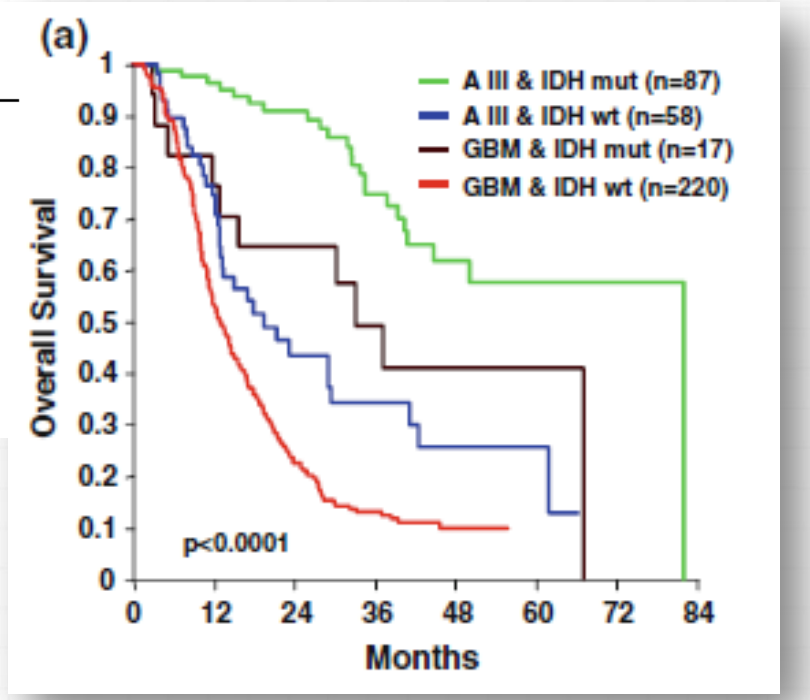
ORIGINAL PAPER

Patients with *IDH1* wild type anaplastic astrocytomas exhibit worse prognosis than *IDH1*-mutated glioblastomas, and *IDH1* mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas

Christian Hartmann · Bettina Hentschel · Wolfgang Wick · David Capper · Jörg Felsberg · Matthias Simon · Manfred Westphal · Gabriele Schackert · Richard Meyermann · Torsten Pietsch · Guido Reifenberger · Michael Weller · Markus Loeffler · Andreas von Deimling

AA IDHwt = GMB

382 pt:
145AA



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AA

1p19q uni- or non-deleted: **Anaplastic oligodendroglioma** **Anaplastic oligoastrocytoma** **Anaplastic astrocytoma**	→	**Fractionated external beam RT[j] (category 1)** **or** **Fractionated external beam RT[j]** **and temozolomide chemotherapy[l]** **or** **PCV or temozolomide chemotherapy[l]**

Table 4 Stratification scheme for high grade lesions based on current data regarding IDH mutational status and the presence or absence of copy number abnormalities associated with chromosomes 7 and 10—WHO III anaplastic glioma stratification with prognosis

Types	+7	+7/-10q
IDH1/2 mutation	Anaplastic astrocytoma: survival >5 years	Anaplastic oligodendroglioma: survival >10 years
IDH wild type	Anaplastic astrocytoma: progression to 2° GBM <2 years	2° GBM: survival <2 years

WHO, World Health Organization.

AA IDHwt = GMB

Vigneswaran et al. Molecular genetics of glioma classification *Ann Transl Med* 2015;3(7):95

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

EBM

RT Adj
Walker 1978,
Walker 1980,
Andersen 1978

COMBINED TREATMENT for 1p/19q loss
Long term EORTC 26951 and RTOG 9402

Open questions
Standard non co-deleti
TMZ vs PVC
RTCT concomitant
Novel drugs
QoL

CATNON (EORTC 26053-22054)

Non 1p/19q deleted

RT-CT (concomitant TMZ) vs RT+CT (adjuvant TMZ)

CODEL (EORTC 26081-22086)

1p/19q co-deleted

RT vs TMZ alone vs RT-CT and adjuvant TMZ

Gliomi di terzo grado: radioterapia, chemioterapia o radiochemioterapia?

Open questions	Trials clinici
Standard non co-deleti	CODEL trial CATNON trials
TMZ vs PVC	
RTCT concomitant	

CATNON (EORTC 26053-22054)

Non 1p/19q deleted

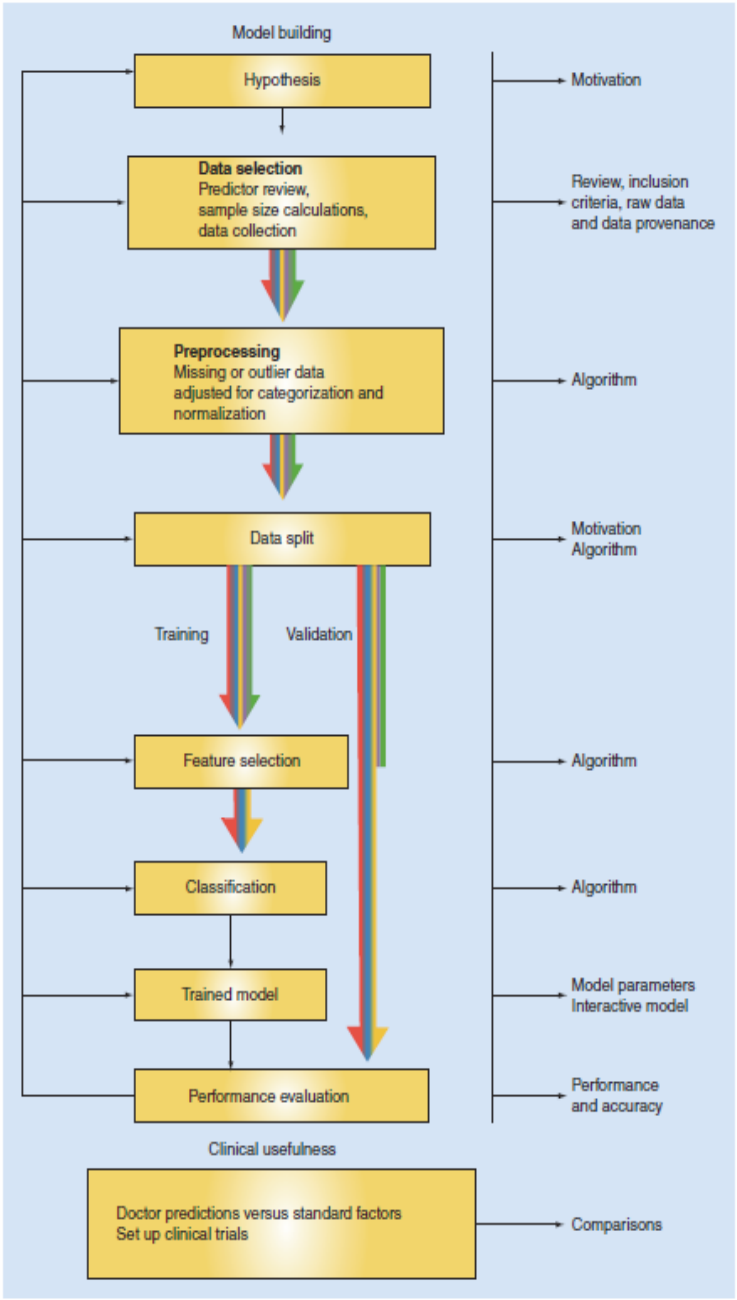
RT-CT (concomitant TMZ) vs RT+CT (adjuvant TMZ)

CODEL (EORTC 26081-22086)

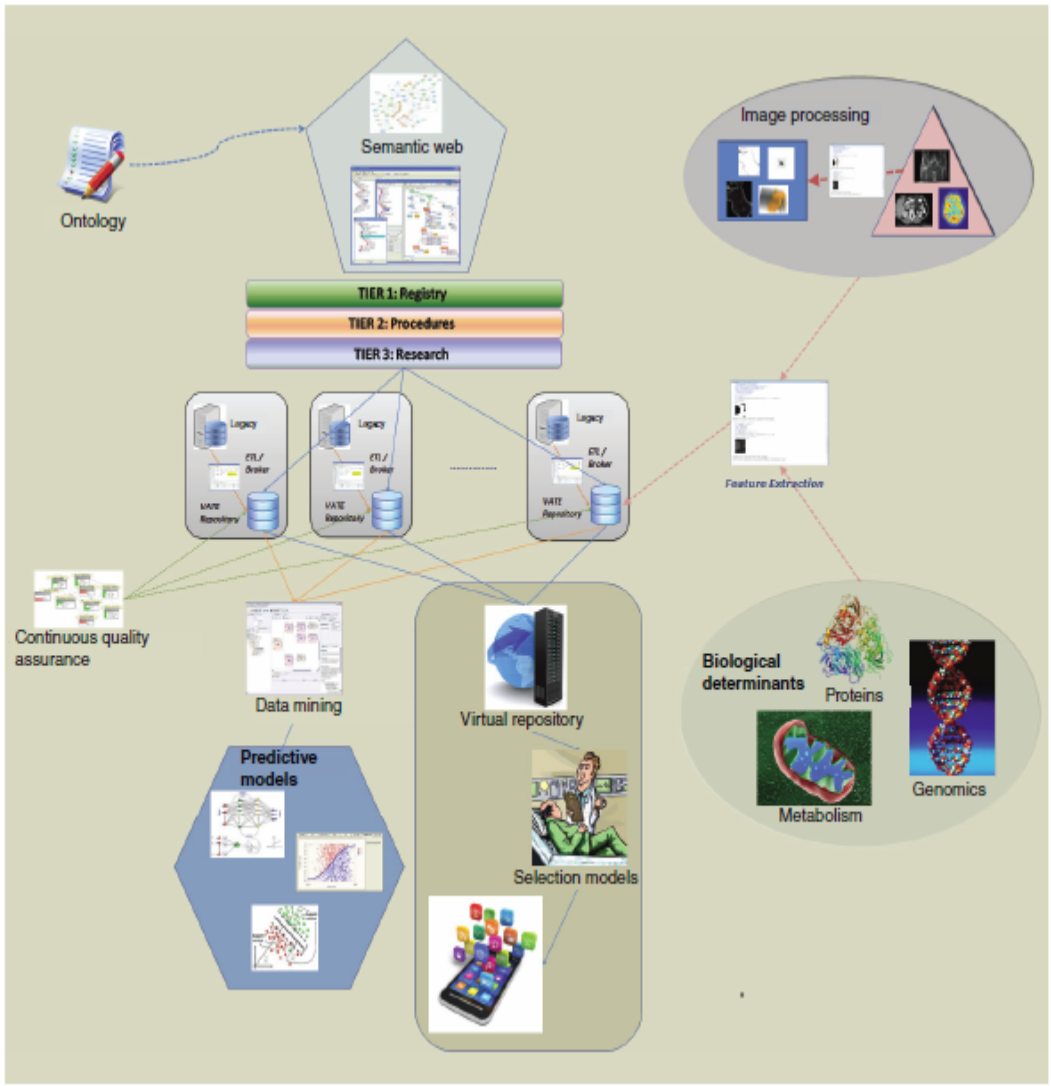
1p/19q co-deleted

RT vs TMZ alone vs RT-CT and adjuvant TMZ

Large-database



Lambin et al., Nat Rev Clin Oncol, 2013



Valentini et al., Colorect Cancer, 2014