REGIONE LAZIO

SAPIENZA UNIVERSITÀ DI ROMA

AZIENDA OSPEDALIERA SANT' ANDREA

FACOLTÀ DI MEDICINA E PSICOLOGIA

Updates and learnings in CNS malignancies and Hodgkin and non-Hodgkin lymphomas

Mattia Falchetto Osti

Updates and learnings in CNS malignancies

- Treatment options for Anaplastic Oligodendroglial tumors
- Perspectives on treatment for elderly patients with Glioblastoma (GBM)

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Anaplastic Oligodendroglioma

- Anaplastic oligodendrogliomas and anaplastic oligoastrocytomas account for up to 25% of all newly diagnosed malignant gliomas
- Standard treatment is surgical resection followed by radiotherapy (RT)
- Median survival time ranges from 3 to 5 years
- 1p/19q codeletion represents a strong and independent favourable prognostic factor

Anaplastic Oligodendroglioma

Evidence that anaplastic oligodendrogliomas were sensitive to PCV chemotherapy prompted 2 studies:

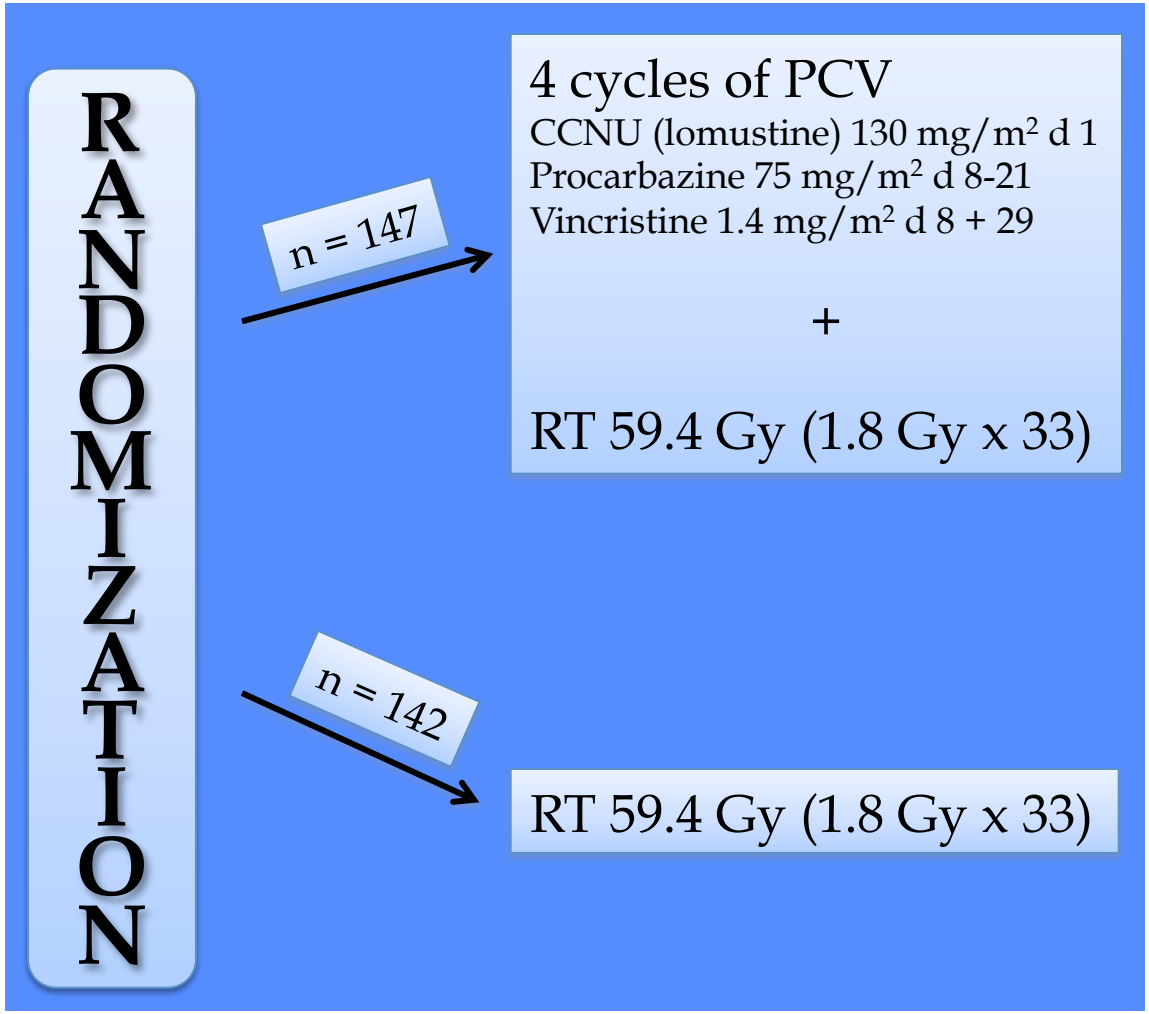
- RTOG 9402 trial in 1994

  PCV + RT 59.4 Gy vs RT 59.4 Gy

- EORTC 26951 trial in 1995

  RT 59.4 Gy + PCV vs RT 59.4 Gy

RTOG 9402: trial design



Cairncross G et al. JCO 2006

RTOG 9402: patient characteristics

Characteristic	PCV/RT (n = 148) No.	%	RT (n = 143) No.	%
Age, years				
Median	43		43	
Range	18-75		19-76	
Age, years*				
< 50	102	69	99	69
≥ 50	46	31	44	31
Sex				
Male	90	61	84	59
Female	58	39	59	41
Neurologic function				
No symptoms	47	32	47	33
Minor symptoms	73	49	69	48
Moderate (active)	17	12	12	8
Moderate (inactive)	11	7	14	10
Unknown	0	0	1	1
KPS*				
60-70	15	10	15	10
80-100	133	90	128	90
Surgery				
Total resection	40	27	53	37
Partial procedure	85	57	75	52
Biopsy only	21	14	14	10
No details	2	1	1	1
Tumor type				
AO	77	52	73	51
AOA (oligodendroglioma dominant)	28	19	37	26
AOA (neither element dominant)	24	16	15	11
AOA (astrocytoma dominant)	19	13	18	13
Tumor grade*				
Moderately anaplastic	80	54	81	57
Highly anaplastic	68	46	62	43
Multifocal tumor				
Yes	15	10	10	7
No	132	89	131	92
Unknown	1	1	2	1
Corticosteroids at baseline				
Yes	92	62	79	55
No	56	38	64	45
Chromosome 1p†				
Known	134		128	
1p deleted	66	49	76	59
1p intact	68	51	52	41
Unknown	14		15	
Chromosome 19q†				
Known	135		129	
19q deleted	85	63	82	64
19q intact	50	37	47	36
Unknown	13		14	
Chromosomes 1p & 19q†				
Known	135		128	
Both deleted	59	44	67	52
One or neither deleted	76	56	61	48
Unknown	13		15	

- 291 pts enrolled (1994 – 2002)

- Newly diagnosed anaplastic oligodendroglial tumors

- Age: ≥ 18 years

RTOG 9402: first report in 2006

(median follow - up: 60 months)

- Progression free survival (PFS), but not overall survival (OS), was prolonged by adding PCV to RT
- 1p/19q codeletion was associated with longer OS independent of treatment
- The addition of PCV to RT was associated with significant toxicity

Cairncross G et al. JCO 2006

RTOG 9402: long-term results in 2012

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

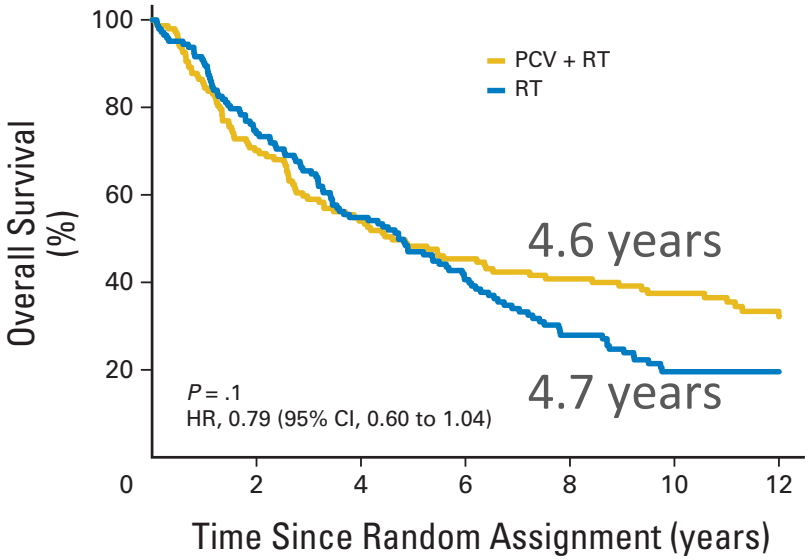
Purpose
Anaplastic oligodendrogliomas, pure (AO) and mixed (anaplastic oligoastrocytoma [AOA]), are chemosensitive, especially if codeleted for 1p/19q, but whether patients live longer after chemoradiotherapy is unknown.

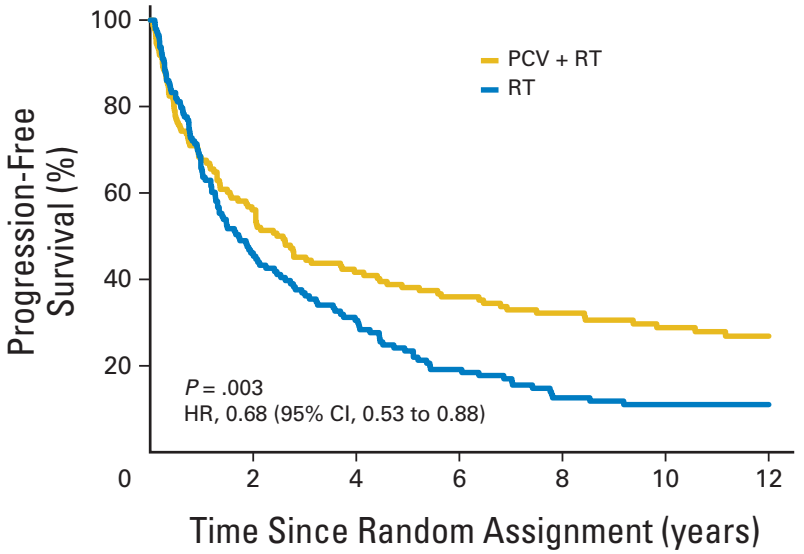
Patients and Methods
Eligible patients with AO/AOA were randomly assigned to procarbazine, lomustine, and vincristine (PCV) plus radiotherapy (RT) versus RT alone. The primary end point was overall survival (OS).

Results
Two hundred ninety-one eligible patients were randomly assigned: 148 to PCV plus RT and 143 to RT. For the entire cohort, there was no difference in median survival by treatment (4.6 years for PCV plus RT *v* 4.7 years for RT; hazard ratio [HR] = 0.79; 95% CI, 0.60 to 1.04; $P = .1$). Patients with codeleted tumors lived longer than those with noncodeleted tumors (PCV plus RT: 14.7 *v* 2.6 years, HR = 0.36, 95% CI, 0.23 to 0.57, $P < .001$; RT: 7.3 *v* 2.7 years, HR = 0.40, 95% CI, 0.27 to 0.60, $P < .001$), and the median survival of those with codeleted tumors treated with PCV plus RT was twice that of patients receiving RT (14.7 *v* 7.3 years; HR = 0.59; 95% CI, 0.37 to 0.95; $P = .03$). For those with noncodeleted tumors, there was no difference in median survival by treatment arm (2.6 *v* 2.7 years; HR = 0.85; 95% CI, 0.58 to 1.23; $P = .39$). In Cox models that included codeletion status, the adjusted OS for all patients was prolonged by PCV plus RT (HR = 0.67; 95% CI, 0.50 to 0.91; $P = .01$).

Conclusion
For the subset of patients with 1p/19q codeleted AO/AOA, PCV plus RT may be an especially effective treatment, although this observation was derived from an unplanned analysis.

RTOG 9402: OS and PFS



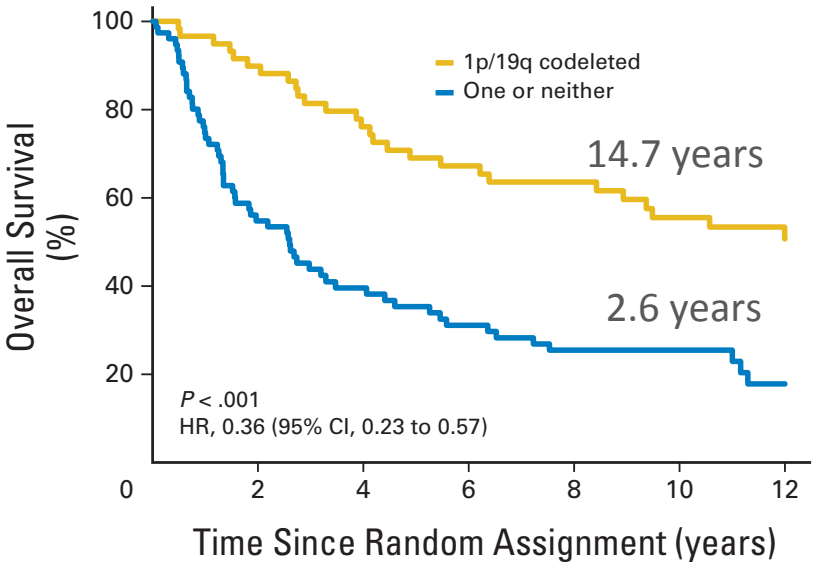


Median FU: 11.3 years

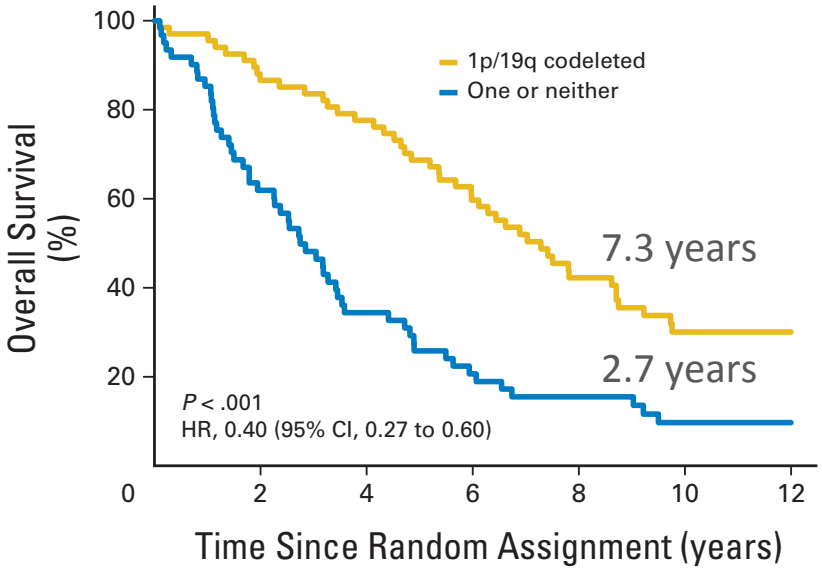
Cairncross G et al. JCO 2012

RTOG 9402: deletion status and survival

PCV + RT



RT



Median FU: 11.3 years

Cairncross G et al. JCO 2012

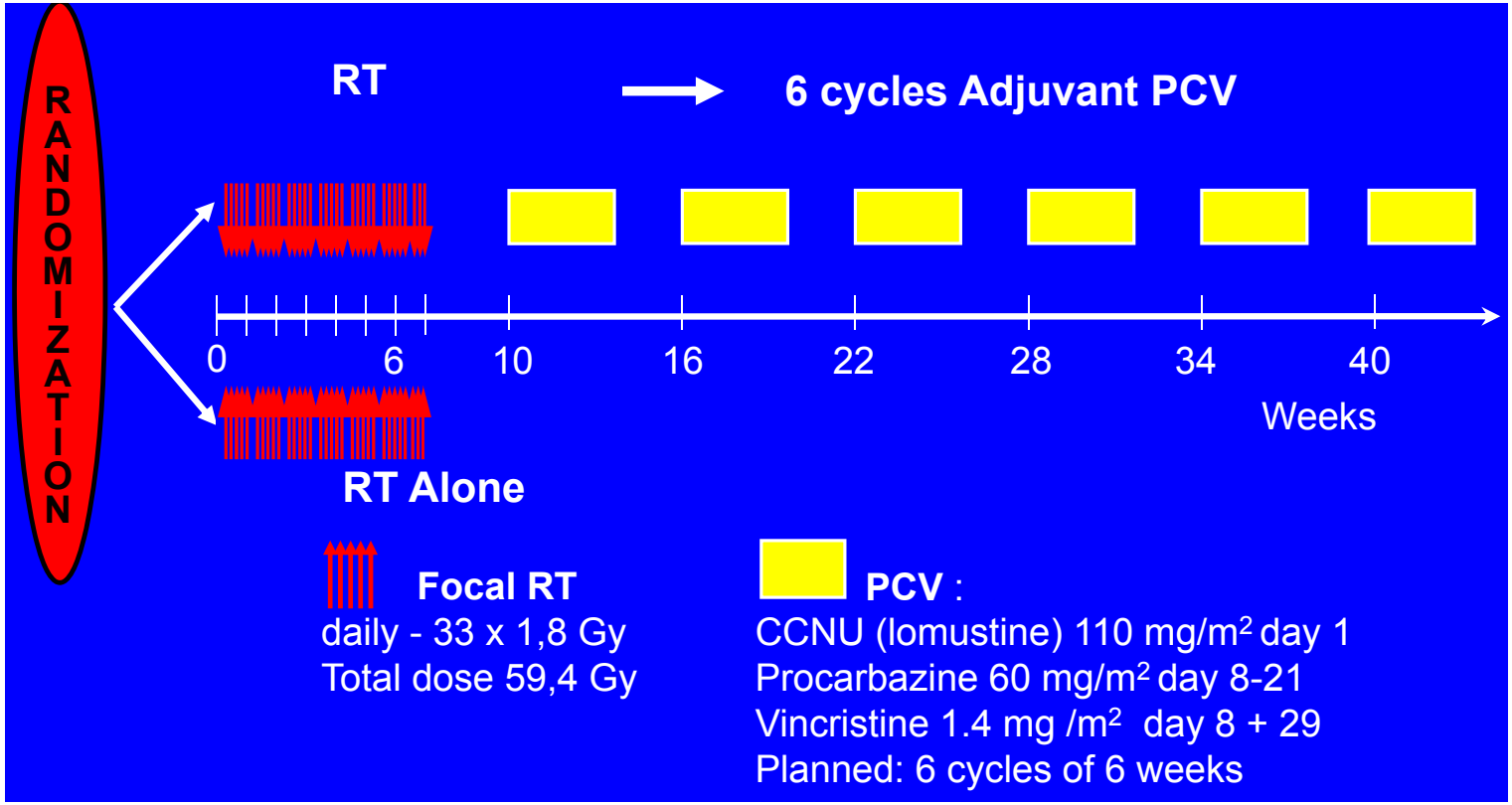
RTOG 9402: conclusions

- PCV + RT may be a highly effective treatment for patients with codeleted anaplastic oligodendroglial tumors

- 1p/19q codeletion is both a predictive and prognostic biomarker

Cairncross G et al. JCO 2012

EORTC 26951: trial design



Van den Bent MJ et al. JCO 2006

EORTC 26951: patient characteristics

Characteristic	Radiotherapy (n = 183) No.	Radiotherapy (n = 183) %	Radiotherapy Plus PCV (n = 185) No.	Radiotherapy Plus PCV (n = 185) %
Age, years				
Median	49.0		48.0	
Range	19.0-68.0		18.0-68.0	
Sex				
Male	110	60.1	102	55.1
Female	73	39.9	83	44.9
Performance status				
0-1	153	83.6	155	83.8
2	30	16.4	30	16.2
Previous surgery for low grade				
No	157	85.8	156	84.3
Yes	25	13.7	27	14.6
Missing	1	0.5	2	1.1
Enhancement of tumor				
No	30	16.4	33	17.8
Yes	141	77.0	145	78.4
Missing	12	6.6	7	3.8
Tumor location				
Frontal	85	46.4	93	50.3
Elsewhere	98	53.6	92	49.7
Mini-mental status examination				
< 27	53	29.0	46	24.9
27-30	114	62.3	116	62.7
Missing	16	8.7	23	12.4
Extent of surgery				
Biopsy	25	13.7	27	14.6
Partial resection	83	45.4	100	54.1
Total resection	75	41.0	58	31.4
Local diagnosis				
Anaplastic oligodendroglioma	126	68.9	140	75.7
Anaplastic oligoastrocytoma	56	30.6	44	23.8
Missing	1	0.5	1	0.5
Central review diagnosis				
Anaplastic oligodendroglioma	84	45.9	91	49.2
Anaplastic oligoastrocytoma	42	23.0	40	21.6
Low-grade glioma	22	12.0	17	9.2
Other high-grade glioma	21	11.5	18	9.7
Other	5	2.7	5	2.7
Missing	9	4.9	14	7.6
1p/19q status				
1p/19 intact	122	66.7	114	61.6
1p/19q codeletion	37	20.2	43	23.2
Missing	24	13.1	28	15.1
MGMT promoter				
Unmethylated	24	13.1	23	12.4
Methylated	62	33.9	74	40.0
Missing	97	53.0	88	47.6
IDH status				
Normal	50	27.3	47	25.4
Mutated	36	19.7	45	24.3
Missing	97	53.0	93	50.3

Abbreviation: PCV, procarbazine, lomustine, and vincristine.

- 368 pts enrolled (1996 – 2002)
- Newly diagnosed anaplastic oligodendroglial tumors
- Age: 16 – 70 years

EORTC 26951: first report in 2006

(median follow - up: 60 months)

- Adjuvant PCV increases progression free survival, not overall survival
- 1p/19q codeletion is prognostic but not predictive for benefit to adjuvant PCV
- The addition of PCV to RT is associated with significant toxicity

Van den Bent MJ et al. JCO 2006

EORTC 26951: long-term results in 2012

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

Martin J. van den Bent, Alba A. Brandes, Martin J.B. Taphoorn, Johan M. Kros, Mathilde C.M. Kouwenhoven, Jean-Yves Delattre, Hans J.J.A. Bernsen, Marc Frenay, Cees C. Tijssen, Wolfgang Grisold, László Sipos, Roelien H. Enting, Pim J. French, Winand N.M. Dinjens, Charles J. Vecht, Anouk Allgeier, Denis Lacombe, Thierry Gorlia, and Khê Hoang-Xuan

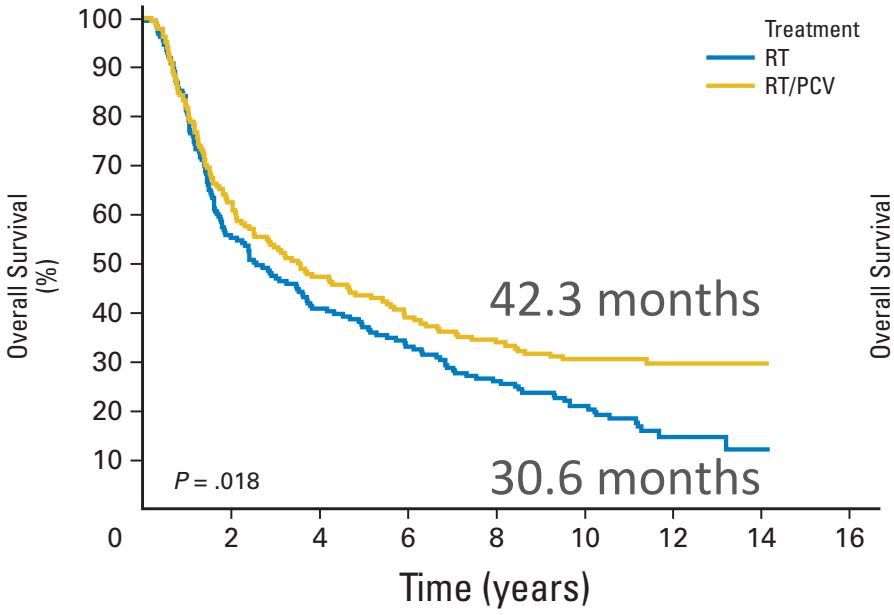
Purpose
Anaplastic oligodendroglioma are chemotherapy-sensitive tumors. We now present the long-term follow-up findings of a randomized phase III study on the addition of six cycles of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy (RT).

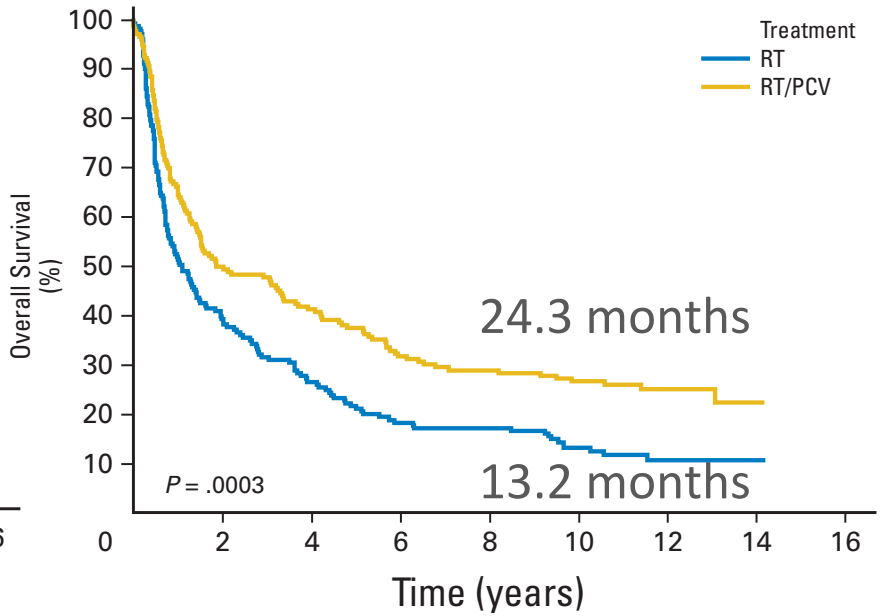
Patients and Methods
Adult patients with newly diagnosed anaplastic oligodendroglial tumors were randomly assigned to either 59.4 Gy of RT or the same RT followed by six cycles of adjuvant PCV. An exploratory analysis of the correlation between 1p/19q status and survival was part of the study. Retrospectively, the methylation status of the methyl-guanine methyl transferase gene promoter and the mutational status of the isocitrate dehydrogenase (*IDH*) gene were determined. The primary end points were overall survival (OS) and progression-free survival based on intent-to-treat analysis.

Results
A total of 368 patients were enrolled. With a median follow-up of 140 months, OS in the RT/PCV arm was significantly longer (42.3 *v* 30.6 months in the RT arm, hazard ratio [HR], 0.75; 95% CI, 0.60 to 0.95). In the 80 patients with a 1p/19q codeletion, OS was increased, with a trend toward more benefit from adjuvant PCV (OS not reached in the RT/PCV group *v* 112 months in the RT group; HR, 0.56; 95% CI, 0.31 to 1.03). *IDH* mutational status was also of prognostic significance.

Conclusion
The addition of six cycles of PCV after 59.4 Gy of RT increases both OS and PFS in anaplastic oligodendroglial tumors. 1p/19q-codeleted tumors derive more benefit from adjuvant PCV compared with non–1p/19q-deleted tumors.

EORTC 26951: OS and PFS



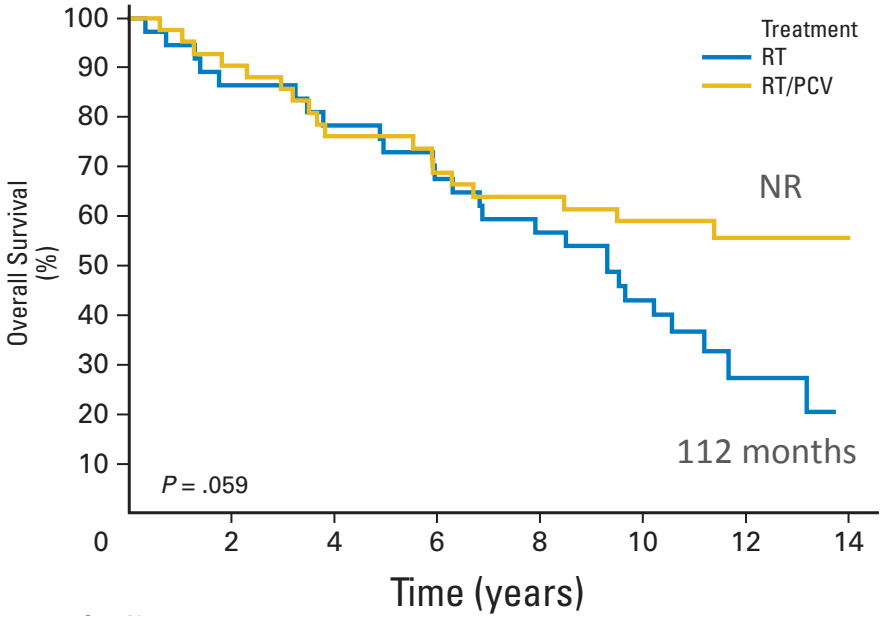


Median FU: 140 months

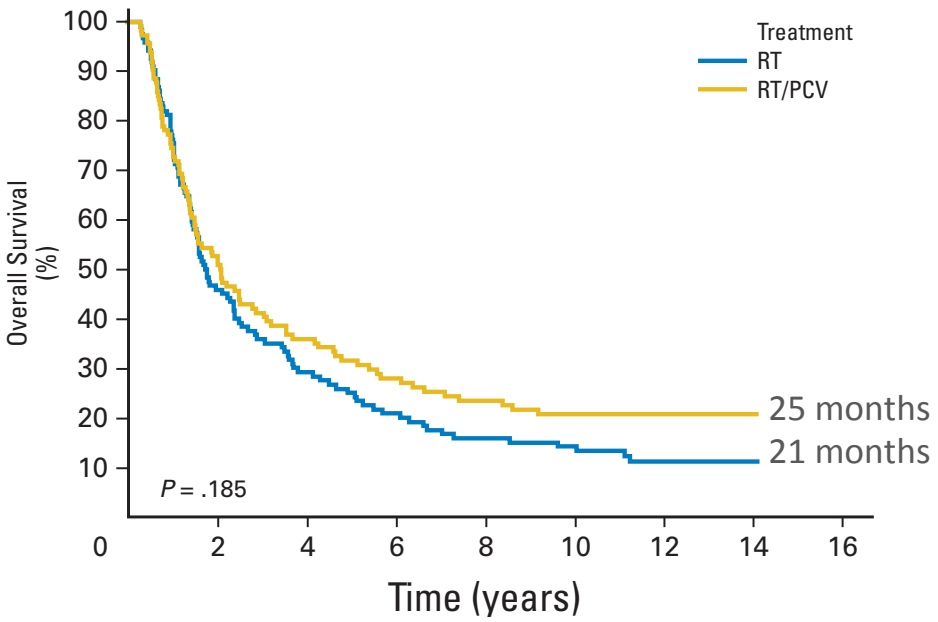
Van den Bent MJ et al. JCO 2012

EORTC 26951: deletion status and OS

1p/19q codeleted (n = 80)



1p/19q non-codeleted (n = 236)

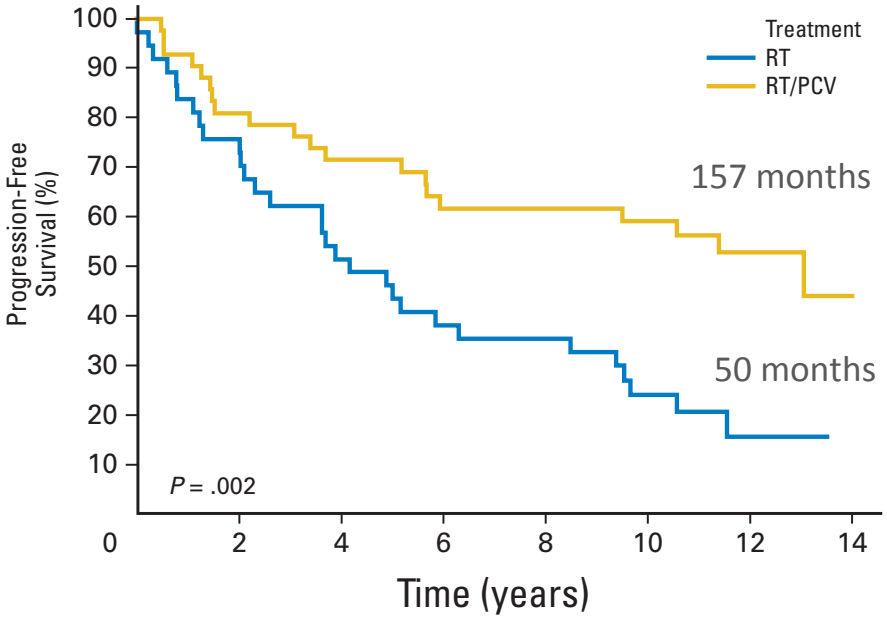


Median FU: 140 months

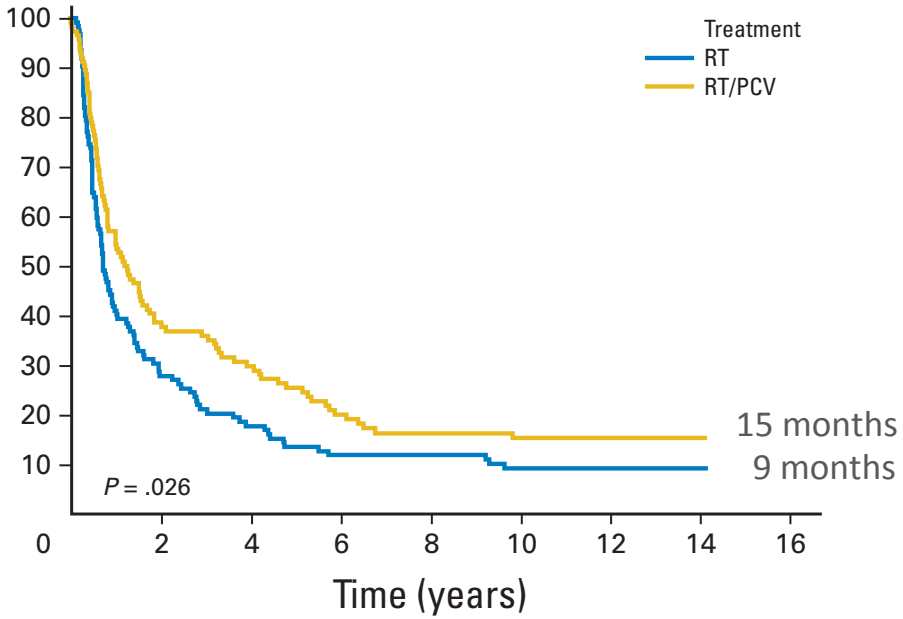
Van den Bent MJ et al. JCO 2012

EORTC 26951: deletion status and PFS

1p/19q codeleted (n = 80)



1p/19q non-codeleted (n = 236)



Median FU: 140 months

Van den Bent MJ et al. JCO 2012

EORTC 26951: conclusions

- Addition of PCV to RT results in improvement of OS and PFS in anaplastic oligodendroglial tumors

- 1p/19q codeleted tumors derive more benefit from PCV compared with non-1p/19q deleted tumors

Van den Bent MJ et al. JCO 2012

Summary

	RTOG 9402	EORTC 26951
Median FU	11.3 years	11.6 years
Overall		
RT	4.7 years	2.5 years
RT/PCV	4.6 years	3.5 years
Codeleted		
RT	7.3 years	9.3 years
RT/PCV	14.7 years	NR
Non-codeleted		
RT	2.7 years	1.7 years
RT/PCV	2.6 years	2.1 years

Open issues

- The combination of RT and PCV should be the new standard of care in codeleted patients?
- Optimal timing of PCV and RT?
- How patients with non-codeleted tumors should be treated?

  Ongoing CATNON trial (EORTC) in non-1p/19q codeleted tumors must further define which patients benefit from chemotherapy

Updates and learnings in CNS malignancies

- Treatment options for Anaplastic Oligodendroglial tumors

- Perspectives on treatment for elderly patients with Glioblastoma (GBM)

Treatment of elderly GBM patients

- Approximately 50% of GBM, the most common primary brain tumor, are diagnosed in patients aged ≥ 65 years

- Concomitant and adjuvant temozolomide (TMZ) in addition to RT is currently the standard treatment for adult patients with GBM

- Treatment of elderly GBM patients remains a challenge

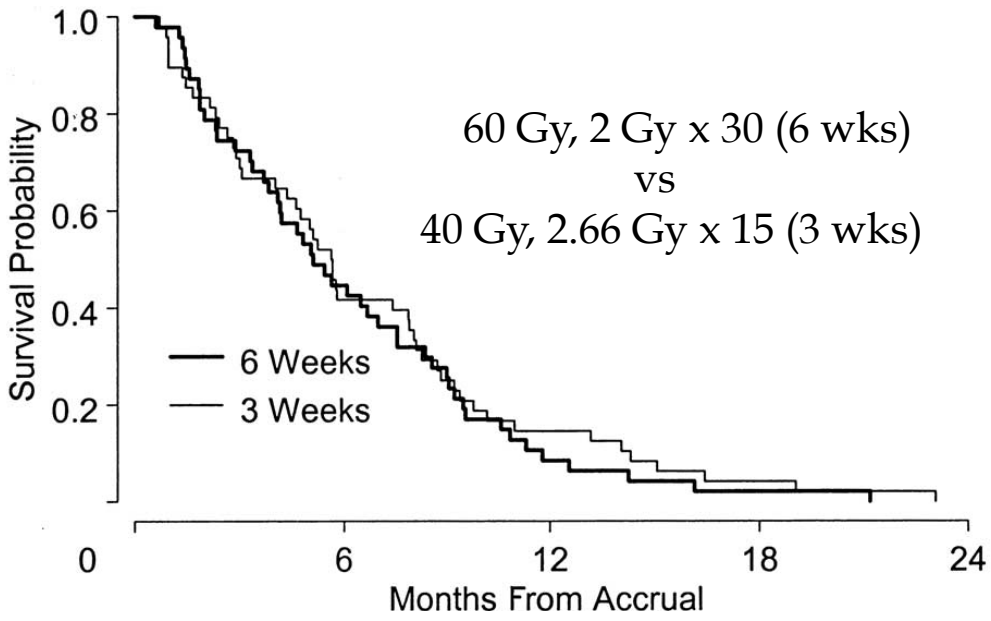
RT in elderly: what do we know?

Abbreviated Course of Radiation Therapy in Older Patients With Glioblastoma Multiforme: A Prospective Randomized Clinical Trial

W. Roa, P.M.A. Brasher, G. Bauman, M. Anthes, E. Bruera, A. Chan, B. Fisher, D. Fulton, S. Gulavita, C. Hao, S. Husain, A. Murtha, K. Petruk, D. Stewart, P. Tai, R. Urtasun, J.G. Cairncross, and P. Forsyth

J Clin Oncol 22:1583-1588. © 2004

Short-course RT is not inferior to standard RT in patients > 65 years



60 Gy, 2 Gy x 30 (6 wks)
vs
40 Gy, 2.66 Gy x 15 (3 wks)

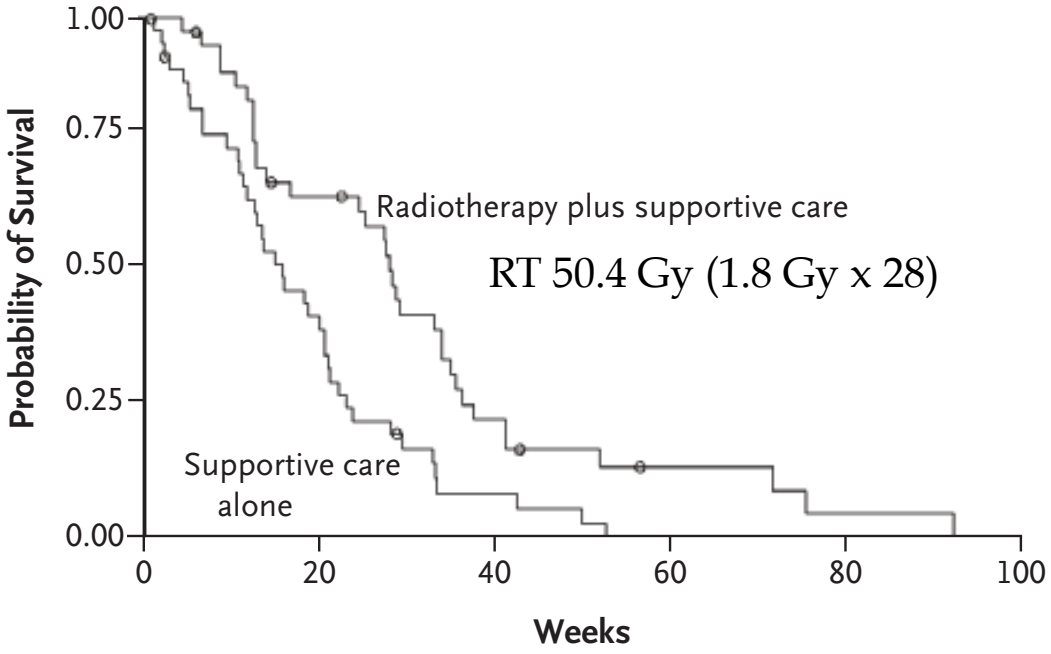
RT in elderly: what do we know?

Radiotherapy for Glioblastoma in the Elderly

Florence Keime-Guibert, M.D., Olivier Chinot, M.D., Luc Taillandier, M.D., Stéphanie Cartalat-Carel, M.D., Marc Frenay, M.D., Guy Kantor, M.D., Jean-Sébastien Guillamo, M.D., Eric Jadaud, M.D., Philippe Colin, M.D., Pierre-Yves Bondiau, M.D., Philippe Meneï, M.D., Hugues Loiseau, M.D., Valérie Bernier, M.D., Jérôme Honnorat, M.D., Maryline Barrié, M.D., Karima Mokhtari, M.D., Jean-Jacques Mazeron, M.D., Anne Bissery, M.D., and Jean-Yves Delattre, M.D., for the Association of French-Speaking Neuro-Oncologists*

N Engl J Med 2007;356:1527-35.

RT is better than best supportive care in patients > 70 years



Treatment of elderly GBM patients: 2012

Results from two randomized phase III trials:

- NOA-08 (Methvsalem) trial (> 65 y)

  RT 60 Gy vs TMZ 7/7

- Nordic trial (> 60 y)

  RT 60 Gy vs RT 34 Gy vs TMZ 5/28

Treatment of elderly GBM patients: 2012

- NOA-08 (Methvsalem) trial (> 65 y)

  RT 60 Gy vs TMZ 7/7

- Nordic trial (> 60 y)

  RT 60 Gy vs RT 34 Gy vs TMZ 5/28

NOA-08 Trial

Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial

Wolfgang Wick, Michael Platten, Christoph Meisner, Jörg Felsberg, Ghazaleh Tabatabai, Matthias Simon, Guido Nikkhah, Kirsten Papsdorf, Joachim P Steinbach, Michael Sabel, Stephanie E Combs, Jan Vesper, Christian Braun, Jürgen Meixensberger, Ralf Ketter, Regine Mayer-Steinacker, Guido Reifenberger, Michael Weller, for the NOA-08 Study Group of the Neuro-oncology Working Group (NOA) of the German Cancer Society*

***Lancet Oncol* 2012; 13: 707–15**

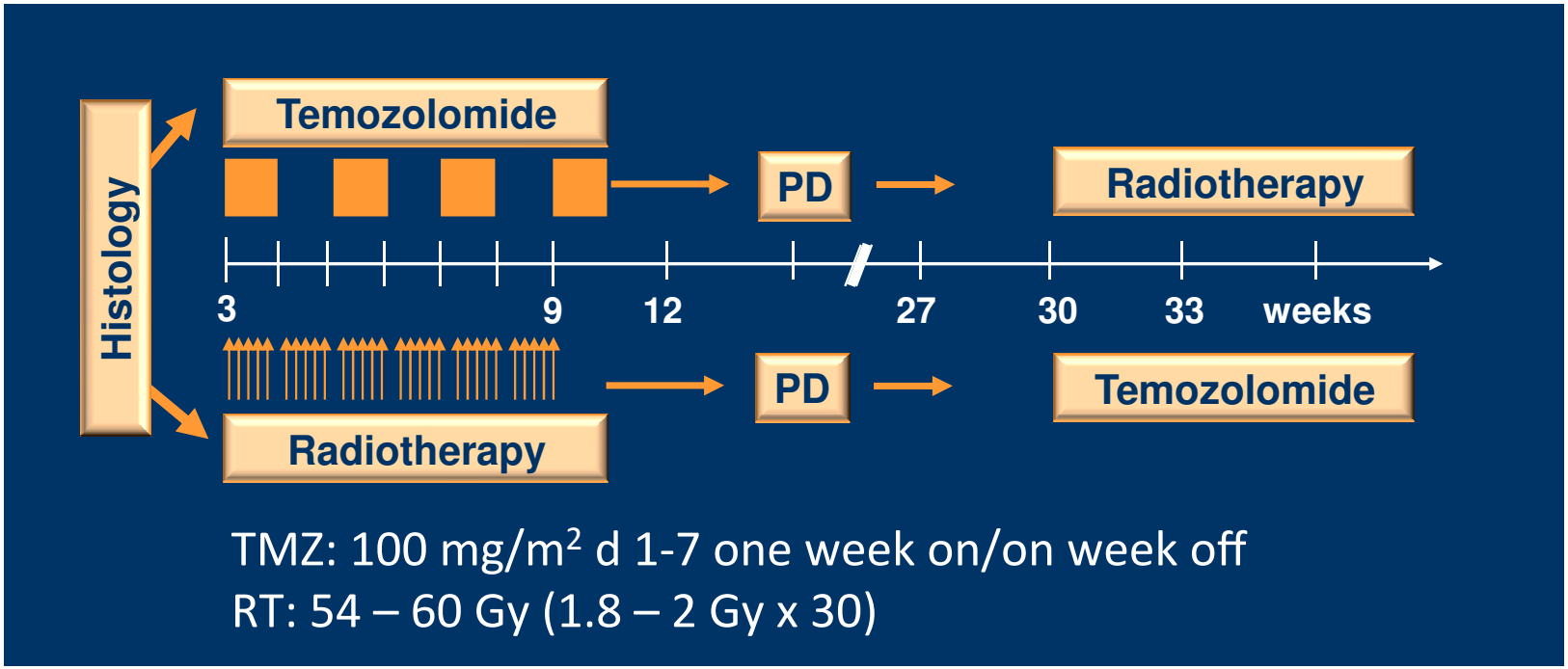
Background Radiotherapy is the standard care in elderly patients with malignant astrocytoma and the role of primary chemotherapy is poorly defined. We did a randomised trial to compare the efficacy and safety of dose-dense temozolomide alone versus radiotherapy alone in elderly patients with anaplastic astrocytoma or glioblastoma.

Methods Between May 15, 2005, and Nov 2, 2009, we enrolled patients with confirmed anaplastic astrocytoma or glioblastoma, age older than 65 years, and a Karnofsky performance score of 60 or higher. Patients were randomly assigned 100 mg/m² temozolomide, given on days 1–7 of 1 week on, 1 week off cycles, or radiotherapy of 60·0 Gy, administered over 6–7 weeks in 30 fractions of 1·8–2·0 Gy. The primary endpoint was overall survival. We assessed non-inferiority with a 25% margin, analysed for all patients who received at least one dose of assigned treatment. This trial is registered with ClinicalTrials.gov, number NCT01502241.

Findings Of 584 patients screened, we enrolled 412. 373 patients (195 randomly allocated to the temozolomide group and 178 to the radiotherapy group) received at least one dose of treatment and were included in efficacy analyses. Median overall survival was 8·6 months (95% CI 7·3–10·2) in the temozolomide group versus 9·6 months (8·2–10·8) in the radiotherapy group (hazard ratio [HR] 1·09, 95% CI 0·84–1·42, $p_{non\text{-}inferiority}$=0·033). Median event-free survival (EFS) did not differ significantly between the temozolomide and radiotherapy groups (3·3 months [95% CI 3·2–4·1] *vs* 4·7 [4·2–5·2]; HR 1·15, 95% CI 0·92–1·43, $p_{non\text{-}inferiority}$=0·043). Tumour *MGMT* promoter methylation was seen in 73 (35%) of 209 patients tested. *MGMT* promoter methylation was associated with longer overall survival than was unmethylated status (11·9 months [95% CI 9·0 to not reached] *vs* 8·2 months [7·0–10·0]; HR 0·62, 95% CI 0·42–0·91, p=0·014). EFS was longer in patients with *MGMT* promoter methylation who received temozolomide than in those who underwent radiotherapy (8·4 months [95e% CI 5·5–11·7] *vs* 4·6 [4·2–5·0]), whereas the opposite was true for patients with no methylation of the *MGMT* promoter (3·3 months [3·0–3·5] *vs* 4·6 months [3·7–6·3]). The most frequent grade 3–4 intervention-related adverse events were neutropenia (16 patients in the temozolomide group *vs* two in the radiotherapy group), lymphocytopenia (46 *vs* one), thrombocytopenia (14 *vs* four), raised liver-enzyme concentrations (30 *vs* 16), infections (35 *vs* 23), and thromboembolic events (24 *vs* eight).

Interpretation Temozolomide alone is non-inferior to radiotherapy alone in the treatment of elderly patients with malignant astrocytoma. *MGMT* promoter methylation seems to be a useful biomarker for outcomes by treatment and could aid decision-making.

NOA-08: trial design



Wick W et al. Lancet 2012

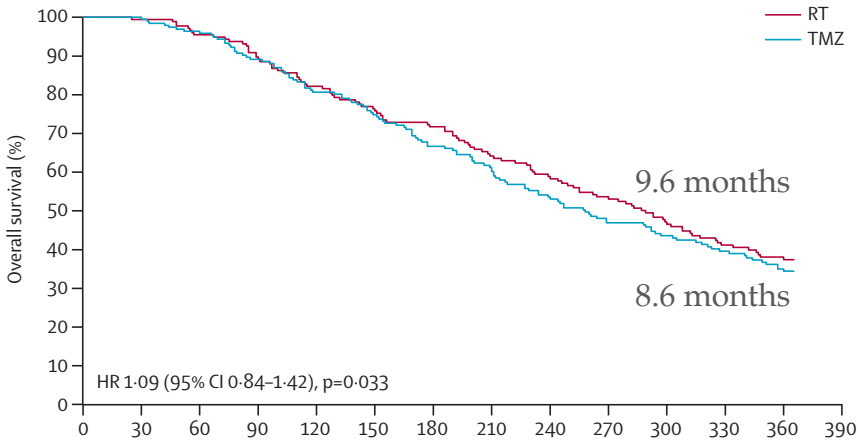
NOA-08: patient characteristics

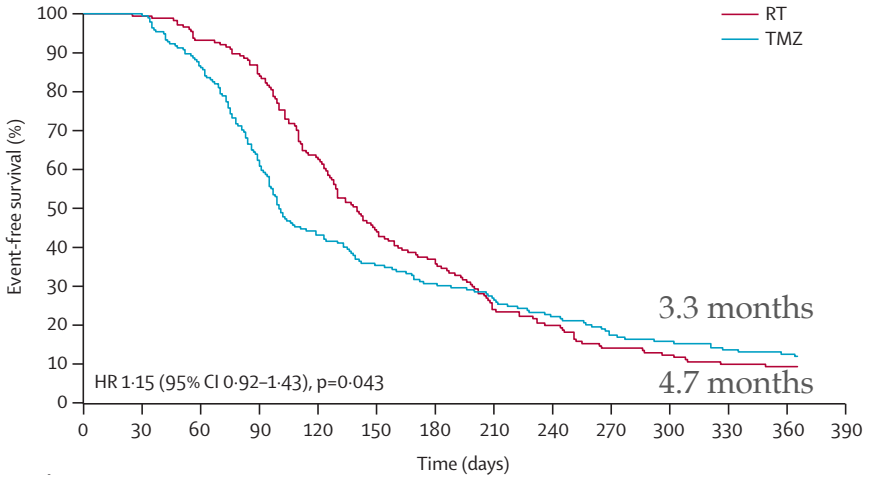
	Temozolomide (n=195)	Radiotherapy (n=178)
Median (range) age (years)	72 (66–84)	71 (66–82)
Sex		
Female	107 (55%)	90 (51%)
Male	88 (45%)	88 (49%)
Central histopathology		
Anaplastic astrocytoma	17 (9%)	23 (13%)
Glioblastoma	178 (91%)	153 (86%)
Not confirmed	0	2 (1%)
Karnofsky performance score		
Overall	80 (60–100)	80 (60–100)
Before treatment*	70 (20–100)	80 (50–100)
After primary treatment†	70 (0–100)	70 (20–100)
Mini-mental state examination score		
Overall	27 (9–30)	27 (13–30)
Before treatment	28·5 (17–30)	28 (12–30)
After primary treatment†	28 (0–30)	27 (11–30)
Resection		
Complete	53 (27%)	51 (20%)
Partial	61 (31%)	62 (35%)
Biopsy	80 (41%)	65 (37%)
Missing	1 (<1%)	0
Steroids		
None	97 (50%)	36 (20%)
At start of treatment only	8 (4%)	26 (15%)
At start and end of treatment	27 (14%)	24 (13%)
At end of treatment only	63 (32%)	90 (51%)
No data	0	2 (1%)
Median (range) duration of treatment (days)	77 (1–1137)	43 (1–65)
Time from surgery to start of study treatment (days)	19·0 (4·0–47·0)	30·5 (11·0–76·0)
MGMT promoter methylation status		
Methylated	31 (16%)	42 (24%)
Unmethylated	77 (39%)	59 (33%)
Missing/inconclusive	87 (45%)	77 (43%)

- 373 pts enrolled (2005 – 2009)
- Newly diagnosed anaplastic astrocytoma or GBM
- Age: > 65 years
- KPS: ≥ 60

Wick W et al. Lancet 2012

NOA-08: OS and EFS

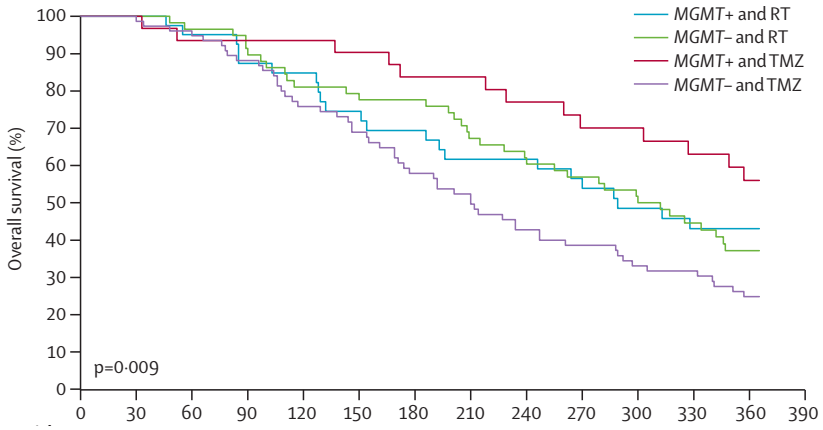


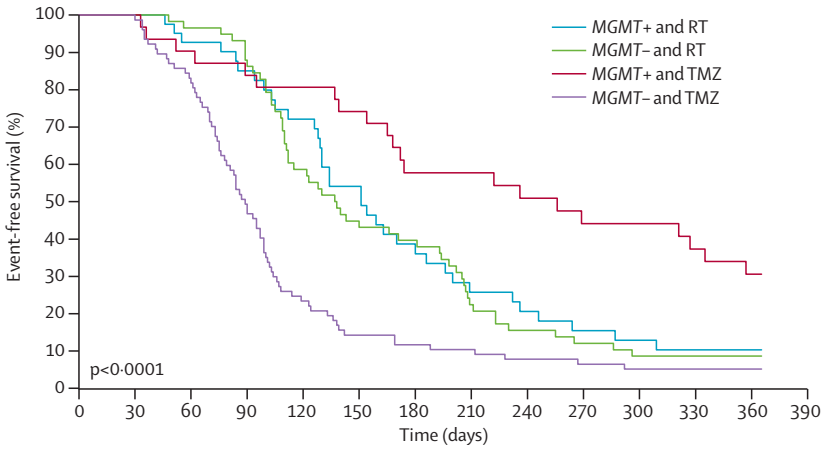


Median FU: 25.2 months

Wick W et al. Lancet 2012

NOA-08: MGMT status and survival





MGMT promoter methylated tumours responded better to TMZ than RT

Wick W et al. Lancet 2012

NOA-08: conclusions

- TMZ alone is non-inferior to RT alone in the treatment of elderly patients with malignant gliomas
- The rate of adverse and serious adverse events is higher with TMZ
- MGMT promoter methylation status is a strong predictive biomarker for outcomes by treatment and could aid decision-making

Wick W et al. Lancet 2012

Treatment of elderly GBM patients: 2012

- NOA-08 (Methvsalem) trial (> 65 y)

  RT 60 Gy vs TMZ 7/7

- Nordic trial (> 60 y)

  RT 60 Gy vs RT 34 Gy vs TMZ 5/28

Nordic Trial

Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial

Annika Malmström, Bjørn Henning Grønberg, Christine Marosi, Roger Stupp, Didier Frappaz, Henrik Schultz, Ufuk Abacioglu, Björn Tavelin, Benoit Lhermitte, Monika E Hegi, Johan Rosell, Roger Henriksson, for the Nordic Clinical Brain Tumour Study Group (NCBTSG)

Lancet Oncol 2012; 13: 916–26

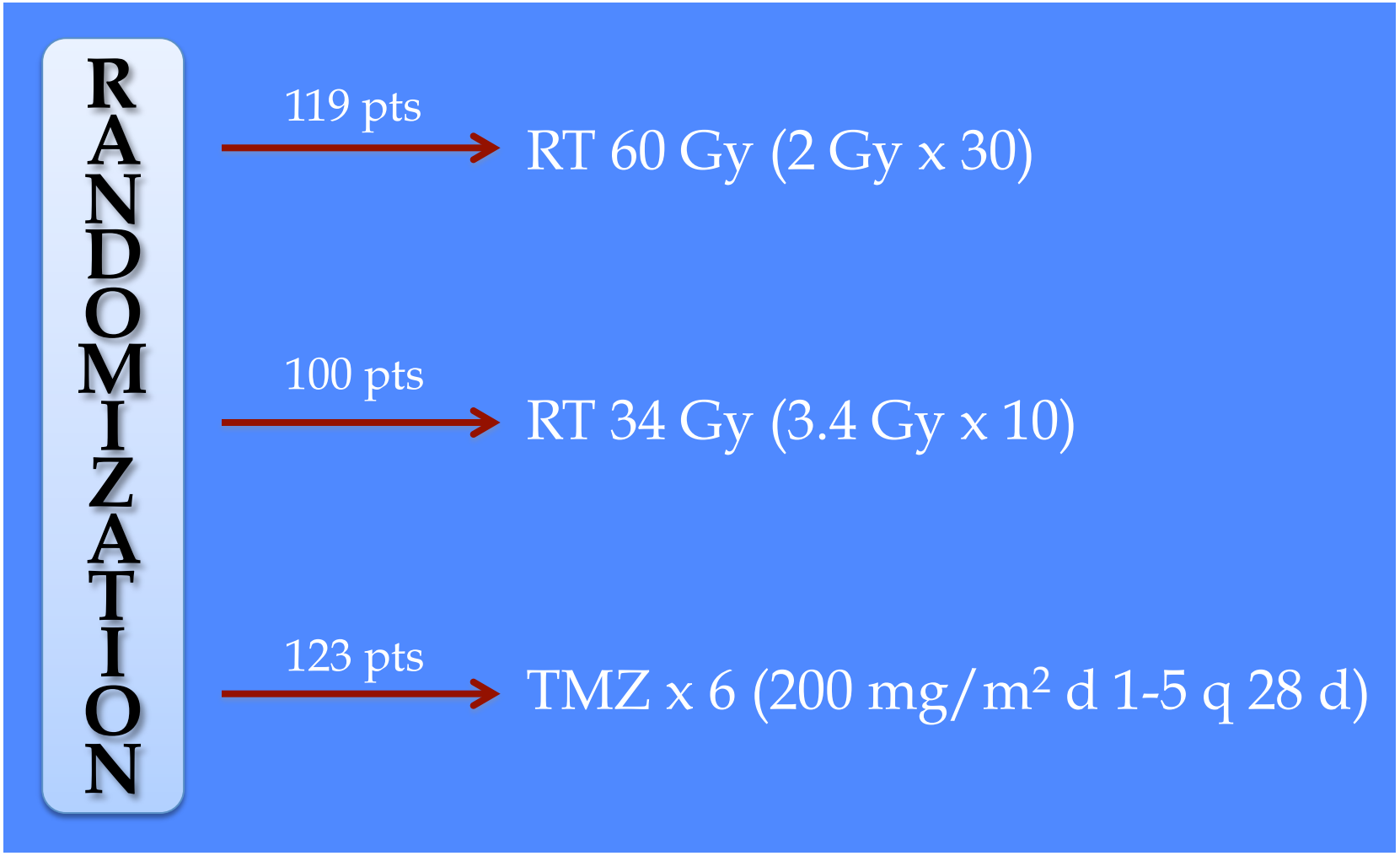
Background Most patients with glioblastoma are older than 60 years, but treatment guidelines are based on trials in patients aged only up to 70 years. We did a randomised trial to assess the optimum palliative treatment in patients aged 60 years and older with glioblastoma.

Methods Patients with newly diagnosed glioblastoma were recruited from Austria, Denmark, France, Norway, Sweden, Switzerland, and Turkey. They were assigned by a computer-generated randomisation schedule, stratified by centre, to receive temozolomide (200 mg/m² on days 1–5 of every 28 days for up to six cycles), hypofractionated radiotherapy (34·0 Gy administered in 3·4 Gy fractions over 2 weeks), or standard radiotherapy (60·0 Gy administered in 2·0 Gy fractions over 6 weeks). Patients and study staff were aware of treatment assignment. The primary endpoint was overall survival. Analyses were done by intention to treat. This trial is registered, number ISRCTN81470623.

Findings 342 patients were enrolled, of whom 291 were randomised across three treatment groups (temozolomide n=93, hypofractionated radiotherapy n=98, standard radiotherapy n=100) and 51 of whom were randomised across only two groups (temozolomide n=26, hypofractionated radiotherapy n=25). In the three-group randomisation, in comparison with standard radiotherapy, median overall survival was significantly longer with temozolomide (8·3 months [95% CI 7·1–9·5; n=93] *vs* 6·0 months [95% CI 5·1–6·8; n=100], hazard ratio [HR] 0·70; 95% CI 0·52–0·93, p=0·01), but not with hypofractionated radiotherapy (7·5 months [6·5–8·6; n=98], HR 0·85 [0·64–1·12], p=0·24). For all patients who received temozolomide or hypofractionated radiotherapy (n=242) overall survival was similar (8·4 months [7·3–9·4; n=119] *vs* 7·4 months [6·4–8·4; n=123]; HR 0·82, 95% CI 0·63–1·06; p=0·12). For age older than 70 years, survival was better with temozolomide and with hypofractionated radiotherapy than with standard radiotherapy (HR for temozolomide *vs* standard radiotherapy 0·35 [0·21–0·56], p<0·0001; HR for hypofractionated *vs* standard radiotherapy 0·59 [95% CI 0·37–0·93], p=0·02). Patients treated with temozolomide who had tumour *MGMT* promoter methylation had significantly longer survival than those without *MGMT* promoter methylation (9·7 months [95% CI 8·0–11·4] *vs* 6·8 months [5·9–7·7]; HR 0·56 [95% CI 0·34–0·93], p=0·02), but no difference was noted between those with methylated and unmethylated *MGMT* promoter treated with radiotherapy (HR 0·97 [95% CI 0·69–1·38]; p=0·81). As expected, the most common grade 3–4 adverse events in the temozolomide group were neutropenia (n=12) and thrombocytopenia (n=18). Grade 3–5 infections in all randomisation groups were reported in 18 patients. Two patients had fatal infections (one in the temozolomide group and one in the standard radiotherapy group) and one in the temozolomide group with grade 2 thrombocytopenia died from complications after surgery for a gastrointestinal bleed.

Interpretation Standard radiotherapy was associated with poor outcomes, especially in patients older than 70 years. Both temozolomide and hypofractionated radiotherapy should be considered as standard treatment options in elderly patients with glioblastoma. *MGMT* promoter methylation status might be a useful predictive marker for benefit from temozolomide.

Nordic: trial design



Malmstrom A et al. Lancet 2012

Nordic: patient characteristics

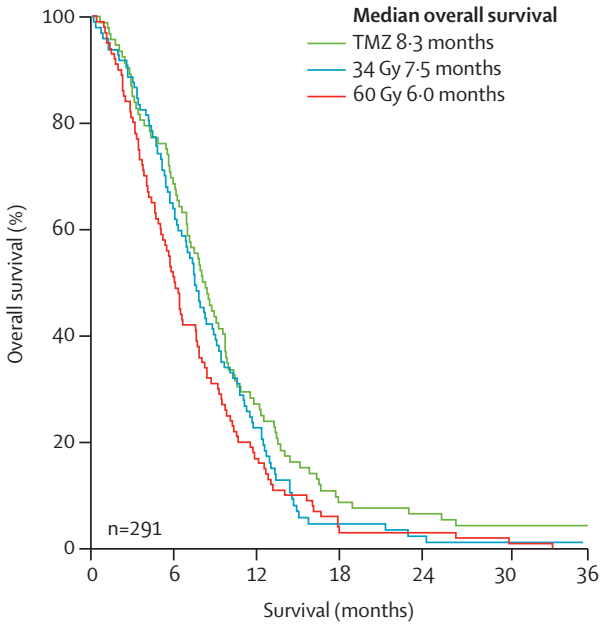
	Temozolomide (n=93)			Hypofractionated radiotherapy (n=98)			Standard radiotherapy (n=100)		
	All	60–70 years (n=51)	>70 years (n=42)	All	60–70 years (n=58)	>70 years (n=40)	All	60–70 years (n=59)	>70 years (n=41)
Sex									
Male	55 (59%)	32 (63%)	23 (55%)	50 (51%)	28 (48%)	22 (55%)	68 (68%)	39 (66%)	29 (71%)
Female	38 (41%)	19 (37%)	19 (45%)	48 (49%)	30 (52%)	18 (45%)	32 (32%)	20 (34%)	12 (29%)
WHO performance score									
0–1	73 (78%)	40 (78%)	33 (79%)	78 (80%)	48 (83%)	30 (75%)	72 (72%)	42 (71%)	30 (73%)
2–3*	20 (22%)	11 (22%)	9 (21%)	20 (20%)	10 (17%)	10 (25%)	28 (28%)	17 (29%)	11 (27%)
Surgery type									
Biopsy	24 (26%)	10 (20%)	14 (33%)	26 (27%)	13 (22%)	13 (33%)	27 (27%)	12 (20%)	15 (37%)
Resection (partial or complete)	69 (74%)	41 (80%)	28 (67%)	72 (73%)	45 (78%)	27 (67%)	73 (73%)	47 (80%)	26 (63%)
Taking steroids at baseline									
Yes	47 (51%)	24 (47%)	23 (55%)	50 (51%)	27 (47%)	23 (57%)	56 (56%)	32 (54%)	24 (59%)
No	32 (34%)	17 (33%)	15 (36%)	37 (38%)	24 (41%)	13 (33%)	30 (30%)	18 (31%)	12 (29%)
Not reported	14 (15%)	10 (20%)	4 (9%)	11 (11%)	7 (12%)	4 (10%)	14 (14%)	9 (15%)	5 (12%)
Median (range) time from surgery† to start of treatment (days)	26 (11–78)	26 (12–78)	27 (11–60)	40 (14–105)	41 (14–73)	38 (20–105)	46 (14–119)	46 (17–96)	46 (14–119)

- 342 pts enrolled (2000 – 2009)
- Newly diagnosed GBM
- Age: ≥ 60 years

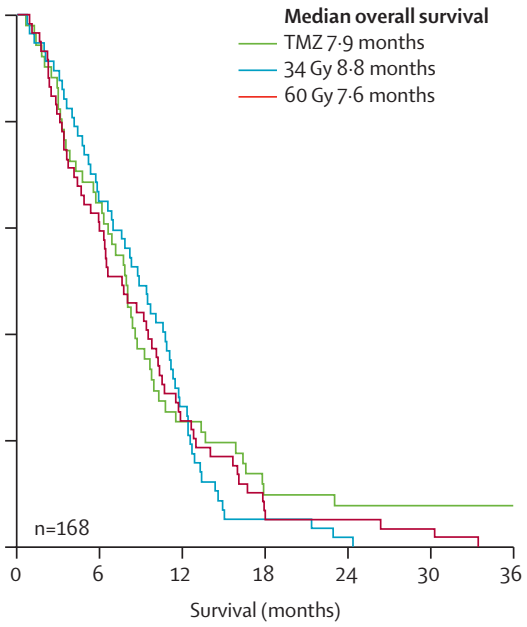
Malmstrom A et al. Lancet 2012

Nordic: Overall Survival

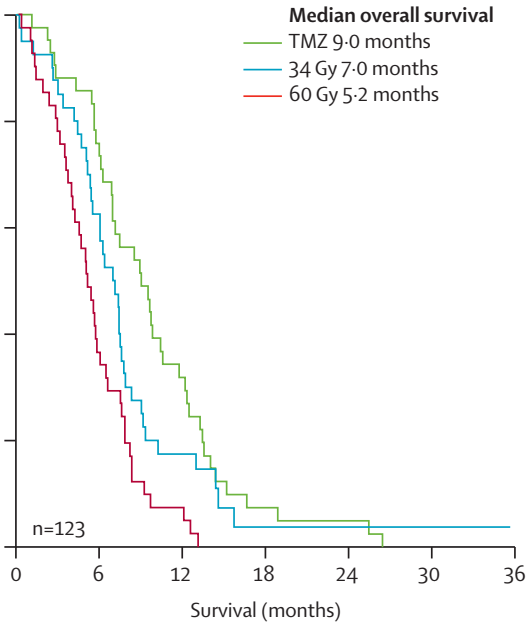
All patients



60 – 70 years

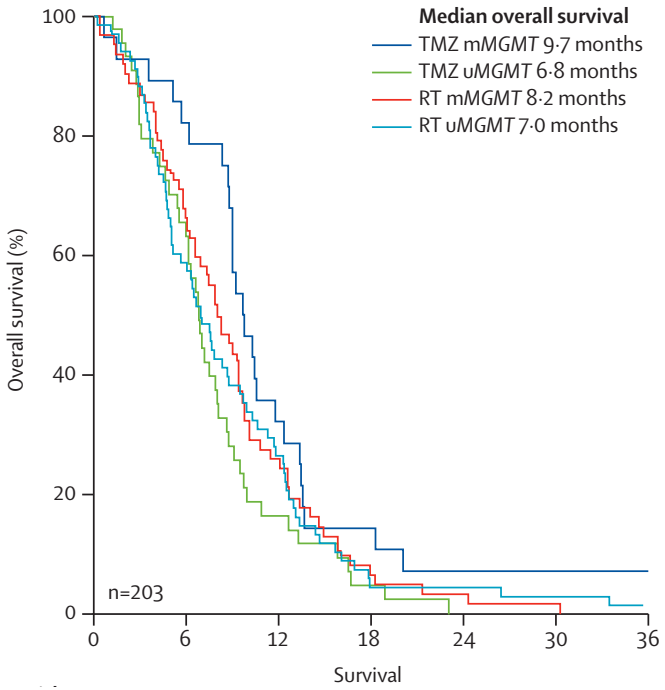


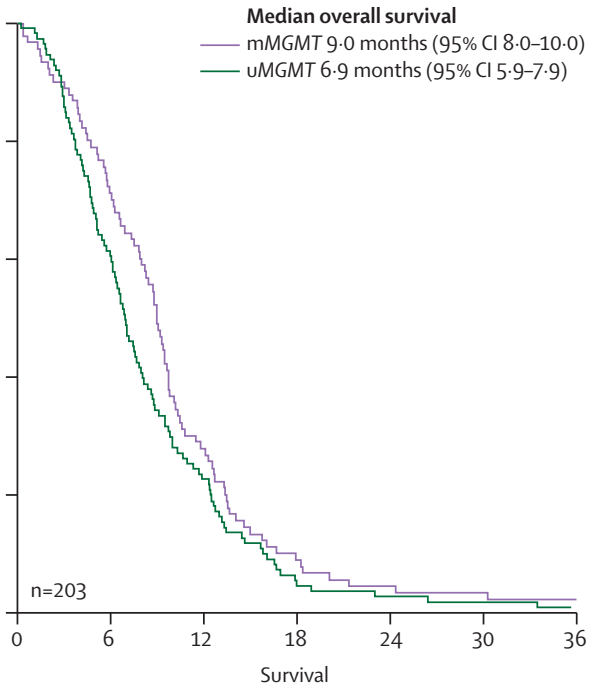
> 70 years



Malmstrom A et al. Lancet 2012

Nordic: MGMT status and OS





Malmstrom A et al. Lancet 2012

Nordic: conclusions

- Standard RT 60 Gy was in no case superior to RT 34 Gy or TMZ alone
- Both TMZ and hypofractionated RT should be considered as standard treatment options in elderly patients with GBM
- MGMT promoter methylation status might be a useful predictive marker for benefit from TMZ

Malmstrom A et al. Lancet 2012

Summary

	NOA-08	Nordic
OS		
TMZ	8.6 months	8.3 months
RT 54-60 Gy	9.6 months	6 months
RT 34 Gy	/	7.5 months
MGMT status		
Methylated	11.9 months	9 months
Unmethylated	8.2 months	6.9 months

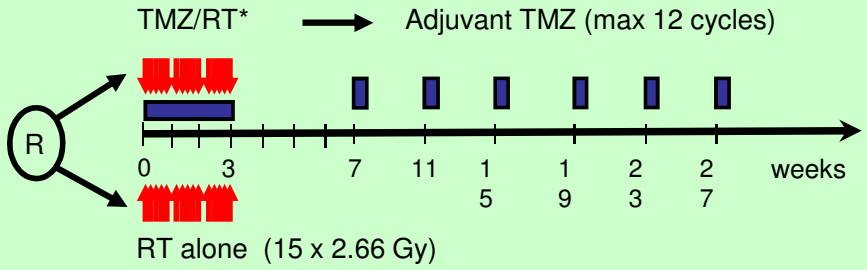
Open issues

- Radiotherapy or temozolomide?
- Or maybe both?

Ongoing EORTC/NCIC Intergroup Trial (EORTC 26062-22061 / NCIC CE.6)

Inclusion Criteria / Design

- Newly diagnosed GBM
- Age ≥ 65 years
- 560 pts to be randomized
- Target hazard ratio < 0.75



- Should we decide on the basis of MGMT promoter methylation status?

Updates and learnings in lymphomas

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma

Updates and learnings in lymphomas

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma

Hodgkin's Disease/Lymphoma Treatment

The treatment of early-stage HL evolved over time, resulting in continuous improvement in the cure rate and reductions in treatment-related toxicity.

Today, *combined modality programs* are considered the standard of care for the majority of these patients, with an expected cure rate exceeding 80% and survival rate exceeding 90%.

Despite these outstanding results, several groups continue to develop treatment programs in the hopes of achieving better cure and safe outcome.

Definition of stage disease and treatment

		Stage III/IV	Stage I/II		
			I/II Bulky Mediastinal	I/II No Bulk	
Stage Grouping	North America	Advanced stage includes stage I/II bulky disease		Early stage	
	GHLSG	Advanced stage	Early-stage unfavorable		Early-stage favorable
Treatment Options	North America	ABVD × 6-8 ± XRT	ABVD × 6-8 + 36 Gy IF-XRT	ABVD × 4 + 30 Gy IF-XRT	ABVD × 2 + 20 Gy IF-XRT
	GHLSG	Esc BEACOPP × 6 ± XRT	Esc BEACOPP × 2 + ABVD × 2 + 30 Gy IF-XRT		ABVD × 2 + 20 Gy IF-XRT

Early-Stage Hodgkin's Lymphoma: in pursuit of perfection.Younes et al. JCO 2012

PRINCIPLES OF RADIATION THERAPY

Therapy with either photons or protons is acceptable.

COMBINED MODALITY-RT DOSES:

- Nonbulky disease (stage I-II): 20*-30 Gy (if treated with ABVD), 30 Gy (if treated with Stanford V)
- Nonbulky disease (stage IB-IIB) and Bulky and nonbulky disease (stage III-IV): 30-36 Gy (if treated with BEACOPP)
- Bulky disease sites (all stages): 30-36 Gy (if treated with ABVD), 36 Gy (if treated with Stanford V)

RT-ALONE DOSES (uncommon, except for LPHL):

- Involved regions: 30-36 Gy (the dose of 30 Gy is mainly used for LPHL)
- Uninvolved regions: 25-30 Gy

RADIATION FIELDS

- When possible, the high cervical regions (all patients) and axillae (women) should be excluded from the radiation fields.
- Consider oophoropexy to preserve ovarian function in pre-menopausal women.

Involved-field: involved lymphoid region(s) only, modified as above

*A dose of 20 Gy following ABVD x 2 is sufficient if the patient has nonbulky stage I-IIA disease with an ESR < 50, no extralymphatic lesions, and only one or two lymph node regions involved. See HODG-A for definition of nodal sites.

Reduced intensity treatment in early-stage Hodgkin's lymphoma

REVIEW

24 November 2011

Blood and Lymphatic Cancer: Targets and Therapy

Abstract: Early-stage Hodgkin's lymphoma which includes patients with Ann Arbor stages I or II, accounts for more than 50% of all cases of the illness and is curable in a high proportion of patients. Long-term follow-up has shown that the mortality in favorable-risk patients with early-stage Hodgkin's lymphoma is exceeded by other causes including secondary malignancies and cardiac disease. Over the decades the treatment paradigm in Hodgkin's lymphoma has evolved from extended field radiotherapy to combined modality therapy using involved field radiotherapy to using chemotherapy alone. The data on long-term complications from using low dose and limited field radiation therapy is still awaited since we know that most of the secondary malignancies occur late (ie, more than 10 years after the treatment). By changing the chemotherapy regimens from mechlorethamine, vincristine, procarbazine, prednisone (MOPP) to doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) the incidence of infertility and leukemia has been reduced. Since the late toxicity was high with radiotherapy, recent studies have focused on using chemotherapy alone. The results of interim positron emission tomography (PET) scans after two cycles of chemotherapy are being tested to see whether minimizing therapy in rapidly-responding patients will still maintain excellent cure rates. Here, we have reviewed some of the important clinical trials in early-stage Hodgkin's lymphoma and focus on some of the recent trials emphasizing reduced intensity treatment in early-stage Hodgkin's lymphoma.

Reduced intensity treatment in early-stage Hodgkin's lymphoma

REVIEW

24 November 2011

Blood and Lymphatic Cancer: Targets and Therapy

Table 2 Trials of radiation therapy alone in early-stage Hodgkin's lymphoma

Author	Treatment	Median follow-up (years)	Outcome (FFP or PFS %)	Overall survival (%)
Liao et al[53]	Mantle irradiation	12.2	75.3 at 10 years 74.2 at 20 years	87.6 at 10 years 65.3 at 20 years
Backstrand et al[54]	Mantle irradiation	5.1	86 at 5 years	100 at 5 years
Mauch et al[55]	Mantle irradiation	2.6	83 at 4 years	100 at 4 years
Zanini et al[56]	Subtotal nodal irradiation	6.5	80 at 7 years	93 at 7 years
Brusamolino et al[57]	Extended mantle or subtotal nodal irradiation	10.0	62 at 10 years	94 at 10 years
Ng et al[58]	Mantle irradiation	9.0	86 at 5 years 84.7 at 10 years	98.2 at 10 years

Note: 94% was reported as the complete remission rate.
Abbreviations: FFP, freedom from progression; PFS, progression free survival.

Since relapse rates were higher than desirable after treatment with radiation therapy alone, and radiation was associated with long-term side effects, clinical trials have focused on combined modality therapy using abbreviated chemotherapy with reduced radiation fields

Reduced intensity treatment in early-stage Hodgkin's lymphoma

REVIEW

24 November 2011

Blood and Lymphatic Cancer: Targets and Therapy

Table 1 Trials of combined-modality treatment in early-stage Hodgkin's lymphoma

Author	Treatment	Median follow-up (years)	Outcome (FFP or PFS %)	Overall survival (%)
EORTC H7 F[13]	EBVPX6+IFRT	9.0	88 at 10 years	92 at 10 years
	STNI		78 at 10 years	92 at 10 years
Bonadonna et al[7]	4× ABVD+IFRT	9.7	94 at 12 years	94 at 12 years
	36–40 Gy	9.7	93 at 12 years	96 at 12 years
	4× ABVD+SNRT			
	36–40 Gy (involved sites) +			
	30.6 Gy (uninvolved sites)			
GHSG HD 7[14]	2× ABVD+EFRT			
	30 Gy EF+10 Gy IF	7.0	88 at 7 years	94 at 7 years
	2× ABVD		67 at 7 years	92 at 7 years
EORTC H9 F[11]	EBVPX6+IF 36 Gy	4.0	87 at 4 years	98 at 4 years
	EBVPX6+IF 20 Gy		84 at 4 years	98 at 4 years
EORTC H8 F[8]	MOPP-ABV+IFRT	7.8	98 at 5 years	97 at 10 years
	STNI		74 at 5 years	92 at 10 years
GHSG HD 10[10]	4× ABVD+IFRT 30 Gy	7.5	93 at 5 years	97 at 5 years
	4× ABVD+IFRT 20 Gy	7.5	93 at 5 years	97 at 5 years
	2× ABVD+IFRT 30 Gy	7.5	91 at 5 years	97 at 5 years
	2× ABVD+IFRT 20 Gy	7.5	91 at 5 years	97 at 5 years

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine, prednisone; EBVP, epirubicin, bleomycin, vinblastine, and prednisone; IFRT, involved-field radiotherapy; EFRT, external field radiotherapy; STNI, subtotal nodal radiotherapy; FFP, freedom from progression; PFS, progression free survival.

Reduction of the dose of radiation therapy has no impact on outcome in patients with favorable early-stage Hodgkin's lymphoma.

Reduced intensity treatment in early-stage Hodgkin's lymphoma

REVIEW

24 November 2011

Blood and Lymphatic Cancer: Targets and Therapy

Table 3 Trials of chemotherapy alone in early-stage Hodgkin's lymphoma

Author	Treatment	Median follow-up in years	Outcome (FFP or PFS %)	Overall survival rate (%)
Biti et al[18]	6× MOPP	5.0	64 at 8 years	56 at 8 years
	EFRT		76 at 8 years	93 at 8 years
Longo et al[19,20]	MOPP	25.0	83 at 25 years	81 at 25 years
	XRT		59 at 25 years	63 at 25 years
Straus et al[21]	6× ABVD	5.6	81 at 5 years	90 at 5 years
	6× ABVD+IFRT or modified EFRT		86 at 5 years	97 at 5 years
Meyer at al[22]	4–6× ABVD	4.2	88 at 5 years	97 at 5 years
	SNRT		87 at 5 years	100 at 5 years
Rueda Dominguez et al[42]	6× ABVD	6.5	88 at 7 years	97 at 7 years
Olcese et al[23]	ABVD	5.0	83 at 4 years	95 at 4 years
	ABVD or Stanford V+ EFRT OR IFRT		80 at 4 years	82 at 4 years
Canellos et al[24]	4–6× ABVD	5.0	92 at 5 years	100 at 5 years
Laskar et al[48]	ABVD+IFRT	5.3	97 at 8 years	100 at 8 years
	ABVD		94 at 8 years	98 at 8 years

Note: In this study, 13% of patients had stage IIIA Hodgkin's lymphoma.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; MOPP, mechlorethamine, vincristine, procarbazine and prednisone; Stanford V, mechlorethamine, doxorubicin, etoposide, vincristine, vinblastine, bleomycin; IFRT, involved-field radiotherapy; EFRT, external field radiotherapy; XRT, radiotherapy; SNRT, subtotal nodal radiotherapy; FFP, freedom from progression; PFS, progression free survival.

ABVD alone could be a reasonable choice of treatment for younger patients with favorable presentations of stage I to II nonbulky disease, especially if they experience prompt and complete response to the first 2 cycles of ABVD

NCCN Recommendations

Stage IA to IIA (Favorable Disease): Combined modality therapy (ABVD plus 20–30 Gy of IFRT or Stanford V chemotherapy plus 30 Gy of IFRT) is the preferred treatment for patients with favorable disease. The panel has also included ABVD alone as an alternative treatment option with a category 2B recommendation. Highly selected patients who are unable to tolerate chemotherapy because of the presence of comorbidities may be treated with radiotherapy alone.

NCCN National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2012
Hodgkin Lymphoma

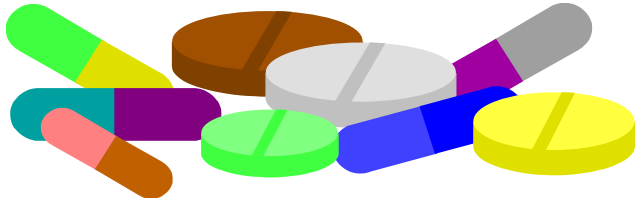
Treatment for Early-Stage Hodgkin Lymphoma: Has Radiotherapy Had Its Day?

VOLUME 30 · NUMBER 31 · NOVEMBER 1 2012

JOURNAL OF CLINICAL ONCOLOGY

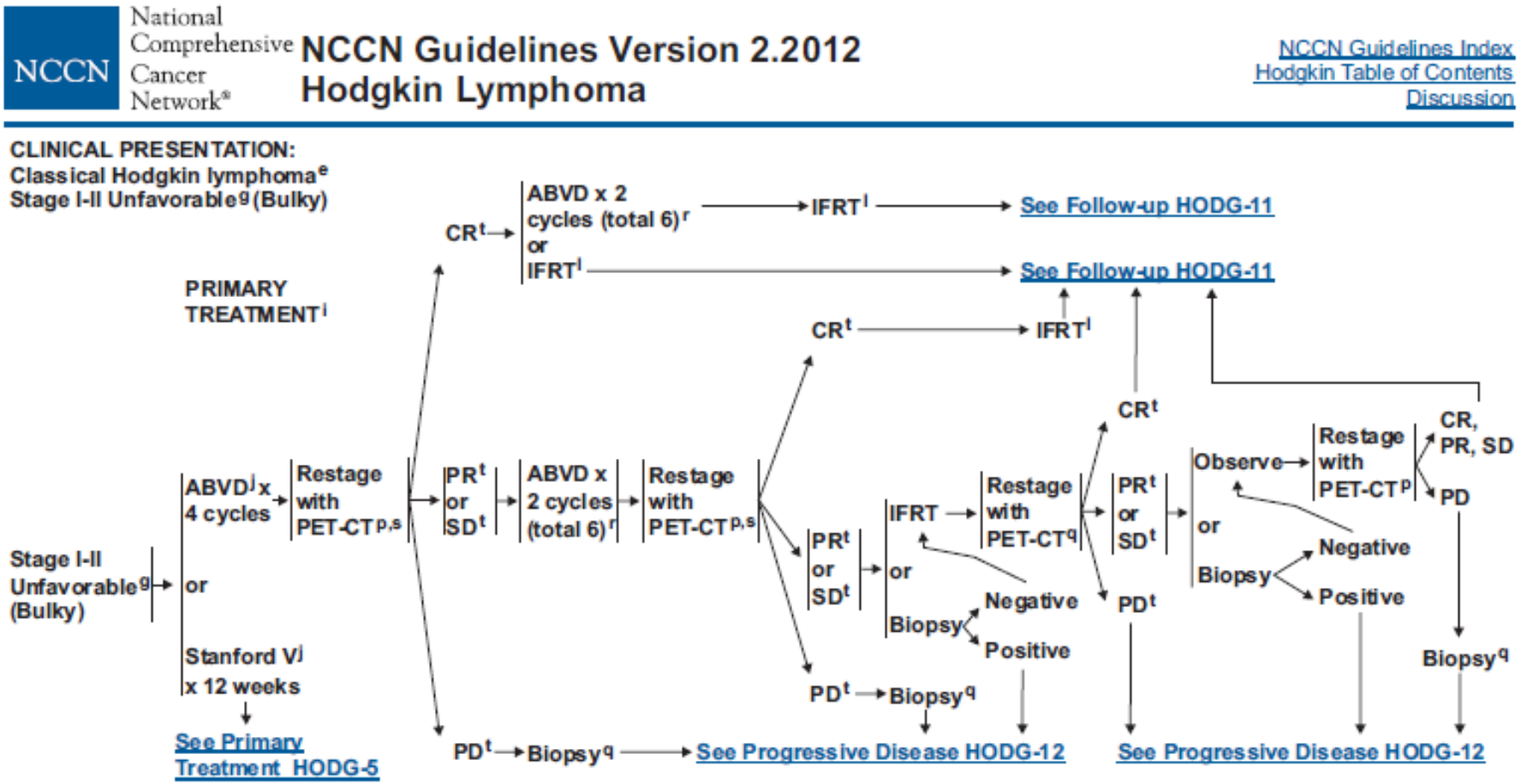
John Radford, *The University of Manchester and the Christie National Health Service Foundation Trust, Manchester, United Kingdom*

The NCIC/ECOG trial demonstrates that four to six cycles of ABVD alone is an effective treatment for many patients with stage IA and IIA nonbulky Hodgkin lymphoma, and this approach is now an option for those patients in whom radiotherapy is considered to pose a particular risk. However, the results of this trial do not support the argument that chemotherapy alone should replace a treatment strategy that incorporates radiotherapy in all cases. STNI is an outdated technique, and modern approaches feature much smaller field sizes and doses that are considered less likely to cause late toxicity.



For these reasons, the GHSG HD10 trial approach of two cycles of ABVD followed by 20 Gy of involved-field radiotherapy retains its position as a highly effective, well-tolerated standard of care for patients with stage IA and IIA, favorable, classical Hodgkin lymphoma. In the future it is hoped that a response-adapted approach may allow the burden of treatment to be reduced even further using PET imaging to identify individuals likely to have an excellent outcome with abbreviated chemotherapy alone, and the results of ongoing trials evaluating this strategy are awaited with interest.

Stage I to II (Unfavorable Disease)



IFRT 30 - 36 Gy

Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Jana Markova, Andreas Lohri, Zdenek Kral, Richard Greil, Max S. Topp, Julia Meissner, Josée M. Zijlstra, Martin Soekler, Harald Stein, Hans T. Eich, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert

JOURNAL OF CLINICAL ONCOLOGY

MARCH 20 2012

Purpose

In patients with early unfavorable Hodgkin's lymphoma (HL), combined modality treatment with four cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and 30 Gy involved-field radiotherapy (IFRT) results in long-term tumor control of approximately 80%. We aimed to improve these results using more intensive chemotherapy.

Patients and Methods

Patients with newly diagnosed early unfavorable HL were randomly assigned to either four cycles of ABVD or an intensified treatment consisting of two cycles of escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by two cycles of ABVD (2 + 2). Chemotherapy was followed by 30 Gy IFRT in both arms. The primary end point was freedom from treatment failure (FFTF); secondary end points included progression-free survival (PFS) and treatment-related toxicity.

Results

With a total of 1,528 qualified patients included, the 2 + 2 regimen demonstrated superior FFTF compared with four cycles of ABVD ($P < .001$; hazard ratio, 0.44; 95% CI, 0.30 to 0.66), with a difference of 7.2% at 5 years (95% CI, 3.8 to 10.5). The difference in 5-year PFS was 6.2% (95% CI, 3.0% to 9.5%). There was more acute toxicity associated with 2 + 2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies.

Conclusion

Intensified chemotherapy with two cycles of BEACOPP escalated followed by two cycles of ABVD followed by IFRT significantly improves tumor control in patients with early unfavorable HL.

Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Jana Markova, Andreas Lohri, Zdenek Kral, Richard Greil, Max S. Topp, Julia Meissner, Josée M. Zijlstra, Martin Soekler, Harald Stein, Hans T. Eich, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert

JOURNAL OF CLINICAL ONCOLOGY

MARCH 20 2012

In conclusion, a dose-intensification with two cycles of BEACOPPesc followed by two cycles of ABVD results in better tumor control with increased PFS as compared with standard treatment with four cycles of ABVD.

The increased rate of acute toxicities in the intensified arm is overcome by fewer relapses and less second-line toxicity.

The regimen of 2 + 2 plus 30 Gy IFRT is the new GHSG standard for patients with early unfavorable HL age 60 years or younger.

Early-Stage Hodgkin's Lymphoma: In Pursuit of Perfection

Anas Younes, *MD Anderson Cancer Center, Houston, TX*

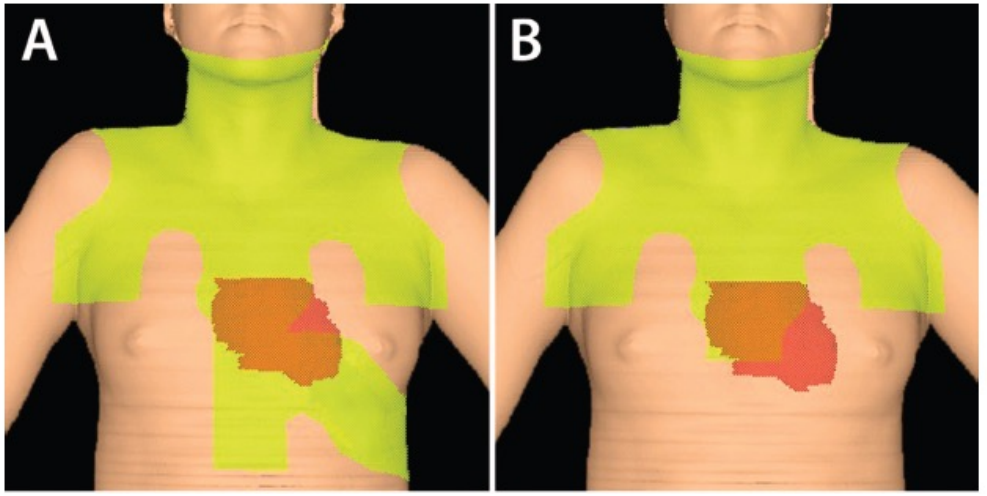
VOLUME 30 · NUMBER 9 · MARCH 20 2012

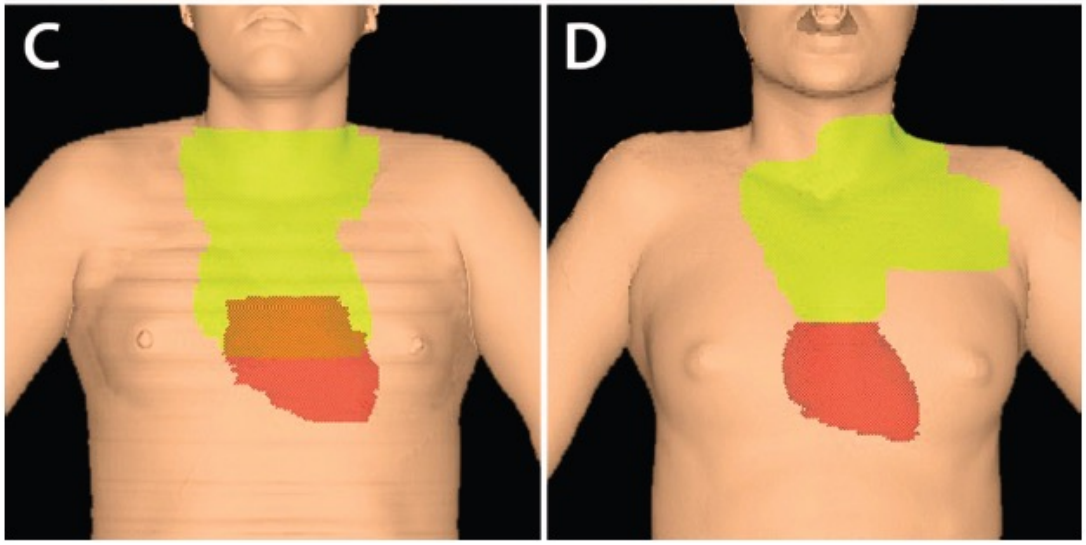
JOURNAL OF CLINICAL ONCOLOGY

What is the added value of the 2+2 regimen compared with the standard four cycles of ABVD in patients with unfavorable-stage I/II disease without bulk or B symptoms?

Given the equal number of cycles and doses of radiation of these two regimens but the increased acute hematologic toxicity associated with the 2+2 regimen, it is likely that patients with unfavorable-stage I/II nonbulky disease who are without B symptoms will continue to be treated with four cycles of ABVD plus 30 Gy of IF-XRT in most parts of the world

Changes in Radiotherapy fields over time





Hematology 2011

Figure 2. Changes in RT fields over time. Figures are 3-dimensional reconstructions of RT fields based on computed tomography imaging. Light green illustrates irradiated field. The true heart position is shown. (A) Mantle and upper abdomen ("spade") field. Note the large volume of heart and left breast irradiated. (B) Mantle field. (C) IFRT for mediastinal disease without axillary disease. Less breast tissue is treated, although inclusion of the subcarinal nodes encompasses the proximal coronary arteries. (D) INRT for a patient with mediastinal, low neck, and high axillary disease. The patient was also treated with active breath hold to decrease heart dose.

Ann Oncol. 2012 Nov

Comparing long-term toxicity and efficacy of combined modality treatment including extended- or involved-field radiotherapy in early-stage Hodgkin's lymphoma.

Sasse S et al. GermanHodgkin Study Group (GHSG).

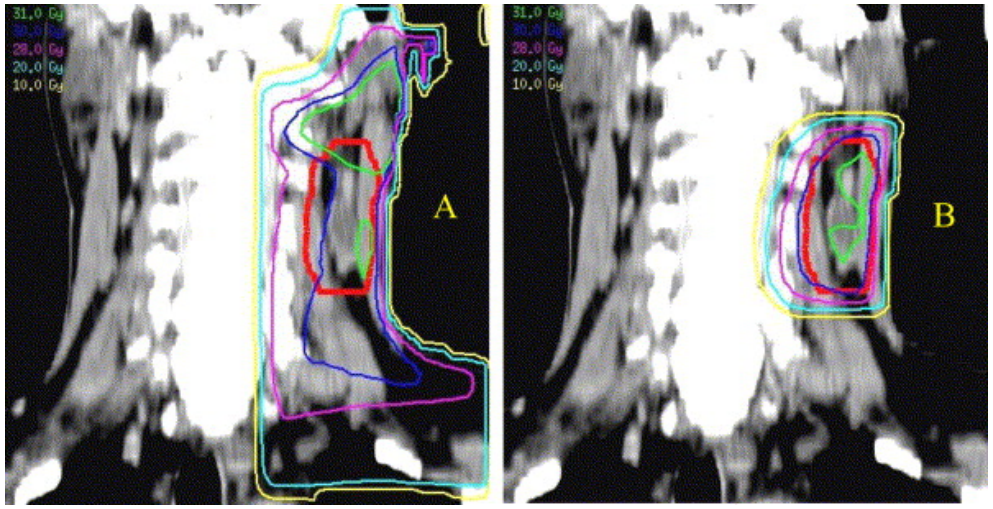
Patients and methods: One thousand two hundred and four patients were randomized to four cycles of chemotherapy followed by either 30 Gy EF- or 30 Gy IF-RT (HD8 trial); 532 patients in each treatment arm were eligible.

Results: At 10 years, no arm differences were revealed with respect to freedom from treatment failure (FFTF) (79.8% versus 79.7%), progression-free survival (79.8% versus 80.0%), and overall survival (86.4% versus 87.3%). Non-inferiority of IF-RT was demonstrated for the primary end point FFTF (95% confidence interval for hazard ratio 0.72-1.25). Elderly patients had a poorer outcome when treated with EF-RT. So far, 15.0% of patients in arm A and 12.2% in arm B died, mostly due to secondary malignancies (5.3% versus 3.4%) or HL (3.2% versus 3.4%). After EF-RT, there were more secondary malignancies overall (58 versus 45), especially acute myeloid leukemias (11 versus 4).

Conclusion: Radiotherapy intensity reduction to IF-RT does not result in poorer long-term outcome but is associated with less acute toxicity and might be associated with less secondary malignancies.

Radiotherapy of Hodgkin's Lymphoma has evolved from extended-field to involved-field (IF) radiotherapy reducing toxicity whilst maintaining high cure rates. Recent publications recommend further reduction in the radiation field to involved-node (IN) radiotherapy

The clinical target volume encompasses the initial volume of the Lymph node(s) before chemotherapy and incorporates the initial Location and extent of the disease taking the displacement of the normal tissues into account. The margin of the planning target volume should be 2 cm in axial and 3 cm in craniocaudal direction. If necessary, it can be reduced to 1-1.5 cm. To minimize Lung and cardiac toxicity, the target definition in the mediastinum is different.



Eich HT et al*. Involved-node radiotherapy in early-stage Hodgkin's lymphoma: Definition and guidelines of the German Hodgkin Study Group (GHSG). *Strahlenther Onkol 2008

Involved-Nodal Radiation Therapy As a Component of Combination Therapy for Limited-Stage Hodgkin's Lymphoma: A Question of Field Size

NOVEMBER 10 2008

JOURNAL OF CLINICAL ONCOLOGY

Belinda A. Campbell, Nick Voss, Tom Pickles, James Morris, Randy D. Gascoyne, Kerry J. Savage, and Joseph M. Connors

Purpose
Combined-modality therapy is the standard of care for limited-stage Hodgkin's lymphoma (HL). Radiation therapy has evolved from extended-field radiation therapy (EFRT) to involved-field radiation therapy (IFRT), reducing toxicity while maintaining high cure rates. Recent publications recommend a further reduction to involved-nodal radiation therapy (INRT), however, this has not been clinically validated.

Patients and Methods
We identified 325 patients with limited-stage HL, diagnosed between May 1, 1989 and April 1, 2005, and treated with chemotherapy and radiation therapy following era-specific guidelines: EFRT until 1996; IFRT from 1996 to 2001; INRT ≤ 5 cm from 2001 to the present. INRT ≤ 5 cm was defined as the prechemotherapy nodal volume with margins ≤ 5 cm to account for physiological movement, set-up variation, and the limitations of conventional simulation and radiation therapy techniques. Exclusion criteria were age younger than 16, fluorine-18 fluorodeoxyglucose positron emission tomography, non–doxorubicin, bleomycin, vinblastine, and dacarbazine-like chemotherapy, and/or more than four chemotherapy cycles.

Results
At diagnosis, median age was 35 years; 52% male; stage IA 29%; stage IIA 71%. Ninety-five percent of patients received two chemotherapy cycles. The three radiation therapy groups were: EFRT, 39%; IFRT, 30%; and INRT ≤ 5 cm, 31%. Median follow-up of living patients was 80 months. Median time to relapse was 37 months. Twelve relapses occurred: four after EFRT (3%); five after IFRT (5%); and three after INRT ≤ 5 cm (3%; $P = .9$). No marginal recurrences occurred after INRT ≤ 5 cm. Locoregional relapse (LRR) occurred in five patients: three after EFRT; two with IFRT; and none with INRT ≤ 5 cm. At 5 years, progression-free survival (PFS) was 97%, and overall survival (OS) was 95%. At 10 years, PFS and OS were 95% and 90%, respectively.

Conclusion
Reduction in field size appears to be safe, without an increased risk of LRR in patients receiving INRT ≤ 5 cm.

Involved-Nodal Radiation Therapy As a Component of Combination Therapy for Limited-Stage Hodgkin's Lymphoma: A Question of Field Size

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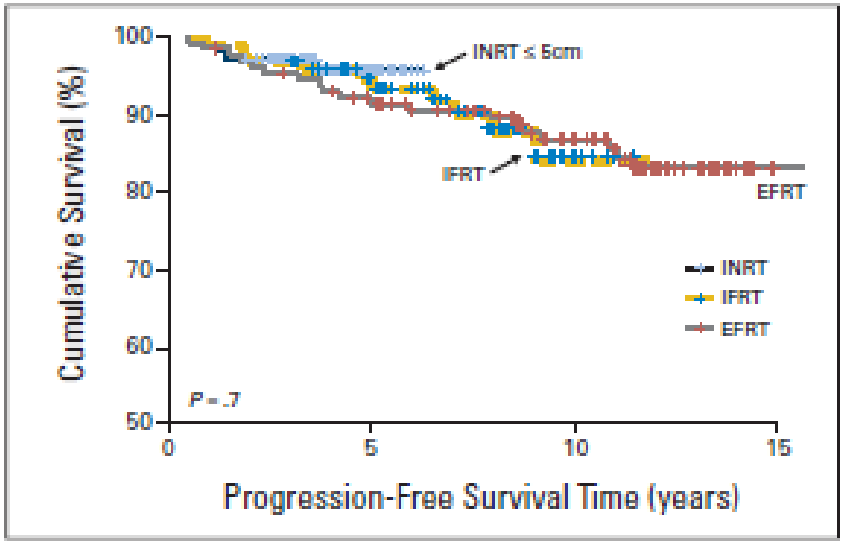

Fig 2. Progression-free survival by radiation field. INRT, involved-nodal radiation therapy; IFRT, involved-field radiation therapy; EFRT, extended-field radiation therapy.

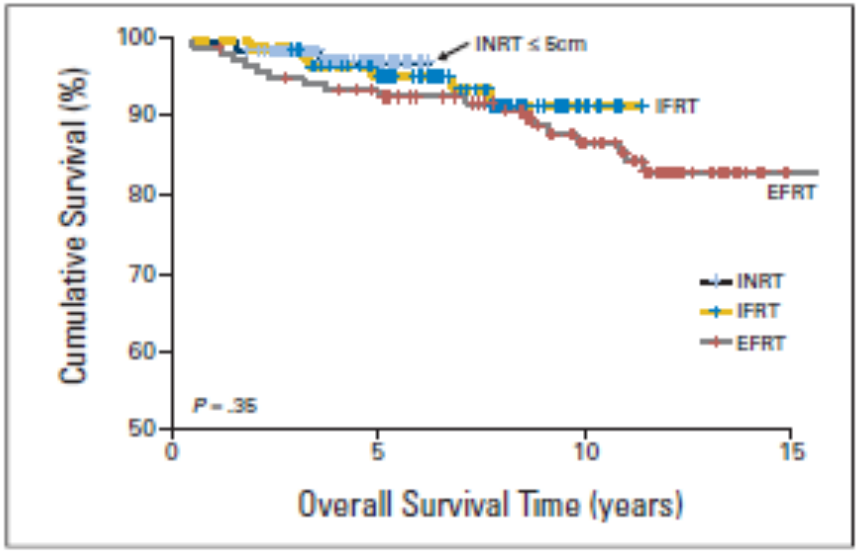

Fig 3. Overall survival by radiation field. INRT, involved-nodal radiation therapy; IFRT, involved-field radiation therapy; EFRT, extended-field radiation therapy.

Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations

Fiandra C, Filippi AR, Catuzzo P, Botticella A, Ciammella P, Franco P, Casanova Borca V, Ragona R, Tofani S, Ricardi U

Radiation Oncology 2012,

Background

Radiotherapy in Hodgkin's Lymphoma (HL) is currently evolving with new attempts to further reduce radiation volumes to the involved-node concept (Involved Nodes Radiation Therapy, INRT) and with the use of intensity modulated radiotherapy (IMRT). Currently, IMRT can be planned and delivered with several techniques, and its role is not completely clear. We designed a planning study on a typical dataset drawn from clinical routine with the aim of comparing different IMRT solutions in terms of plan quality and treatment delivery efficiency.

A total of 10 young female patients affected with early stage mediastinal HL and treated with 30 Gy INRT after ABVD-based chemotherapy were selected from our database. Five different treatment techniques were compared: 3D-CRT, VMAT (single arc), B-VMAT ("butterfly", multiple arcs), Helical Tomotherapy (HT) and Tomodirect (TD). Beam energy was 6 MV, and all IMRT planning solutions were optimized by inverse planning with specific dose-volume constraints on OAR (breasts, lungs, thyroid gland, coronary ostia, heart). Dose-Volume Histograms (DVHs) and Conformity Number (CN) were calculated and then compared, both for target and OAR by a statistical analysis (Wilcoxon's Test).

Conclusions

IMRT techniques showed superior target coverage and OAR sparing, with, as an expected consequence, larger volumes of healthy tissues (lungs, breasts) receiving low doses. Among the different IMRT techniques, HT and VMAT showed higher levels of conformation; B-VMAT and HT emerged as the planning solutions able to achieve the most balanced compromise between higher conformation around the target and smaller volumes of OAR exposed to lower doses (typical of 3D-CRT).

Different IMRT solutions vs. 3D-Conformal Radiotherapy in early stage Hodgkin's lymphoma: dosimetric comparison and clinical considerations

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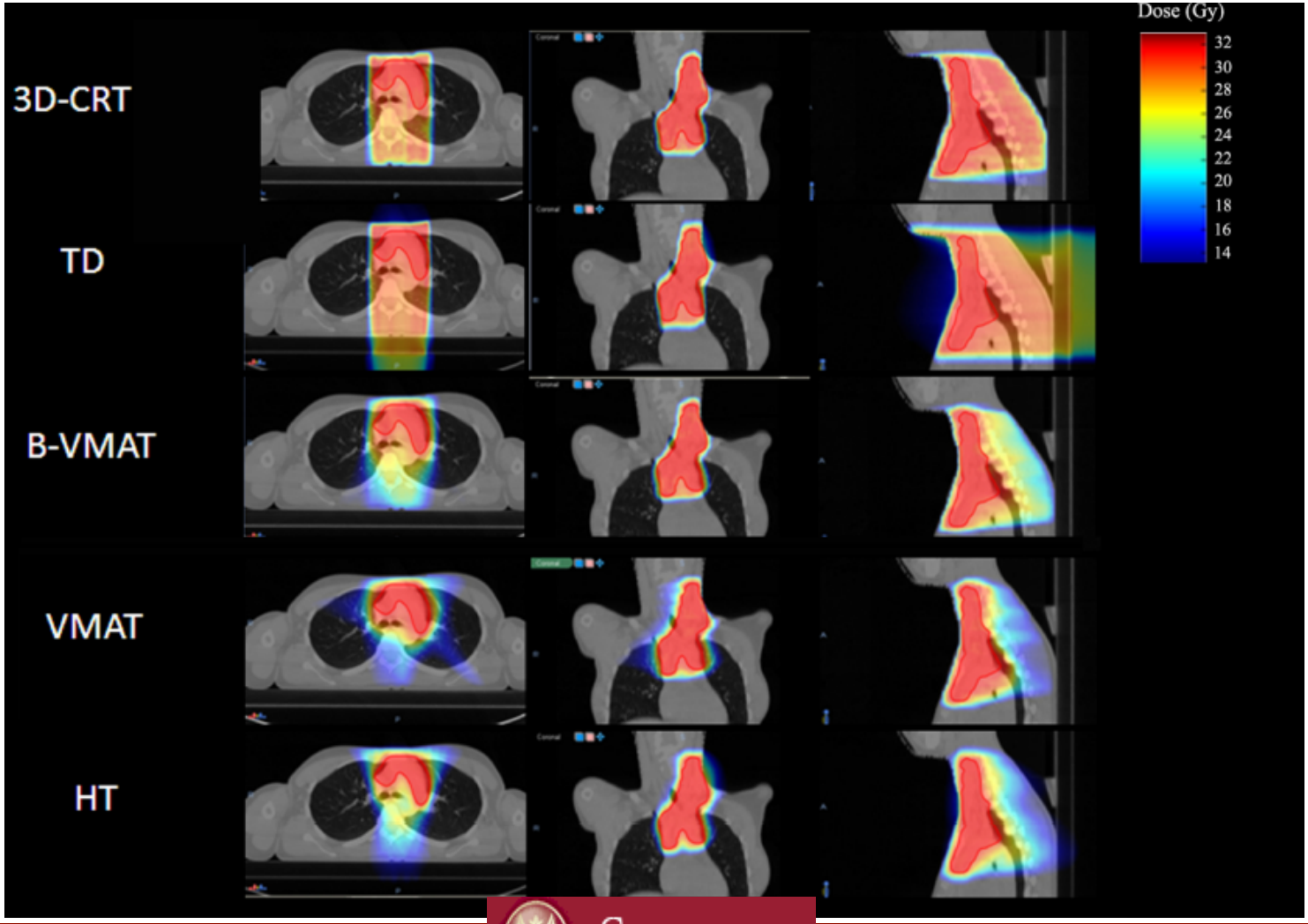
Radiation Oncology 2012,



Intensity modulated radiotherapy in early stage Hodgkin lymphoma patients: Is it better than three dimensional conformal radiotherapy?

Vitaliana De Sanctis[1], Chiara Bolzan[2], Marco D'Arienzo[3], Stefano Bracci[1*], Alessandro Fanelli[1], Maria Christina Cox[4], Maurizio Valeriani[1], Mattia F Osti[1], Giuseppe Minniti[1], Laura Chiacchiararelli[2] and Riccardo Maurizi Enrici[1]

RADIATION ONCOLOGY 2012,

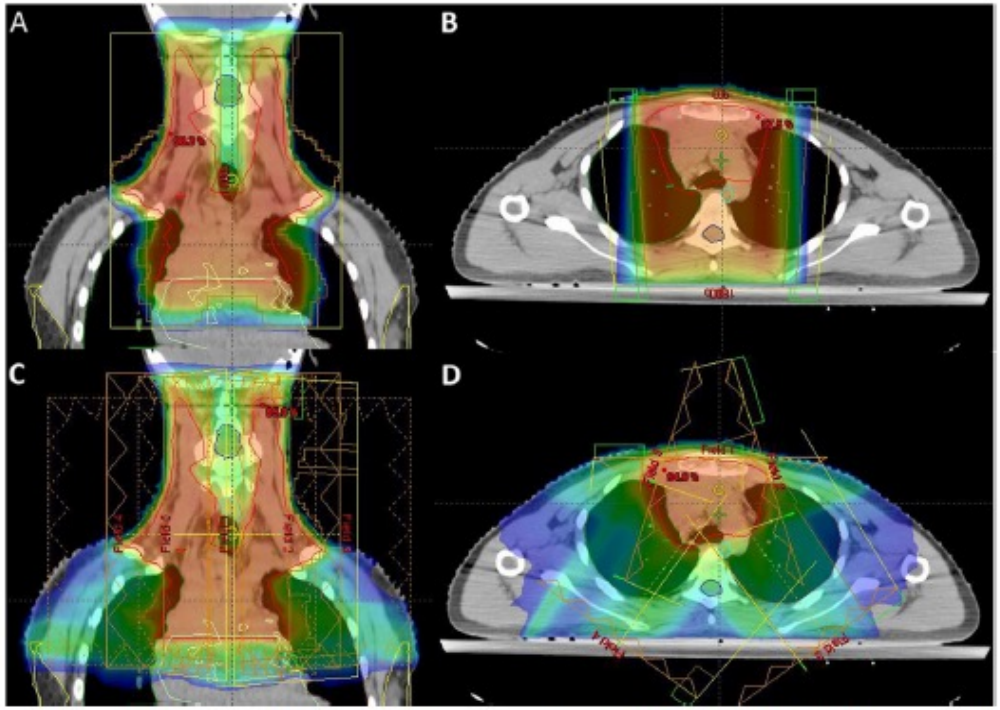
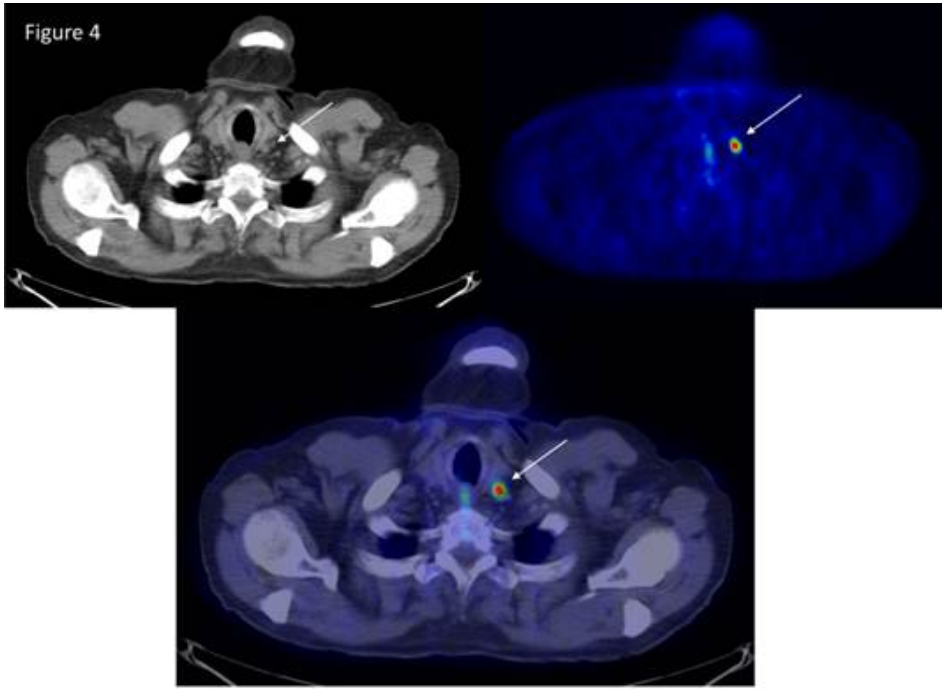


Figure 1 Comparison of dose distribution and PTV (red line) coverage of 3D-CRT (A,B) vs IMRT (C,D) plans in coronal (A,C) and axial (B,D) section.

Conclusions: In HL male patients IMRT seems feasible and accurate while for women HL patients IMRT should be used with caution.

Keywords: Hodgkin, IMRT, 3D-CRT, NTCP

Use of PET/CT to evaluate response to therapy in lymphoma



1) initial staging
2) assessment of early response to chemotherapy
3) assessment of residual masses at completion of initial treatment
4) follow-up
5) radiotherapy planning

^{18}F-FDG PET After 2 Cycles of ABVD Predicts Event-Free Survival in Early and Advanced Hodgkin Lymphoma

Juliano J. Cerci[1], Luís F. Pracchia[2], Camila C.G. Linardi[2], Felipe A. Pitella[1], Dominique Delbeke[3], Marisa Izaki[1], Evelinda Trindade[4], José Soares Junior[1], Valeria Buccheri[2], and José C. Meneghetti[1]

THE JOURNAL OF NUCLEAR MEDICINE • Vol. 51 • No. 9 • September 2010

Our objective was to assess the prognostic value of ^{18}F-FDG PET after 2 cycles of chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in Hodgkin lymphoma (HL) patients overall and in subgroups of patients with early and advanced stages and with low and high risks according to the International Prognostic Score (IPS). **Methods:** One hundred fifteen patients with newly diagnosed HL were prospectively included in the study. All underwent standard ABVD therapy followed by consolidation radiotherapy in cases of bulky disease. After 2 cycles of ABVD, the patients were evaluated with PET (PET2). Prognostic analysis compared the 3-y event-free survival (EFS) rate to the PET2 results, clinical data, and IPS. **Results:** Of the 104 evaluated patients, 93 achieved complete remission after first-line therapy. During a median follow-up of 36 mo, relapse or disease progression was seen in 22 patients. Treatment failure was seen in 16 of the 30 PET2-positive patients and in only 6 of the 74 PET2-negative patients. PET2 was the only significant prognostic factor. The 3-y EFS was 53.4% for PET2-positive patients and 90.5% for PET2-negative ones ($P < 0.001$). When patients were categorized according to low or high IPS risk and according to early or advanced stage of disease, PET2 was also significantly associated with treatment outcome. **Conclusion:** PET2 is an accurate and independent predictor of EFS in HL. A negative interim ^{18}F-FDG PET result is highly predictive of treatment success in overall HL patients, as well as in subgroups with early or advanced-stage disease and with low or high IPS risk.

TABLE 5. Major Studies Evaluating Prognostic Impact of PET2 in HL

Study	Year	Number of cycles	Number of patients	EFS		Follow-up (mo)
				PET-positive	PET-negative	
Hutchings et al. (*12*)	2005	2 or 3	85	46%	96%	6–125
Hutchings et al. (*11*)	2006	2	77	0%	96%	2–41
Gallamini et al. (*13*)	2006	2	108	6%	96%	2–47
Gallamini et al. (*14**)	2007	2	97	13%	95%	4–62
Present study	2009	2	104	24%	90%	28–40
Total			471	18%	95%	

Use of PET/CT to evaluate response to therapy in lymphoma

Q J NUCL MED MOL IMAGING 2011;55:633-47

TABLE IV.—*Main ongoing trials with Interim PET response-adapted therapies in limited stage HL.*

Study	Group	Risk factors	PET timing	Treatment
RAPID	UK NCRI	non bulky	post 3 cycles ABVD	PET neg→randomize to RT versus No further therapy; PET pos→complete 1 ABVD+RT
HD16	GHSG	only favourable	post 2 cycles ABVD	Standard arm: 30 Gy IFRT regardless of PET Experimental: PET neg→No further therapy; PET pos→30 Gy IFRT
H10	EORTC, GELA,IIL	favourable and unfavourable (even bulky)	post 2 cycles ABVD	Standard arm: complete ABVD+ 30 Gy INRT regardless of PET Experimental: PET neg→complete 2 or 4 ABVD but no RT; PET pos→2 BEACOPPesc+30 Gy INRT
50604	CALGB	non bulky	post 2 cycles ABVD	PET neg→complete 2 ABVD; PET pos→6 BEACOPPesc
50801	CALGB	bulky	post 2 cycles ABVD	PET neg→complete 4 ABVD; PET pos→4 BEACOPPesc+RT

TABLE V.—*Main ongoing trials with Interim PET response-adapted therapies in advanced-stage HL*

Study	Group	Projected accrual	PET timing	Treatment
HD18	GHSG	1500	Post 2 cycles BEACOPPesc	PET neg→randomize to 2 *versus* 6 more cycles (no RT); PET pos→randomize to 6 BEACOPPesc with *versus* without Rituximab; post-chemotherapy PET pos on resides>2.5cm→IFRT
HD0607	GITIL	450	Post 2 cycles ABVD	PET neg→ complete ABVD; if still PET neg→randomize to RT *versus* no RT; PET pos→randomize to BEACOPPesc with, *versus* without, Rituximab
RATHL	UK NCRI	1200	Post 2 cycles ABVD	PET neg→randomize to 4ABVD *versus* 4AVD (no RT); PET pos→6 BEACOPP 14 or BEACOPPesc
HD0801	IIL	300	Post 2 cycles ABVD	PET neg→complete ABVD; if still PET neg→randomize to RT *versus* no RT; PET pos→high-dose therapy with autologous BMT
S0816	SWOG	230	Post 2 cycles ABVD	PET neg→further 2 ABVD; PET pos→6 BEACOPPesc

Late Effects in the Era of Modern Therapy for Hodgkin Lymphoma

Hematology 2011

David C. Hodgson[1]

[1]*Department of Radiation Oncology and Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON*

Extended-field and subtotal nodal radiation therapy (RT), developed in the 1960s, was the first reliably curative treatment for early-stage Hodgkin lymphoma (HL). However, the large volume of normal tissue irradiated resulted in significant delayed toxicity, including cardiac disease and second cancers (SCs). The 30-year cumulative incidence of heart disease among adult survivors receiving 40-45 Gy of extended-field or mantle RT is approximately 30%; the incidence of SCs is similar. Improving disease control while reducing the toxicity of treatment has been a major objective of HL trials for more than 2 decades. Contemporary involved-field RT (IFRT) reduces irradiated volumes and produces significant reductions in normal tissue dose compared with historic treatments. Recent data indicate that, compared with mantle RT, IFRT reduces the relative risk of breast cancer among young females receiving mediastinal RT by approximately 60% and also reduces cardiac dose. The recent transition to involved-node RT allows further reductions in normal tissue dose. Response-adapted therapy is being evaluated in clinical trials as a means of identifying those patients most likely to benefit from treatment reduction or intensification, enhanced screening will facilitate early intervention to reduce the clinical burden of late effects, and there is increasing interest in elucidating the genetic correlates of treatment toxicity.

Late Effects in the Era of Modern Therapy for Hodgkin Lymphoma

David C. Hodgson[1]

Hematology 2011

[1]*Department of Radiation Oncology and Department of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON*

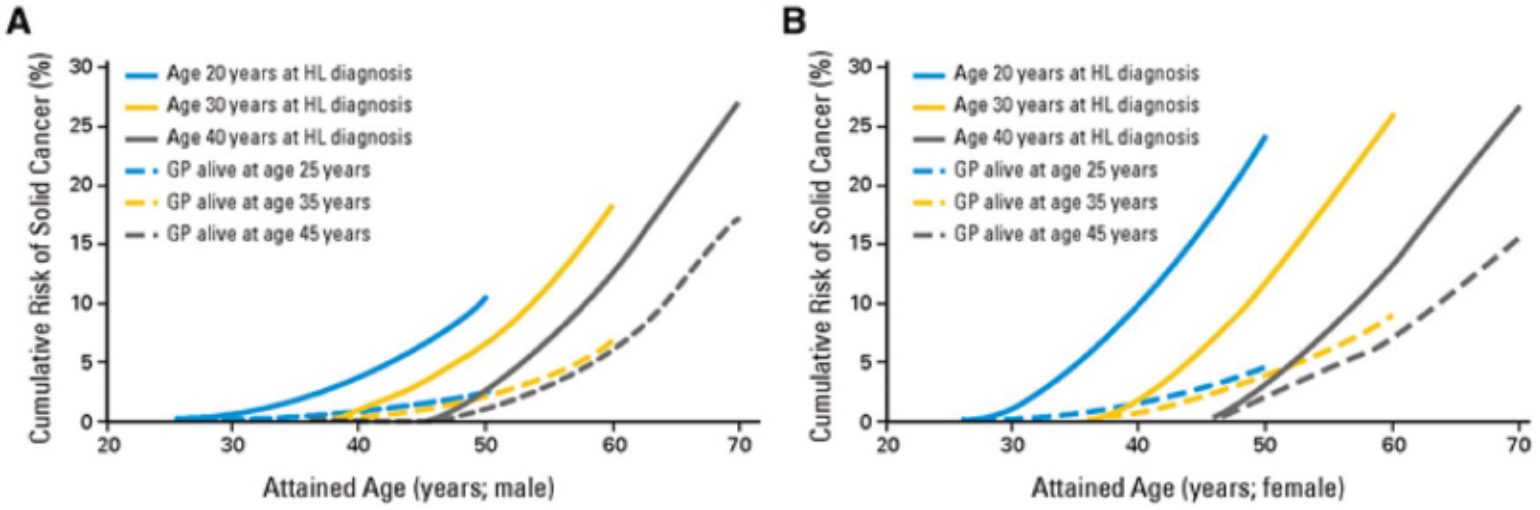


Figure 1. Cumulative incidence of solid cancers among 5-year survivors of HL compared with controls of the same age in the general population. (A) Males (n = 10 619 survivors). (B) Females (n = 8243 survivors). (From Hodgson et al.[8] Reprinted with permission. Copyright 2007, American Society of Clinical Oncology. All rights reserved.)

Future research should continue to work to eliminate treatment related toxicity while maintaining or even improving the cure rate for patients with early- and advanced-stage HL.

DECREASING THE FIELD SIZE AND DOSE OF RADIATION THERAPY REDUCED THE RISK OF SECONDARY MALIGNANCIES AND OTHER ORGAN DAMAGE.

Updates and learnings in lymphomas

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma

TABLE 4: WHO classification of the mature B-cell, T-cell, and NK-cell neoplasms (2008)

Mature B-cell neoplasms

Chronic lymphocytic leukemia/small lymphocytic lymphoma
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic lymphoma/leukemia, unclassifiable
*Splenic diffuse red pulp small B-cell lymphoma**
Hairy cell leukemia-variant*
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Heavy chain diseases
Alpha heavy chain disease
Gamma heavy chain disease
Mu heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
Pediatric follicular lymphoma
Primary cutaneous follicular center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), NOS
T-cell/histiocyte-rich large B-cell lymphoma
EBV+ DLBCL of the elderly
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
Primary cutaneous DLBCL, leg type
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV-8–associated multicentric Castleman disease
Primary effusion lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classic Hodgkin lymphoma

Mature T-cell and NK-cell neoplasms

T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells*
Aggressive NK cell leukemia
Systemic EBV+ T-cell lymphoproliferative disease of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell leukemia/lymphoma
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30+ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
*Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma**
*Primary cutaneous CD4+ small/medium T-cell lymphoma**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK+
*Anaplastic large cell lymphoma, ALK−**

Hodgkin lymphoma

Nodular lymphocyte-predominant Hodgkin lymphoma
Classic Hodgkin lymphoma
Nodular sclerosis classic Hodgkin lymphoma
Lymphocyte-rich classic Hodgkin lymphoma
Mixed cellularity classic Hodgkin lymphoma
Lymphocyte-depleted classic Hodgkin lymphoma

Posttransplantation lymphoproliferative disorders (PTLDs)

Early lesions
Plasmacytic hyperplasia
Infectious mononucleosis-like PTLD
Polymorphic PTLD
Monomorphic PTLD (B and T/NK-cell types)†
Classic Hodgkin lymphoma type PTLD†

*Provisional entities for which the WHO Working Group thought there was insufficient evidence to recognize as distinct diseases at this time.
†These lesions are classified according to the leukemia or lymphoma to which they correspond. Diseases shown in italics were newly included in the 2008 WHO classification.

Radiotherapy in Non-Hodgkin Lymphomas

Knowledge of histology, extent and pattern of disease is essential to select the appropriate therapeutic strategy.

Most patients with localized non-Hodgkin lymphoma (NHL) who receive radiotherapy (RT) are treated with the intent of achieving local control of disease. A palliative approach is used only when, due to the condition of the patient and/or the extent or location of the disease, a radical course of treatment carries no chance of local control.

Involved field RT is routinely used, whether for cure or local control.

Radiotherapy in non-Hodgkin Lymphomas

Uncertainty remains regarding the optimal ***radiation dose*** required.

The studies were mainly retrospective series of heterogeneous populations. Radiation fields and techniques varied within and across studies,

The difficulties in comparison between studies and application of results from older studies to current practice are compounded by the use of many different histological classification systems for NHL over the past 50 years.

Radiotherapy in non-Hodgkin Lymphomas

M. Gospodarowicz[1]

Annals of Oncology 2010

The dose of RT required to achieve local control varies depending upon histological type and tumor bulk. Follicular lymphoma and MALT lymphoma are more responsive to RT, and a dose of 30 Gy delivered in 15–20 fractions over 3–4 weeks results in local control rates in excess of 95%. For small cutaneous or orbital lesions RT doses of 25 Gy are sufficient to achieve 90–95% local control. Large cell lymphomas are less sensitive and require doses in the range 35–45 Gy. For low bulk disease treated with full courses of chemotherapy, excellent local control rates are obtained with 30 Gy [10], whereas for bulky lymphomas treated with CMT, a minimum dose of 35 Gy is required. Some centers routinely administer doses of 40 Gy, or up to 45–50 Gy in the combined modality setting. There are no randomized trials designed to determine the optimal dose of RT, and the practice has developed based on institutional experience, although higher doses are difficult to justify with excellent local control reported in patients who are in CR after chemotherapy.

Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Lisa Lowry [a], Paul Smith [a], Wendi Qian [b], Stephen Falk [c], Kim Benstead [d], Tim Illidge [e], David Linch [f], Martin Robinson [g], Andrew Jack [h], Peter Hoskin [i,*]

Radiotherapy and Oncology 100 (2011) 86–92

Purpose: This multicentre, prospective, randomised-controlled trial compared efficacy and toxicity of differing radiotherapy doses in non-Hodgkin lymphoma (NHL).

Patients and methods: Patients with any histological subtype of NHL, requiring radiotherapy for local disease control, whether radical, consolidative or palliative, were included. Three hundred and sixty one sites of indolent NHL (predominantly follicular NHL and marginal zone lymphoma) were randomised to receive 40–45 Gy in 20–23 fractions or 24 Gy in 12 fractions. Six hundred and forty sites of aggressive NHL (predominantly diffuse large B cell lymphoma as part of combined-modality therapy) were randomised to receive 40–45 Gy in 20–23 fractions or 30 Gy in 15 fractions. Patients with all stages of disease, having first-line and subsequent therapies were included; first presentations of early-stage disease predominated.

Results: There was no difference in overall response rate (ORR) between standard and lower-dose arms. In the indolent group, ORR was 93% and 92%, respectively, ($p = 0.72$); in the aggressive group, ORR was 91% in both arms ($p = 0.87$). With a median follow-up of 5.6 years, there was no significant difference detected in the rate of within-radiation field progression (HR = 1.09, 95%CI = 0.76–1.56, $p = 0.64$ in the indolent group; HR = 0.98, 95%CI = 0.68–1.4, $p = 0.89$ in the aggressive group). There was also no significant difference detected in the progression free or overall survival. There was a trend for reduced toxicities in the low-dose arms; only the reduction in reported erythema reached significance.

Conclusion: In a large, randomised trial, there was no loss of efficacy associated with radiotherapy doses of 24 Gy in indolent NHL and 30 Gy in aggressive NHL, compared with previous standard doses of 40–45 Gy.

Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

Lisa Lowry [a], Paul Smith [a], Wendi Qian [b], Stephen Falk [c], Kim Benstead [d], Tim Illidge [e], David Linch [f], Martin Robinson [g], Andrew Jack [h], Peter Hoskin [i,*]

Radiotherapy and Oncology 100 (2011) 86–92

... To minimising clinical side-effects, the use of lower doses of radiation results in fewer hospital attendances for the patient, and a reduction in the use of radiotherapy resources. Another approach to reduce toxicity from radiotherapy is to reduce the volume treated …

… In conclusion, this large, randomised trial shows that doses of radiotherapy can safely be reduced to ***24 Gy in indolent lymphoma and 30 Gy in more aggressive histological subtypes***, without compromising local tumour control in the short- or long-term. ***These radiation doses should become the new standard of care for patients receiving radiotherapy for NHL***. Even lower doses of radiotherapy may be as efficacious in some settings, but this has yet to be confirmed in the setting of large, randomised trials. In follicular lymphoma doses of 4 Gy in two fractions have been shown to achieve effective local control. We are currently recruiting patients into a randomised, phase III trial of 24 Gy vs. 4 Gy palliative or radical radiotherapy in patients with FL or MZL …

Clinical Oncology xxx (2012) 1–10

Guidelines

Recommendations for the Use of Radiotherapy in Nodal Lymphoma

P.J. Hoskin *, P. Díez *, M. Williams †, H. Lucraft ‡, M. Bayne § on Behalf of the Participants of the Lymphoma Radiotherapy Group[a]

These guidelines have been developed to define the use of radiotherapy for lymphoma in the current era of combined modality treatment taking into account increasing concern over the late side-effects associated with previous radiotherapy. The role of reduced volume and reduced doses is addressed integrating modern imaging with three-dimensional planning and advanced techniques of treatment delivery. Both wide-field and involved-field techniques have now been supplanted by the use of defined volumes based on node involvement shown on computed tomography (CT) and positron emission tomography (PET) imaging and applying the International Commission on Radiation Units and Measurements concepts of gross tumour volume (GTV), clinical target volume (CTV) and planning target volume (PTV). The planning of lymphoma patients for radical radiotherapy should now be based upon contrast enhanced 3 mm contiguous CT with three-dimensional definition of volumes using the convention of GTV, CTV and PTV. The involved-site radiotherapy concept defines the CTV based on the PET-defined pre-chemotherapy sites of involvement with an expansion in the cranio-caudal direction of lymphatic spread by 1.5 cm, constrained to tissue planes such as bone, muscle and air cavities. The margin allows for uncertainties in PET resolution, image registration and changes in patient positioning and shape. There is increasing evidence in both Hodgkin and non-Hodgkin lymphoma that traditional doses are higher than necessary for disease control and related to the incidence of late effects. No more than 30 Gy for Hodgkin and aggressive non-Hodgkin lymphoma and 24 Gy for indolent lymphomas is recommended; lower doses of 20 Gy in combination therapy for early-stage low-risk Hodgkin lymphoma may be sufficient. As yet there are no large datasets validating the use of involved-site radiotherapy; these will emerge from the current generation of clinical trials. Radiotherapy remains the most effective single modality in the treatment of lymphoma. A reduction in both treatment volume and overall treatment dose should now be considered to minimise the risks of late sequelae. However, it is important that this is not at the expense of the excellent disease control currently achieved.

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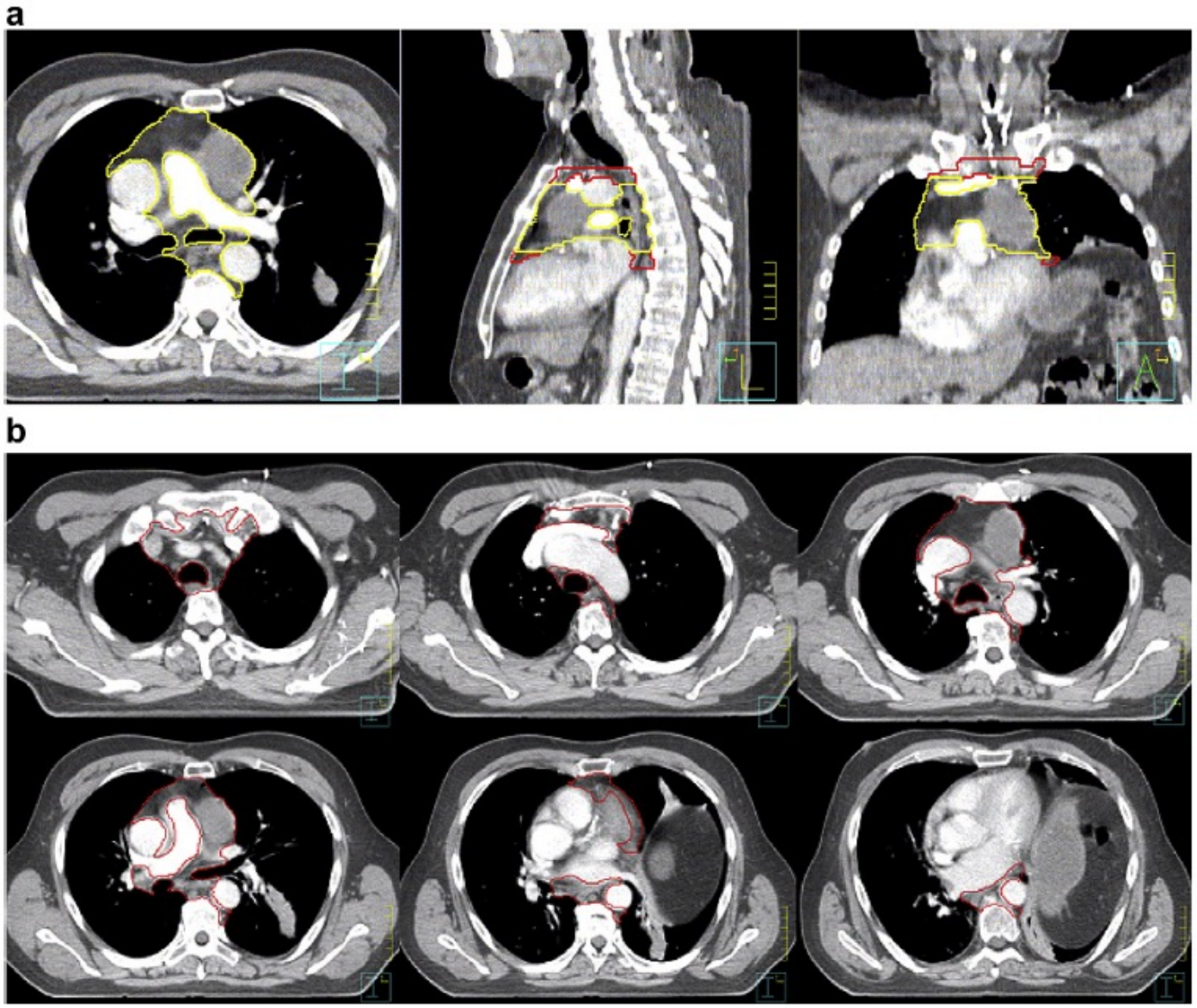

Fig 1. (a) Transverse sagittal and coronal views of a mediastinal lymphoma patient. In yellow, the pre-chemotherapy nodal area superior–inferior extent. In red, the involved-site radiotherapy clinical target volume. (b) Transverse view of the most superior to the most inferior extent of the mediastinum involved-site radiotherapy clinical target volume.

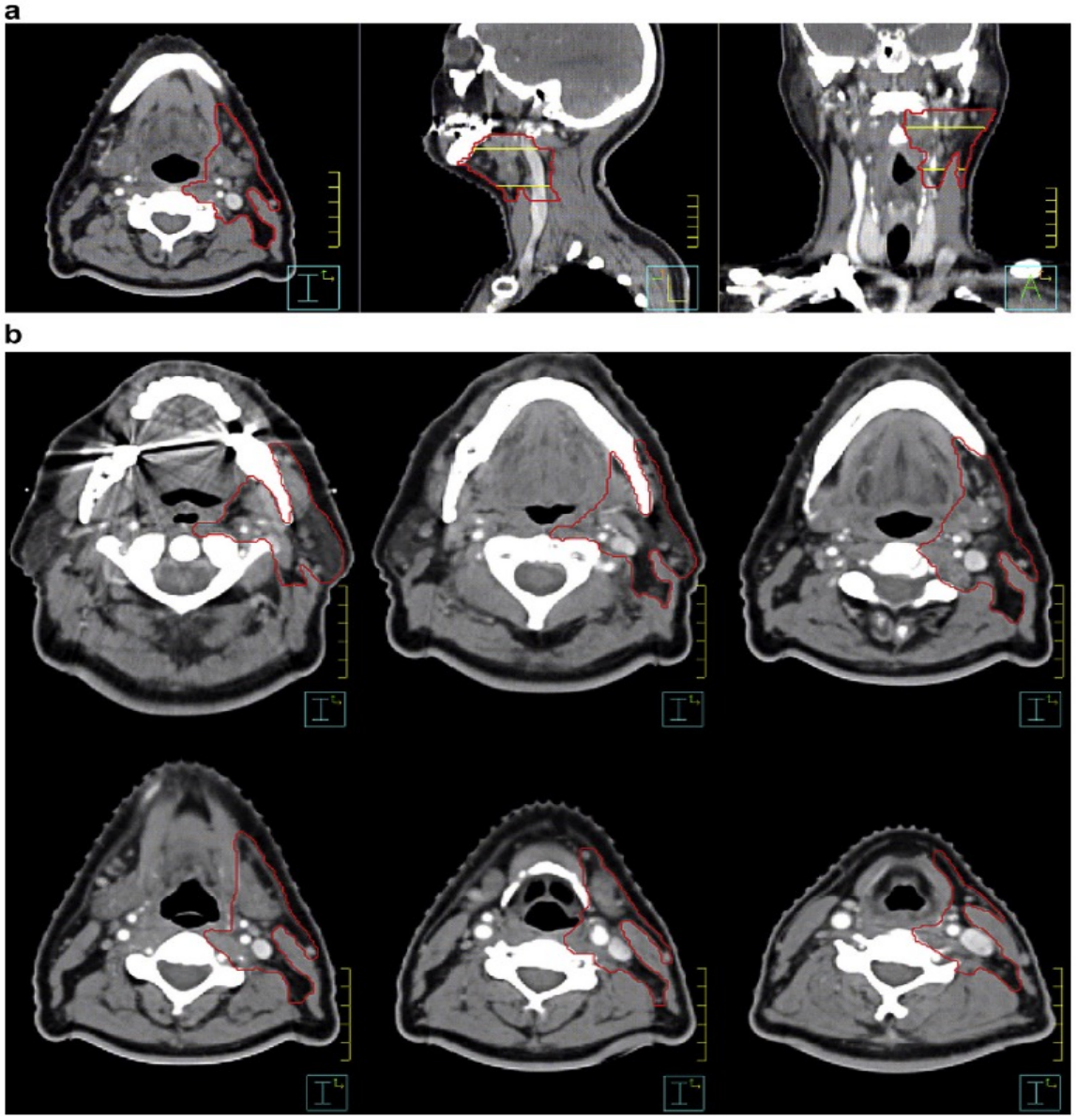

Fig 2. (a) Transverse sagittal and coronal views of a neck lymphoma patient. In yellow, the pre-chemotherapy nodal area superior–inferior extent. In red, the involved-site radiotherapy clinical target volume. (b) Transverse view of the most superior to the most inferior extent of the neck involved-site radiotherapy clinical target volume.

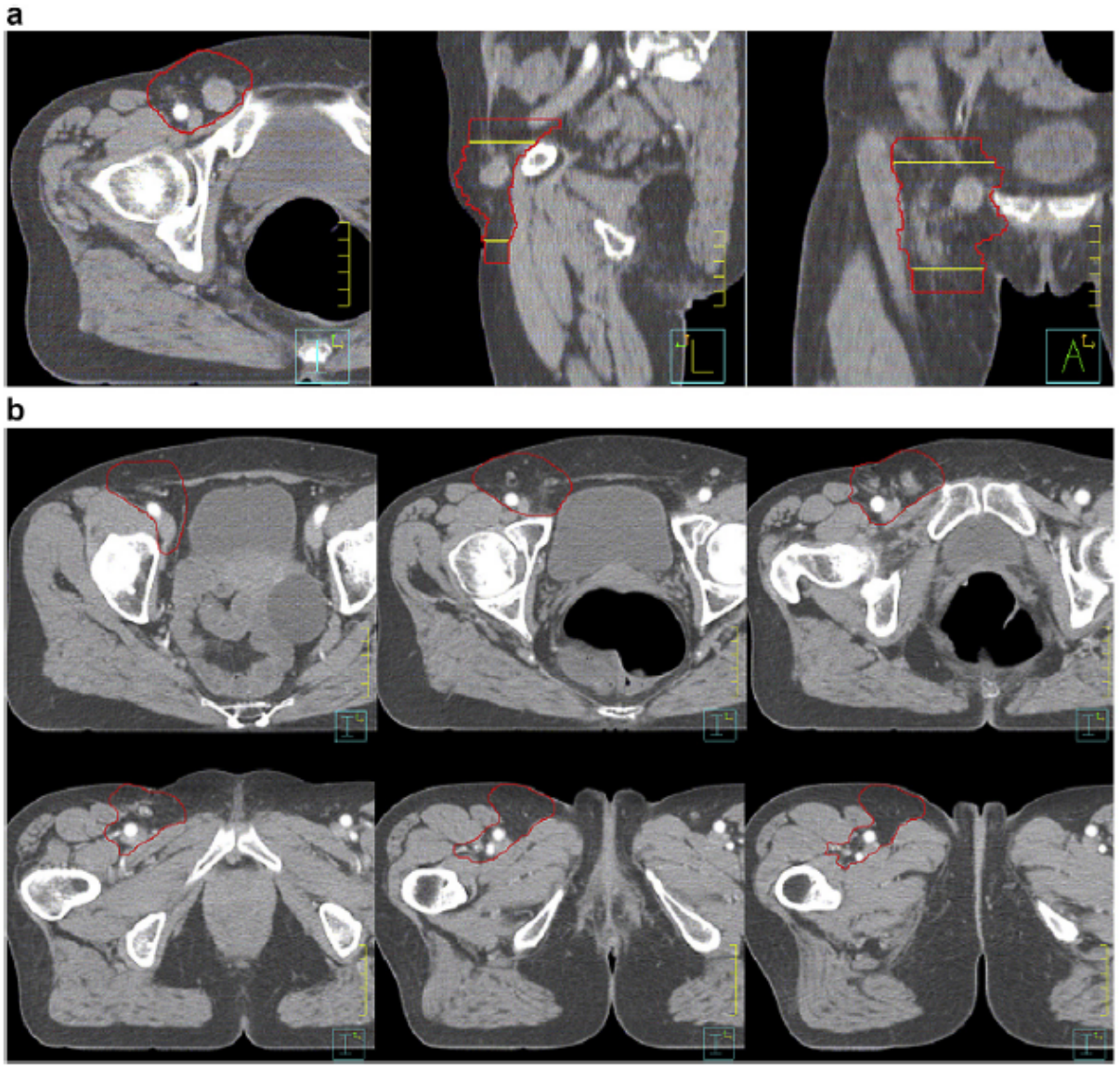

Fig 3. (a) Transverse sagittal and coronal views of an inguinal lymphoma patient. In yellow, the pre-chemotherapy nodal area superior–inferior extent. In red, the involved-site radiotherapy clinical target volume. (b) Transverse view of the most superior to the most inferior extent of the inguinal involved-site radiotherapy clinical target volume.

Overview

Radiotherapy Studies and Extra-nodal Non-Hodgkin Lymphomas, Progress and Challenges

L. Specht

Clinical Oncology 24 (2012) 313–318

Abstract

Extra-nodal lymphomas may arise in any organ, and different histological subtypes occur in distinct patterns. Prognosis and treatment depend not only on the histological subtype and disease extent, but also on the particular involved extra-nodal organ. The clinical course and response to treatment for the more common extra-nodal organs, e.g. stomach, Waldeyer's ring, skin and brain, are fairly well known and show significant variation. A few randomised trials have been carried out testing the role of radiotherapy in these lymphomas. However, for most extra-nodal lymphomas, randomised trials have not been carried out, and treatment decisions are made on small patient series and extrapolations from nodal lymphomas. Hopefully, wide international collaboration will make controlled clinical trials possible in the less common extra-nodal lymphomas.

Modern highly conformal radiotherapy allows better coverage of extra-nodal lymphomatous involvement with better sparing of normal tissues. The necessary radiation doses and volumes need to be defined for the different extra-nodal lymphoma entities. The challenge is to optimise the use of radiotherapy in the modern multimodality treatment of extra-nodal lymphomas.

Use of PET/CT to evaluate response to therapy in lymphoma

Q J NUCL MED MOL IMAGING 2011;55:633-47

TABLE VI.—*Main ongoing trials with Interim PET response-adapted therapies in aggressive NHL*

Study	Group	Patients	PET timing	Treatment
PET CHOP	Alberta Cancer Board	DLBCL	post 2 cycles R-CHOP	PET pos→salvage with high-dose chemotherapy +ASCT
LNH2007-3B	GELA	DLBCL	post 2 cycles R-CHOP	PET pos→salvage with high-dose chemotherapy +ASCT
–	British Columbia Cancer Agency	Advanced DLBCL	post 4 cycles R-CHOP	PET pos→ 4 cycles R-ICE
–	Johns Hopkins	Aggressive NHL	post 2-3 cycles (R)-CHOP	PET pos→salvage with high-dose chemotherapy +ASCT
PETAL	University Hospital, Essen	Aggressive NHL	post 2 cycles (R)-CHOP	PET neg→ 4 R-CHOP PET pos→ 6 (R)-CHOP *versus* Burkitt regimen (B-ALL protocol)

Generally, the scientific literature published so far, has found lower predictive values than in HL..
The lower NPV (Negative predictive value) is probably due to the intrinsically worse prognosis of NHL. The lower PPV (Positive predictive value) is instead related to the higher risk of infections among patients treated with higher dose-density and intensity strategies and among typically older patients.

In addition the use of Rituximab may produce a high incidence of false positive results by Inducing an inflammatory response by activation of antibody dependent cellular cytotoxicity and complement dependent cytotoxicity.

Combined Modality Treatment for PET-Positive Non-Hodgkin Lymphoma: Favorable Outcomes of Combined Modality Treatment for Patients With Non-Hodgkin Lymphoma and Positive Interim or Postchemotherapy FDG-PET

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Purpose: To evaluate outcomes of patients treated for aggressive non-Hodgkin lymphoma (NHL) with combined modality therapy based on [^{18}F]fluoro-2-deoxy-2-D-glucose positron emission tomography (FDG-PET) response.

Methods and Materials: We studied 59 patients with aggressive NHL, who received chemotherapy and radiation therapy (RT) from 2001 to 2008. Among them, 83% of patients had stage I/II disease. Patients with B-cell lymphoma received R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone)-based chemotherapy, and 1 patient with anaplastic lymphoma kinase-negative anaplastic T-cell lymphoma received CHOP therapy. Interim and postchemotherapy FDG-PET or FDG-PET/computed tomography (CT) scans were performed for restaging. All patients received consolidated involved-field RT. Median RT dose was 36 Gy (range, 28.8-50 Gy). Progression-free survival (PFS) and local control (LC) rates were calculated with and without a negative interim or postchemotherapy FDG-PET scan.

Results: Median follow-up was 46.5 months. Thirty-nine patients had negative FDG-PET results by the end of chemotherapy, including 12 patients who had a negative interim FDG-PET scan and no postchemotherapy PET. Twenty patients were FDG-PET-positive, including 7 patients with positive interim FDG-PET and no postchemotherapy FDG-PET scans. The 3-year actuarial PFS rates for patients with negative versus positive FDG-PET scans were 97% and 90%, respectively. The 3-year actuarial LC rates for patients with negative versus positive FDG-PET scans were 100% and 90%, respectively.

Conclusions: Patients who had a positive interim or postchemotherapy FDG-PET had a PFS rate of 90% at 3 years after combined modality treatment, suggesting that a large proportion of these patients can be cured with consolidated RT. © 2012 Elsevier Inc.

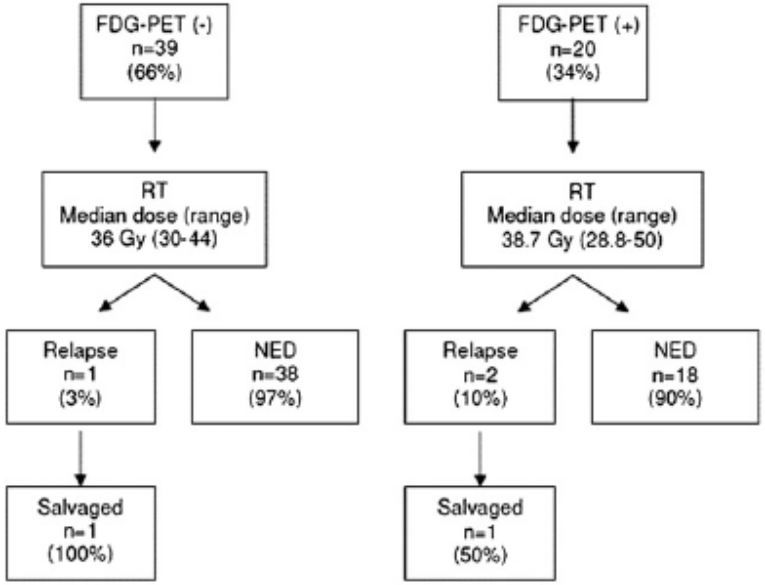

Fig. 2. Outcome based on interim and postchemotherapy FDG-PET scans. NED = no evidence of disease; RT = radiotherapy.

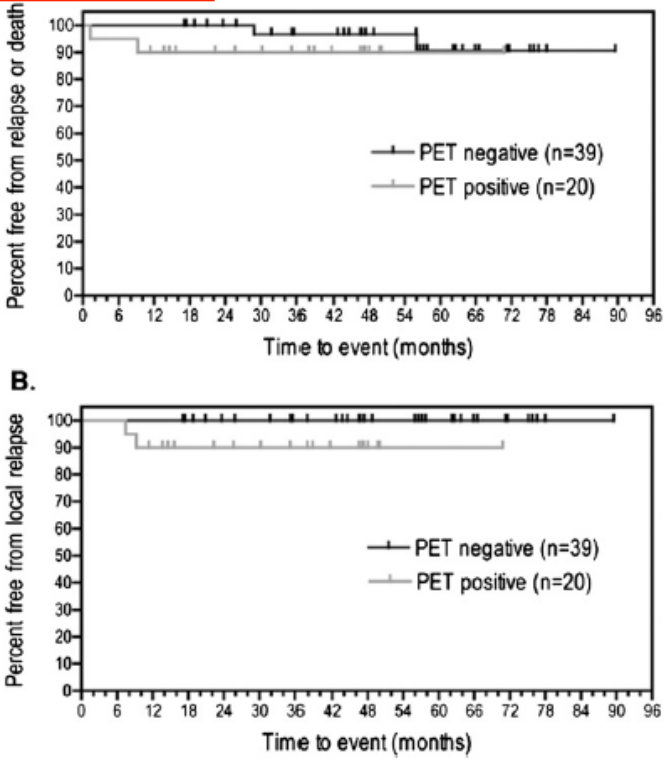

Fig. 3. (A) Kaplan-Meier curves of PFS rates stratified by FDG-PET response. (B) Kaplan-Meier curves of LC stratified

Is there a role for consolidative radiotherapy in the treatment of aggressive and localized Non-Hodgkin Lymphoma? A systematic review with meta-analysis

BMC Cancer
BMC Cancer 2012,

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Background: Chemotherapy is the mainstay of non-Hodgkin lymphoma (NHL) treatment. Based on expert opinion, the use of radiotherapy (RT) is currently preferred in some institutions as consolidative treatment for patients with localized disease. The lack of conclusive data coming from conflicting studies about the impact of treatment demands a systematic review, which could provide the most reliable assessment for clinical decision-making. We evaluate the addition of RT post-CT, for aggressive and localized NHL (ALNHL).

Methods: Randomized controlled trials (RCT) that evaluated chemotherapy alone versus chemotherapy plus RT were searched in databases. The outcomes were overall survival (OS), progression-free survival (PFS), overall response rate (ORR) and toxicity. Risk ratio (RR) and hazard ratio (HR) with their respective 95% confidence intervals (CI) were calculated using a fized-effect model.

Results: Four trials (1,796 patients) met the inclusion criteria. All trials tested the use of RT after systemic therapy comprising anthracycline-based chemotherapy. This systematic review showed that RT enhances PFS after chemotherapy (hazard ratio [HR] 0.81; 95% CI 0.67-0.98; $p = 0.03$), with no impact on ORR and OS. Some heterogeneity between trials could limit the conclusions about OS. Toxicity data could not be pooled due to differences in reporting adverse events.

Conclusions: This systematic review with meta-analysis shows no improvement in survival when adding RT to systemic therapy for ALNHL. Our conclusions are limited by the available data. Further evaluations of new RT technologies and its association with biologic agents are needed.

Leuk Lymphoma. 2012 Oct 26

Risk of second malignant neoplasms after cyclophosphamide-based chemotherapy with or without radiotherapy for non-Hodgkin's lymphoma

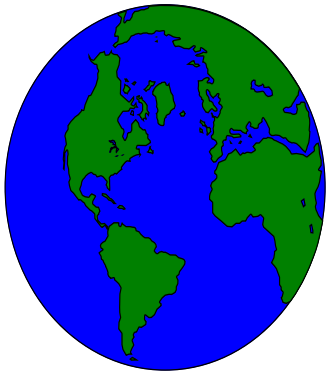
Yuanlin Xu, Huaqing Wang, Shiyong Zhou

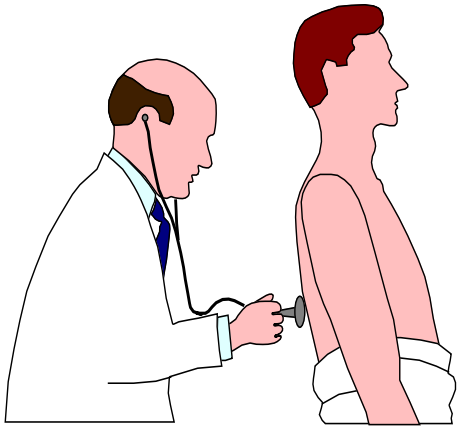
- **Abstract**

Relatively little information is available on quantitative risks of therapy-induced second malignant neoplasm (SMN) in patients with non-Hodgkin's lymphoma (NHL). A nested case-control study was conducted in a cohort of **3,412 patients treated for NHL between 1990 and 2006, including 118 patients with SMN and 472 controls**. ***Risks of leukemia / lung / breast / colorectal and bladder cancer were higher in NHL compared with general population. A higher risk of leukemia was restricted to patients given cumulative dose of cyclophosphamide more than 11250 mg/m(2).*** However, no significant association was found between SMN risk with rituximab, fludarabine, anthracyclines, epipodophyllotoxins and platinum, respectively. ***In combined modality, involved regional-field radiation therapy (IRRT) had a higher risk for second solid cancers as compared to involved-nodal radiation therapy (INRT). With patients receiving radiation doses exceeding 40Gy, the risk of lung cancer and breast cancer was increased*****.** In conclusion, we found that cyclophosphamide-based therapy increased the risk of SMN in NHL. Leukemia risk was linked with high dose cyclophosphamide. Received larger radiation field or higher radiation dose also could be important risk factor for the development of SMN.

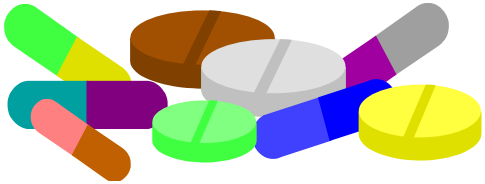
Lymphomas are characterized by a high degree of radioresponsiveness and therefore RT is an important modality in controlling these malignancies. Recent progress in biology and histopathology as well as cytogenetic techniques have allowed us to study homogeneous patient populations and have given an opportunity to reassess the role of RT in their management.

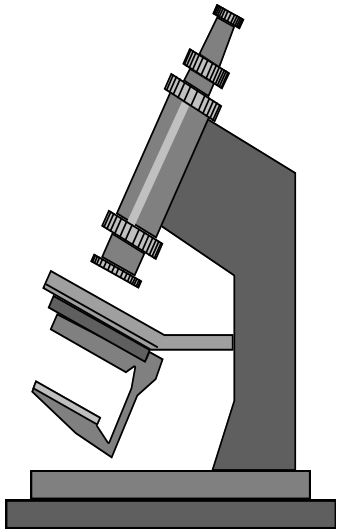
Late effects of treatment manifesting as normal tissue toxicity and especially second cancers are continuing concerns following curative therapy. Attention to late morbidity while we devise treatments to improve the cure rate remains an important goal.





In the era of Personalized medicine, treatment is likely to become more adaptive to the individual clinical situation





Grazie per l'attenzione…..