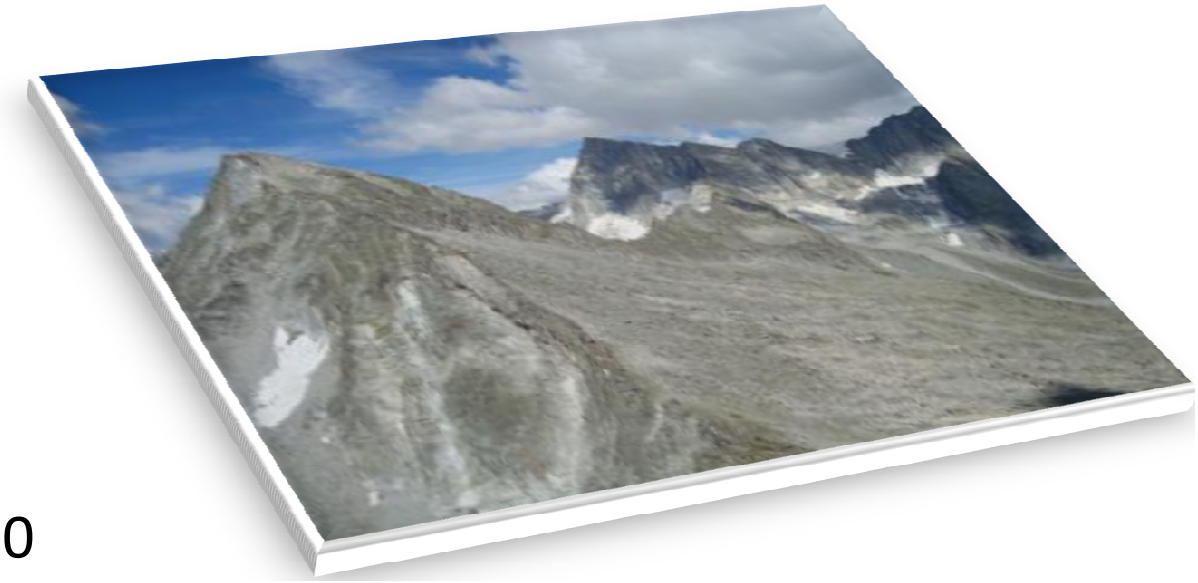
UNIVERSITA' DEGLI STUDI DI BRESCIA

Radiotherapy: Which Role in Non Hodgkin Indolent Lymphoma ?

Stefano Magrini



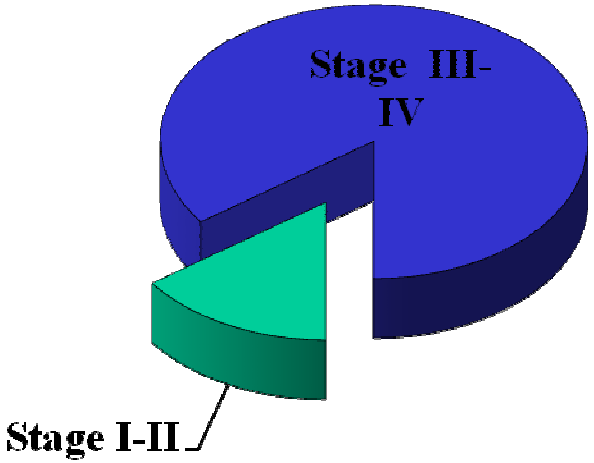
Brescia -14 Maggio 2010

REAL / WHO classification

Phénotype B	Phénotype T
Indolents	
Lymphocytique	
Lymphoplasmocytaire	
Splénique zone marginaale	
MALT zone marginale	
Ganglionnaire zone marginale	
Folliculaire	
Manteau[a]	
Agressifs	
Diffus à grandes cellules	Anaplasique à grandes cellules T
	T périphérique
	T angio-immunoblastique
Très agressifs	
Burkitt	Lymphoblastique
Lymphoblastique	

40% of the NHL

Indolent Lymphomas



Staging, *treatment* ?

ANN ARBOR CLASSIFICATION

Modified Ann Arbor staging (Costwald).

Stade I	Atteinte d'une seule aire ganglionnaire
Stade IE	Atteinte associée à une atteinte de contiguïté localisée
Stade II	Atteinte de plusieurs aires ganglionnaires du même côté du diaphragme
Stade IIE	Atteinte associée à une atteinte de contiguïté localisée
Stade III	Atteinte ganglionnaire située de part et d'autre du diaphragme
Stade IIIS	Atteinte associée à une atteinte splénique
Stade IIIE	Atteinte associée à une atteinte de contiguïté localisée
Stade IIIES	Atteinte associée à une atteinte de contiguïté localisée et splénique
Stade IV	Atteinte viscérale extralymphatique avec ou sans atteinte ganglionnaire
A/B	Symptômes B = perte de poids > 10 %, fièvre, sueurs nocturnes

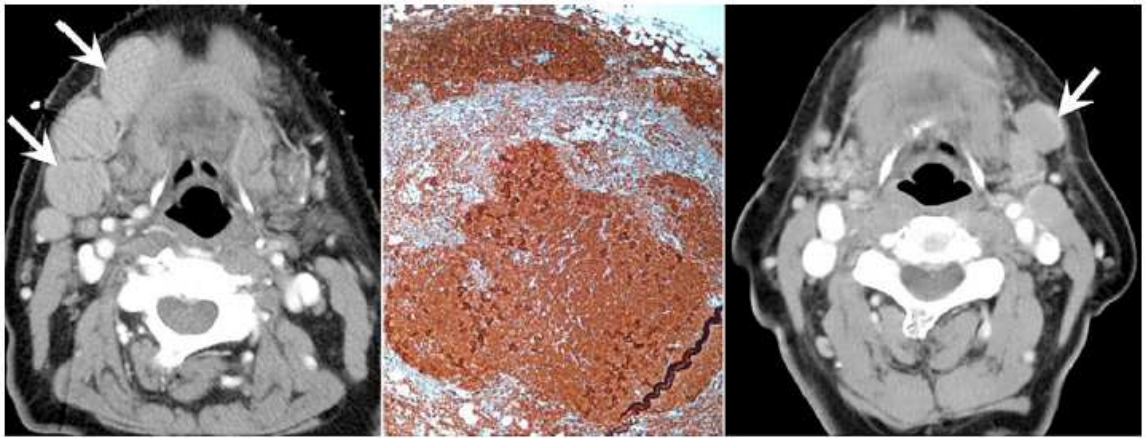
FLIPI (Follicular Lymphoma International Prognostic Index)

- age,
- stage of disease, performance status
- number of extranodal (other than the lymph nodes) sites,
- elevated lactate dehydrogenase (LDH),
- Hb

FLIPI 2

- Beta 2 microglobulin increased
- largest lymphnode diameter > 6 cm
- Bone marrow involvement
- Hb < 12
- Age > 60 yrs

Stage I-II



Stage I-II

Radiotherapy remains the treatment of choice for early stage low grade follicular lymphomas ?

Clinical Stage I - II

RADIOTHERAPY ALONE IS "STANDARD THERAPY" ?

Stanford, 177 pts, CS I - II, median f.up 7.7 aa,
RT alone (J Clin Oncol, 14: 1282, 1996)

	5 aa	10 aa	15 aa	20 aa
OS	82 %	64 %	44 %	35 %
RFS	55 %	*44 %*	*40 %*	*37 %*

"Radiotherapy remains the treatment of choice for early stage low grade follicular lymphomas"

Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone

*P. M. Petersen, **M. Gospodarowicz**, R. Tsang, M. Pintilie, W. Wells, D. Hodgson, A. Sun, M. Crump, B. Patterson and D. Bailey - **Princess Margaret Hospital, Toronto**, ON, Canada*

Journal of Clinical Oncology, 2004, Vol 22, No 14S (July 15 Supplement), 2004: 6521

Methods: **669 patients with stage I and II FL** were seen between 1968 and 1999. The records on these patients were systematically collected in an institutional database. The analysis focused on those initially treated with **involved-field RT alone (n=460).** Median RT dose was **35 Gy** (16.0 –47.5 Gy) given over 3–4 wks

Results: Median **follow-up duration was 12.5 yrs** (range 1.1 –32.2 yrs). The clinical stage was: stage IA: 337 pts, IIA: 115 pts, IB: 2 pts and IIB: 5 pts. Histology was: grade 1: 35%, 2: 38%, and 3: 27%. 25% presented with extranodal disease. 43% had Karnofsky performance status (KPS) of 100% · **OS at 5 and 10 yrs were 79% and 62% and DFS 56% and 41%,** respectively. Local disease control was excellent; 450 patients achieved CR and **only 5.5% relapsed in radiation fields**. Most relapses occurred in distant sites. The probability of relapse between 5 and 10 yrs was only 11%, and beyond 15 yrs, 2%.

Conclusions: **Involved-field radiation therapy provides long-term clinical disease control in over 40% of pts.** While 30% of all relapses occur after 5 years, risk of very late relapse is low. Long-term follow-up is recommended.

Clinical Radiology 65 (2010) 408–420

Contents lists available at ScienceDirect

Clinical Radiology

journal homepage: www.elsevierhealth.com/journals/crad

Pictorial Review

Follicular non-Hodgkin's lymphoma

D. Hayashi [a,*], J.C. Lee [b], B. Devenney-Cakir [a], S. Zaim [c], S. Ounadjela [c], P. Solal-Céligny [d], M. Juweid [e], A. Guermazi [a]

Cancer/Radiothérapie 13 (2009) 471–478

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Revue générale

Place de la radiothérapie dans le traiteme… …dgkiniens

Radiotherapy indications in non-Hodgkin ly…

L. Quero [a,*], C. Hennequin [a], P. Brice [b]

[a] Service de cancérologie-radiothérapie, hôpital Saint-Louis, AP-HP…

[b] Service d'hématologie, hôpital Saint-Louis, AP-HP, 1, avenue C…

According also to the more recent literature available, radiotherapy remains the treatment of choice for early stage low grade follicular lymphomas

Nodal Follicu…

The Role of Radiotherap… …and II

Frank Heinzelmann[1], Marianne E… …hard[2], Hellmut Ottinger[3], Michael Bamberg[1], Martin Weinmann[1]

Strahlenther Onkol 2010;186:191–6
DOI 10.1007/s00066-010-2090-9

Randomized trials F CT

According to the available randomized trials, radiotherapy remains the treatment of choice for early stage low grade follicular lymphomas"

1. RT vs RT + CVP ma
2. RT vs RT + CVP
3. RT vs RT + Vincristine, Streptonigrin, Prednisone (Cancer, 19
4. RT vs RT + CVP (RTO, 1984, 2: 301),
5. RT vs RT + CHOP (Cancer, 1993, 71:2342);
6. RT vs RT + Chlorambucil (Med Oncol, 1994, 11:19);

No survival advantage with the addition of CHT but some advantage in DFS for higher grade, more bulky CS I-II disease

Standard treatment options:

1. **Involved-field radiation therapy**

2. Watchful waiting
3. **Chemotherapy with radiation therapy**
4. **Extended (regional) radiation therapy** to cover adjacent prophylactic nodes
5. Rituximab, an anti-CD20 monoclonal antibody, either alone or in combination with chemotherapy and extrapolated from trials of patients with advanced-stage disease.
6. Other therapies as designated for patients with advanced-stage disease

Last Modified: *04/23/2010*

Management of nodal indolent (non marginal-zone) non-Hodgkin's lymphomas: practice guidelines from the Italian Society of Hematology, Italian Society of Experimental Hematology and Italian Group for Bone Marrow Transplantation

Giovanni Barosi
Angelo Carella
Mario Lazzarino
Monia Marchetti
Maurizio Martelli
Alessandro Rambaldi
Corrado Tarella
Umberto Vitolo
Pier Luigi Zinzani
Sante Tura

The Italian Society of Hematology (SIE) and the two affiliated societies (SIES and GITMO) commissioned a project to develop clinical practice guidelines for the treatment of nodal indolent non-Hodgkin's lymphomas (NHL). Key questions clinically relevant to the management of patients with nodal indolent NHL were formulated by an Advisory Committee and approved by an Expert Panel composed of eight senior hematologists. After a comprehensive, systematic review of the literature, the Expert Panel formulated therapy recommendations and graded them according to the supporting evidence. An explicit approach to consensus methodologies was used for evidence interpretation and for providing recommendations based on poor evidence. The Expert Panel formulated recommendations on when to start a lymphoma-specific therapy, which first-line therapy to choose and which therapy to adopt for patients with relapsed, refractory and transformed disease. Treatment deferral was recommended for patients with stage III-IV disease without systemic symptoms, high tumor burden, extranodal disease, cytopenia due to marrow involvement, leukemic phase, serous effusion and high lactate dehydrogenase levels. Patients with stage I-II disease and a low tumor burden should receive frontline external involved-field radiotherapy, while patients with a high tumor burden or a severe prognostic score should receive front-line chemotherapy plus involved-field radiotherapy. Younger patients with stage III-IV disease should receive front-line therapy with anthracycline- or fludarabine-based regimens combined with rituximab, while older patients who are candidates for treatment should receive single-agent alkylating therapy. By using a systematic literature review and an explicit approach to consensus among experts, recommendations for the key therapeutic decisions in patients with nodal indolent NHL are provided.

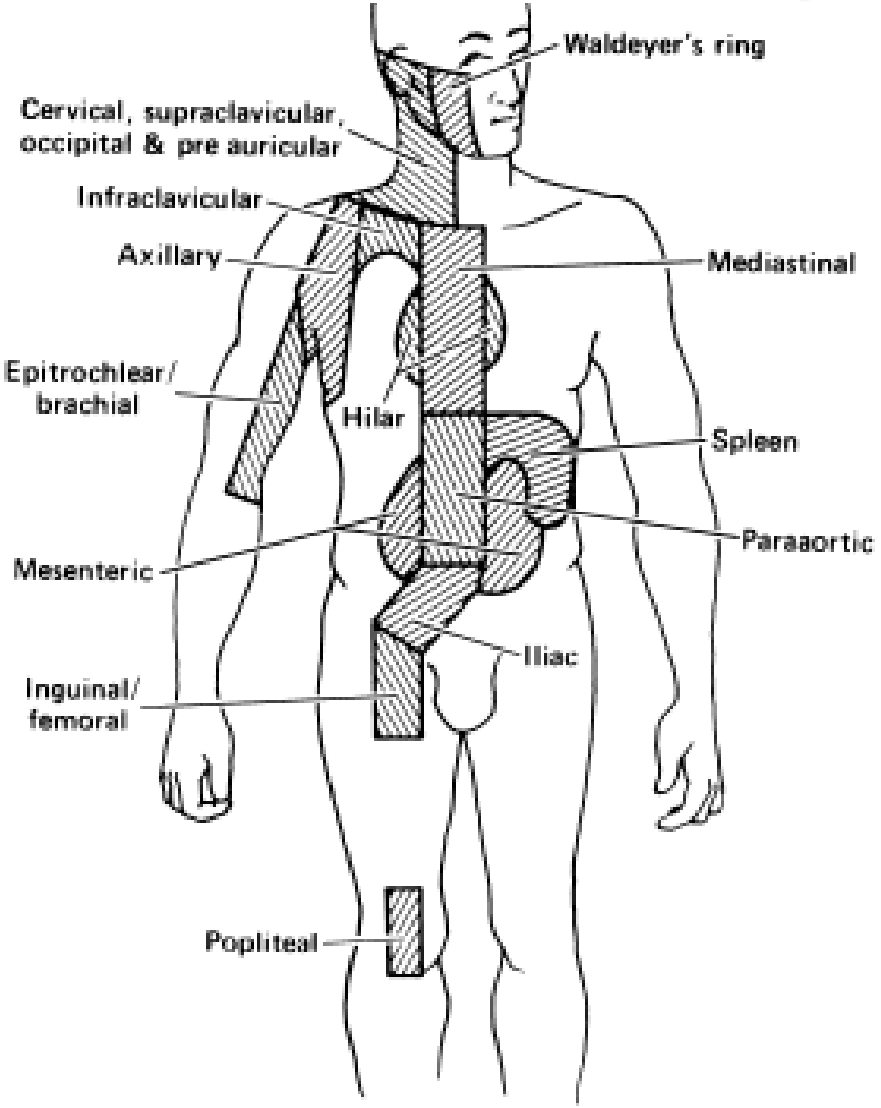
Key words: non-Hodgkin's lymphoma, clinical practice guidelines, systematic review, rituximab, chemotherapy

Haematologica 2005; 90:1236-1257

VOLUMES?

IFI (Involved Field)
irradiation of all involved sites

EFI (Extended Field)
IFI + adjacent regions of clinically noninvolved lymph nodes,
e.g.,supradiaphragmatic mantle field

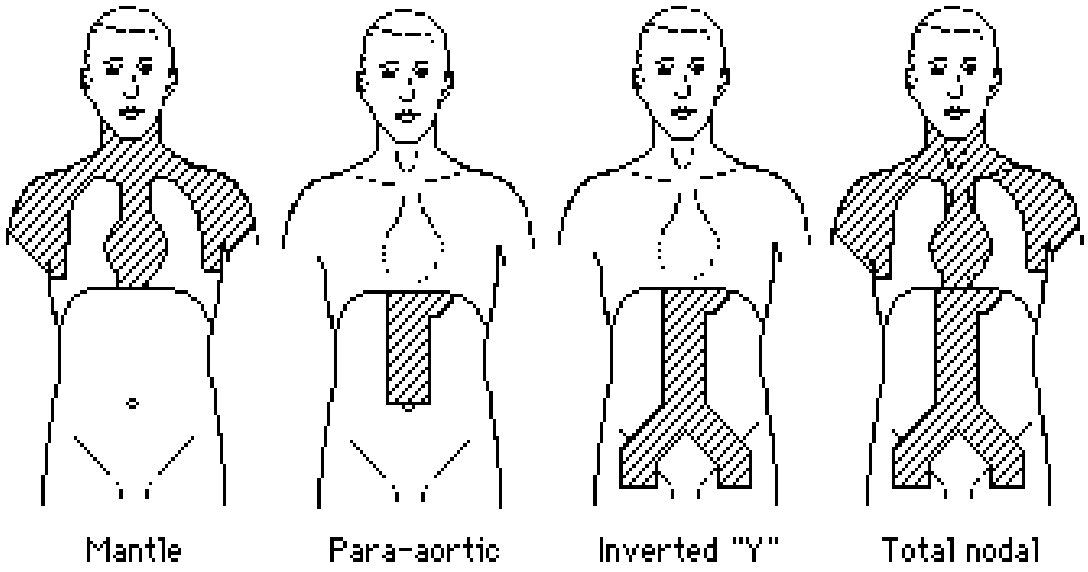


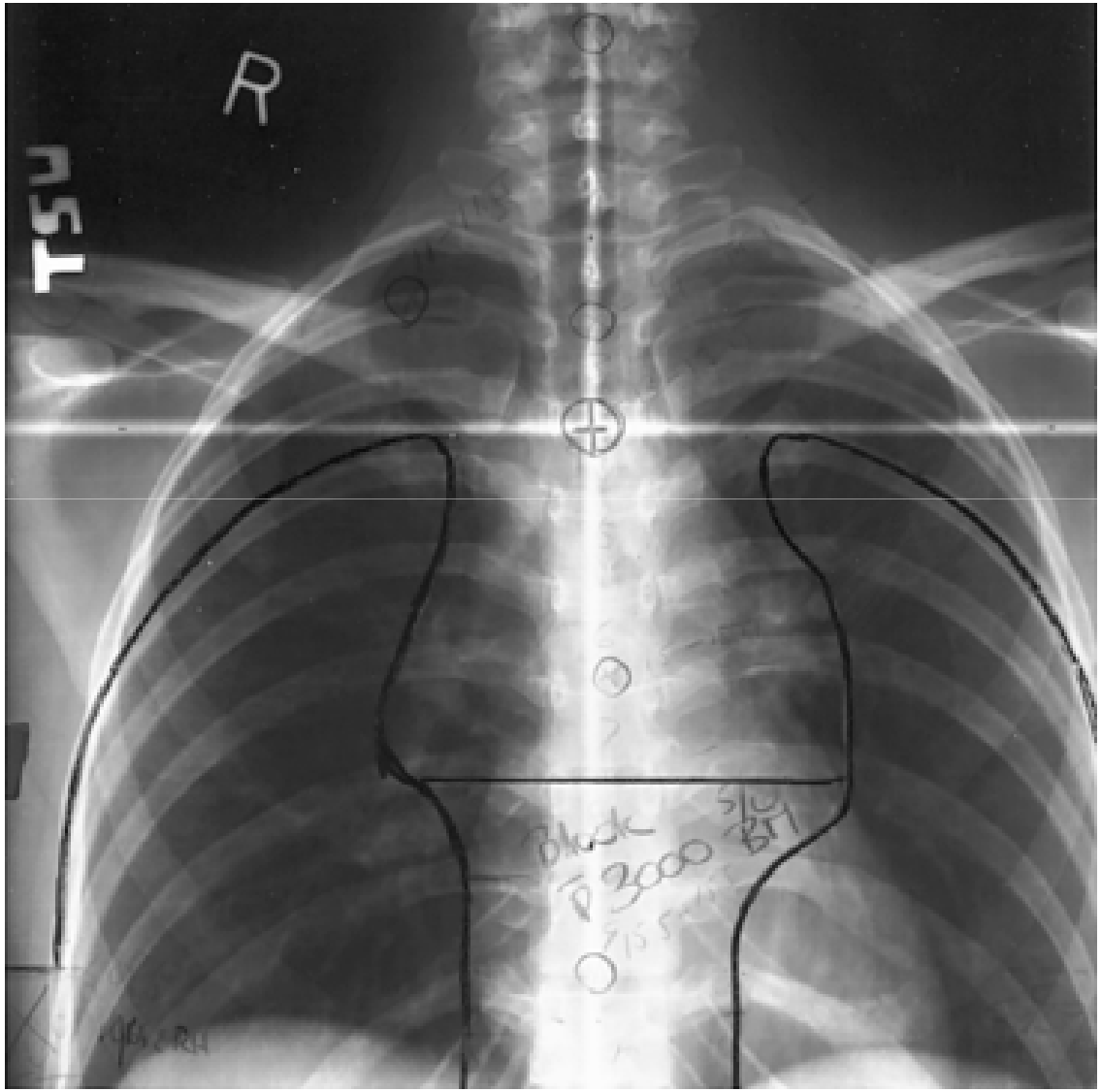
TNI (Total Nodal Irradiation) supradiaphragmatic mantle field + Infradiaphragmatic inverted Y including the spleen

TCLI (Total Central Lymphoid Irradiation) TNI + abdomen ± Waldeyer's ring

TLI (Total Lymphoid Irradiation) TNI + whole abdomen + Waldeyer ring

TBI Total Body Irradiation

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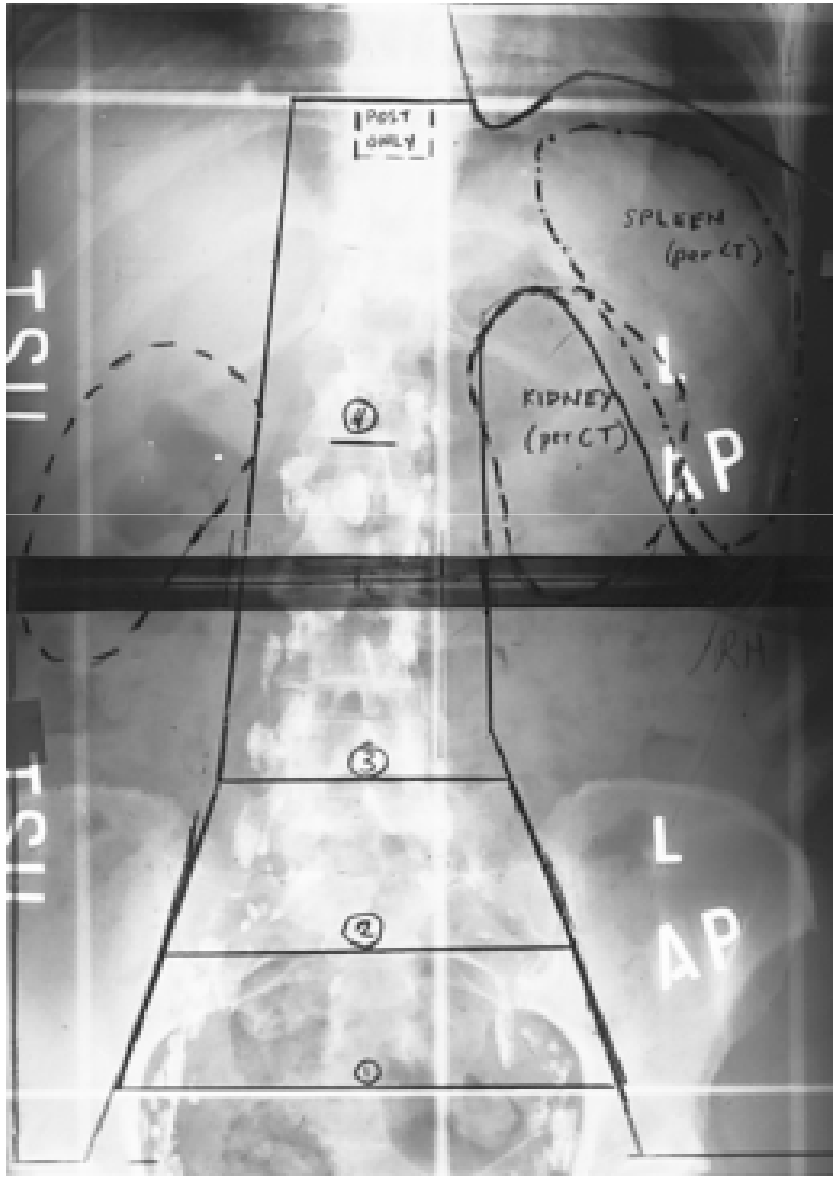
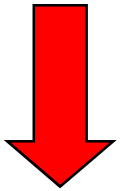

POST
ONLY
SPLEEN
(per CT)
KIDNEY
(per CT)
TSII
TSII
AP
L
AP

In patients with stage I and II nodal Follicular Lymphoma, **RT alone** with **different radiation techniques** (IF-EF-TNI-TLI) produces excellent disease control (95%)



At 15 years: **DFS** 40%

OS 93%

First author, year	Patients (n)	Technique Dose (Gy)	Follow-up (years)	PFS 5 years (%)	PFS 10 years (%)	PFS 15 years (%)	OS 5 years (%)	OS 10 years (%)	OS 15 years (%)
Paryani, 1983 [38]	124	IFI/EFI/TLI	5.5	62	54	42	84	68	40
Gospodarowicz, 1984 [11]	190	IFI/EFI 20–40	12	56	53	–	73	58	
McLaughlin, 1986 [30]	50	IF/EFI 30–40	4	37	–	–	73	–	–
Epelbaum, 1992 [8]	48	IFI/EFI 30–50	6.3	71	57	–	83	68	–
Vaughan Hudson, 1994 [56]	149	NS. 35	10	–	47	–	–	64	–
Pendlebury, 1995 [40]	58	IFI/EFI 40 (30–54)	NS.	59	43	–	93	79	–
MacManus, 1996 [28]	177	IFI/EFI/STLI/ TLI 35–50	7.7	55	44	40	82	64	44
Stuschke, 1997 [51]	117[a]	EFI/TCLI 26 + 10	5.7	71	59 (8 years)	–	86	86 (8 years)	–
Gospodarowicz, 1999 [12]	595	IFI 35	10.6	56	41	–	81	66	–
Kamath, 1999 [22]	72	IFI/EFI/TLI NS	NS	62	59	47	73	46	40
Voss, 2001 [58]	228	IFI 30–35	NS	94	82	75	87	62	52
Wilder, 2001 [59]	80	IFI/EFI 40 (26–50)	19	63	57	41	82	65	43
Ott, 2003 [37]	58[b]	IFI/EFI/TNI/ TLI 40 (26–50)	8.8	74	64	–	86	69	–
Neumann, 2003 [33]	116	IFI/EFI/TNI 35 (20–50)	4	62	48	–	76	51	–
Petersen, 2004 [41]	460	IFI 35 (16–47.5)	12.5	56	41	–	79	62	–
Guadagnolo, 2006 [14]	79	IFI/EFI 36.7 (30–42)	19	–	47	43	–	74	62
Eich, 2009 [5]	65[c]	IFI/EFI/TNI/ TLI 40 (26–46)	9.1	55	37	–	86	55	–

[a]including n = 17 with limited stage III; [b]including n = 10 with limited stage III; [c]including n = 8 with limited stage III

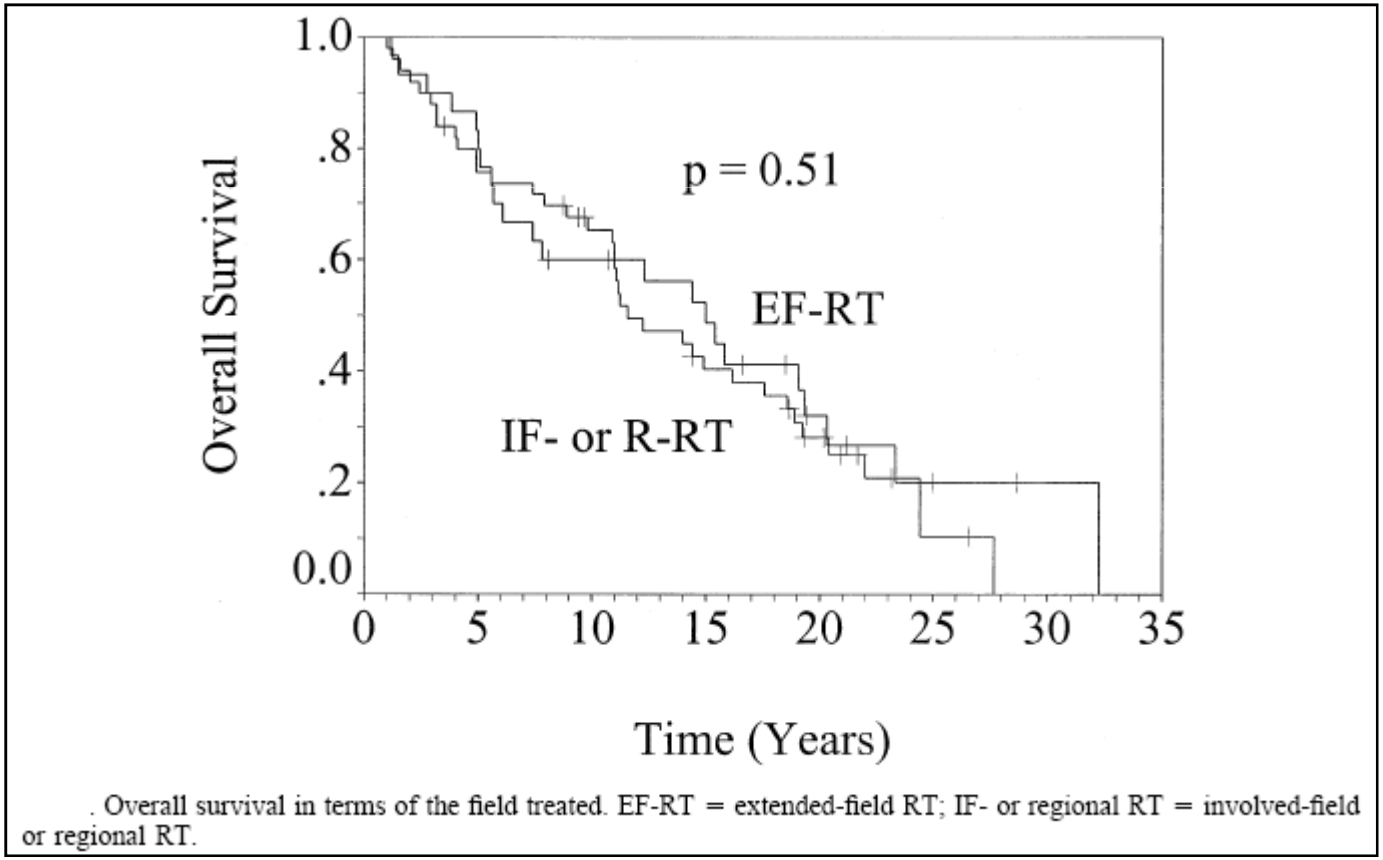
The main cause of failure is out of field recurrence: IF RT led to higher relapse rates.

Increased target volumes results in a reduction of relapse, but there is no significant effect on OS.

	FFR (10 aa)	OS (10 aa)
One side of the diaphragm	**36 %**	**60 %**
Both sides of the diaphragm	**67 %**	**70 %**
P	**0.0012**	**NS**

Stanford, 177 cases, RT alone

Wilder et al, 2001: a retrospective analysis that found no significant differences in cause specific survival and OS between patient treated with EF-RT as compared to patients treated with IF-RT.



. Overall survival in terms of the field treated. EF-RT = extended-field RT; IF- or regional RT = involved-field or regional RT.

Larger irradiation volumes might enhance

the risk of

acute toxic side effects (hematotoxicity, gastrointestinal toxicity)

late sequelae (organ toxicity, higher mortality rate, incidence of secondary malignancies)

DOSES?

…The international experience suggests that radiation doses of

25-30 Gy to subclinical disease

36-40 Gy to involved sites

are appropriate to control Follicular Lymphoma

(or not ?).

In the German multicenter phase II study, **TCLI** (total central lynphatic irradiation) and **EF-RT** were applied to a total dose of **26 Gy** (2 Gy single dose daily) with the exception of the whole abdomen irradiated to a total dose of 25.5 Gy (1.5 Gy single dose daily).

In addition, a **boost of 10 Gy was administered to macroscopically involved lymph nodes**.

More than **one third of all recurrences occurred within radiation fields** alone.

Multivariate Analysis of the Association of Patient Characteristics and Treatment Variables with Outcome

	End points			
	Survival	Relapse at any site	Lymph node recurrences	Lymph node in-field recurrences
Patient characteristics				
Age (yrs)	RR = 10 (2.8–36)	n.s.	n.s.	n.s.
>60 vs. ≤60	$P = 0.0005$			
Hemoglobin	RR = 3.4 (1.1–10)	n.s.	n.s.	n.s.
< vs. ≥ lower normal	$P = 0.02$			
Treatment variables				
Dose deviation > 20%	n.s.	RR = 5.3 (2.6–11)	RR = 7.0 (3.2–15)	RR = 14 (4.3–44)
Yes vs. no		$P < 0.0001$	$P < 0.0001$	$P < 0.0001$
Break of ≥7 days	n.s.	n.s.	n.s.	RR = 4.4 (1.5–13)
Yes vs. no				$P = 0.008$

RR: relative risk; n.s.: not significant.

Patients who received < 80% of prescribed dose had a significantly higher risk of in-field recurrence than those treated without dose violations. Dose deviations were mainly observed in regions with enlarged lymph nodes not subjected to boost therapy.

Stuschke et al, 1997. Results of a Prospective Multicenter Study

Guadagnolo et al, 2006: 106 patients with Stage I–II, Grade 1–2 follicular lymphoma treated with RT alone or radiation and chemotherapy (RT/CT)

The study reported a dose dependence for freedom from treatment failure

Univariate analyses for freedom from treatment failure and overall survival

	n	10-yr FFTF	15-yr FFTF	*p* Value	10-yr OS	15-yr OS	*p* Value
Entire cohort	106	46%	39%		75%	62%	
RT alone	79	47%	43%		74%	62%	
RT/CT	27	46%	31%	0.72	78%	57%	0.94
REG/IF RT alone	75	46%	42%	0.76	72%	59%	0.80
RT dose <36.7 Gy	54	35%	35%		74%	53%	
RT dose >36.7 Gy	52	58%	44%	0.03	81%	71%	0.23
Age <60 yr	68	47%	38%		84%	72%	
Age ≥60 yr	38	47%	47%	0.90	59%	43%	0.001

Abbreviations: CT = chemotherapy; FFTF = freedom from treatment failure; IF = involved field; OS = overall survival; REG = regional field; RT = radiation therapy.

Perspectives for CS I-II disease

The EORTC initiated a randomized phase III trial with **low dose TBI irradiation (1.5 Gy) and IFRT (26-40 Gy) versus IFRT (26-40 Gy)** alone based on promising Phase II data.

Richaud PM, Soubeyran P, Eghbali H, et al. Place of low-dose total body irradiation in the treatment of localized follicular non-Hodgkin's lymphoma: results of a pilot study. Int J Radiat Oncol Biol Phys 1998;40:387–90.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Rituximab and Involved Field Radiotherapy in Early Stage Follicular Lymphoma (MIR)

This study is currently recruiting participants.

Verified by University of Heidelberg, January 2010

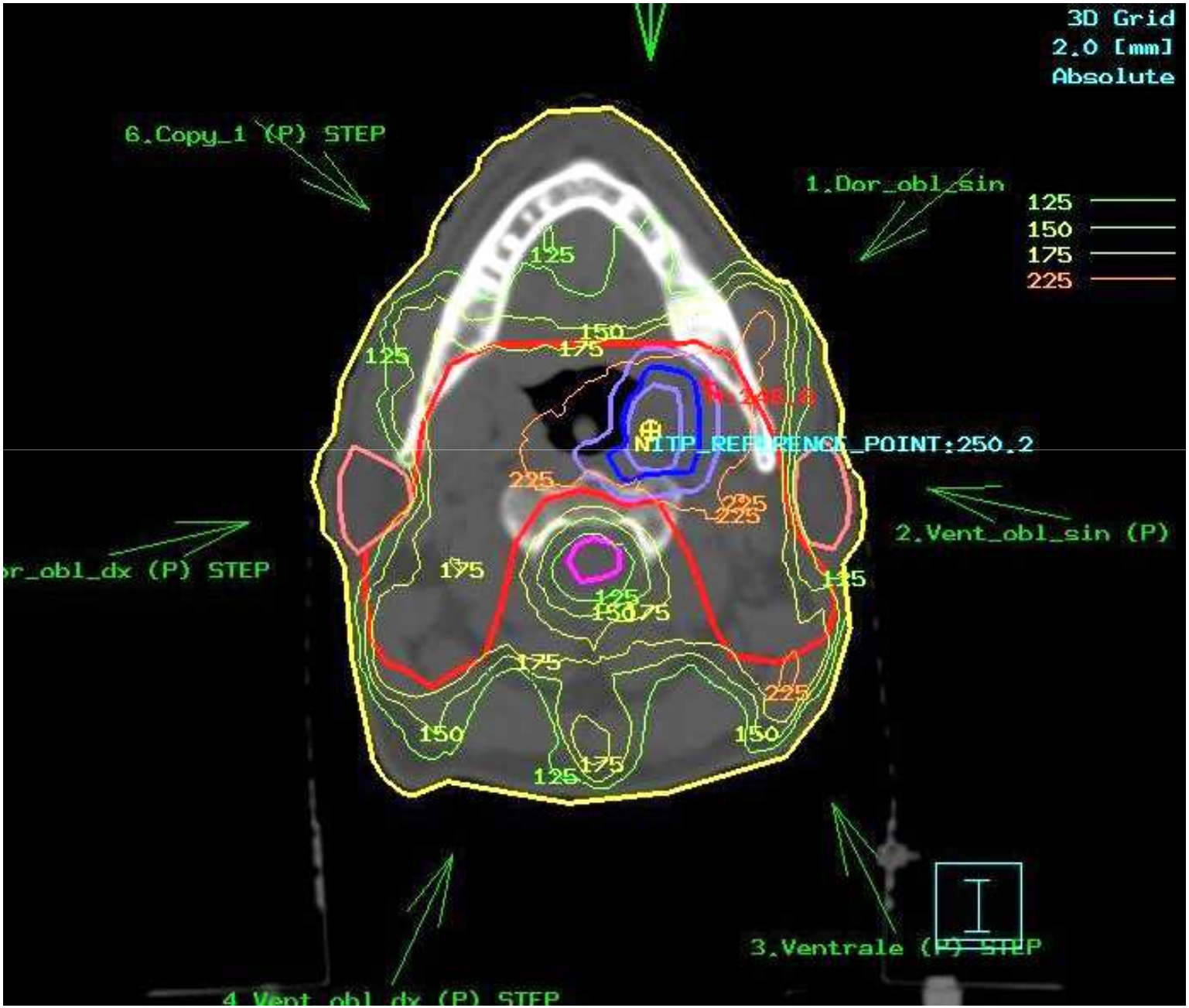
First Received: July 30, 2007 Last Updated: January 19, 2010

Sponsor:	University of Heidelberg
Collaborators:	**German Low Grade Lymphoma Study Group** **Roche Pharma AG**
Information provided by:	University of Heidelberg
ClinicalTrials.gov Identifier:	NCT00509184

Another option may be the use of **radioimmunotherapy**, but data for its relevance in limited-stage FL are not yet available.

In order to reduce morbidity in sensitive sites with enhanced risk of acute/late sequelae like the head and neck region/the abdomen, the use of **intensity-modulated therapy** to minimize salivary gland tissue and mucosa exposure might be beneficial.

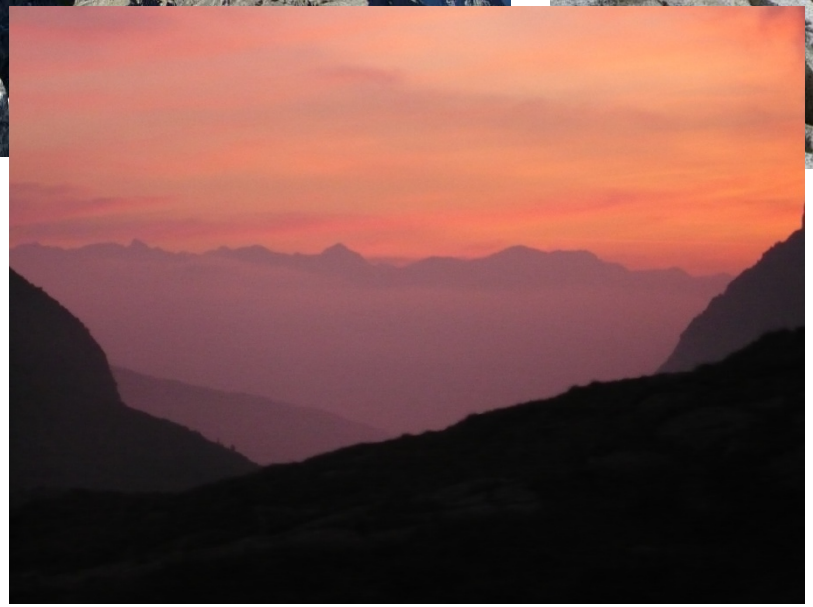
Parotid sparing ?



Stage III-IV

Radiotherapy has any role apart from palliation ?

The *scenario* …. Has many faces…



Treatment strategies include

- A watch-and-wait strategy
- Chemoimmunotherapy
- Monotherapy with rituximab
- Radioimmunotherapy (as an experimental approach)

Asymptomatic patients can be managed expectantly (**watch-and-wait strategy**)

In **symptomatic*** patients, **chemoimmunotherapy** is regarded as standard therapy.

* B-symptoms
Hematopietic impairment
Bulky disease
Rapid lymphoma progression

First author, year	Patients (n)	Therapy	Follow-up (months)	ORR (%)	CR (%)	Median EFS/TTF	OS (%)
Hiddemann, 2005 [33]	205	CHOP	18	90	17	29 months	90 (2 years)
	223	R-CHOP		96	20	NR	95 (2 years)
						p < 0.001	p = 0.016
Herold, 2007 [32]	96	MCP	47	75	25	26 months	74 (4 years)
	105	R-MCP		92	60	NR	87 (4 years)
						p < 0.0001	p = 0.0096
Marcus, 2008 [51]	159	CVP	53	57	10	15 months	77 (4 years)
	162	R-CVP		81	41	34 months	83 (4 years)
						p < 0.0001	p = 0.029
Salles, 2008 [69]	183	CHVP-I	60	85	34	35 months	79 (5 years)
	175	R-CHVP-I		94	63	NR	84 (5 years)
						p = 0.0004	p = 0.1552

Chemoimmunotherapy versus chemotherapy alone in previously untreated advanced follicular NH lymphomas

In symptomatic elderly patients with relevant comorbidities, **rituximab ± single-agent chemotherapy**, or **low-dose involved-field radiotherapy** might be appropriate.

For younger patients with chemoresistant/relapsed disease, **allogeneic HSCT** might be considered, since advances in supportive care and better patient selection have resulted in improved outcomes.

Which role for Radiotherapy?

In the pre - rituximab era, the use of RT (30–40 Gy) after chemotherapy induction significantly improved DFS/OS compared to chemotherapy alone (68%/89% vs. 41%/71%) in the first-line treatment of patients with bulky stage III/IV FL, possibly implying cure in selected patients

(Aviles etal, 2002): between 1981 and 1995, 469 patients with follicular lymphoma were treated with combined chemotherapy, mostly anthracycline-based regimens; patients who achieved complete response were randomly assigned either to receive adjuvant radiotherapy to sites or to nodal bulky disease or not (control group)

DFS

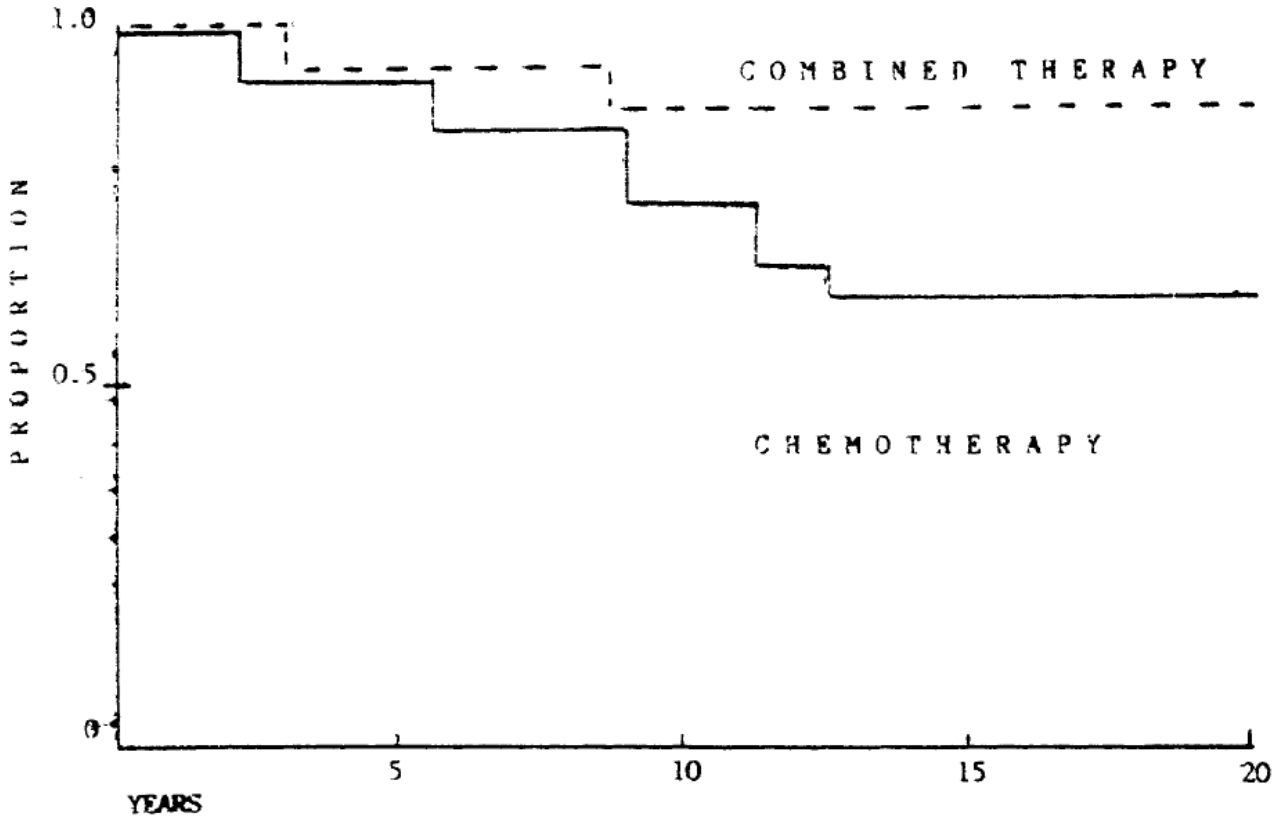
CHT 41%

CHT+RT 68%

OS

CHT 71%

CHT+RT 89%



Overall survival.

Currently, the role of RT is poorly defined, since novel strategies like chemo- and radioimmunotherapy lead to substantially improved PFS/OS rates with tolerable toxicity in the first-line treatment of advanced FL.

Ganem G, Lambin P, Socie G, et al. Potential role for low dose limited-field radiation therapy (2 × 2 grays) in advanced low-grade non-Hodgkin's lymphomas. Hematol Oncol 1994;12:1–8.

Girinsky T, Guillot-Vals D, Koscielny S, et al. A high and sustained response rate in refractory or relapsing low-grade lymphoma masses after low-dose radiation: analysis of predictive parameters of response to treatment. Int J Radiat Oncol Biol Phys 2001;51:148–55.

Haas RL, Poortmans P, de Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. J Clin Oncol 2003;21:2474–80.

Ng M, Wirth A, Ryan G, et al. Value of low-dose 2 × 2 Gy palliative radiotherapy in advanced low-grade non-Hodgkin's lymphoma. Australas Radiol 2006;50:222–7.

In the palliative setting, low-dose involved-field RT (4 Gy given in two fractions) has been reported to provide a long-lasting response with minimal side effects

In case of failure of low-dose RT, full-dose involved-field RT (30–40 Gy) plays a key role in providing symptom relief and local control.

Currently, nontoxic involved-field RT (2 × 2 Gy) is compared with standard chemotherapy chlorambucil in the phase III randomized HOVON 47/EORTC 20013 trial in previously untreated patients

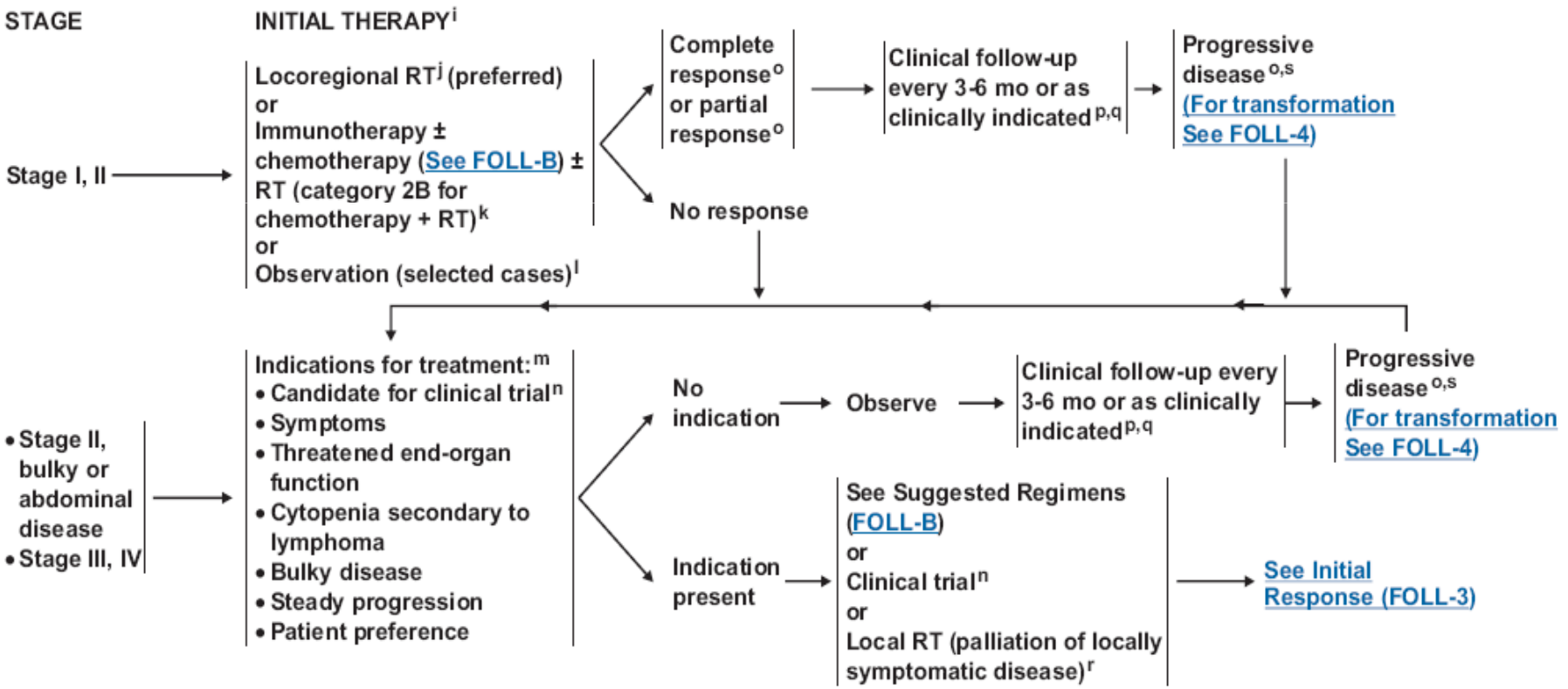
Haas RL, Girinsky T. HOVON 47/EORTC 20013: chlorambucil vs 2×2 Gy involved field radiotherapy in stage III/IV previously untreated follicular lymphoma patients. Ann Hematol 2003;82:458–62.

In the palliative setting, low-dose involved-field irradiation constitutes an effective treatment option in order to control local symptoms with potential long-lasting response.

NCCN® Practice Guidelines in Oncology – v.1.2010

Follicular Lymphoma (grade 1-2)

Guidelines Index
NHL Table of Contents
Staging, Discussion, References



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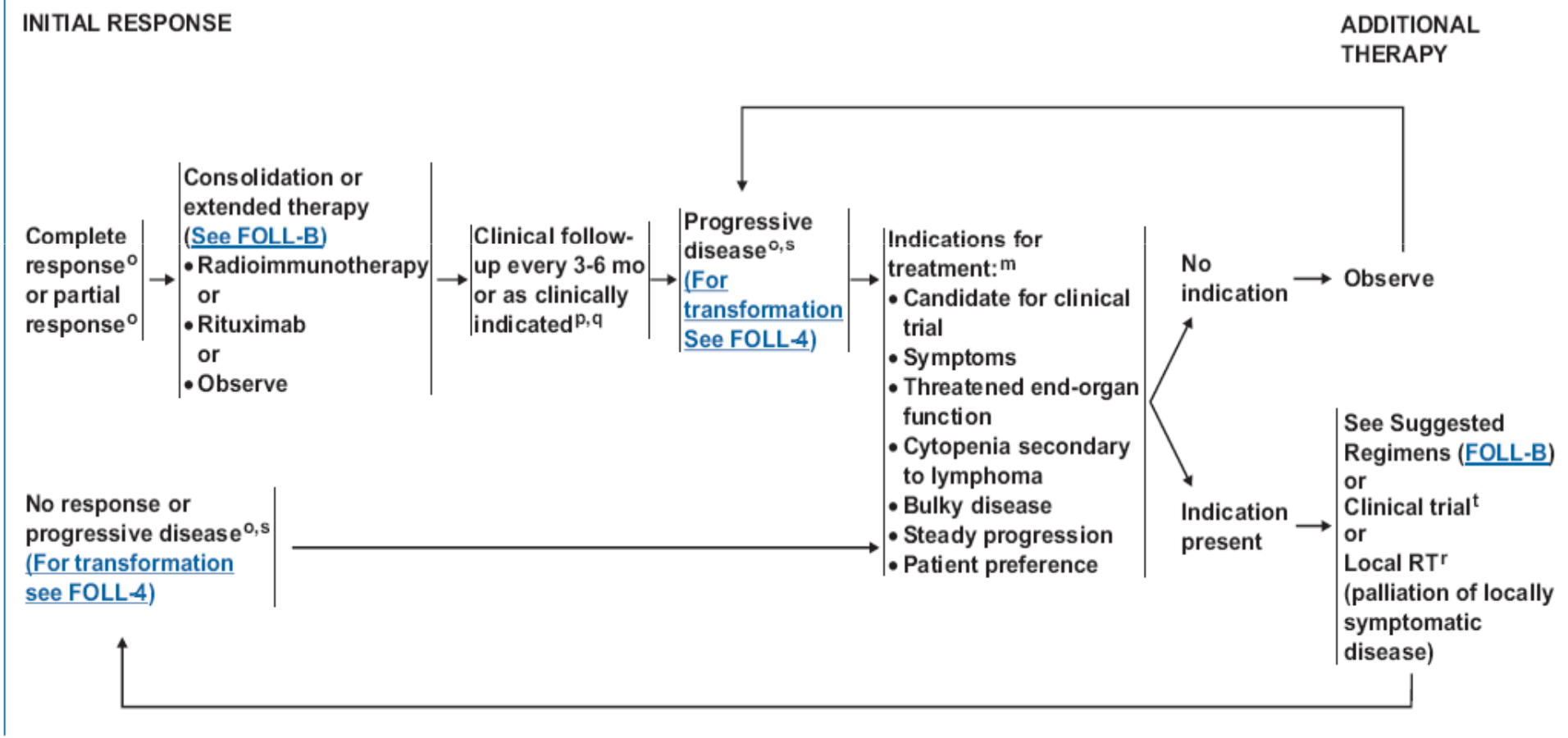
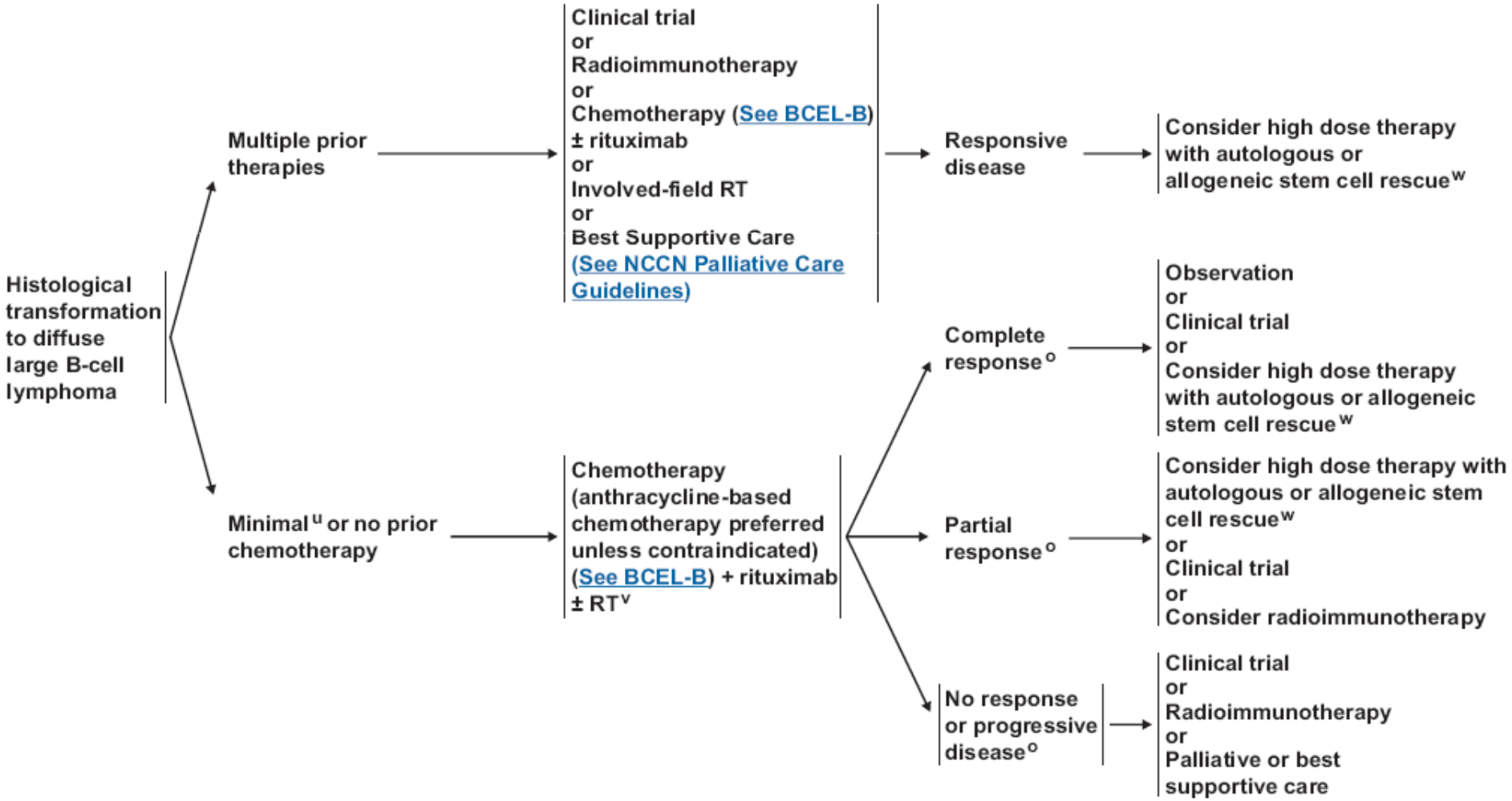


HISTOLOGICAL TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA



FOLL-B

UNIVERSITA' DEGLI STUDI DI BRESCIA
Facoltà di Medicina e Chirurgia

NCCN® Practice Guidelines in Oncology – v.1.2010

Follicular Lymphoma

Guidelines Index
NHL Table of Contents
Staging, Discussion, References

SUGGESTED TREATMENT REGIMENS[a,b]
(in alphabetical order)

First-line Therapy[c,d]
- Bendamustine + rituximab
- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) + rituximab (category 1)
- CVP (cyclophosphamide, vincristine, prednisone) + rituximab (category 1)
- Fludarabine + rituximab
- FND (fludarabine, mitoxantrone, dexamethasone) + rituximab
- Radioimmunotherapy[e,f] (category 2B)
- Rituximab

First-line Therapy for Elderly or Infirm (if none of the above are tolerable)
- Radioimmunotherapy
- Rituximab, preferred
- Single agent alkylators (eg, chlorambucil or cyclophosphamide)

For patients with locally bulky or symptomatic disease, consider IFRT 4-30 Gy ± additional systemic therapy.

First-line Consolidation or Extended Dosing
- Chemotherapy followed by radioimmunotherapy[e,f,g] (category 1)
- Rituximab maintenance[h,i,j] (category 2B) [It is strongly recommended this treatment be on a prospective clinical study.]

Second-line and Subsequent Therapy
- Chemoimmunotherapy (as in first-line therapy)
- FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) (category 1)
- High dose therapy with autologous stem cell rescue[k]
- High dose therapy with allogeneic stem cell rescue, for highly selected patients[l]
- Radioimmunotherapy[g,h] (category 1)
- See Second-line Therapy for DLBCL (BCEL-C 1 of 3)[m]

Second-line Extended Dosing
- Rituximab maintenance[j] (category 1)

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clinical recommendations

Annals of Oncology 20 (Supplement 4): iv119–iv120, 2009
doi:10.1093/annonc/mdp148

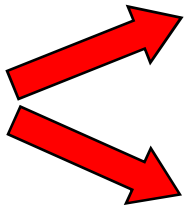
Newly diagnosed and relapsed follicular lymphoma: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

M. Dreyling
On behalf of the ESMO Guidelines Working Group*
Department of Medicine III, University Hospital Grosshadern, LMU Munich, Germany

First line, stage I–II → IFRT or EFRT (30–40 Gy)

In patients with large tumor burden systemic therapy as indicated for advanced stages may be applied prior to optional radiation.

Stage III–IV, induction



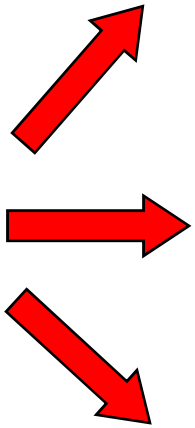
Observation

Chemotherapy
only upon the occurrence of symptoms including B-symptoms, hematopoietic impairment, bulky disease or rapid lymphoma progression

• If complete remission and long progression-free survival is to be achieved, **rituximab** in combination with chemotherapy should be applied.

• Antibody monotherapy (rituximab, radioimmunotherapy) or single agent alkylators remain an alternative in patients with low risk profile or contraindications for a more intensive immuno-chemotherapy

Stage III–IV, consolidation



Rituximab (first line)

Radioimmunotherapy

Myeloablative radiochemotherapy followed by autologous stem cell transplantation

Relapsed disease

repeat biopsy to rule out
a secondary transformation
into aggressive lymphoma

Early relapses (<12 months), a **non cross-resistant scheme** should be preferred (e.g. fludarabine after CHOP).

Rituximab should be added if the previous antibody-containing scheme achieved a >12 months duration of remission→ prolongs PFS

Myeloablative consolidation followed by autologous stem cell transplantation → prolongs PFS & OS

Radio-immunotherapy (preferable as consolidation) and potentially curative **allogenic stem cell transplantation** may be discussed

MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996;14:1282–90.

Wilder RB, Jones D, Tucker SL, et al. Long-term results with radiotherapy for stage I–II follicular lymphomas. Int J Radiat Oncol Biol Phys 2001;51:1219–27.

Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, grade 1–2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2006;64:928–34.

Stuschke M, Hoederath A, Sack H, et al. Extended field and total central lymphatic radiotherapy in the treatment of early stage lymph node centroblastic-centrocytic lymphomas: results of a prospective multicenter study. Study Group NHL-frühe Stadien. Cancer 1997;80:2273–84.

Aviles A, Delgado S, Fernandez R, et al. Combined therapy in advanced stages (III and IV) of follicular lymphoma increases the possibility of cure: results of a large controlled clinical trial. Eur J Haematol 2002;68:144–9.

Additional CHT mostly failed to improve treatment results achieved with RT alone

Randomized trials with small patients numbers in the 1970s/1980s and recently published data from non randomized trials did not confer a definitive OS advantage with additional adjuvant CHT

Carde P, Burgers JM, van Glabbeke M, et al. Combined radiotherapy-chemotherapy for early stages non-Hodgkin's lymphoma: the 1975–1980 EORTC controlled lymphoma trial. Radiother Oncol 1984;2:301–12.

Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, grade 1–2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2006;64:928–34.

Kelsey SM, Newland AC, Hudson GV, et al. A British National Lymphoma Investigation randomised trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkin's lymphoma. Med Oncol 1994;11:19–25.

Monfardini S, Banfi A, Bonadonna G, et al. Improved five year survival after combined radiotherapy-chemotherapy for stage I–II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1980;6:125–34.

Nissen NI, Ersboll J, Hansen HS, et al. A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I–II non-Hodgkin's lymphomas. Cancer 1983;52:1–7.

Yahalom J, Varsos G, Fuks Z, et al. Adjuvant cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Results of a prospective randomized study. Cancer 1993;71:2342–50.

The use of autologous hematopoietic stem cell transplantation (HSCT) for patients in first remission or chemosensitive relapse prolongs progression-free survival while the effect on overall survival remains unclear compared to standard chemotherapy.

However, long-term results are flawed by high relapse rates and risk of secondary malignancies.

In patients with relapsed/chemoresistant disease, allogeneic HSCT constitutes the only curative approach but is associated with high treatment-related mortality.