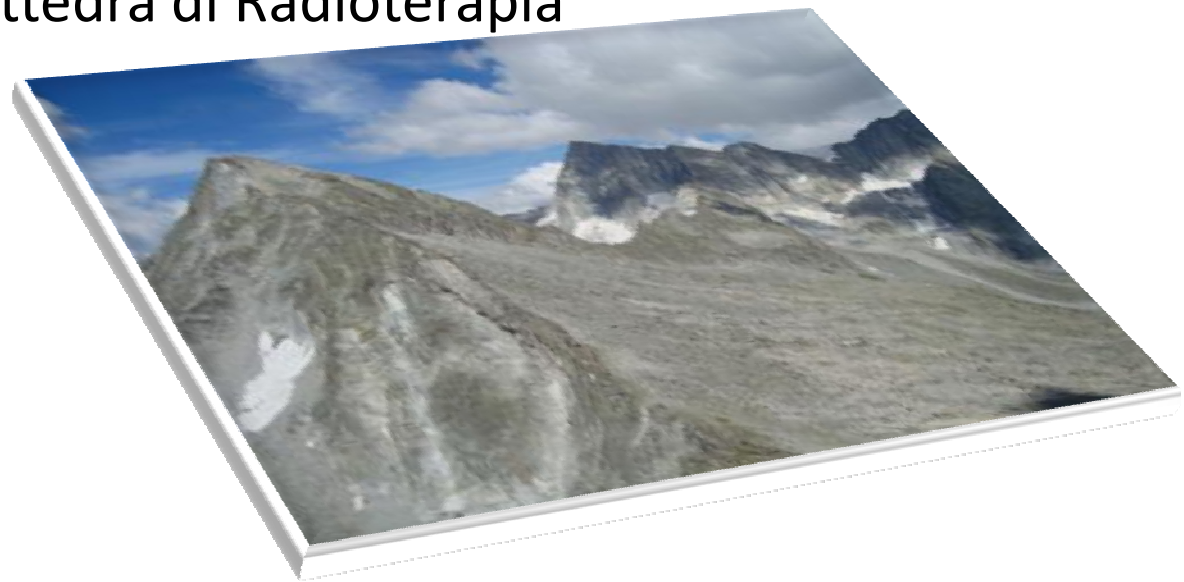
UNIVERSITA' DEGLI STUDI DI BRESCIA

Radiotherapy in Non Hodgkin Lymphoma: dose

Michela Buglione di Monale
Cattedra di Radioterapia



Brescia -14 Maggio 2010

Radiotherapy in NHL's

- dose needed to control disease?

  nodal DLCL stage I-II vs III-IV
  extranodal DLCL

- dose-related toxicity?

Radiosensibility: where do we stand with lymphomas?
We all know since many years that...

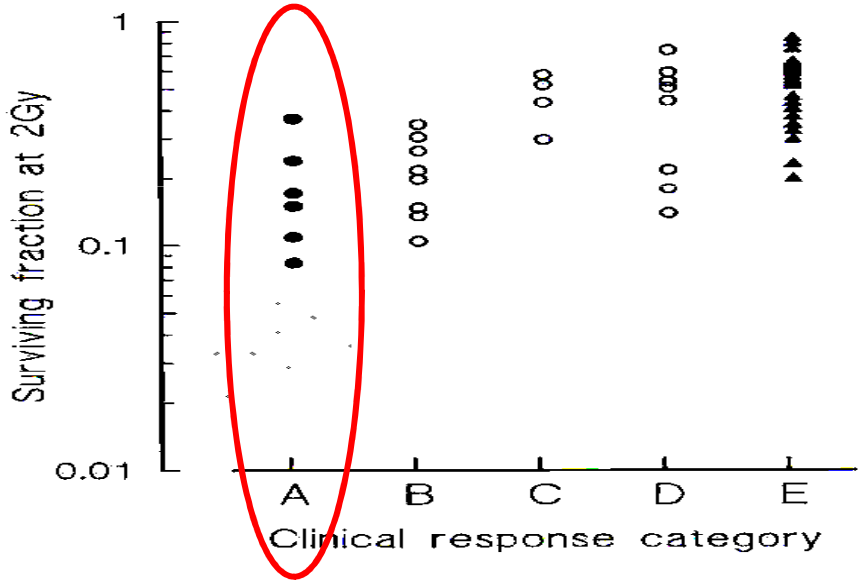


Figure 17.6 *Surviving fraction at 2 Gy for 51 human tumour cell lines, arranged in five categories of clinical radioresponsiveness. From Deacon* et al. *(1984), with permission.*

A: LINFOMA, MIELOMA, NEUROBLASTOMA
B: MEDULLOBLASTOMA, SCLC
C: CA MAMMARIO, VESCICALE, CERVICE UTERINA
D: CA PANCREAS, COLORETTALE, NSCLC
E: MELANOMA, OSTEOSARCOMA, GLIOBLASTOMA

Stage I-II DLBC lymphoma in the clinic

First question

Is the radiotherapy dose needed to control disease equal to zero? (null hypotesis)

Second question

If not, what dose is needed to control disease?

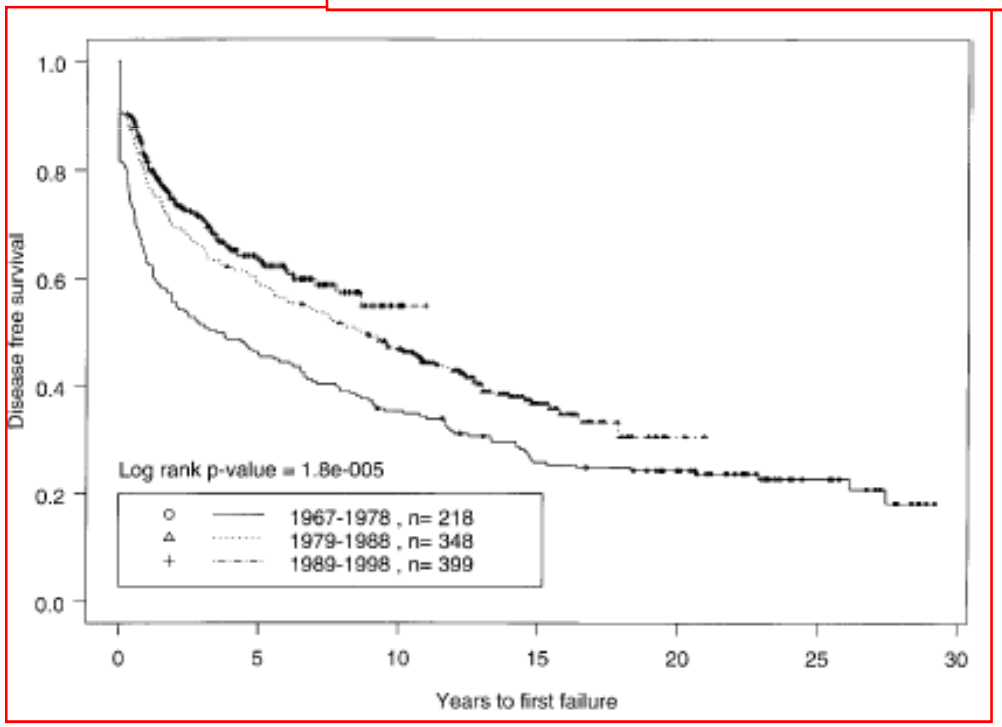
I-II DLBC NHL

Radiotherapy is useful ….. But not alone..

1967-1998

R.W. Tsang · M.K. Gospodarowicz

Management of localized (stage I and II) clinically aggressive lymphomas



Ann Hematol (2001) 80:B66–B72

Radiotherapy in I-II DLBC NHL

combined modality treatment – randomized trials					
	n° PTS	Stage	treat	FFP/RFS	OS
SWOG 8736 Miller (NEJM 1998)	401	I or IEA (b/non b) II or IIEA (non b)	Cx3 →IFRT vs CHOP x8	77% vs 68%	92% vs 72%
ECOG 1484 Horning (JCO 2004)	215	I (b or EN only) II (b/non b)	Cx8 if CR →RT vs no RT if PR → RT	70% 53% 63%	79% 67% 69%
GELA LNH 93-1 Reyes (NEJM 2005)	647	Age <60 (10%b; 50%EN; no AA IPI factors)	Intensive CHT alone vs Cx3 → RT	82% 74%	90% 81%
GELA LNH 93-4 Bonnet (JCO 2007)	576	Age >60 (8%b; 56% EN; no AA IPI factors)	Cx4 → RT vs Cx4	66% vs 68%	72% vs 68%

Radiotherapy in I-II DLBC NHL

combined modality treatment – randomized trials		
	treat	**dose**
SWOG 8736 Miller (NEJM 1998)	Cx3 →IFRT vs CHOP x8	**40-55 Gy** (no stated criteria ; probably PR pts had >40Gy; the n° of pts with PR is unknown)
ECOG 1484 Horning (JCO 2004)	Cx8 if CR →RT vs no RT if PR → RT	CR → **30 Gy** PR → **40 Gy** (outcome similar for CR pts after CHT alone)
GELA LNH 93-1 Reyes (NEJM 2005)	Intensive CHT alone vs Cx3 → RT	Planned dose **40 Gy** Given dose **36-40 Gy** (lower; no decision criteria; 26 pts were not given RT)
GELA LNH 93-4 Bonnet (JCO 2007)	Cx4 → RT vs Cx4	Planned **40 Gy** Given dose **36-44 Gy** (39 pts were not given RT)

Radiotherapy is therefore an essential part of integrated treatment, but data reported on RT doses are often poor quality data.... Especially when the reporting author is not a radiation oncologist

!

QUALITY OF RADIOTHERAPY REPORTING IN RANDOMIZED CONTROLLED TRIALS OF HODGKIN'S LYMPHOMA AND NON-HODGKIN'S LYMPHOMA: A SYSTEMATIC REVIEW

JUSTIN E. BEKELMAN, M.D.,* AND JOACHIM YAHALOM, M.D.*

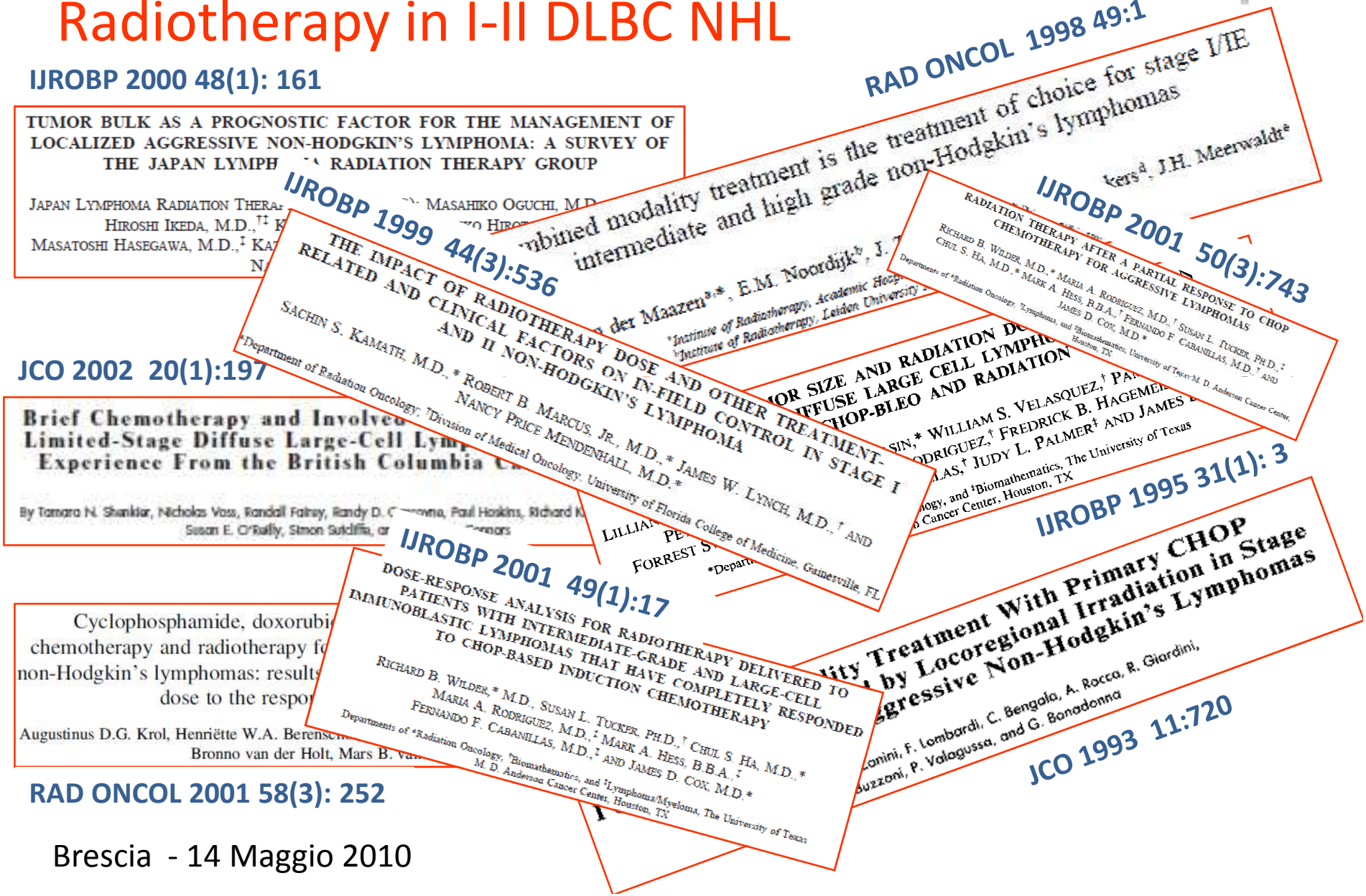
	n/tot	%
Dose	57/61	89
Dose/fraction	39/61	64
Point of prescription	13/61	21

Radiation oncology author		
yes	35	66
no	26	19
	p	<0.001

IJROBP (2009) 73: 492

UNIVERSITA' DEGLI STUDI DI BRESCIA

Radiotherapy in I-II DLBC NHL



Brescia - 14 Maggio 2010

Radiotherapy in I-II DLBC NHL

Dose in different trials							
Center	n° pts	stage	**dose**	CR	5yDSS	5y PFS	note
JLRTG (IJROBP '00)	787	I-II; EN	**20-70 Gy**	nn	nn	69%	**>=40 Gy** no better EFS; no ↑ in bulky
BCCA (JCO '00)	308	I-IIA; EN	**10x3Gy; 20x1.75Gy**	97%	87%	81%	Survival is IPI strongly related
Holland (rad oncol '01)	128	I; EN	**CR 26 Gy PR 40 Gy**	91%	nn	74%	no better outcome in CR pts with **40 Gy**;
MDACC (IJROBP '95)	190	I-II-III ; EN	**30-40 Gy + 10-15 Gy**	nn	62%	58%	Local control 97% **>=40** and 83% **30-40 Gy**; 88% and 71% when **bulky**
Holland (rad oncol '98)	94	I A e B; EN	**36 Gy (6-8) 40 Gy (3-4)**	nn	89%	83%	**RT dose** varying with **CHT cycles N°**
INT (JCO '93)	183	I-II (no> 3)	**40-44 Gy**	98%	nn	83%	**36 Gy** on uninvolv regions
Univ of Florida (IJROBP '99)	213	I-II	**30-50 Gy**	nn	nn	66%	**>40Gy** → Better outcome in pts with bulky disease and PR
MDACC (IJROBP '01)	172	I-II; EN	**30-50.4Gy (BED 29-51 Gy)**	Nn	nn	nn	BED **29-39 Gy** → poorer local control in **bulky**;

Radiotherapy in I-II DLBC NHL

combined modality treatment – randomized trials					Dose in different trials						
	n° PTS	Stage	treat	FFP /RF	n° pts	stage	**dose**	CR	5yDSS	5y PFS	note
SWOG 8736 Miller (NEJM 1998)	401	I or IEA (b/n							nn	69%	>=40 Gy no better EFS; no in b
										81%	Survival IPI strongly related
ECOG 1484 Horning (JCO 2004)											on sig trend better tcome in 40 Gy CR;
											ontrol 97% d 83% 30-40 % and 71% hen b
GELA LNH 93-1 R (NEJM 2005)											
											Gy on uninvolv regions
GELA LNH 93-4 Bonnet (JCO 2007)		no A factors)					Gy)	Nn	nn	nn	>40Gy →Better outcome in pts with b disease and PR
											BED 29-39 Gy →poorer local control in b;

NO RANDOMIZED TRIALS TO EVALUATE THE DOSE AVAILABLE.

- **=> 40 Gy is probably better;**
- **some authors suggest 30-36 Gy after 6-8 CHOP is enough..but: do we need > 6 CHOP? Patient selection?**
- **in patients in RP or with CR but bulky disease a 40-46 Gy dose is warranted**

Stage III-IV DLBC lymphoma in the clinic

First question

Is the radiotherapy dose needed to control disease equal to zero? (null hypotesis)

Second question

If not, what dose is needed to control disease?

Radiotherapy dose should be > 0 ?

Probably YES!

Dose in different trials							
Centre	n° pts	stage	**dose**	CR	5yDSS	5y PFS	note
Aviles IJROBP 1994	341 in CR after CHT	IV b	**In CR pts 40 Gy vs no RT**			82% vs 55%	**5 y OS** 87% vs 66%
Schlernbach (MDACC) IJROBP 2000	59	III-IV	**CHOP → 30-50 Gy vs no RT**	89% vs 52%		85% vs 51% *	• LC 89% vs 33% in **>4cm*** • Small and bulky lesion • no diff in OS
Aviles MEDICAL ONCOL 2005	106	III-IV	**In PR after CHT 30 Gy Vs no RT**			86% vs 32%	**10 y OS** 89% vs 68%
Moser IJROBP 2006	238 (114 in PR)	III-IV	**In PR after CHT 40 Gy vs 2° line CHT (or ASCT)**	61% Vs 21% (75%)		Better with RT	**5 y OS after CR** 61% vs 32% (68%)

Are there subgroups getting a larger benefit from RT……?

May be the bulky cases ?!

Dose in different trials							
Centre	n° pts	stage	**dose**	CR	5yDSS	5y PFS	note
Ferreri ONCOLOGY 2000	94	III-IV in CR after CHT	**30-46 Gy vs no RT (medical decision)**			41 vs 18 months	**•bulky >10 cm** • OS and PFS improved in CMT in **low** risk pts • **>=36 Gy** better OS
Rube (NHLB-94) ANNAL HEMATOL 2001	366 (in CR after CHT) pts; **84 (b)**		**CHOP vs CHOP + RT (bulky pts 36 Gy)**			74% (3 y)	**• bulky >7.5 cm** • No differences in DFS in bulky and no bulky • rt riduces the heavy of bulky prognostic factor
Krieger ONKOLOGIE 2001	71	49 St III-IV	**MACOP B→ In bulky CR pts 40 Gy**			42%	**• bulky =>5 cm** • out of field relapse • RT not well defined
Bartlett (Stanford) CANCER 1993	47	27 st III-IV	**MACOP B→ In bulky CR pts 35-40 Gy**				**• bulky >=8 cm** • better OS and FFP • difficult to define the role of RT dose

Radiotherapy plays (possibly) a role…… but..

Dose in different trials						
Centre	n° pts	stage	dose	CR	yDSS	5y PFS
Aviles IJROBP 1994	341	IV b	**In CR pts 40 Gy vs**			82% vs 55%
Schlern bach IJRO 2						
A ML ONCO 2005						86% vs
Moser IJROBP 2006	238	III-IV	**40 Gy vs 2° line CHT (or ASCT)**	61% Vs 21% (75%)		

Dose in different trials							
Centre	n° pts	stage	dose	CR	5yDSS	5y PFS	note
Ferreri ONCOLOGY 2000	94	III-IV	**Gy (n deci**				• OS and PFS improved in CMT in **low** risk pts • **>=36 Gy** better OS
Ru (N	84	III-IV	**CH CH (bu**				No differences OS in bulky nd no bulky
			MACOP B→ In b CR pts 40 Gy			42%	• **b= >5 cm** • out of field relapse • RT not well defined
Bartlett (Stanford) CANCER 1993	47	27 st III-IV	**MACOP B→ In b CR pts 35-40 Gy**				• **b>=8 cm** • better OS and FFP • difficult to define the role of RT dose

Different patients, different bulky definition

Different CHT regimen

Different RT doses

UNIVERSITA' DEGLI STUDI DI BRESCIA

Radiotherapy in III-IV DLBC NHL

Dose in different trials				
Centre	n° pts	stage	dose	CR
Aviles IJROBP 1994	341	IV b	**In CR pts 40 Gy**	
Schlernbach IJROBP 2000	59	……		
Aviles MEDICAL ONCOL 2005	106	……		
Moser IJROBP 2006	238	…….	**2° line ASCT**	

… trials		
5yD SS	5y PFS	note
		• OS and PFS improved in CMT in **low** risk pts • **>=36 Gy** better OS
		• No differences in OS in bulky and no bulky
		• **b= >5 cm** • out of field relapse • RT not well defined
		• **b>=8 cm** • better OS and FFP • difficult to define the role of RT dose

1993

NO definitive RANDOMIZED TRIALS TO EVALUATE

- DOSE

- INDICATIONS

- **RT could have a role in stage III-IV bulky disease pts and in those with residual mass after chemotherapy**
- **40 Gy RT represent the standard**

Radiotherapy in DLBC NHL

NO definitive RANDOMIZED TRIALS TO EVALUATE THE DOSE

STAGE I-II

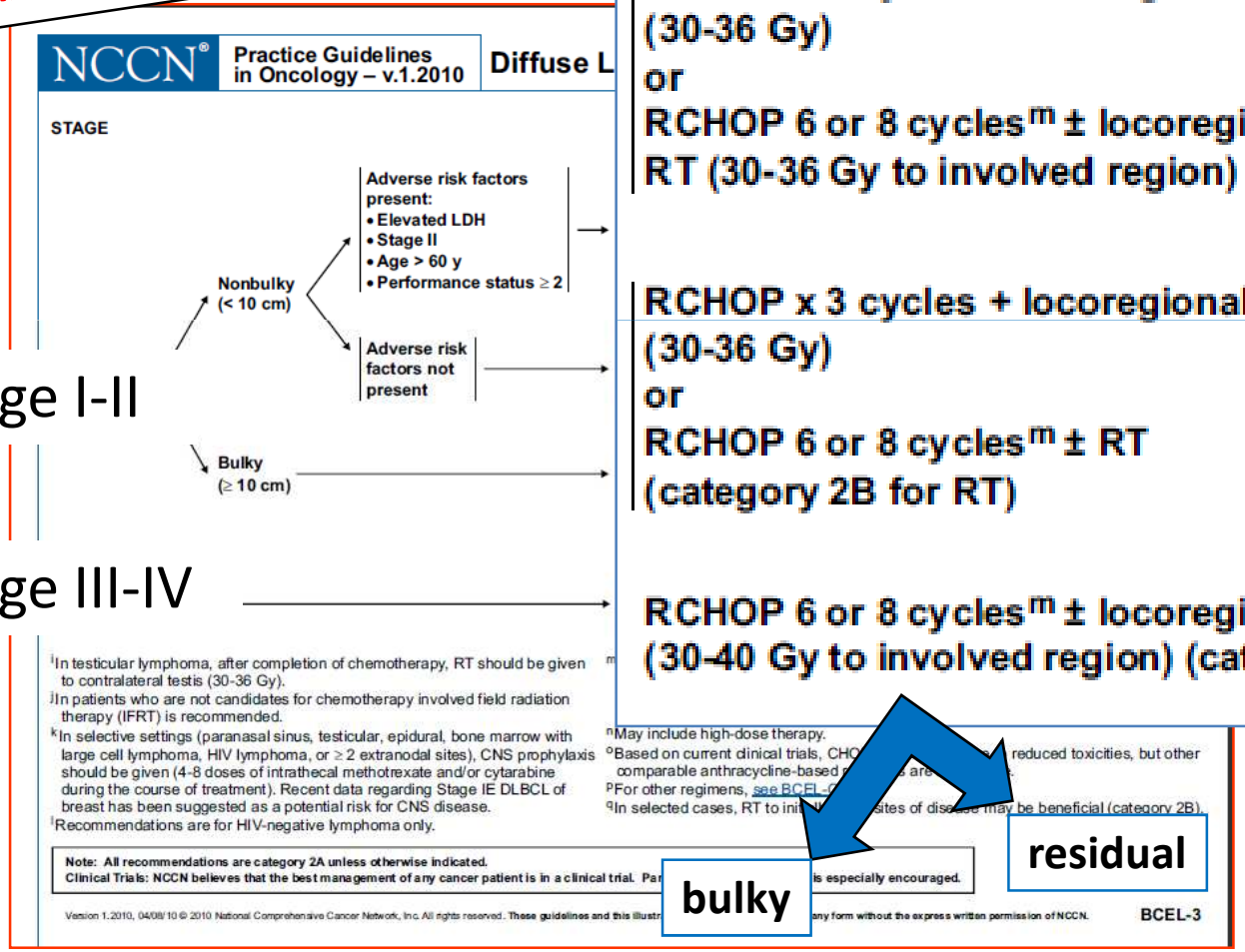
- **40 Gy after 3-4 CHOP**
- **(30-36 Gy for CR pts after 6-8 CHOP?)**
- **in patients in RP or CR but bulky disease a 40-46 Gy dose is warranted**

NO definitive RANDOMIZED TRIALS TO EVALUATE
-DOSE
- INDICATIONS

STAGE III-IV

- **RT could have a role in stage III-IV bulky disease and in pts with residual mass after chemotherapy**
- **40 Gy RT represent the standard**

The current guidelines however refer to patients treated with the addition of Rituximab and after PET staging



Radiotherapy dose in DLBC :

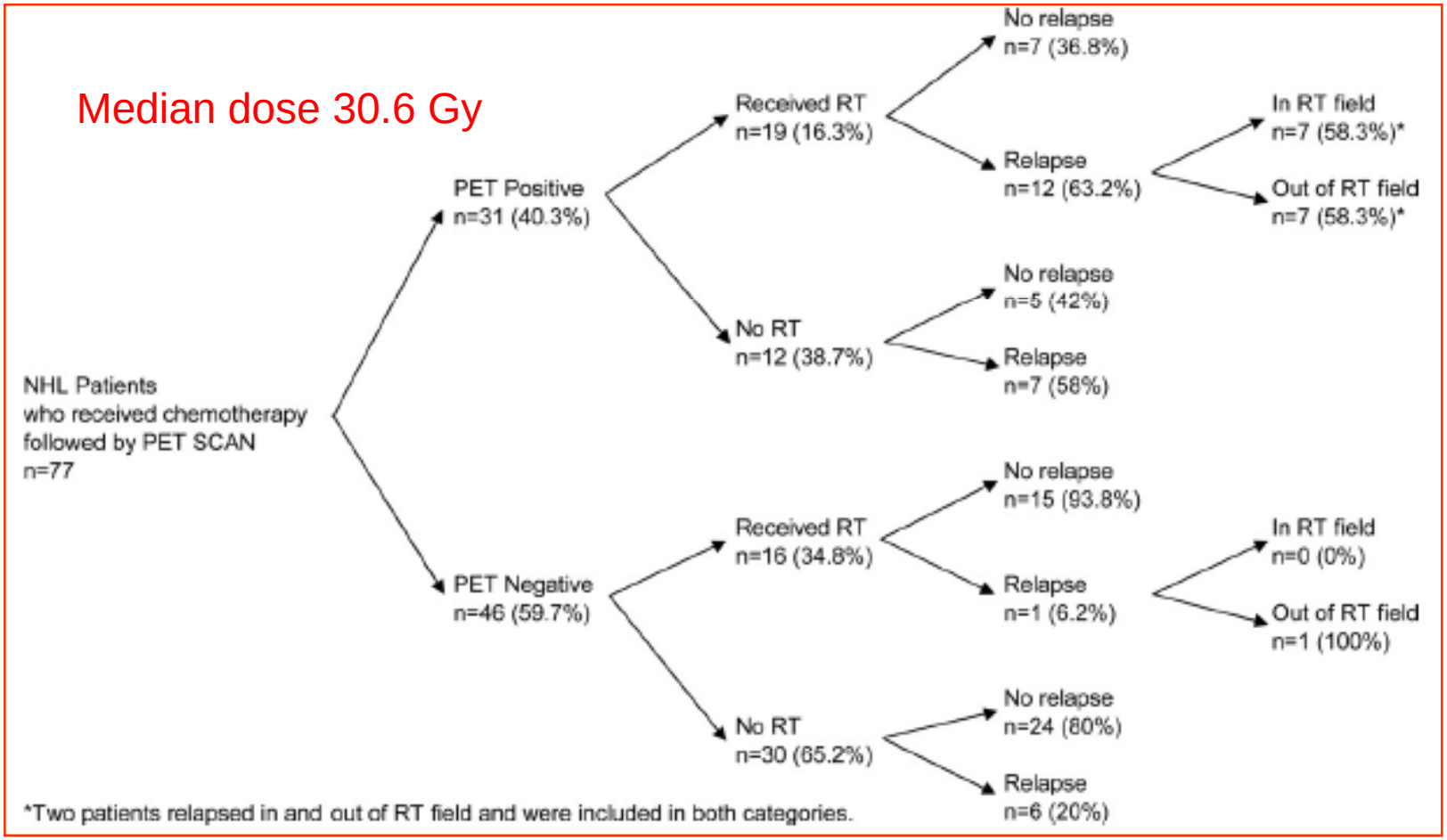
- role of PET: - predict the outcome;

  - decision on RT dose?

- role of association with Rituximab

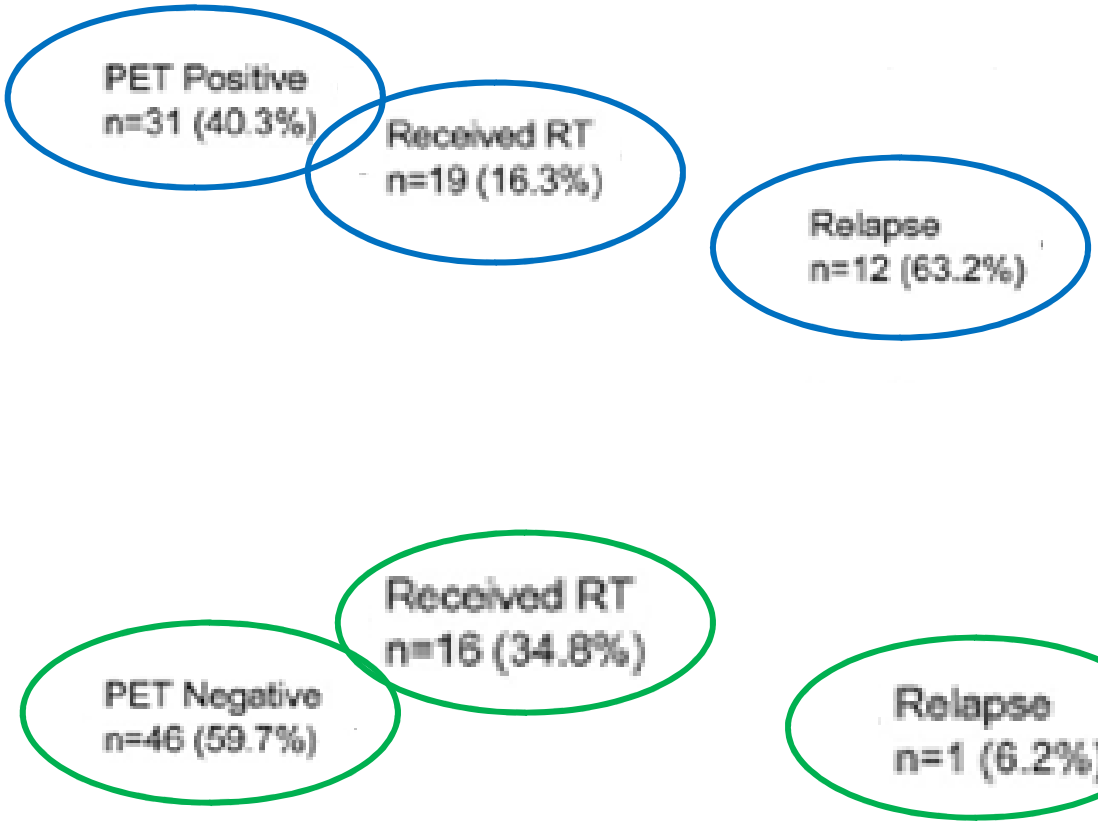
  - need for change of RT dose?

PET to predict the outcome and to help to define RT dose



IJROBP 2006 66(4): 961

PET to predict the outcome and to help to define RT dose

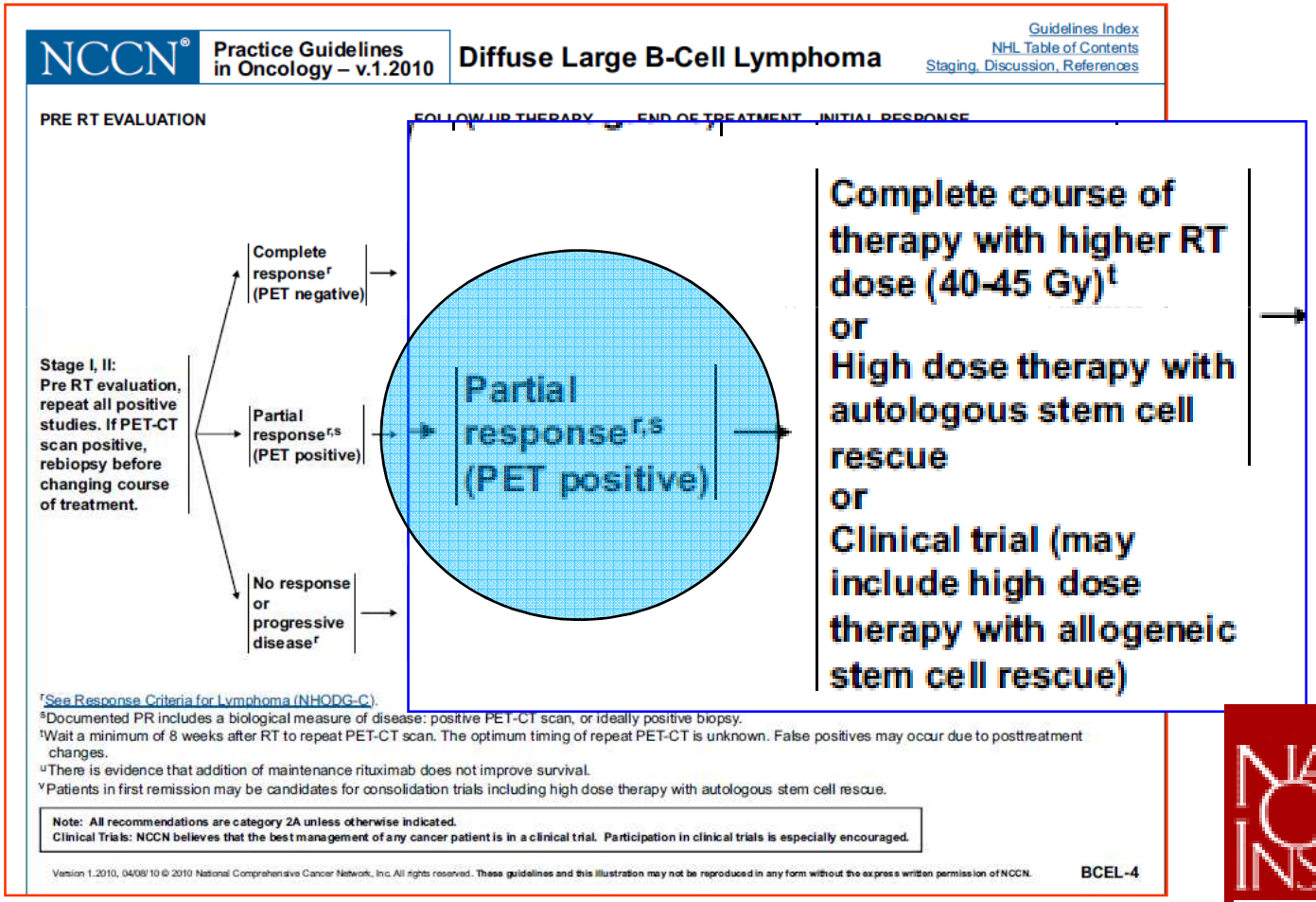


Median dose 30.6 Gy

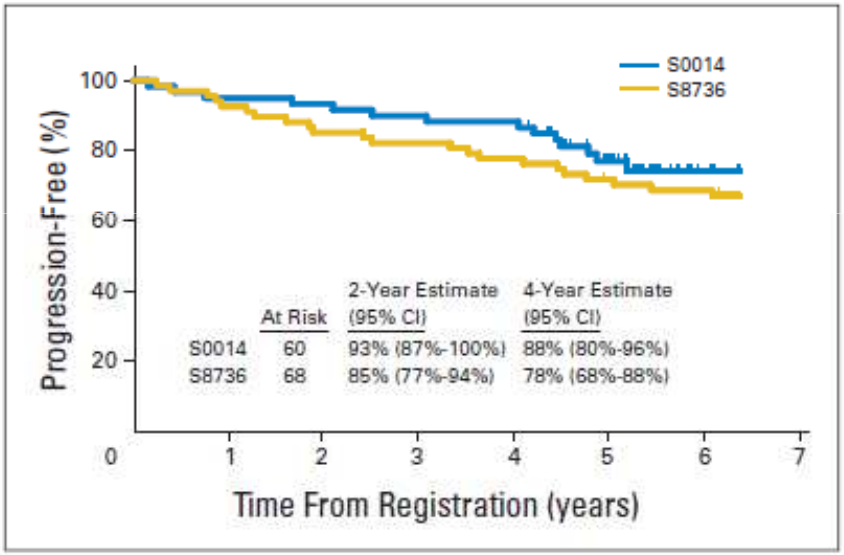
• higher RT doses may be required in CHT resistent/PET + patients

IJROBP 2006 66(4): 961

Is this the reason why….?

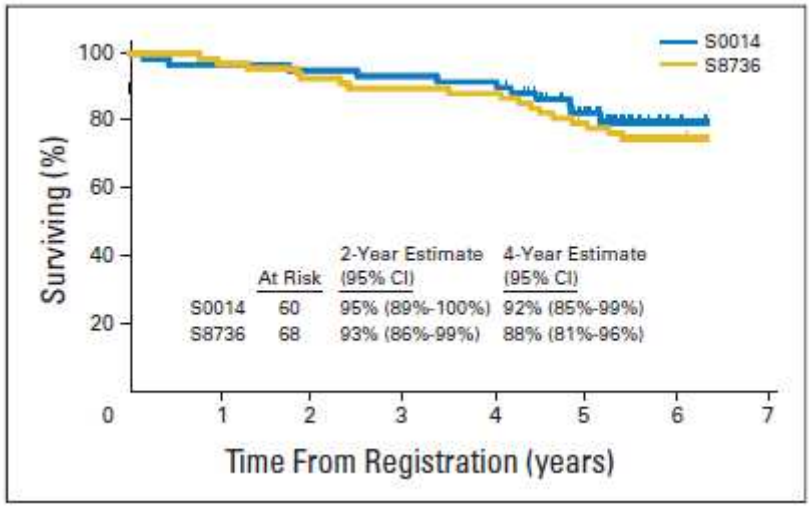


Role of association with Rituximab



SWOG 0014

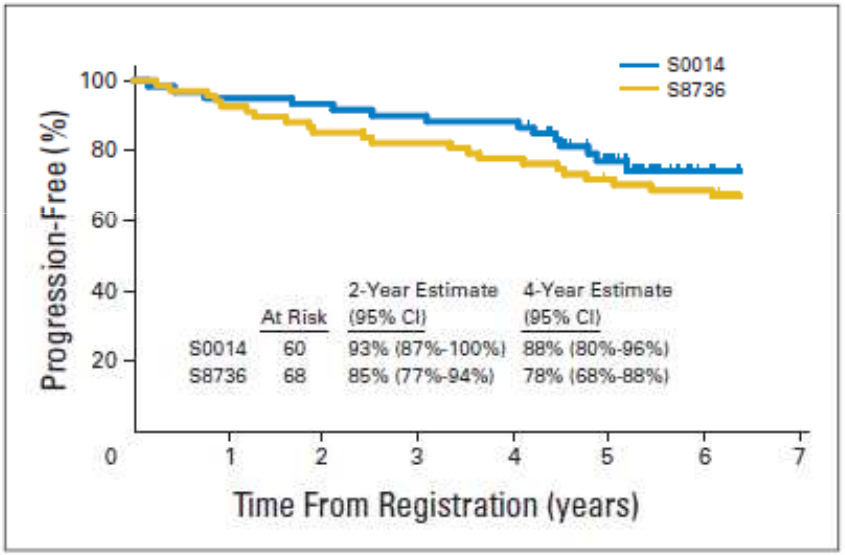
- **ph 2**
- **CHOP+ Rituximab +RT**
- **low risk**



- **Comparision with previous trial**

JCO 2008 26 (14): 2258

Role of association with Rituximab



- **Comparision with previous trial**

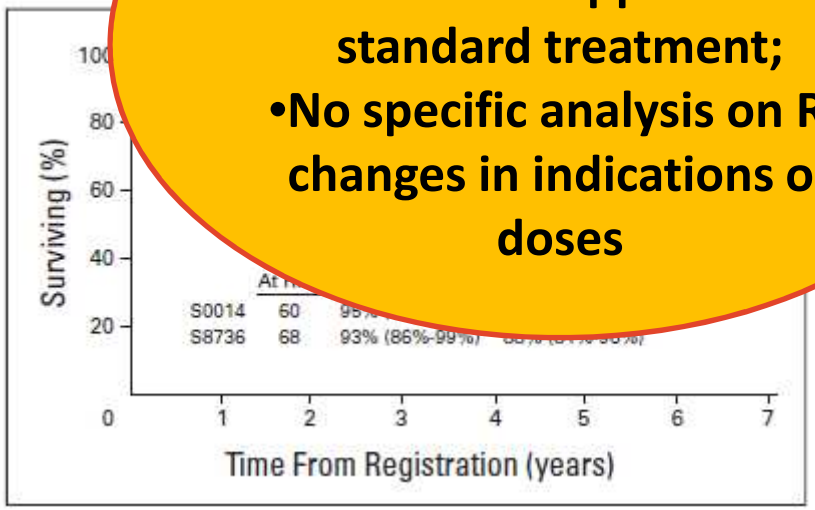
JCO 2008 26 (14): 2258

NEJM 2002 346: 235

JCO 2005 23: 4117

SWOG 0014

- **ph 2**
- **CHO**
- **lo**



- **In trial comparing CHOP vs R-CHOP RT is not studied but applied as a standard treatment;**
- **No specific analysis on RT changes in indications or doses**

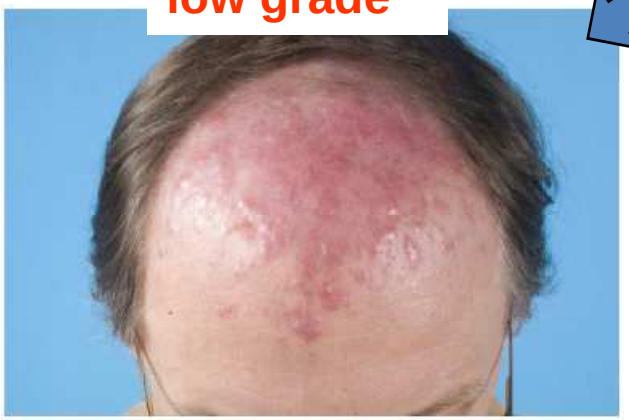
Radiotherapy for extranodal (DLBC) lymphoma

- Substantially the same questions could be posed
- Substantially similar answers are obtained

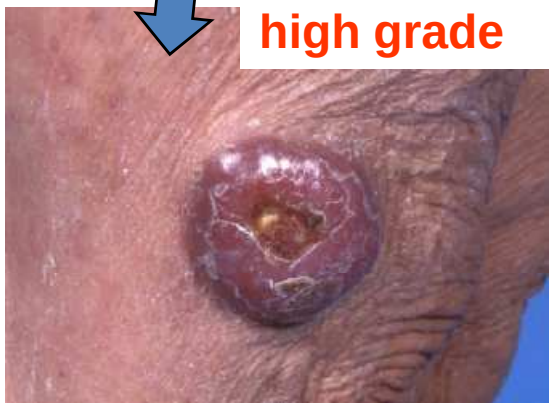
We will only give a few examples

Cutaneous lymphoma

low grade



HISTOLOGY / DOSE of RT / OUTCOME				
HISTOLOGY	**Dose Gy**	**N°PTS**	**CR %**	**Relapse %**
PCMZL	**30-45**	132	99	46
PCFCL	**20-54**	460	99	47
PCLBCL	**>= 40**	101	88	58



high grade

RT alone: 30-36 Gy

RT alone: 40-46 Gy

BLOOD 2008 112(5):1600

Head and neck DLBC

• RT obtain a **good local control**, however **almost 50%** of patients (even in early stage) relapse 22-42% in extranodal sites, **out of RT portals; high percentage of local relapse without RT**

RT alone:
40-50 Gy

Combined modality treat:
CHOP + RT
CR: 30-36 Gy
PR or bulky: 40-46 Gy

Tumori 2005 91 (6): 456
Leuk & lymph 2008 49 (12):2263

DLBC NHL: breast

Ann Oncol 2008 19: 233

Primary diffuse large B-cell lymphoma of the breast: prognostic factors and outcomes of a study by the International Extranodal Lymphoma Study Group

RT dose (ipsilateral breast, $n = 110$)	Median	40 Gy	
	Range	4–60 Gy	
	Distribution		
	<30 Gy	4	4
	30–39.9 Gy	34	31
	40–49.9 Gy	61	55
	≥50 Gy	11	10

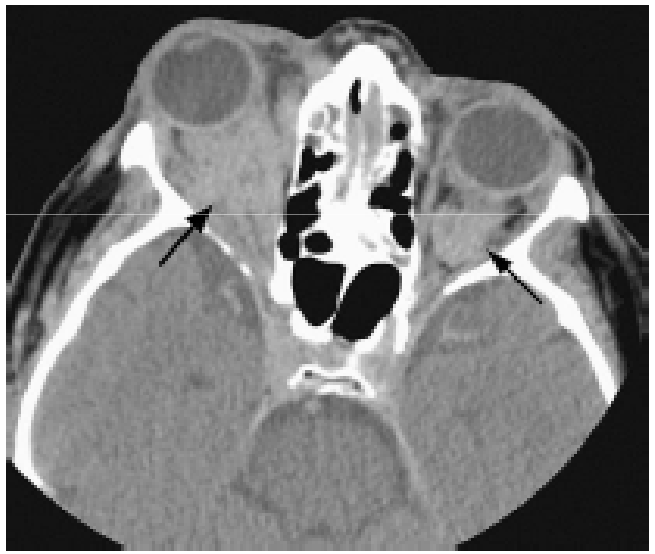
- good IPI,
- anthracycline-containing cht
- radiotherapy (RT)

• CMT
• RT 36-46 Gy

Orbital NHL

- **the median dose for low-grade tumors was 30 -36 Gy**

- **the median dose for intermediate and high-grade tumors was 40 – 46 Gy**



IJROBP 2002 54(3): 818

testicular Oncol Hematol 2008 65:183

DLBC L – Stage I-II

CMT:
CHOP + RT
CR: 30-35 Gy
PR: 35-45 Gy

25-30 Gy

mediastinal

IJROBP 2000 47(5): 1281

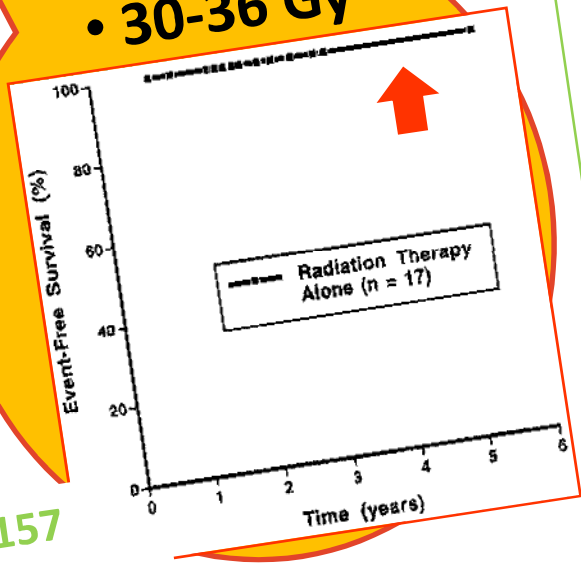
Hematol Oncology 2007 25:157

CMT :
CHOP + RT
40 Gy

stomac MALT

- **25 – 30 Gy**

- **30-36 Gy**



JCO 2003 21: 4157

JCO 1998 16:1916

JCO 2005 23: 6415

IJROBP 2010 76(3) suppl.

Late toxicity: Quantec or not to Quantec?

QUANTEC: ORGAN PER **Thorax: Heart**

RADI SE–VOLUME EFFECTS IN THE HEART

GIOVANNA GAGLIARDI, S. CONSTINE, M.D.,† VITALI MOISEENKO, PH.D.,‡
CANDACE CORREA, M. IERCE, M.D.,§ AARON M. ALLEN, M.D.,‖

QUANTEC: ORGAN-SPECIFIC PAPER **Head and Neck: Parotid**

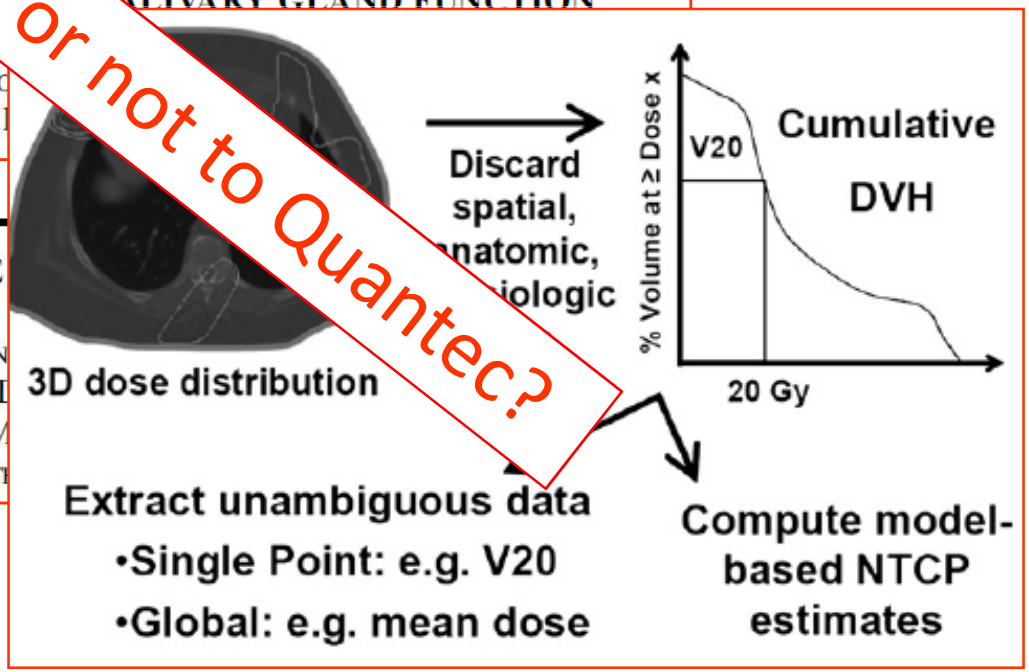
RADIOTHERAPY DOSE–VOLUME EF ALIVARY GLAND FUNCTION

JOSEPH O. DEASY, PH.D.,* VITALI MOISEENKO
K. S. CLIFFORD CHAO, M.D.,§ JIHO NAM, PH.

QUANTEC: ORGAN-SPECIFIC PAPER

RADIATION DOSE–VOLUME

LAWRENCE B. MARKS, M.D.,* SOREN M. BEN
FENG-MING (SPRING) KONG, M.D., PH.D.,§ JEFFREY
ISSAM EL NAQA, PH.D.,‡ JESSICA L. HUBBS, M
ROBERT D. TIMMERMAN, M.D.,¶ MARY K. MARTI



Late toxi… Quantec or not to Quantec?

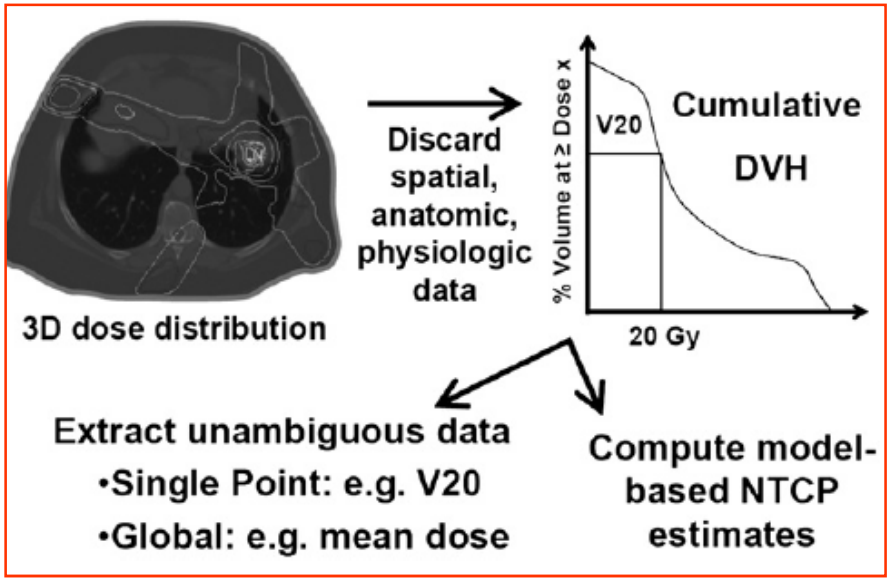
POINT of discussion

…dream of a NTCP-based planning will probably remain a (dangerous?) dream for a very long time and the variety of treated volumes involved in DLCB lymphomas precludes a meaningful summary of the reported toxicities.

However, an accurate reporting of toxicity data is the pre-requisite to answer the question of organ-specific toxicity for low dose treatments such as those needed for the treatment of DLCB L.

Lung, salivary glands and heart are often considered major dose limiting organs in the treatment of lymphomas.

While good quality long term data are missing for the dose levels actually used, the additional toxicity from CHT should be considered.



Late toxicity

IJROBP 2010 76(3) suppl. S77

QUANTEC: ORGAN SPECIFIC PAPER **Thorax: Heart**

RADIATION DOSE–VOLUME EFFECTS IN THE HEART

* Louis S. Constine, † Vitali M
Lori J. Pie M.D.,§ A
nce B. ks, M.D.¶

- for partial irradiation NTCP **V25>10% → <1%** cardiac mortality in 15 y
- **30 Gy whole heart** well tolerated but is better to limit the **dose ~15 Gy** in pts treated with antracycline-cht
- pericarditis: the risk increase with **m dose >26Gy and/or V30>46%**

- **Patient risk factors**
- **Treatment risk factors**

Rew of literature
- **Ischemic heart disease → >= 30 Gy**
- **congestive heart failure → m dose > 40 Gy**
- **valvular disease → m dose 43 Gy**

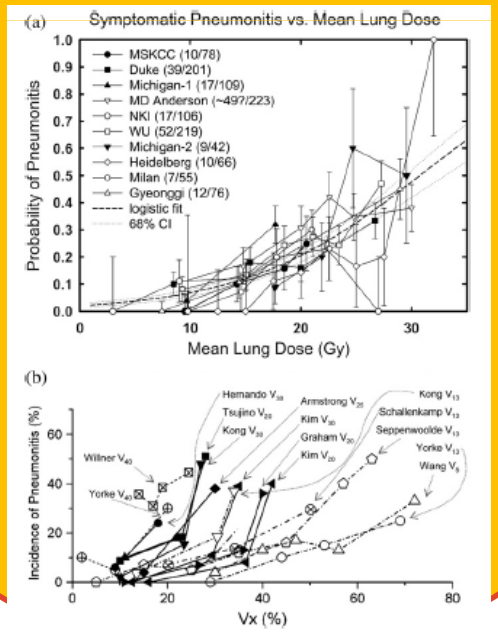
Late toxicity

IJROBP 2010 76(3) suppl. S70

RADIATION DOSE–VOLUME EFFECTS IN THE LUNG

LAWRENCE B. MARKS, M.D. * ... BENTZEN, ... FENG-MING ... JEFF ... D. BRADLEY, ... L. HUBBS ... S.,* JOOS V. L ... ARY K. MA ... PH.D.,# AND ...

Review of literature



- **Pts risk factors (pre-RT lung function)**
- **Treat risk factors**

- the acceptable risk level varies with the *clinical scenario*
- limit **V20 to <=30-35%**
- median lung dose **<= 20-23 Gy**

→ risk of **Radiation Pneumonitis <=20%**

Late toxicity

IJROBP 2010 76(3) suppl. S58

QUANTEC: ORGAN-SPECIFIC PAPER **Head and Neck: Parotid**

RADIOTHERAPY DOSE–VOLUME EFFECTS ON SALIVARY GLAND FUNCTION

JOSEPH O. DEASY, PH.D.,* VITALI MOISENKO, PH.D.,† LA
K. S. CLIFFORD , M.D.,§ JIHO NAM, D.,‡ AND AVRA

- **sparing at least one parotid gland** and sparing at least one submandibular gland
- xerostomia is avoided if at least **one parotid gland** has been spared to a **m dose <20 Gy** or if **both glands** have been spared to a **m dose < 25 Gy**

- **Pts risk factors (pre-RT function)**
- **Treat risk factors**

Rew of literature
- **Minimal xerostomia at m dose <10–15 Gy**
- **Gradual improvement at m dose 20–40 Gy**
- **severe xerostomia (>75%) at >40 Gy**
- **spare other salivary glands**

Late toxicity

IJROBP 2001 49(5) 1327

CLINICAL INVESTIGATION — **Hodgkin's Disease**

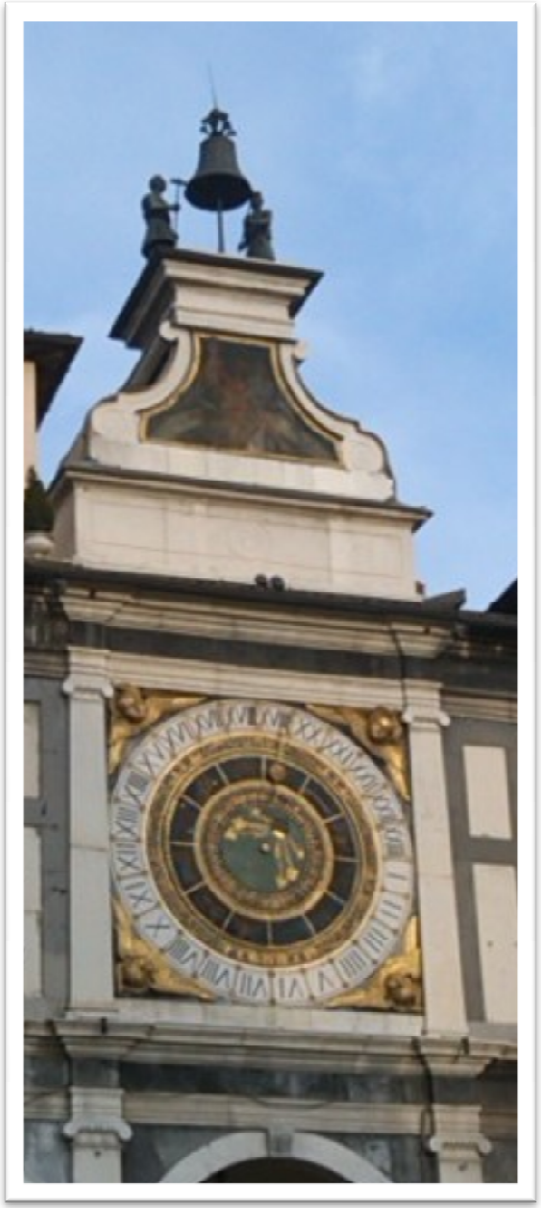
THE RISK OF SECOND MALIGNANT TUMORS AND ITS CONSEQUENCES FOR THE OVERALL SURVIVAL OF HODGKIN'S DISEASE PATIENTS AND FOR THE CHOICE OF THEIR TREATMENT AT PRESENTATION: ANALYSIS OF A SERIES OF 1524 CASES CONSECUTIVELY TREATED AT THE FLORENCE UNIVERSITY HOSPITAL

Ann Oncol 2006 17:1749

Second malignancy risk associated with treatment of Hodgkin's lymphoma: meta-analysis of the randomised trials

Same conclusions:
1. the risk of second tumors is slighly increased in patients *long survivors* after combined treatment for HD;
2. the not negligible impact on OS do not juntify any change in the therapeutic approch!

... no more time now!.....



thank you !

Brescia - 14 Maggio 2010