RADIATION THERAPY FOR NHL
CURRENT CONSENSUS

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RADIATION THERAPY FOR AGGRESSIVE NODAL NHL

MALIGNANT LYMPHOMAS

Uniquely sensitive to ionizing radiation.

For majority of anatomic locations, the sensitivity of the tumor is greater than that of the surrounding normal tissue, usually by a considerable amount, a luxury not available when treating most solid tumors.

Background

Radiation Therapy for Early Stage Disease (Stage I & II)

Radiation Therapy for Advanced Stage Disease (Stage III & IV)

Radiation Therapy Treatment Volume

Radiation Dose

THE ANN ARBOR/ COTSWOLDS STAGING CLASSIFICATION

Stage I	Involvement of a single lymph node region or single extralymphatic organ or site (I_E)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site (II_E) and one lymph node region on the same side of the diaphragm. The number of anatomic regions involved is indicated by a subscript (e.g., II_3).
Stage III	Involvement of lymph node regions on both sides of the diaphragm, which may also be accompanied by involvement of the spleen (III_S) or by localized contiguous involvement of only one extranodal organ site (III_E), or both (III_{SE}).
III_1	With or without involvement of splenic hilar, celiac, or portal nodes
III_2	With involvement of para-aortic, iliac, and mesenteric nodes
Stage IV	Diffuse or disseminated involvement of one or more extranodal organs or tissues, with or without associated lymph node involvement

Designations applicable to any disease state

A	No symptoms
B	Fever (temperature >38Â°C), drenching night sweats, unexplained loss of >10% body weight within the preceding 6 mo
X	Bulky disease (a widening of the mediastinum by more than one-third or the presence of a nodal mass with a maximal dimension >10 cm)
E	Involvement of a single extranodal site that is contiguous or proximal to the known nodal site
CS	Clinical stage
PS	Pathologic stage (as determined by a laparotomy)

J Clin Oncol 1989;7:1630-1636,

INTERNATIONAL PROGNOSTIC INDEX (IPI)

International NHL Prognostic Factors Project

Factors Included:

Age > 60 years
Stage III to IV
> 1 Extranodal Site
Performance Status ≥ 2
LDH > normal

Outcomes Based on IPI

Risk Groups	Factors	CR (%)	5 Yr RFS (%)	5 Yr OS (%)
All Patients				
Low	0 or 1		70	73
Low Intermediate	2	67	50	51
High Intermediate	3	55	49	43
High	4 or 5	44	40	26
Pts. <60 yrs. (age adjusted IPI)				
Low	0	92	86	83
Low Intermediate	1	78	66	69
High Intermediate	2	57	53	46
High	3	46	58	32

NEJM 1993

RADIATION THERAPY FOR STAGE I & II

Br. J. Cancer (1994), **69**, 1088–1093

Clinical stage 1 non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy

B. Vaughan Hudson[1], G. Vaughan Hudson[1], K.A. MacLennan[2], L. Anderson[1] & D.C. Linch[1]

[1]*The British National Lymphoma Investigation, Departments of Haematology and Oncology, University College London School of Medicine, London W1N 8AA, UK;* [2]*Institute for Cancer Studies, St James' University Hospital, Leeds LS9 7TF, UK.*

Patients: 451
Patients in BNLI Studies (1974-1991)
Stage I/ IE, No B Symptoms
Age: > 16 Years (Median-56 Yrs)

High Grade: 243
Nodal – 145 (60%)
E. Nodal – 98 (40%)

RT Technique: ?? EFRT (Not Documented for all pts.)
RT Dose: 40Gy/ 20#

10 Year DFS: 45%, 10 Year CCS: 61%

Br J Cancer 1994

British Journal of Cancer (2004) 90, 1151 – 1155

www.bjcancer.com

Long-term follow-up of patients treated with radiotherapy alone for early-stage histologically aggressive non-Hodgkin's lymphoma

J Spicer[1], P Smith[2], K Maclennan[2], P Hoskin[3], B Hancock[4], D Linch[2] and R Pettengell[*,1,5]

[1]Department of Oncology, St George's Hospital Medical School, Cranmer Terrace, London SW17 ORE, UK; [2]British National Lymphoma Investigation (BNLI), Cancer Research UK and UCL Cancer Trials Centre, 222 Euston Road, London NW1 2DA, UK; [3]Mount Vernon Hospital, Rickmansworth Road, Northwood, Middlesex HA6 2RN, UK; [4]University of Sheffield, Weston Park Hospital, Whitham Road, Sheffield S10 2SJ, UK; [5]Department of Haematology, St George's Hospital Medical School, Cranmer Terrace, London SW17 ORE, UK

Patients: 377
Patients in BNLI Studies (1974-1997)
Stage I/ II, No B Symptoms
Age: > 16 Years
All High Grade

RT Technique: IFRT
RT Dose: 35-40Gy
CR: 294/377 (78%)
10 Year DFS: 44%, 10 Year OS: 51%, 10 Year CCS: 63%

Br J Cancer 1994

INFERENCES

BNLI Update

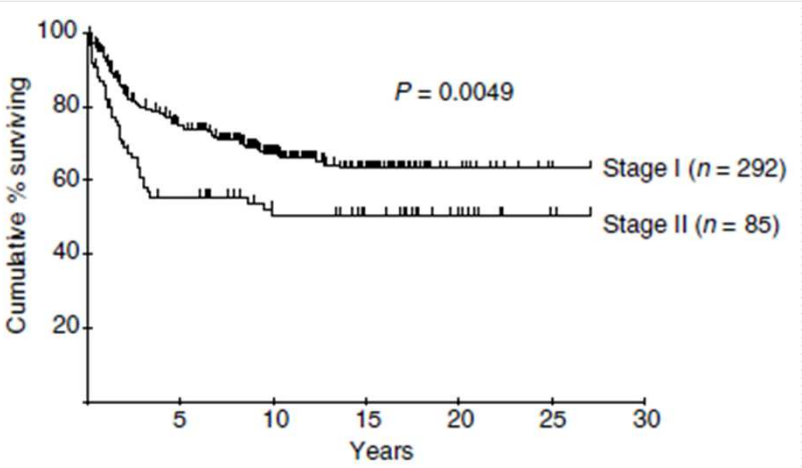

Figure 3 Cause-specific survival according to stage of patients with early aggressive NHL

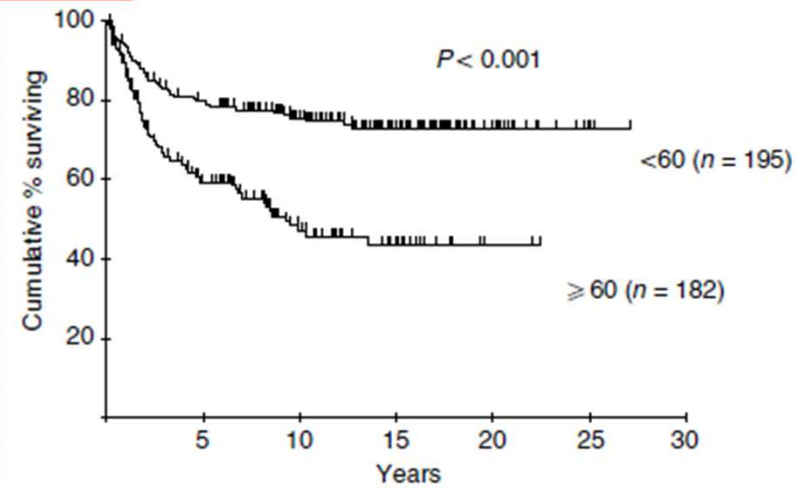

Figure 4 Cause-specific survival according to age of patients with early aggressive NHL

CR Rates superior in Pts. <60 Yrs, Stage I
Inferior OS in older age due to unsuccessful salvage
Similar results reported by:

Timothy et al, 1980
Hagberg et al, 1989

Br J Cancer 1994

Is only Radiation Therapy Adequate for Early Stage NHL

A RANDOMIZED STUDY OF RADIOTHERAPY VERSUS RADIOTHERAPY PLUS CHEMOTHERAPY IN STAGE I-II NON-HODGKIN'S LYMPHOMAS.

Randomized Trial

N= 73

Stage I & II

Treatment:
Extended field radiotherapy alone (RT) vs.
RT + CT (vincristine, streptonigrin, cyclophosphamide and prednisone)

Median follow up of 5 years

DFS:

RT: 45%
RT + CT: 80% , p=0.01

Dead due to disease progression:

RT: 59%
RT + CT: 9% , p=0.01

Nissen et al, Cancer 1983
Monfardini et al, IJROBP 1980

Is only Chemotherapy Adequate for Early Stage NHL

CHEMO VS CHEMO + RT IN EARLY STAGE DLBCL RANDOMIZED TRIALS

Study	Stage	No.	F/U	Treat	Results	P-value
SWOG 8736	St I or IE (Bulky+Non Bulky) St II or IIE (Non Bulky only)	401	4.4yrs	CHOPx3 + IFRT (40-55Gy) CHOPx8	5-y PFS: 77% 5-y OS: 92% 5-y PFS: 64% 5-y OS: 72%	0.03 0.02
ECOG	St I (Bulky or EN only) St II (Bulky+Non Buky)	215	12yrs	CHOPx8: If CR: IFRT 30Gy No RT If PR: IFRT 40Gy	 6-y DFS:69% 6-y FFS:70% 6-y OS:79% 6-y DFS:53% 6-y FFS:53% 6-y OS:67% 6-y FFS:63% 6-y OS:69%	0.05 0.05 0.23
LNH-93-1 (GELA Group)	Age <60 (10% bulky, 50% EN, 0 aaIPI)	647	7.7yrs	ACVBPx3 + MTX, Ifos, VP16, ara-C CHOPx3+IFRT (30-40Gy)	5-y EFS:82% 5-y OS:90% 5-y EFS:74% 5-y OS:81%	0.004 0.001
LNH-93-4 (GELA Group)	Age >60 (8% bulky, 56% EN)	576	6.8yrs	CHOPx4+IFRT (40Gy) CHOPx4	EFS:66% OS:72% EFS:68% OS:68%	0.7 0.6

SWOG 8736 STUDY

Study not designed to address the need for IFRT.
Study designed to address the possibility to reduce CT with IFRT

5 Yr DFS & OS superior in CT + RT arm

Life-threatening toxic effects (Myelosupression):

CHOP :	40% (p=0.06)
CHOP+RT:	30%

Left Ventricular Dysfunction:

CHOP :	7 pts (p=0.02)
CHOP+RT:	Nil

Updated Results (Median FU 8.2yrs):

No difference in DFS & OS i.e late relapses in CT+RT

Analysis based on IPI (CT+RT arm) – 5 Yr OS

0 Risk Score: 94%
1 Risk Score: 70%
3 Risk Score: 50%

Late relapses in pts. with risk factors suggest that 3# CT is inadequate in the presence of risk factors

ECOG STUDY

DESIGN: CHOPx8

If CR: IFRT 30Gy vs. No RT

If PR: IFRT 40Gy

12 Yr DFS, FFS, & OS superior in CT + RT arm

Improved outcome with CT+RT despite imbalance in proportion of bulky disease: 26% in CT+RT arm vs. 17% in CT only arm

CR was achieved only in 61% pts.

Partial responders to CT who received adjuvant IFRT (40Gy) had 6-Yr FFS (63%) & OS (69%) comparable to pts. Achieving CR after CT only.

GELA GROUP: LNH93-1 TRIAL

DESIGN:

ACVBPx3 + MTX, Ifos, VP16, ara-C (Maint. CT)
vs
CHOPx3+IFRT (30-40Gy)

5 Yr EFS & OS superior in the Intensive CT arm

Patterns of Relapse:

ACVBP arm:	41% at primary site of disease
CHOP+RT arm:	23% at primary site of disease

Inference: Adjuvant RT cannot replace inadequate CT
Adjuvant RT reduces relapse rates at the primary site

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ORIGINAL REPORT

Phase II Study of Rituximab Plus Three Cycles of CHOP and Involved-Field Radiotherapy for Patients With Limited-Stage Aggressive B-Cell Lymphoma: Southwest Oncology Group Study 0014

Daniel O. Persky, Joseph M. Unger, Catherine M. Spier, Baldassarre Stea, Michael LeBlanc, Matthew J. McCarty, Lisa M. Rimsza, Richard I. Fisher, and Thomas P. Miller

Patients and Methods

Southwest Oncology Group (SWOG) study S0014 enrolled patients with newly diagnosed, aggressive, CD20-expressing non-Hodgkin's lymphoma (NHL). Patients had limited-stage disease and at least one adverse risk factor as defined by the stage-modified International Prognostic Index (nonbulky stage II disease, age > 60 years, WHO performance status of 2, or elevated serum lactate dehydrogenase). Four doses of rituximab were infused on days –7, 1, 22, and 43, and CHOP was administered on days 3, 24, and 45, followed 3 weeks later by 40 to 46 Gy of IFRT.

Results

Sixty patients with aggressive NHL were eligible. With the median follow-up of 5.3 years, treatment resulted in a progression-free survival (PFS) of 93% at 2 years and 88% at 4 years. Overall survival (OS) was 95% at 2 years and 92% at 4 years. These results were compared with those from a historic group of patients treated without rituximab on S8736, demonstrating PFS of 78% and OS of 88% at 4 years.

Conclusion

In limited-stage DLBCL, the addition of rituximab to three cycles of CHOP plus IFRT met prespecified study criteria of efficacy, with 2-year PFS of at least 84%, meriting further investigation. There is a pattern of continuing relapse with modest survival gains. We hypothesize that such a pattern may be the result of biologic differences between limited- and advanced-stage lymphoma.

SUMMARY OF RANDOMISED TRIALS FOR EARLY STAGE

Combined modality treatment remains the standard of care

Adjuvant radiation therapy improves outcome (DFS, FFS)

Adjuvant radiation therapy cannot compensate for inadequate chemotherapy

Intensive chemotherapy is associated with significant toxicity

Optimal number of cycles of chemotherapy is still an area of debate

Optimal dose of IFRT in the context of combined modality therapy is not clearly established

Currently no randomised trial comparing
R-CHOP/ CHOP like regimens vs. R-CHOP/ CHOP + IFRT

CURRENT RECCOMENDATIONS FOR EARLY STAGE

LOW RISK GROUP:

CHOP ± R (CD 20+ve) x 3 # + IFRT 40-45Gy

ADVERSE RISK GROUP:

CHOP ± R (CD 20+ve) x 6-8 # + IFRT 36-40Gy

PARTIAL RESPONDERS TO CHEMO:

Adjuvant IFRT 40-45Gy

RADIATION THERAPY FOR STAGE III & IV

CURRENT STANDARD OF CARE

Multiagent Chemotherapy ± IFRT

IFRT for Initial Sites of Bulky Disease after Complete Response to Chemotherapy

ADJUVANT RADIOTHERAPY TO SITES OF PREVIOUS BULKY DISEASE IN PATIENTS STAGE IV DIFFUSE LARGE CELL LYMPHOMA.

Randomised Trial

N= 218

Treatment: CEOP-bleo (cyclophos, epirubicin, vincristine, prednisone, bleomycin) alternating with DAC (dexamethasone, cytosine arabinoside, and cisplatinum)

CR: 155 pts

Bulky disease: 88

Adjuvant IFRT (40-50Gy):	43 pts.
No Adjuvant RT:	45 pts.

5 Yr DFS:

Adjuvant IFRT (40-50Gy):	72%
No Adjuvant RT:	35%

5 Yr OS:

Adjuvant IFRT (40-50Gy):	81%
No Adjuvant RT:	55%

Aviles et al, IJROBP 1994

IFRT for Partial Responders After Chemotherapy

IMPACT OF INVOLVED FIELD RADIOTHERAPY IN PARTIAL RESPONSE AFTER DOXORUBICIN-BASED CHEMOTHERAPY FOR ADVANCED AGGRESSIVE NON-HODGKIN'S LYMPHOMA

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UMBERTO TIRELLI, M.D., PH.D.,‖ BERTHE M. P. ALEMAN, M.D.,# JOKE BAARS, M.D., PH.D.,**
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Purpose: Whether salvage therapy in patients with advanced aggressive non-Hodgkin's lymphoma (NHL) in partial remission (PR) should consist of radiotherapy or autologous stem-cell transplantation (ASCT) is debatable. We evaluated the impact of radiotherapy on outcome in PR patients treated in four successive European Organization for Research and Treatment of Cancer trials for aggressive NHL.

Patients and Methods: Records of 974 patients (1980–1999) were reviewed regarding initial response, final outcome, and type and timing of salvage treatment. After 8 cycles of doxorubicin-based chemotherapy, 227 NHL patients were in PR and treated: 114 received involved field radiotherapy, 16 ASCT, 93 second-line chemotherapy, and 4 were operated. Overall survival (OS) and progression-free survival (PFS) after radiotherapy were estimated (Kaplan-Meier method) and compared with other treatments (log–rank). Impact on survival was evaluated by multivariate analysis (Cox proportional hazards model).

Results: The median PFS in PR patients was 4.2 years and 48% remained progression-free at 5 years. Half of the PR patients converted to a complete remission. After conversion, survival was comparable to patients directly in complete remission. Radiotherapy resulted in better OS and PFS compared with other treatments, especially in patients with low to intermediate International Prognostic Index score, bulky disease, or nodal disease only. Correction by multivariate analysis for prognostic factors such as stage, bulky disease, and number of extranodal locations showed that radiotherapy was clearly the most significant factor affecting both OS and PFS.

Conclusion: This retrospective analysis demonstrates that radiotherapy can be effective for patients in PR after fully dosed chemotherapy; assessment in a randomized trial (radiotherapy vs. ASCT) is justified.

IJROBP 2006

Combination chemotherapy with adriamycin, cyclophosphamide, vincristine, methotrexate, etoposide and dexamethasone (ACOMED) followed by involved field radiotherapy induces high remission rates and durable long-term survival in patients with aggressive malignant non-Hodgkin's lymphomas: long-term follow-up of a pilot study

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Abstract

The aim of the present study was to evaluate the feasibility and efficacy of the intensified induction chemotherapy regimen ACOMED for patients with aggressive non-Hodgkin's lymphoma (NHL). Untreated adult patients with aggressive NHL, presenting with Ann Arbour stage II–IV disease or stage I with bulky disease, and with at least one of the following risk factors: age > 60 years, advanced disease, elevated serum lactate dehydrogenase level, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, presence of extranodal sites of disease and bulky disease, were treated with the ACOMED regimen consisting of 4–6 cycles of adriamycin 25 mg/m^2 i.v. on days 4–5, cyclophosphamide 250 mg/m^2 i.v. on days 1–5, vincristine 2 mg i.v. absolute on day 1, methotrexate 500 mg/m^2 i.v. on day 1 with leucovorin-rescue after 24 h 30 mg/m^2 i.v. and 3 × 15 mg p.o., etoposide 100 mg/m^2 i.v. on days 3–5, dexamethasone 10 mg/m^2 p.o. on days 1–5 and granulocyte colony-stimualting factor support, repeated on day 21. Twenty-two patients were treated within this study at a single center. After 4–6 cycles of ACOMED followed by additional involved field radiotherapy in 18 patients, the complete and overall response rates were 86% (19 of 22 patients) and 95% (21 of 22 patients), respectively. After a median observation time of 10 years and 2 months, 16/22 (73%) patients are alive in continuous complete reponse without evidence of any late toxicities. ACOMED followed by involved field radiation presents a highly effective regimen for remission induction and long-term survival in patients with aggressive NHL, and merits further investigation.

Leukemia & Lymphoma 2005

Table III. Response rates and 10-year survival rates.

Response after 4–6 cycles	Response after radiation	10-year survival
CR 45%	CR 86%	EFS 73%
OR 90%	OR 95%	OS 73%

CR, Complete response; OR, overall response; EFS, event-free survival; OS, overall survival.

The results of our study show that patients treated with the non-myeloablative ACOMED regimen followed by radiotherapy achieved high response rates (CR 86%, OR 95%) and exceptional long-term survival rates (10-year survival rate 73%).

IFRT for Bulky Sites/ Partial Response After High Dose Chemo & Stem Cell Transplant

HIGH DOSE CHEMOTHERAPY AND STEM CELL RESCUE FOR AGGRESSIVE NON-HODGKIN'S LYMPHOMA: PATTERN OF FAILURE AND IMPLICATIONS FOR INVOLVED-FIELD RADIOTHERAPY

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Purpose: To evaluate the pattern of failure and outcome of patients with aggressive non-Hodgkin's lymphoma (NHL) undergoing high-dose chemotherapy (HDCT) and autologous stem cell rescue (SCR) with an emphasis on the role of adjuvant involved-field radiotherapy (IFRT).

Method and Materials: Fifty-three adult patients with aggressive NHL (46 intermediate-and 7 high-grade) underwent HDCT with SCR. All patients underwent induction chemotherapy prior to high dose intensification. Seven (13.2%) received IFRT to 10 disease sites either prior to or following HDCT. Indication included symptomatic or bulky disease, persistent disease, or to consolidate a complete response (CR). Sites of relapse were designated as old (involved prior to HDCT) or new (previously uninvolved). Median followup was 20.1 months (range, 1.2–69.3 months).

Results: The 4-year actuarial progression-free (PFS) and cause-specific (CSS) survivals of the entire group were 30.0 and 50.2%, respectively. Excluding toxic deaths, 24 patients (52.2%) relapsed. Sixteen (34.7%) failed in old and 15 (32.6%) in new sites. Patients treated with IFRT had a lower rate of relapse in old sites (0 vs. 41%) ($p = 0.04$) than patients treated with HDCT alone. Of the 141 sites present prior to induction, 127 (90.1%) were amenable to IFRT. Excluding irradiated sites, the overall 4-year local control (LC) of all amenable sites was 61.1%. Amenable sites failing to achieve a CR to induction had a poorer LC (32.0 vs. 95.1%) ($p < 0.0001$) than sites in CR. The 4-year LC of sites failing to achieve a CR to HDCT was 29.4%. Adjuvant IFRT improved the 4-year LC of all sites (100 vs. 61.1%) ($p = 0.05$), persistent sites following induction (100 vs. 32.0%) ($p = 0.01$) and persistent sites following HDCT (100 vs. 29.4%) ($p = 0.01$). Adjuvant IFRT was not associated with any untoward acute or late toxicity.

Conclusions: The predominant site of relapse in patients with aggressive NHL undergoing HDCT and SCR is in sites of disease present prior to HDCT. However, the risk of relapse of prior disease sites varies greatly depending upon their response to chemotherapy. Sites at greatest risk are those failing to achieve a CR to induction regardless of their response to HDCT. IFRT is capable of reducing the high risk of relapse in these sites, the majority of which are amenable to IFRT. These results demonstrate a rationale for and possible benefit to IFRT in patients with aggressive NHL undergoing HDCT and SCR.

IJROBP 1997

INVOLVED FIELD RADIATION AFTER AUTOLOGOUS STEM CELL TRANSPLANT FOR DIFFUSE LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA

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Purpose: For patients with recurrent or refractory large B-cell non-Hodgkin's lymphoma, high-dose chemotherapy and autologous stem cell transplant (ASCT) is the treatment of choice. We evaluated the role of involved field radiation therapy (IFRT) post-ASCT for patients initially induced with cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) or, more recently, rituximab-CHOP (R-CHOP).

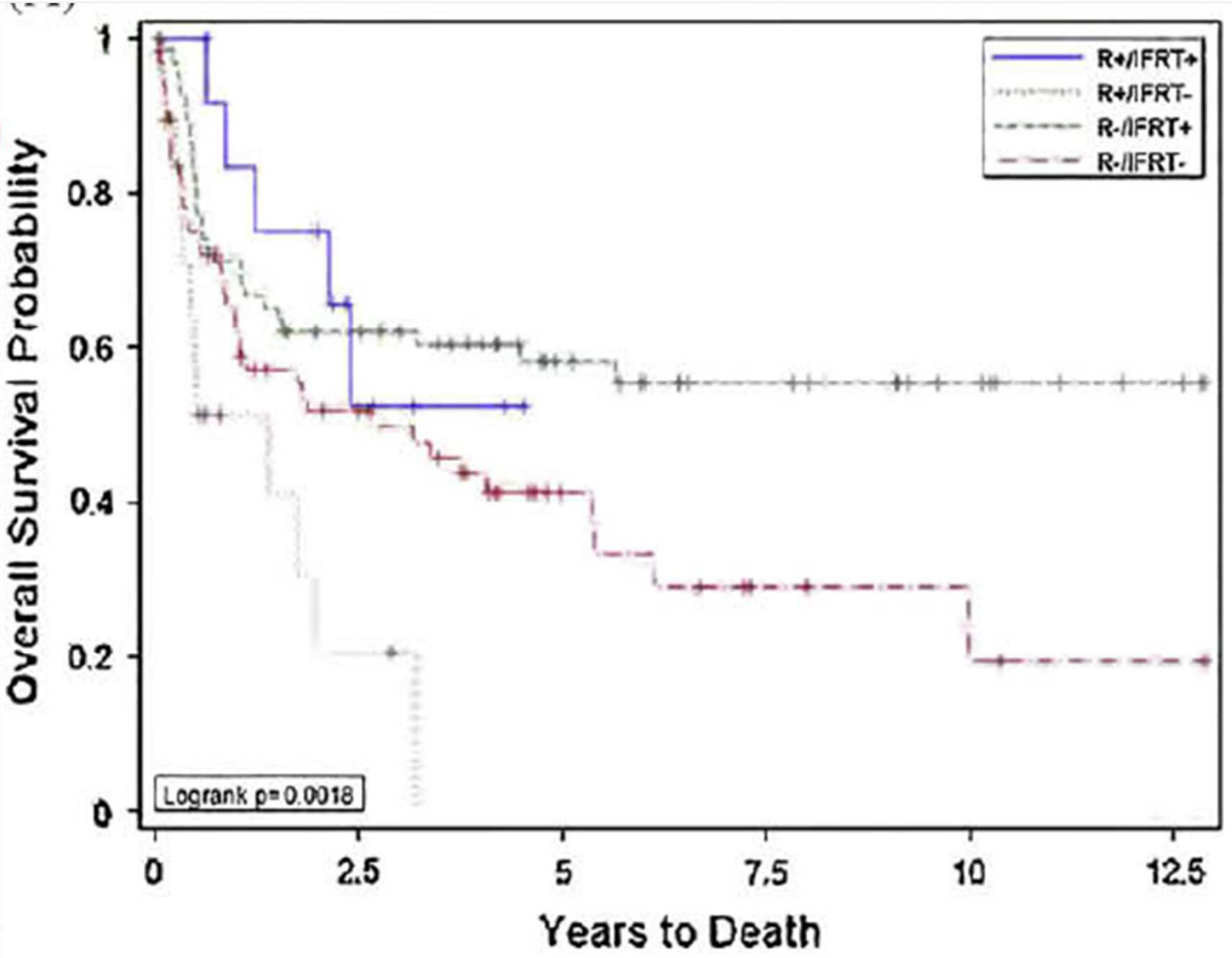
Materials and Methods: Between May 1992 and April 2005, 176 patients underwent ASCT for recurrent or refractory large B-cell non-Hodgkin's lymphoma; 164 patients were evaluable for endpoint analysis. Fifty percent of the CHOP group ($n = 131$), and 39% of the R-CHOP group ($n = 33$), received IFRT. Follow-up from the time of transplant was a median/mean of 1.7/3 years (range, 0.03-13 years).

Results: The 5-year overall survival (OS) and disease-specific survival (DSS) improved with IFRT in both the R-CHOP ($p = 0.006$ and 0.02, respectively) and CHOP ($p = 0.02$ and $p = 0.04$, respectively) groups. IFRT was associated with a 10% ($p = 0.17$) reduction in local failure, alone or with a distant site. On univariate analysis, IFRT was associated with superior OS (hazard ratio [HR] = 0.50 [95% CI 0.32, 0.78]; $p = 0.002$) and DSS (HR = 0.53 [95% CI 0.33, 0.86]; $p = 0.009$). Presence of B symptoms was adverse ($p = 0.03$). On multivariate analysis, only IFRT was associated with significant improvement in OS (HR = 0.35 [0.18, 0.68]; $p = 0.002$) and DSS (HR = 0.39 [95% CI 0.18, 0.84]; $p = 0.01$).

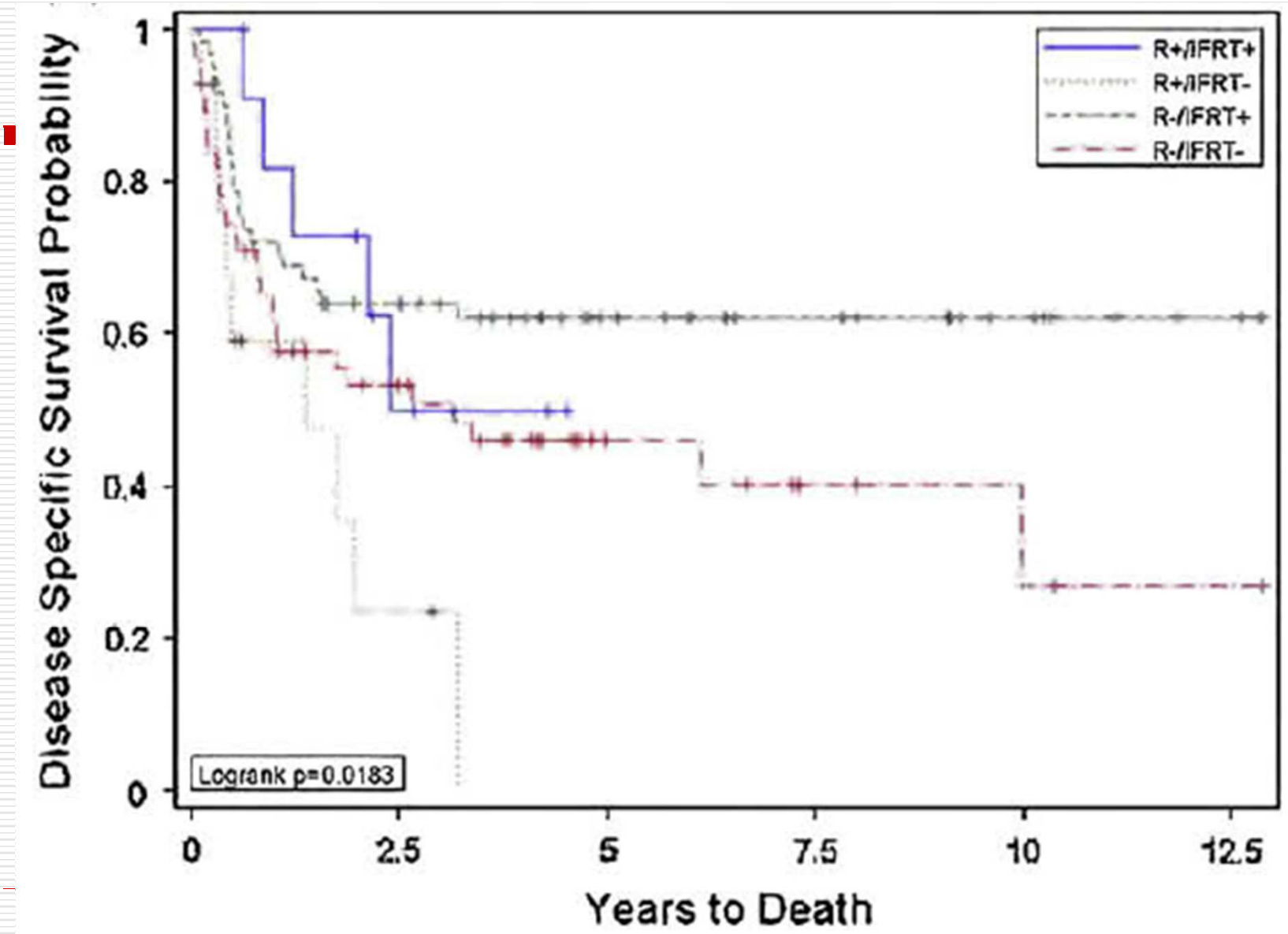
Conclusions: Recognizing that positive and negative patient selection bias exists for the use of IFRT post-ASCT, patients initially treated with CHOP or R-CHOP and who undergo ASCT for recurrent or refractory disease may benefit from subsequent IFRT presumably due to enhanced local control that can translate into a survival advantage.

IJROBP 2009

OS WITH RITUXIMAB ± IFRT



DFS WITH RITUXIMAB ± IFRT



SUMMARY OF RT FOR ADVANCED STAGE

IFRT improves DFS, FFS, OS in patients with poor prognostic factors (bulky disease)

IFRT increases response rates and DFS/ FFS in partial responders to chemo

IFRT improves DFS/ FFS in pts with bulky disease after achieving complete Response to chemotherapy

IFRT improves DFS/FFS/ OS in patients with resistant/ refractory disease undergoing HDCT & SCT

RADIATION THERAPY GUIDELINES FOR AGGRESSIVE NODAL LYMPHOMAS

Stage	Treatment	Radiotherapy Dose	
		Complete Response	Partial Response
$I_{A,}$ II_{A}	CTh x 4 cycles + IFRT	35-40Gy	45Gy
$I_{AX,}$ II_{AX}	CTh x 6-8 cycles + IFRT	35-40Gy	40-45Gy
IIB, III, IV	CTh x 6-8 cycles ± IFRT	No RT	40-45Gy
II_{BX}, III_{X}, IV_{X}	CTh x 6-8 cycles + IFRT	35-40Gy	40-45Gy

Use conformal fields (3D-CRT/ IMRT) wherever applicable

RT to be started 12-14 days after completion of CTh