Incontri Bresciani di Radioterapia Oncologica - Edizione 2010
“HODGKIN AND NON HODGKIN LYMPHOMAS: A NEW ROLE FOR RADIATION THERAPY?”
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Extranodal NHL: the case of CNS. The role of radiotherapy

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Primary Central Nervous System Lymphoma (PCNSL)

Immunocompetent patient

- *4% of primay brain tumors*
- *More common in the sixth or seventh decade*
- *Prevalent in males*
- *No racial differences*
- *Multifocal in CNS in approximately 1/3 of cases*
- *Approximately 75% of PCNSL tumors are supratentorial masses*
- *ocular involvement occurs in 10–20% of patients*
- *Increasing incidence*
- *0-20% association with Epstein-Barr virus*
- *The great majority of PCNSLs are high grade, DLBCL*
- *Typically express MUM-1, a marker of activated B-cells, and BCL-6, a marker of germinal centers*
- *Median survival: 12-18 months after radiation monotherapy*

↑RT has a role for cure.

Immunodeficient patient (AIDS, etc.)

- *Fourth decade*
- *Prevalent in males*
- *Multifocal in 30% to 75%*
- *Second most common cerebral mass lesion after toxoplasmosis*
- *2-13% of patients with previous AIDS diagnosis*
- *Incidence of AIDS PCNSL declined since the introduction of HAART (Highly Active AntirRetorviral Therapy: survival not yet improved appreciably: 30%)*
- *Risk factors: low CD4 count (5100,000) and a high viral load*
- *95% B-cell origin*
- *95% associated with Epstein-Barr virus infection*
- *Membrane protein-1 positive (in 45%)*
- *Wide variety of radiographic appearances , can be cortical or subcortical*
- *Median survival: 1 month with no treatment, 3 months with RT, before HAART*

A possible radiosensitizing role for HAART? ↑

Cancer, 2004

Hematol Oncol Clin N Am , 2005

Main arguments about RT:

- **RT volume;**
- **RT dose (and timing);**

⇕

- **Associated treatment with chemotherapy;**

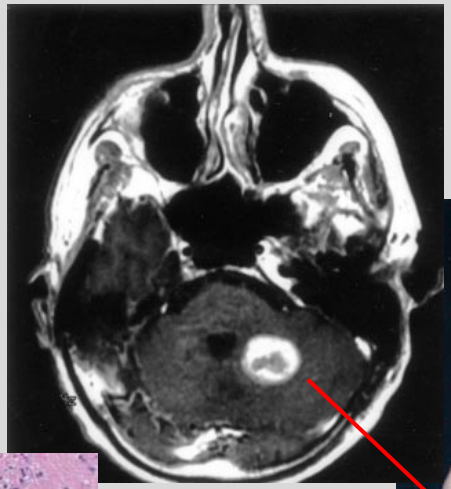
⇕

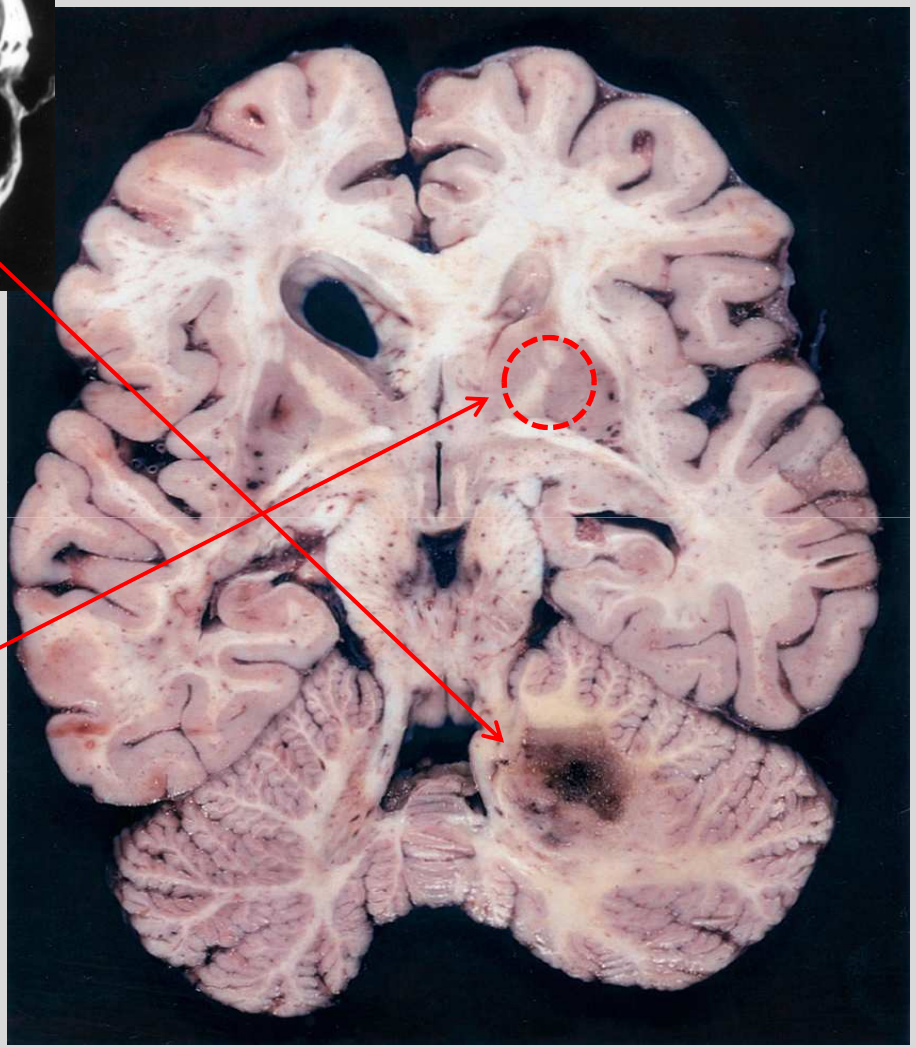
- **Toxicity of chemo-RT;**

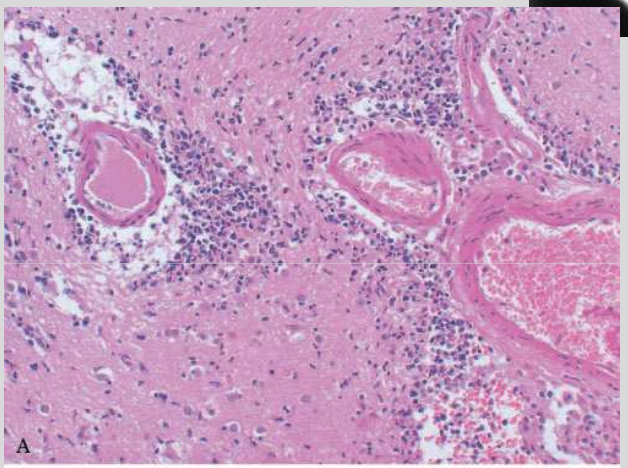
⇕

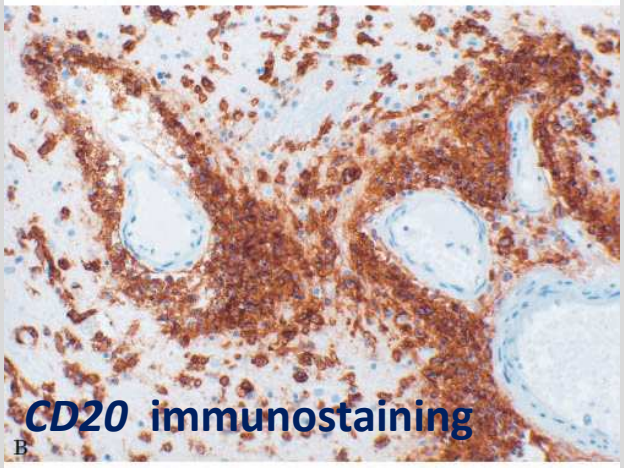
- **Selection of patients (inherent natural history variables might prevail over therapy strategies).**

Volume:









Lay, Rosenblum and De Angelis, NEUROLOGY 2002;59:1557-62

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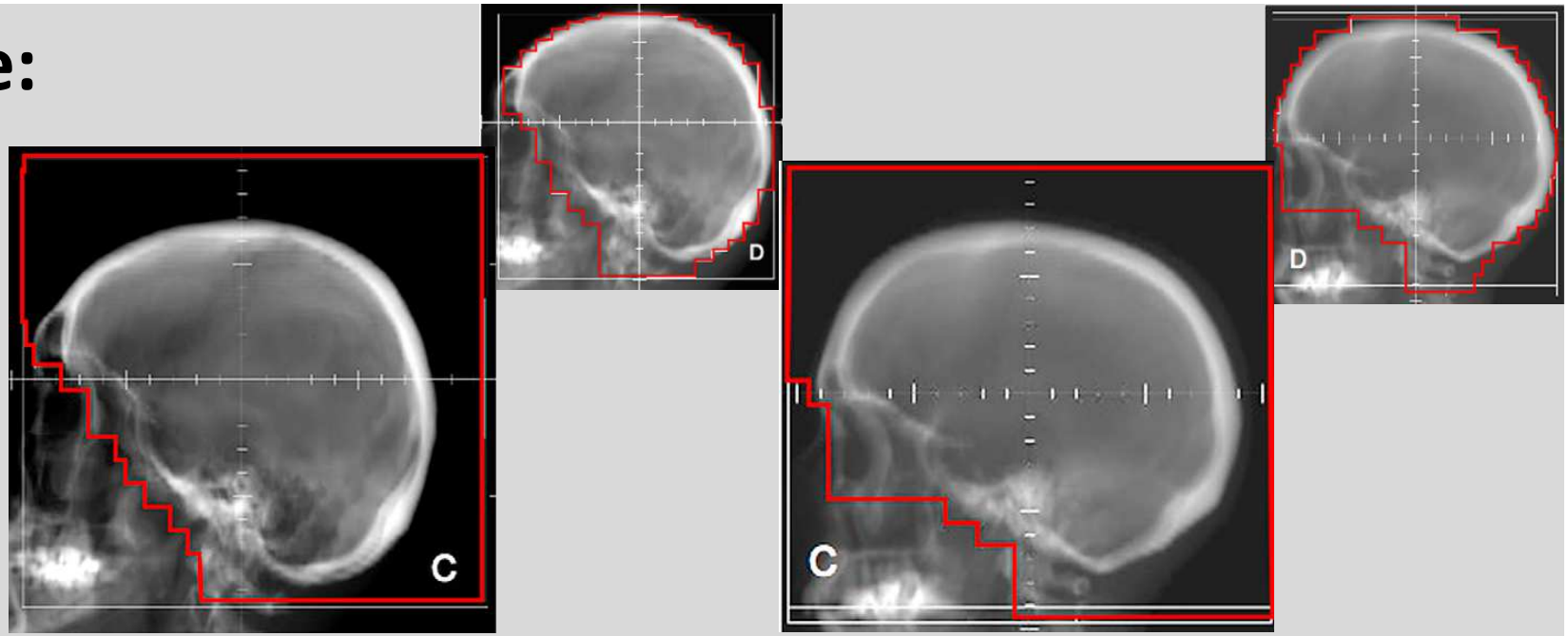
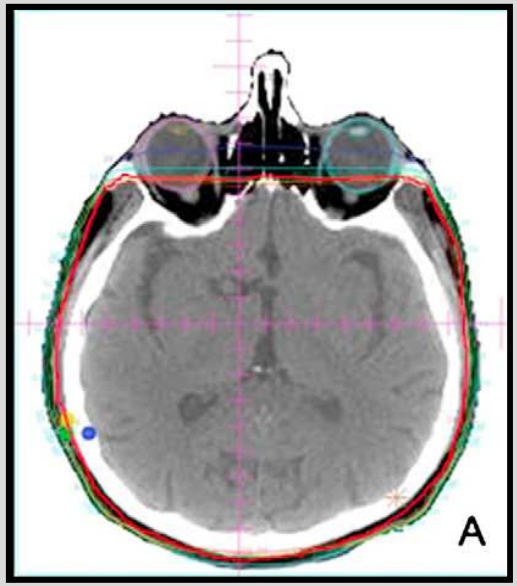
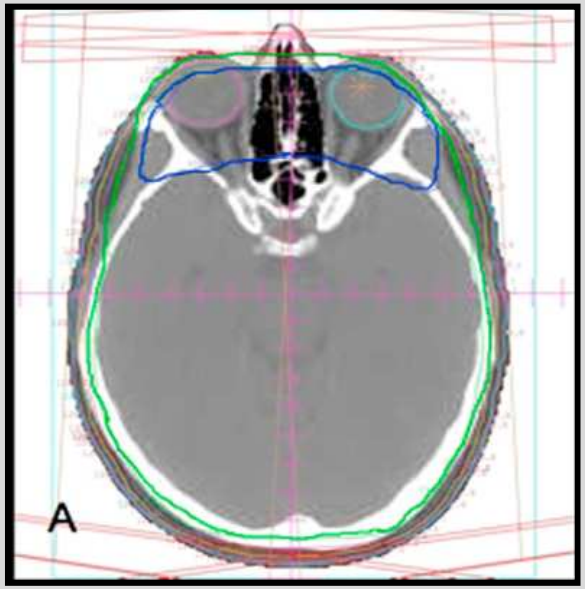


(… and dose distribution)





Schultz and Bovi,
IJROBP 2010;76:666

Early reports of the results of radiation monotherapy.

Murray et Al, J NEUROSURG 1986; 65:600

Dose-response information is difficult to obtain. Sagerman, *et al.*,[73] found no local control or long-term survival in patients who had received less than 3000 rads. Cox, *et al.*,[16] in a review of time-dose relationships for malignant lymphoreticular tumors, noted improved local control in patients with primary CNS disease given greater than 45 Gy. Berry and Simpson[9] suggested an improved survival time in patients receiving doses greater than 50 Gy to the whole brain, with a 2-year survival in two of 10 patients compared to 0 of 8 with lower doses. Loeffler, *et al.*,[54] noted that their long-term survivors had received a median dose of over 50 Gy to the tumor.

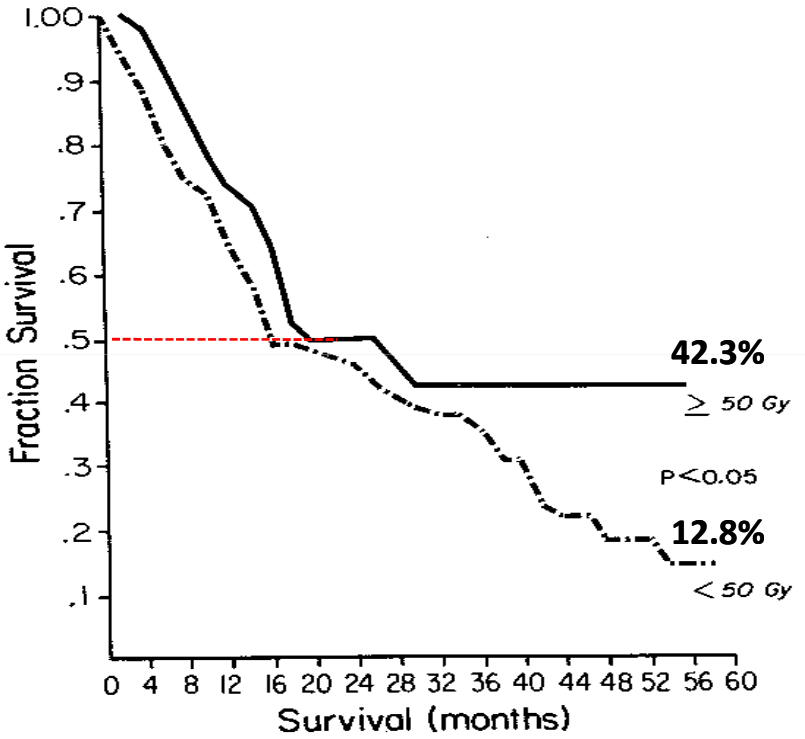


FIG. 2. Graph showing survival times in 188 cases collected from the literature and 10 cases in the present series in which irradiation dosage is available. *Solid line* indicates those patients receiving a dosage of 50 Gy or above; *broken line* represents those receiving a dosage of less than 50 Gy. The difference was statistically significant ($p < 0.05$).

The subject of dose-escalation in radiation monotherapy was addressed by RTOG 83-15: 41 Pts.

Nelson et Al, IJROBP 1992; 23:9

40 Gy in 1.8 fractions
20 Gy boost by 2 or 3 field technique to the contrast enhancing lesion(s) plus a 2 cm border

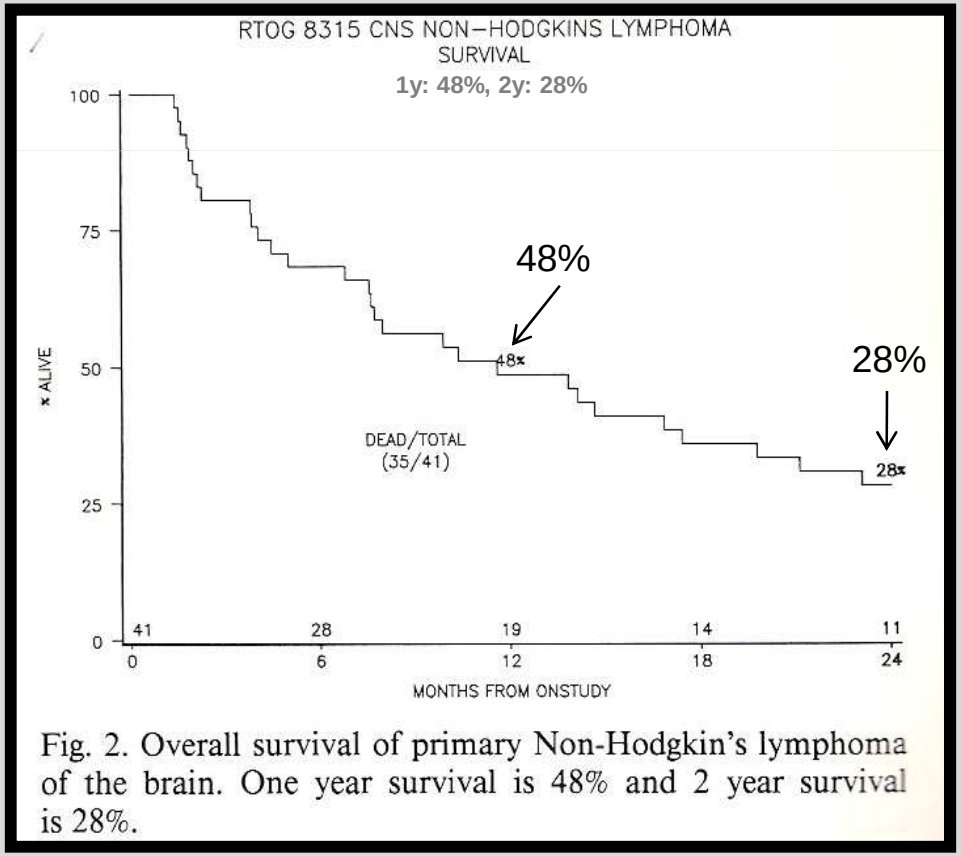


Fig. 2. Overall survival of primary Non-Hodgkin's lymphoma of the brain. One year survival is 48% and 2 year survival is 28%.

Survival, UNIVARIATE ANALYSIS:

	1y	2y	p
KPS 70-100	71%	46%	
KPS 40-60	25%	10%	<.001
Age < 60	70%	47%	
Age ≥ 60	37%	19%	.004
NFP work	73%	36%	
NFP home	55%	33%	
NFP hospital	10%	10%	.005
Female	29%	6%	
Male	62%	44%	.005

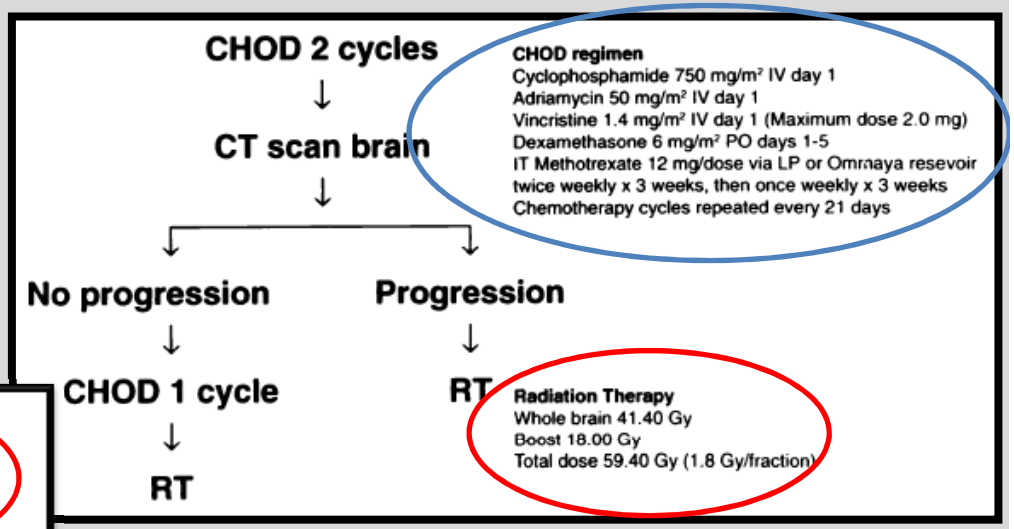
MULTIVARIATE ANALYSIS

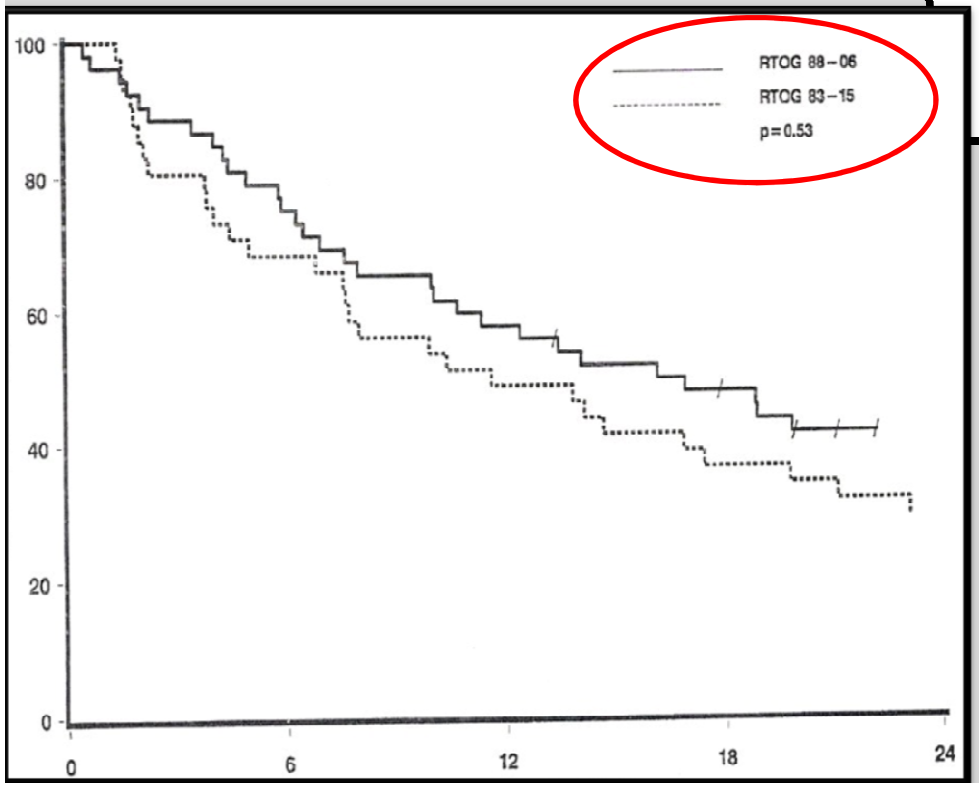
	RR	Stat. Significance
KPS	3.55	.002
Sex	2.43	.032

The subject of chemotherapy* + RT was addressed in RTOG 88-06: 52 Pts. (note: * CHT not penetrating BBB, i.e.: CHOD)

Schultz et Al, J CLIN ONCOL 1996;14:556

- Follow up: 20 months
- 12/52 patients alive without evidence of progression
- Median survival time: 16.1 months
- 2 y survival rate: 42%





Note: the most frequent localization of recurrence was the primary, both in RTOG 83-15 and 88-06 studies.

The subject of Complete Response (CR) was addressed in a secondary analysis of RTOG 83-15 and 88-06 studies

Corn et Al, IJROBP 2000;47:299

- **The main endpoint of the RTOG 83-15 and 88-06 studies was OS**
- **The secondary analysis of the database was approved by RTOG to formally assess radiographic response based on central review of imaging studies submitted to RTOG head-quarters in Philadelphia.**
- **Complete response: absence of enhancement on follow-up scans when compared with the postoperative, pretherapy study**
- **Partial response: tumor size reduction of at least 50%in the product of the largest cross-sectional diameter and the largest perpendicular diameter**
- **Tumor progression: a 25% increase in the product of these quantities**

Table 2. Primary CNS lymphoma: tumor response data

Response	RTOG 83-15	RTOG 88-06
CR	24 (83%)	23 (85%)
PR	4	3
Progression	1	1
Missing	17	25

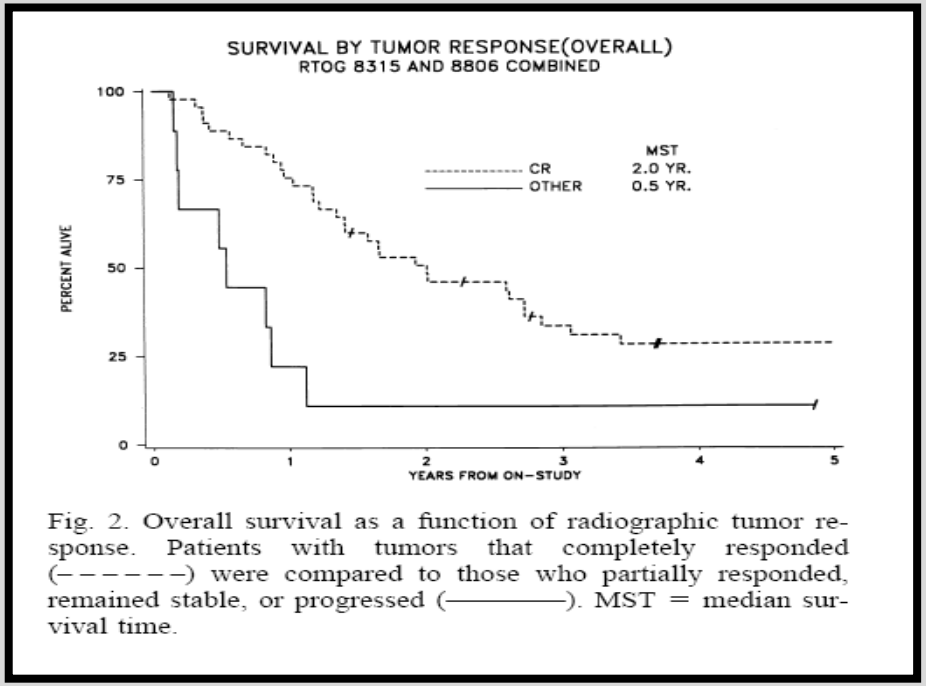


Fig. 2. Overall survival as a function of radiographic tumor response. Patients with tumors that completely responded (– – – – – –) were compared to those who partially responded, remained stable, or progressed (————). MST = median survival time.

Conclusions

- **RT (60 Gy, conventionally fractionated) achieves very high rates of CR**
- **CR strongly correlates with a significantly improved survival**
- **the progression of previously present microscopic disease may occur also in a substantial proportion of CRs, sometimes arising far from primary site**
- **<u>Additional dose-escalation strategies to improve the rate of of CRs were not warranted</u>**

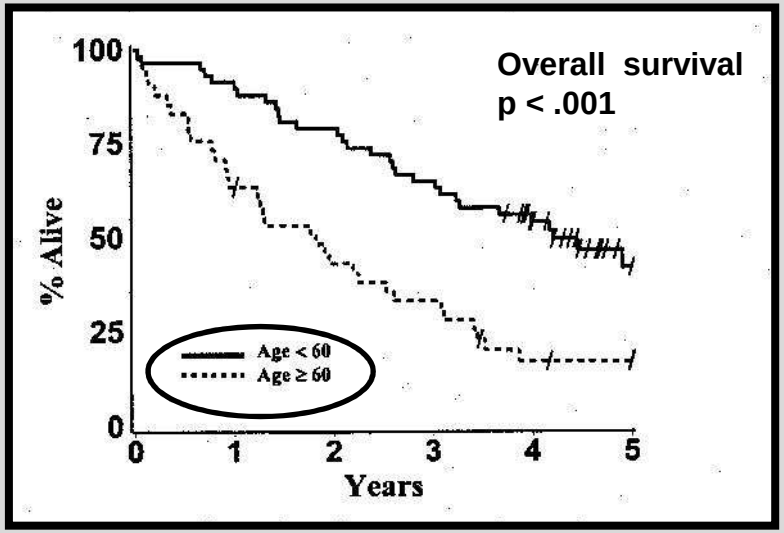
The subject of BBB-penetrating chemotherapy + RT was addressed in RTOG 93-10: 102 Pts.

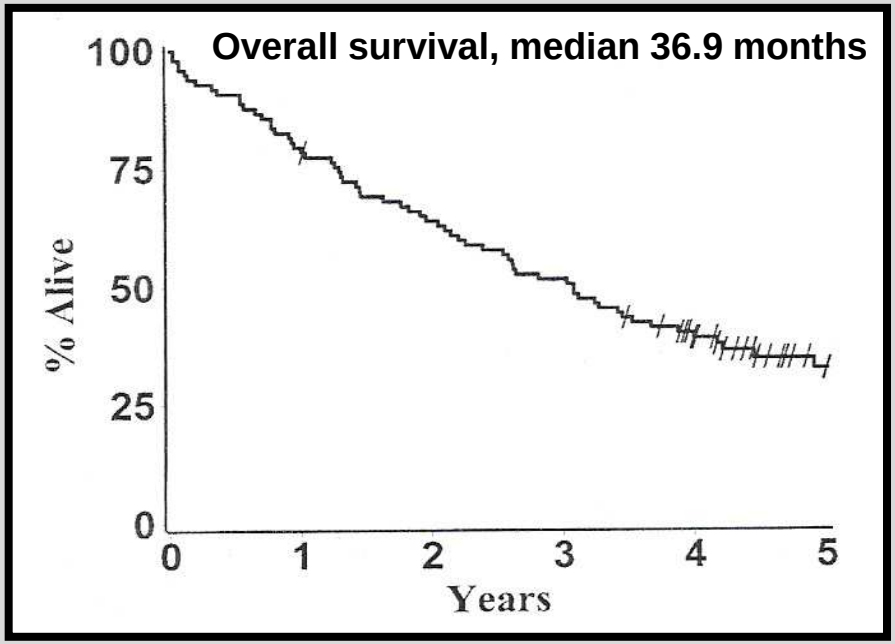
De Angelis et Al, J CLIN ONCOL 2002;20:4643

- **102 pts → 98 evaluable**
- **CHT: 5 cycles: ivMTX 2.5 g/mq, vincristine, procarbazine, intraventricular MTX 12 mg**
- **WBRT in 82 pts, no boost; 45 Gy initially;**

*** halfway modified protocol: 36 Gy (1.2 Gy x 2 /day) in CRs**

- **High dose cytarabine after RT**





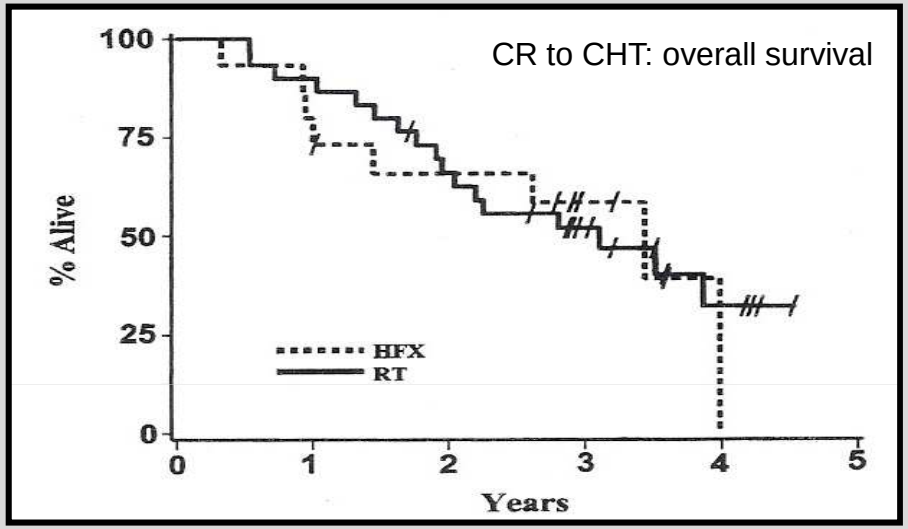
*** Toxicity: severe, delayed neurotoxicity due to HD MTX + RT was observed in a previuos study [Abrey et Al, J CLIN ONCOL 2000; 18:3144] and in other reports**

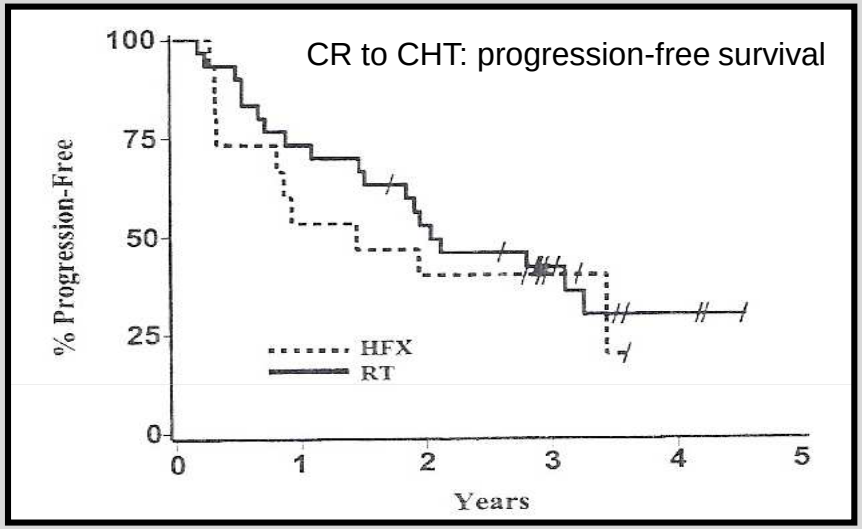
Neurotoxicity in the RTOG 93-10 study:
12 pts (15%) showed leukoencephalopathy, 8 fatal
Age < 60: 7/50, 14%
Age ≥ 60: 6/32, 18,75%
Among CRs: 3 /13 pts (23%) undergoing HF RT developed grade 4-5 neurotoxicity (vs 1/27 – 3% - G3 neurotoxicity in CF RT)

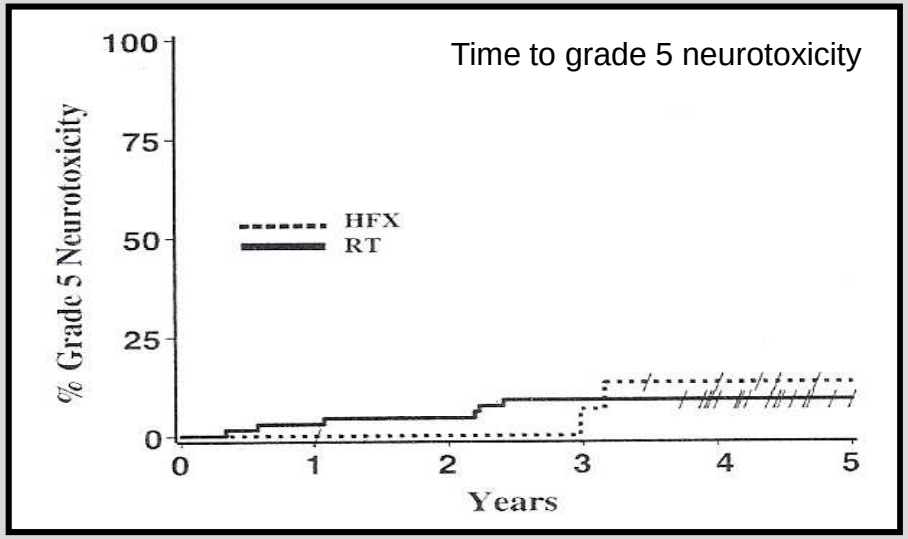
Results and toxicity of HD MTX–based CHT + HF RT (36 Gy) in CRs were the subject of a subset analysis of RTOG 93-10

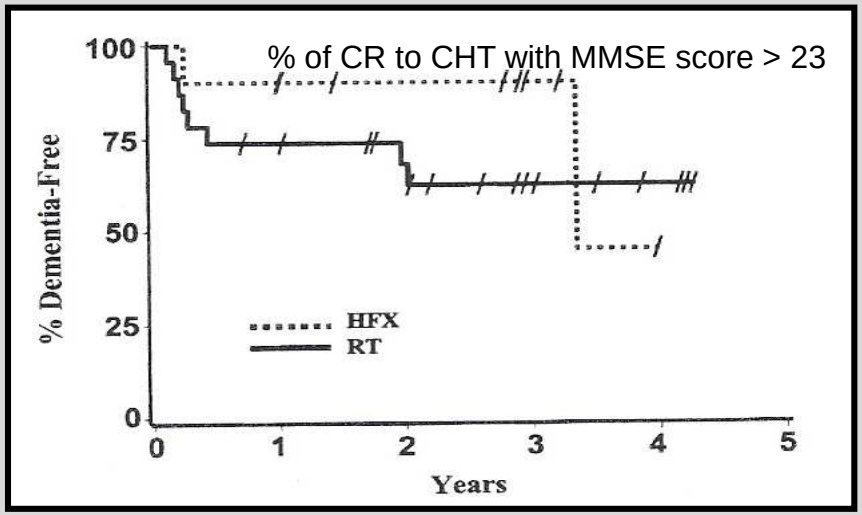
Fisher et Al, J NEURO-ONCOL 2005;74:201

<u>Note</u>: CRs, 27 after CF RT, 13 after HF RT









The subject of MTX + Rituximab + TMZ pre-RT + TMZ post-RT (HF WB 36 Gy) is presently addressed in RTOG 02-27

Glass et Al, XI NEURONCOLOGY MEETING, 2006

Phase I 13 Pts.

Purpose: to determine the maximum tolerated dose of TMZ in combination with MTX

RTX 375 mg/mq 3 days before the first cycle of i.v. MTX 3.5 mg/mq (leucovorin rescue on weeks 1, 3, 5, 7 and 9)
TMZ daily for 5 days on weeks 4 and 8 (Arm 1, 100 mg/sm: 7 pts; Arm 2, 150 mg/sm: 7 pts [1 inelig.]; Arm 3, 200 mg/sm: stop.
HF RT (36 Gy) on weeks 11, 12, 13
TMZ 200 mg/sm/day for 5 days on weeks 14, 18, 22, 26, 30, 34, 38, 42, 46 and 50

Results: **TMZ 100 mg/mq: 1 DLT (grade IV kidney toxicity)**
TMZ 150 mg/mq: 3 DLTs (grade III-IV liver toxicity -2pts- grade III kidney toxicity-1pt-)

Conclusion: **MTD of TMZ in the "induction" phase: 100 mg/sm**

Phase II

therapeutic results, ongoing

Furthermore, many other studies addressed the issue of combining different CHT schedules with different timing and schedules of RT …

Data by Schultz and Bovi, IJROBP 2010;76:666

	First author (Ref)	Median age	Chemotherapy	Penetrating Yes	Penetrating No	IT/IO therapy	Radiation WBRT (boost)	XRT at relapse	PFS	OS	Neurotoxicity
XRT alone	Nelson (23)	66	None			None	40 Gy (20 Gy)		NS	1 y 48% 2 y 28%	None
Chemo + XRT	DeAngelis (26)	56.5	MTX, Vin, Pro, Leu, Dex, Cyt after XRT	X		IO MTX	45 Gy		24 mo	2 y 64% 3 y 52% 5 y 32%	53% Grade 3, 4/w chemo, 15% leuko, no change in MMSE
	Poortmans (60)	51	MBVP	X		IT MTX Ara-C Hydrocortisone	40 Gy		NS	2 y 69% 3 y 58%	None
	Gavrilovic (61)	65	MTX, Vin, Pro	X		IO MTX	45 Gy		Not reached	Pts >60 y 29 mo	26% <60 y 75% ≥60 y
	Fisher (36)	NS	MTX, Vin, Pro, Leu, Dex, Cyt after XRT	X		IO MTX	45 Gy 25 fx (STD) or 36 Gy 30 fx 3 wk (HFX)		24.5 mo STD FX 23.3 mo HFX	Med 36.9 mo	10% Grade 5
	O'Brien (62)	58	MTX	X		None	45 Gy (5.4)		2 y 65%	2 y 65%	22% at 30 mo
	Blay (63)	51	C5R	X		IT MTX Hydrocortisone	20 Gy (30 Gy)		NS	2 y 70% 3 y 56%	None
	Abrey (64)	65	MTX Leu Pro Vin	X		IO MTX	45 Gy		NS	Med 60 mo	25% overall 83% in pts >60 y
	Abrey (65)	59	MTX Leu	X		IO MTX	40 Gy (14.4 Gy)		NS	5 y 22.3%	2 pts <50 y 80% > 60 y
	Bessell (28)	59	CHOD/BVAM	X		None	45 Gy (10 Gy)		NS	5 y 31%	8% in pt <60 62% in pt >60
	O'Neill (24)	63.5	CHOP/HDAC		X	None	50.4 Gy		1 y 35% 3 y 11%	1 y 44% 3 y 14%	Higher in pt >60
	Schultz (25)	NS	CHOD		X	None	41.4 Gy		Median 9.2 mo	2 y 42%	1 encephalomalacia
	Brada (66)	51	MACOP-B		X	None	40 Gy (15 Gy)		5 y 32%	5 y 36%	1 pt unclear if treatment related
Chemotherapy alone	Pels (67)	62	MTX, Vin, Ifos, Dex Pred, ARA-C	X		IT MTX		28%	NS	2 y 69% 5 y 43%	35% MRI white matter changes, asymptomatic
	Gerstner (68)	60	MTX	X		None		52%	Median 12.8 mo	Med 55.4 mo	No leuko reported
	Batchelor (69)	60	MTX	X		None		52%	Median 12.8 mo	Not reached	NS
	Hoang-Xuan (70)	72	MTX Lom Pro methylpred	X		IT MTX cytarabine		NS	1 y 40% Median 6.8 mo	Med 14.3 mo	8% MMSE decrease
	Sandor (71)	57	MTX Leu Thio Vin Dex	X		IT MTC ARA-C		57%	Median 16.5 mo 57 mo 34.3%	4.5 y 68.8%	2 pt w/ grade 3 leuko
	Dahlborg (72)	52.3	CMPD	X		None		31%	NS	Med 40 mo	No neuropsychologic deficit reported
	Gavrilovic (61)	65	MTX Vin Pro	X		IO MTX		NS	7 mo	3 y 55% 5 y 31%	1 pt

"Integrated" RT→

RT at relapse →

Abbreviations: ARA-C = cytarabine; C5R = cyclophosfamide, vincristine, methotrexate, hydrocortisone, methylprednisolone, adriamycin, cytarabine; CHOD/BVAM = cyclophosfamide, doxorubicin, vincristine, dexamethasone, carmustine, vincristine, cytarabine, methotrexate; CHOP/HDAC = cyclophosfamide, adriamycin, vincristine, prednisone, high-dose cytarabine; CMPD = cyclophosfamide, methotrexate, procarbazine, dexamethasone; Dex = dexamethasone; HFX = hyperfractionation; Ifos = ifosfamide; IO MTX = intraommaya methotrexate; IT-MTX = intrathecal methotrexate; Leu = leucovorin; leuko = leukoencephalopathy; Lom = lomustine; MACOP-B = cyclophosfamide, doxorubicin, methotrexate, vincristine, prednisolone; MBVP = methortrexate, teniposide, carmustine, methylprednisolone; Methylpred = methylprednisolone; MMSE = mini mental status exam; MTX = methotrexate; NS = not stated; pred = prednisone; OS = overall survival; Pro = procarbazine; pt = patient; STD = standard fractionation; Thio = thiotepa; Vin = vincristine; WBRT = whole-brain radiotherapy.

… often achieving good therapeutic results and sometimes acceptable toxicity… but the bias of patient selection can never be excluded, due to the lack of random trials …

Data by Schultz and Bovi IJROBP 2010;76:666

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	Blay (63)	5								70% 56%	None
	Abrey (64)	6								60 mo	25% overall 83% in pts >60 y
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	Dahlborg (72)	52.3	CMPD	X		None		31%	NS	Med 40 mo	No neuropsychologic deficit reported
	Gavrilovic (61)	65	MTX Vin Pro	X		IO MTX		NS	7 mo	3 y 55% 5 y 31%	1 pt

"Integrated" RT→

RT at relapse →

	2y survival	5y survival
Integrated RT	42% - 70%	22% - 36%
RT at relapse	up to 69%	31% - 68.8%(4.5y)

Severe early and delayed toxicity, in some reports

Abbreviations: ARA-C = cytarabine; C5R = cyclophosfamide, vincristine, methotrexate, hydrocortisone, methylprednisolone, adriamycin, cytarabine; CHOD/BVAM = cyclophosfamide, doxorubicin, vincristine, dexamethasone, carmustine, vincristine, cytarabine, methotrexate; CHOP/HDAC = cyclophosfamide, adriamycin, vincristine, prednisone, high-dose cytarabine; CMPD = cyclophosfamide, methotrexate, procarbazine, dexamethasone; Dex = dexamethasone; HFX = hyperfractionation; Ifos = ifosfamide; IO MTX = intraommaya methotrexate; IT-MTX = intrathecal methotrexate; Leu = leucovorin; leuko = leukoencephalopathy; Lom = lomustine; MACOP-B = cyclophosfamide, doxorubicin, methotrexate, vincristine, prednisolone; MBVP = methortrexate, teniposide, carmustine, methylprednisolone; Methylpred = methylprednisolone; MMSE = mini mental status exam; MTX = methotrexate; NS = not stated; pred = prednisone; OS = overall survival; Pro = procarbazine; pt = patient; STD = standard fractionation; Thio = thiotepa; Vin = vincristine; WBRT = whole-brain radiotherapy.

Selection of patients:

- **the current statements about therapy of PCNSL derive from non-random studies, due to the rarity of the disease**
- **inherent natural history variables might prevail over therapy strategies, as prognostic determinants**

Inherent prognostic factors Score Systems:

1) Nottingham - Barcelona

Bessel et Al, IJROBP 2004;59:501

2) International Extranodal Lymphoma Study Group (IELSG)

Ferreri et Al, J CLIN ONCOL 2003;21:266

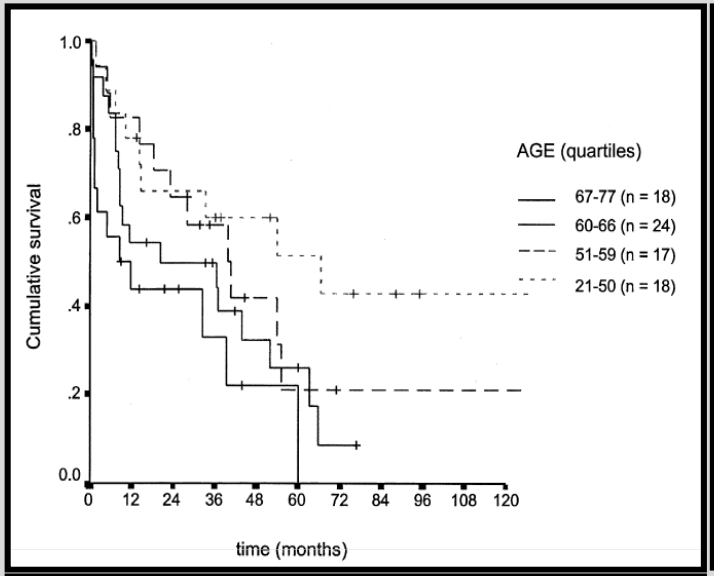
3) Memorial Sloan-Kettering Cancer Center (MSKCC)

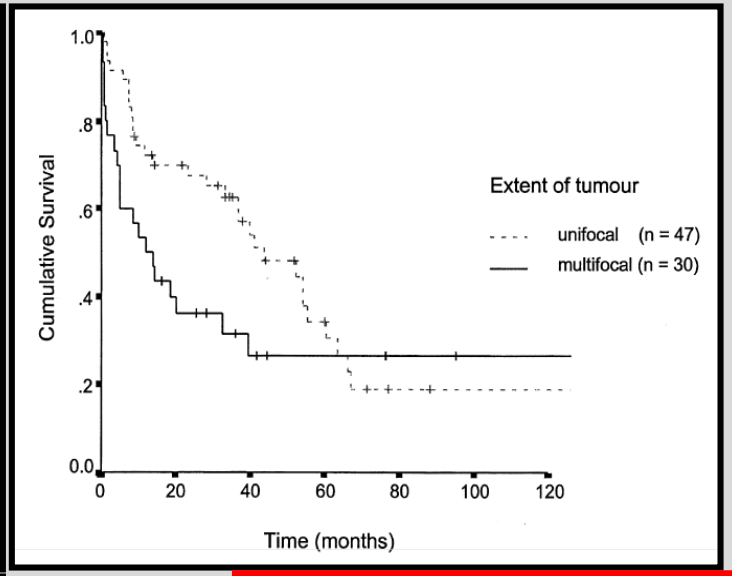
Abrey et Al, J CLIN ONCOL 2006;24:5711

The Nottingham – Barcelona system

- 77 consecutive pts, collected over 15 years (1986-2001), undergoing various schedules of CHT (BVAM; CHOD/BVAM) and RT (45 Gy + boost CF; 30.6 Gy HF)
- The main prognostic facors were age, ECOG PS and unifocal / multifocal – meningeal disease
- Long-term survival was demonstrated in 35 pts <60y undergoing BVAM or CHOD/BVAM and RT, similar to that of other LBC NHL of other organs

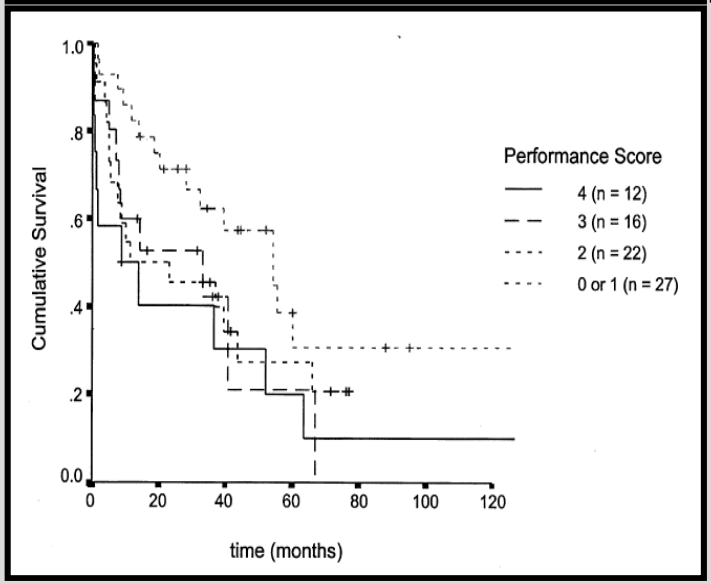
The Nottingham – Barcelona system

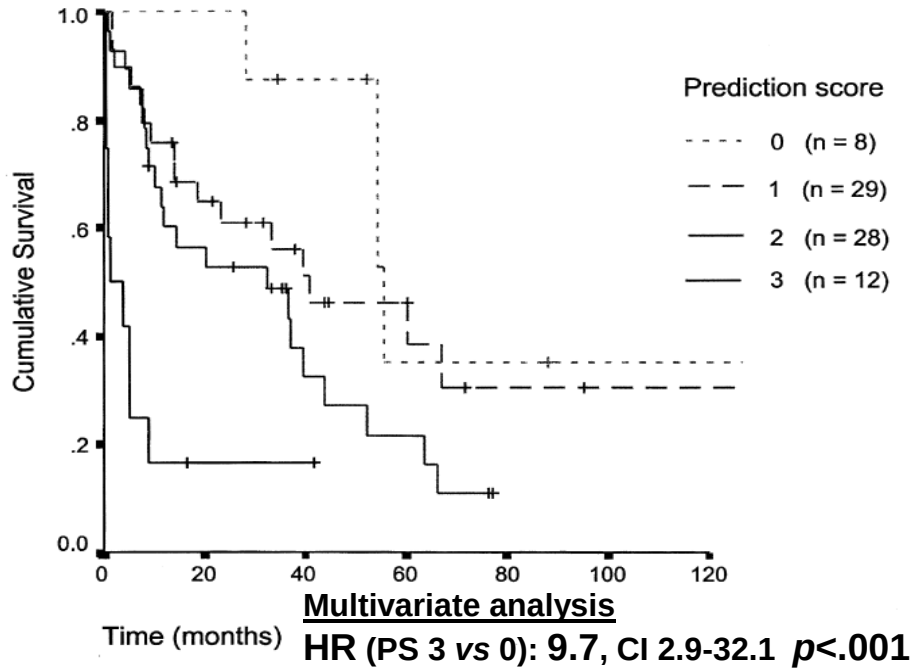




Scoring system
1 point for each unfavorable factor:

- **Age ≥ 60y**
- **PF ≥ 2**
- **Multifocal/Mening.**





Multivariate analysis
HR (PS 3 *vs* 0): 9.7, CI 2.9-32.1 *p*<.001

The International Extranodal Lymphoma Study Group (IELSG) system

- **378 pts from 48 centers, collected over 20 years: only 105 had complete data for inclusion in the model**
- **The median follow-up time was only 24 months**
- **RT, CHT, CHT + RT or no treatment; MTX was the most commonly used drug; RT dose was in the range 34 -55 Gy**
- **the analysis (uni- and multivariate) was performed according to the intention-to-treat**

The International Extranodal Lymphoma Study Group (IELSG) system

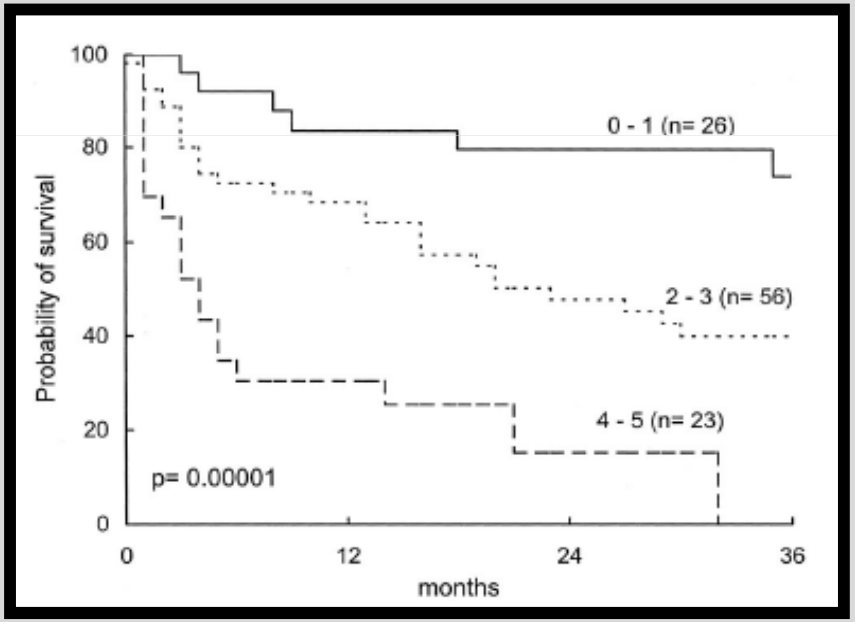
Table 3. Multivariate Analysis: Clinical and Therapeutic Variables Associated With Survival

Independent variables

Variable	Subgroup	Entire Series (N = 370) Odds Ratio	95% CI	P
Age	Continuous variable	1.02	1.01-1.03	.0001
Sex	Female/male	1.24	0.95-1.62	.11
ECOG PS	0-1/2-4	1.64	1.21-2.23	.001
Histotype	A-C/D-K	0.97	0.73-1.31	.87
Systemic symptoms	A/B	2.31	0.51-9.12	.27
LDH serum level	Normal/elevated	1.41	1.01-2.08	.05
CSF protein level	Normal/elevated	1.71	1.03-2.79	.03
No. of lesions	Single/multiple	0.98	0.73-1.31	.91
Meningeal disease	No/yes	1.28	0.81-2.01	.28
Ocular disease	No/yes	0.81	0.45-1.49	.51
Deep lesions	No/yes	1.45	1.11-1.91	.007
Planned treatment	RT/RT-CHT/CHT/CHT-RT	0.91	0.83-0.99	.05
HD-MTX	Yes/no	1.32	1.01-1.89	.05
HD cytarabine	Yes/no	1.15	0.78-1.69	.45
Anthracycline	Yes/no	1.01	0.68-1.48	.97
Alkylating agents	Yes/no	1.27	0.81-2.01	.28
Intrathecal CHT	Yes/no	1.21	0.85-1.72	.28
Year of diagnosis	Continuous variable	0.99	0.96-1.02	.81

Scoring system:
- **Age: ≤60y, >60y**
- **ECOG PS: 0-1 vs 2-4**
- **LDH sl: norm. vs elev.**
- **Prot. CSF conc.: norm. vs elev.**
- **Deep involv.: no vs yes**

For each: 0 (favorable), 1 (unfavorable)
Final score: the sum



Survival analysis for 105 pts with complete data for all the 5 variables

The International Extranodal Lymphoma Study Group (IELSG) system

Table 3. Multivariate Analysis: Clinical and Therapeutic Variables Associated With Survival

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Scoring system:
- **Age: ≤60y, >60y**
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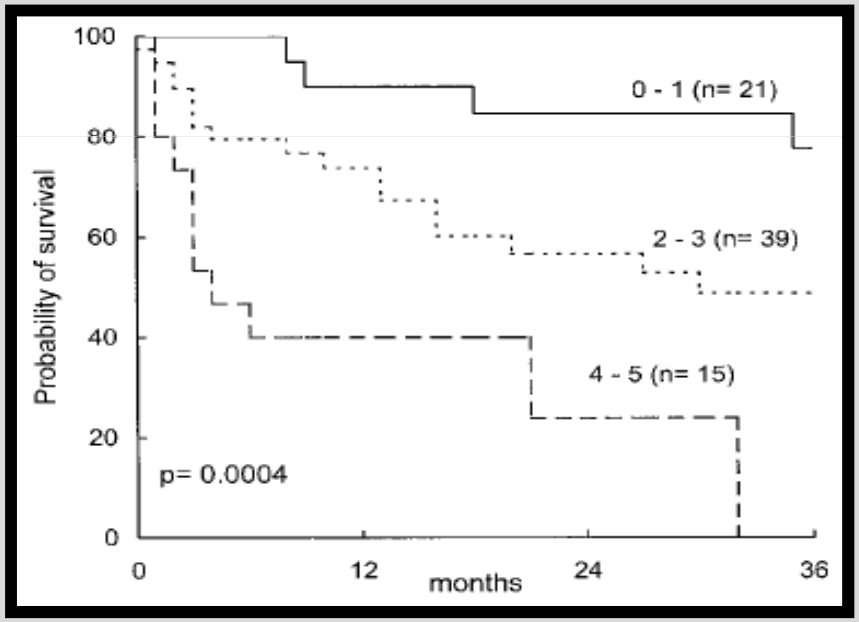
- **LDH sl: norm. vs elev**
- **Prot. CSF conc.: norm. vs elev.**
- **Deep involv.: no vs yes**

For each: 0 (favorable), 1 (unfavorable)
Final score: the sum



Survival analysis for 75 pts undergoing HD MTX-based CHT and RT

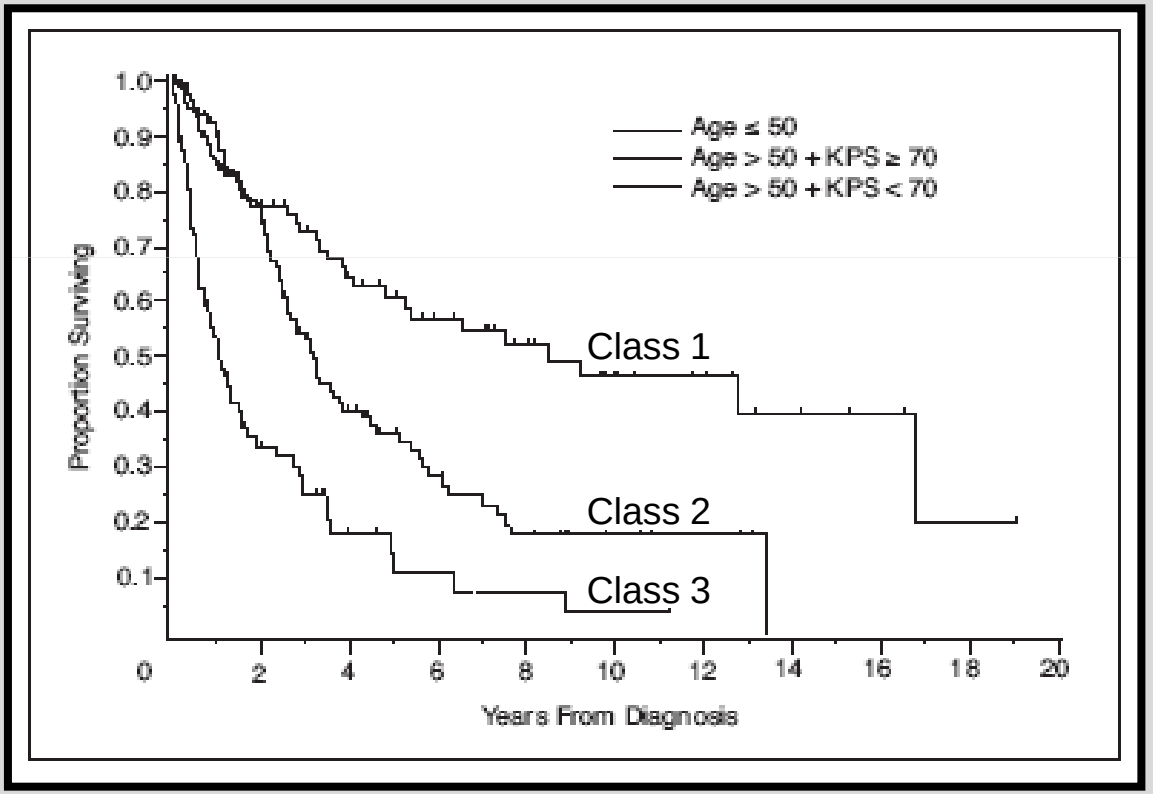
The Memorial Sloan-Kettering (MSKCC) prognostic model

- 338 consecutive pts with PCNSL, 1983-2003: uni- and multivariate analysis of prognostic factors; formal cut point for age (the most significant prognostic factor)
- 79%: MTX-based CHT; 54% WB RT as part of the primary treatment
- 71% CRs at the end of primary treatment
- Recursive partitioning analysis (RPA) used to create independent prognostic classes
- RPA of 282 pts identified three distinct prognostic classes:
  - Class 1: pts < 50y
  - Class 2: pts ≥ 50y, KPS > 70
  - Class 3: pts ≥ 50y, KPS < 70
- These classes significantly identified prognosis (both OS and FFS)

The Memorial Sloan-Kettering (MSKCC) prognostic model

Class	OS	FFS	p
Median, years			
1	8.5	2.0	<.001
2	3.2	1.8	
3	1.1	0.6	
RTOG data 88-06 and 93-10 for external validation (194 pts)			
1	5.2	4.9	<.001
2	2.1	1.7	
3	0.9	0.9	
IELSG score system (OS only, internal validation: 226 pts)			
0 - 1	7.9		=.006
2 - 3	2.9	p =.10	
4 - 5	1.0		

RPA analysis of Overall Survival of 282 pts



PCNS lymhoma: what is the present role for radiotherapy?

- Optimal therapy for PCNS is far from being defined: this statement applies also to RT timing and dose/fractionation;
- Presently, on the ground of the available data, the best reachable therapeutic results could probably be obtained mainly after a careful selection of patients;
- Primary therapy should include BBB-penetrating CHT (HD/IT MTX - based), and sequentially integrated WBRT (45 Gy if CF, 36 Gy if HF);
- The above statement about WBRT is reasonably valid for CRs to CHT;
- In PRs, salvage CHT was suggested as an alternative, or previously to WBRT;
- Elderly patients (>50y or >60y ?) deserve a particular consideration, due to the inherent bad prognosis and an increased risk for neurotoxicity: deferred WBRT at relapse should be considered;
- Patients should be enrolled in prospective, well-designed trials, even if it is difficult to hypothesize phase 3 trials; necessity of large databases (≥ nationwide) also for biologic characterization.