

Ruolo della Radioterapia nei linfomi indolenti non follicolari

Dr. Mario Levis

Ricercatore a tempo determinato tipo B

Dipartimento di Oncologia

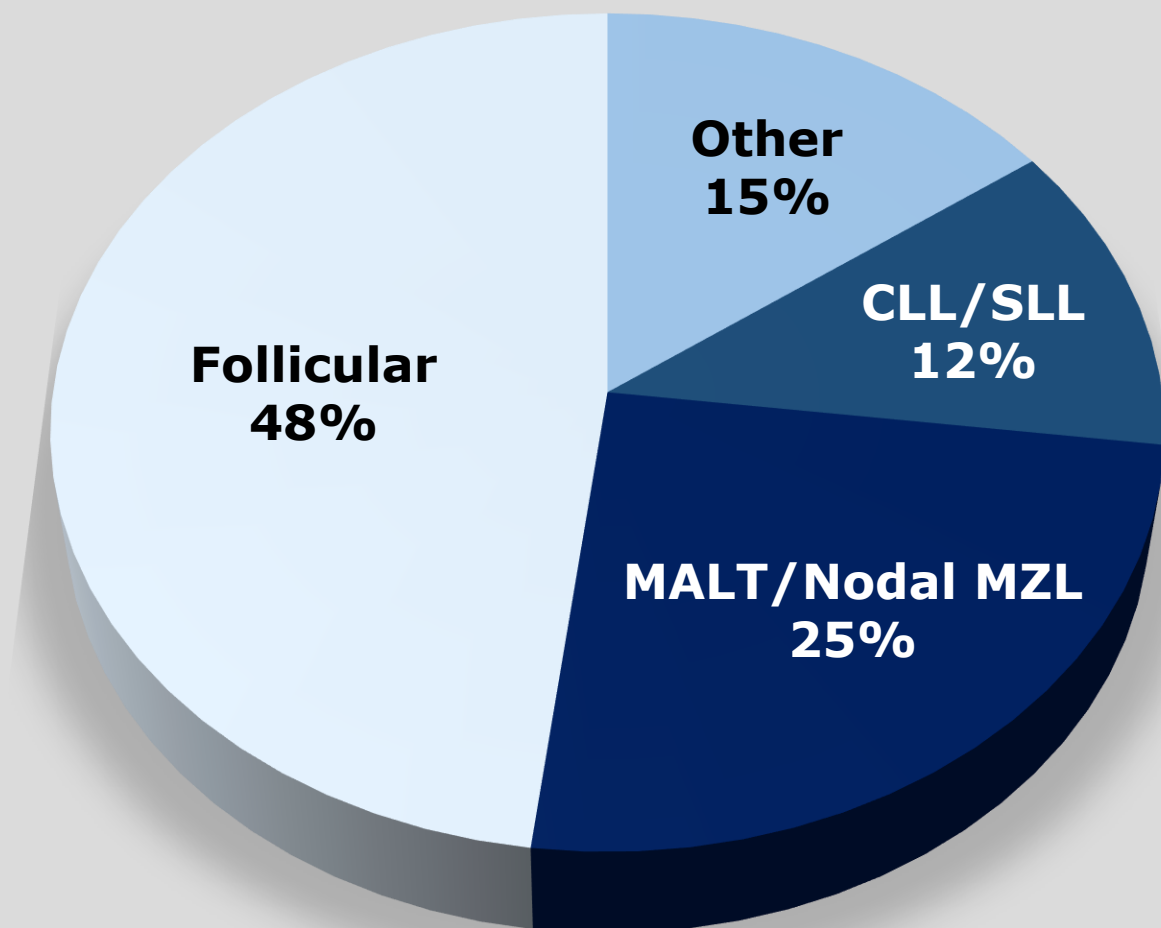
Università degli Studi di Torino

Torino, 16 Dicembre 2019

Indolent Lymphomas

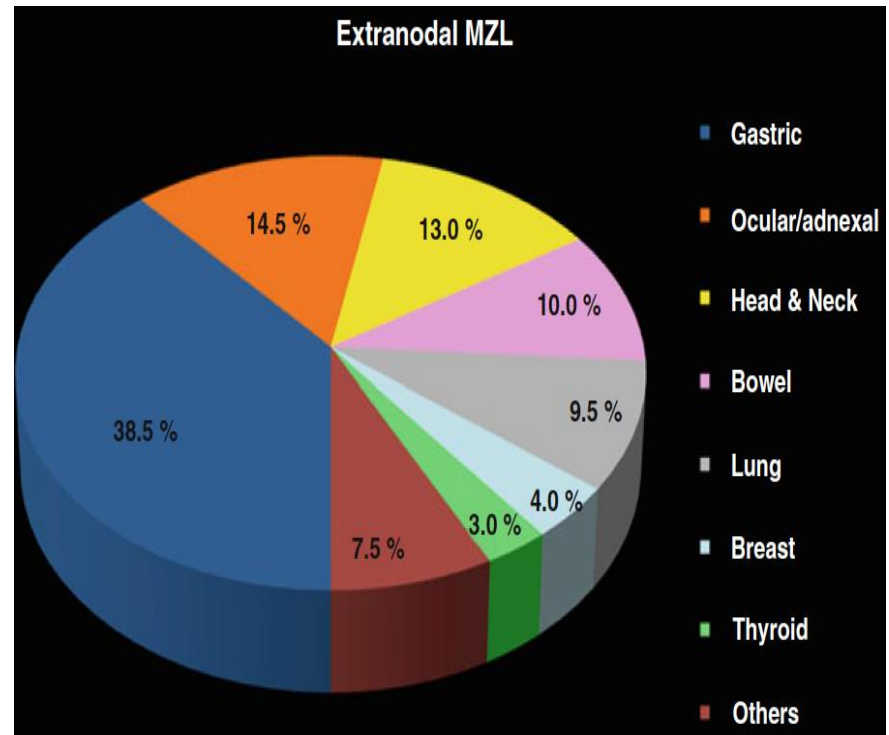
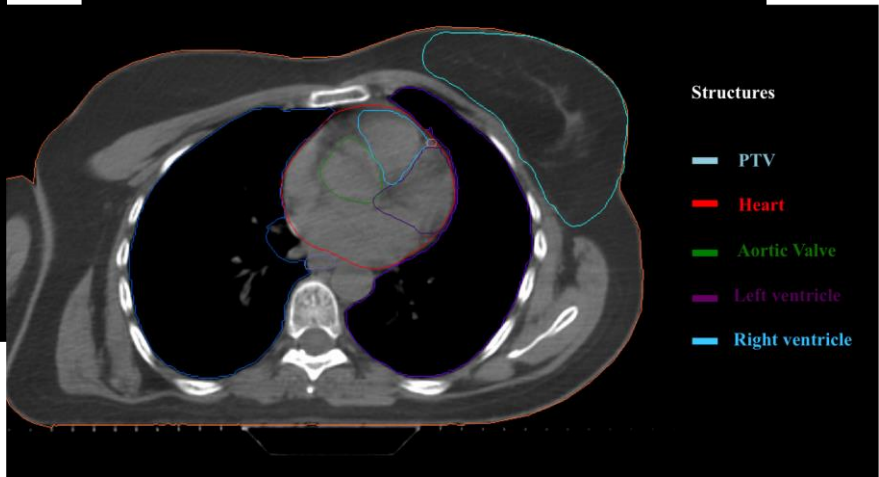
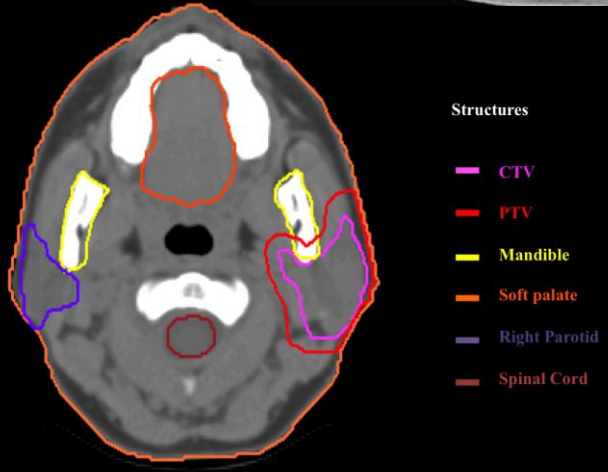
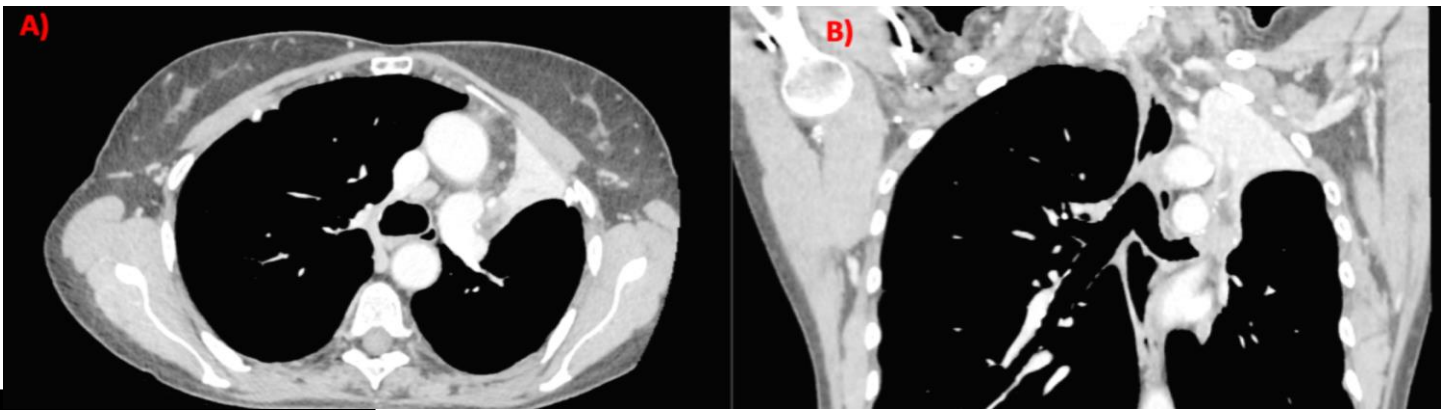
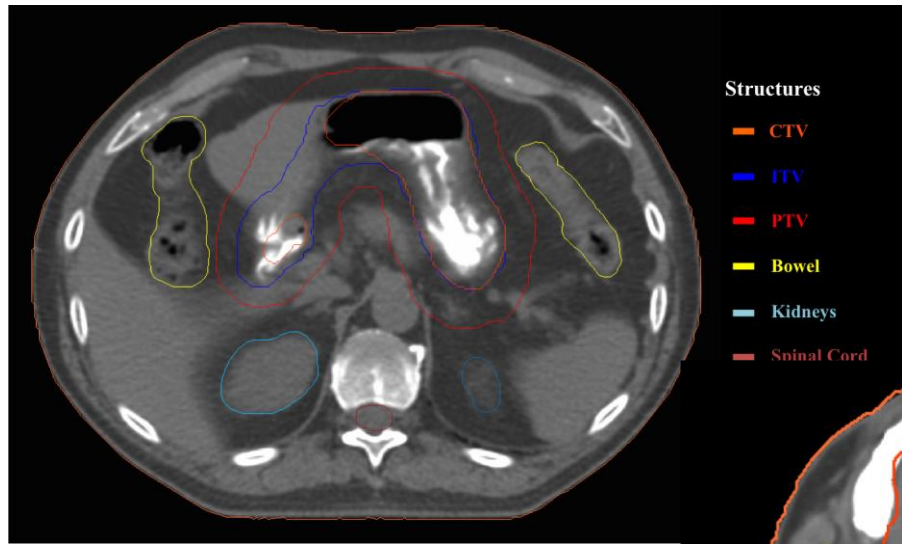
- Approximately 40–45 % of all NHL
- Minority of patients present with localized disease
- Thorough staging with bone marrow biopsy and FDG-PET essential (debated in MZL)
- Highly radiosensitive
- Therapy guidelines
 - Stage I/II: radiotherapy
 - Stage III/IV: systemic treatment, when needed

Indolent Lymphomas



Marginal Zone Lymphomas

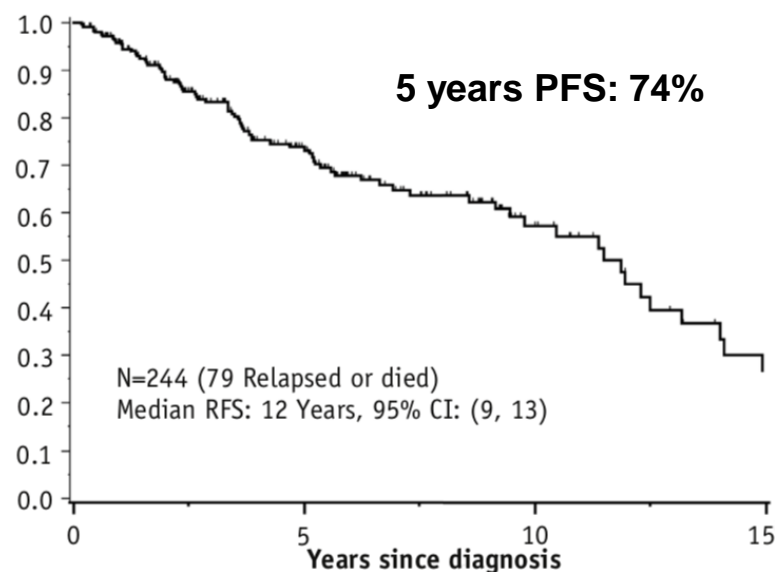
- ✓ Rarely involving nodal sites
- ✓ Frequently affecting extranodal sites
- ✓ Rarely presenting in Limited Stage
- ✓ ISRT in a valuable treatment for limited stage disease
- ✓ Omission of RT is detrimental in Stage I disease also for nodal MZL (OS 69% vs 54% @ 10 years, $p < 0.001$) Ling et al. Pract Radiat Oncol 2016



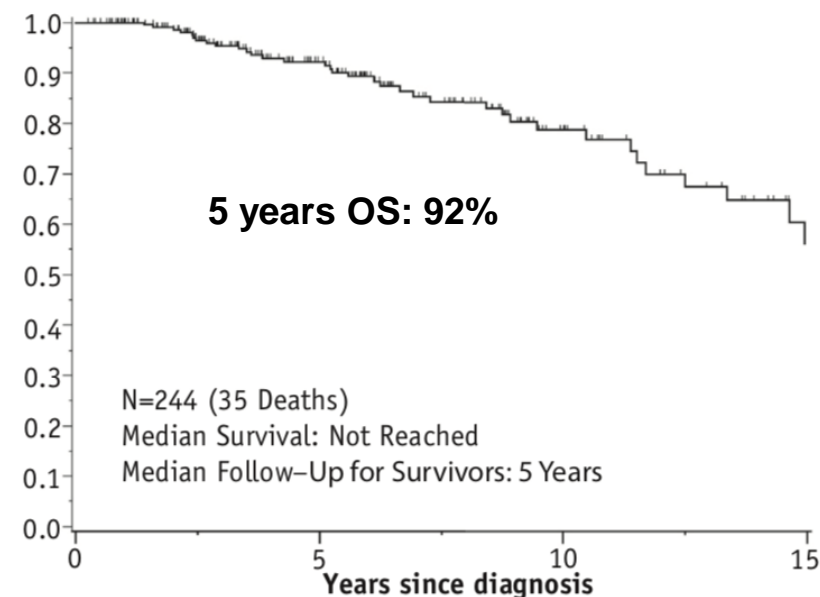
Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent



PFS



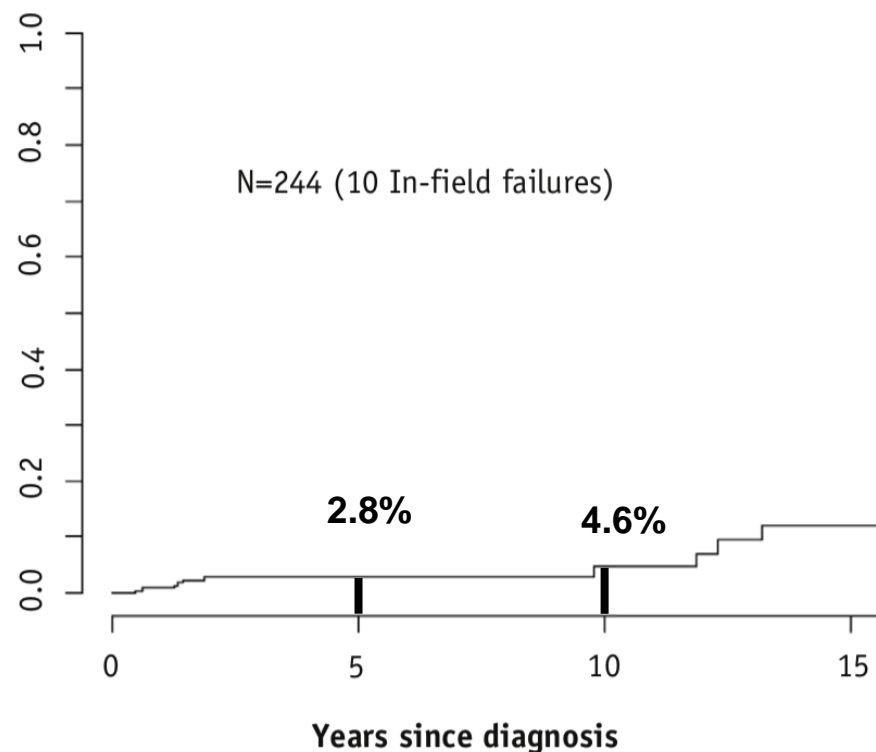
OS



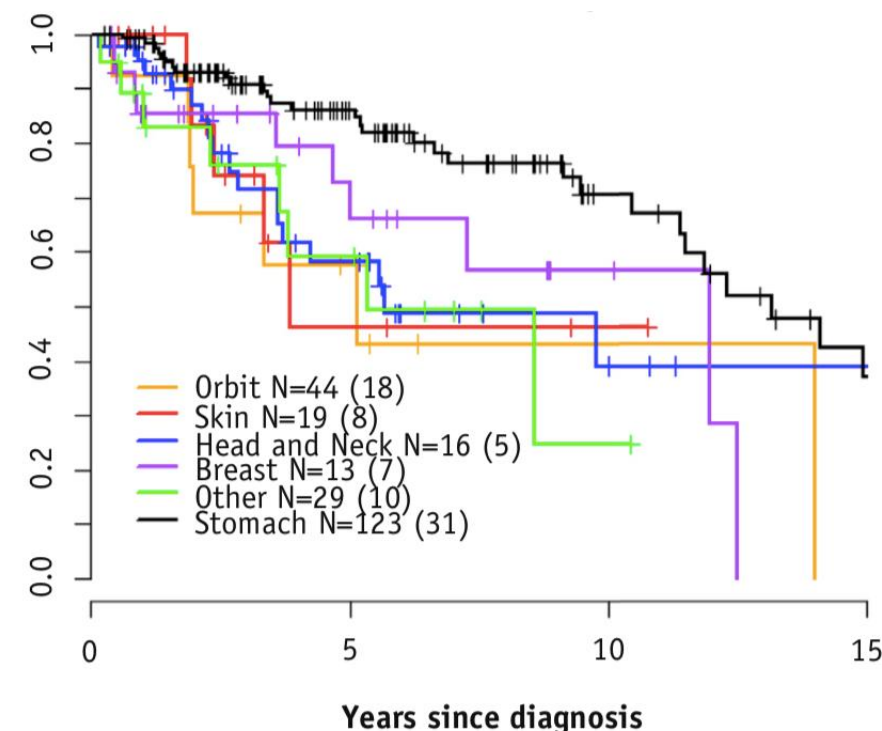
Long-Term Outcomes and Patterns of Relapse of Early-Stage Extranodal Marginal Zone Lymphoma Treated With Radiation Therapy With Curative Intent



In field relapses



PFS by site of disease



GASTRIC MALT LYMPHOMA

- ☐ Often associated with HP gastritis (90%)
- ☐ Regression in 60% of cases

- ☐ HP eradication first line
- ☐ Patients predicted NOT to respond:



(Koch *et al*, 2005).

Histological type	Frequency (%)
Diffuse large B-cell lymphoma	59
With MALT component	14
Without MALT component	45
MALT lymphoma of the marginal zone	38
Mantle lymphoma	1
Follicular lymphoma	0-5
Peripheral T-cell lymphoma	1-5

- ☐ HP negative
- ☐ Invasion beyond submucosa
- ☐ t(11,18) translocation (present in up to 40%)
- ☐ Nodal involvement

GASTRIC MALT LYMPHOMA

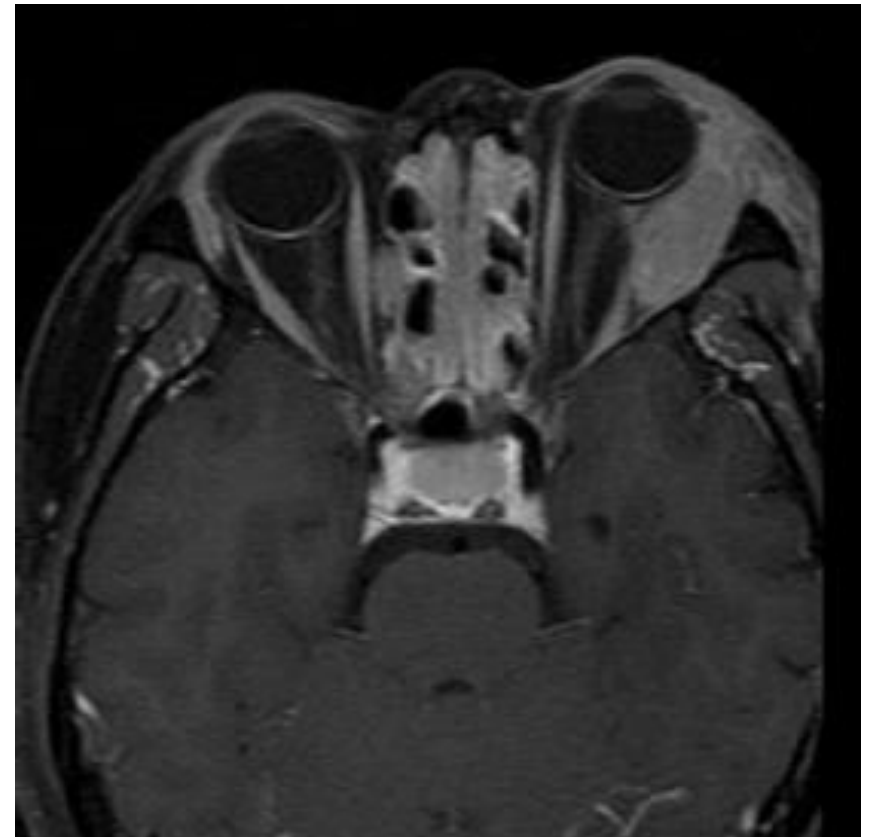
- ☐ RT standard of treatment
- ☐ CR > 90%
- ☐ FFP 80-90%

Reference, year	No. of patients	Treatment	RR (%)	EFS (%)	Survival (%)
Schechter et al. 1998 [71]	17	RT to the stomach and adjacent lymph nodes: 30 Gy/20 fr (range 28.5–43.5 Gy)	ND	27 months 100	27-month OS 100
Yahalom et al. 2002 [91]	51	RT to the stomach and adjacent nodes: median 30 Gy	CR 96	4-year FFTF 89	4-year OS 83 4-year CSS 100
Tsang et al. 2003 [84]	10	RT to the stomach and local nodes: 20–35 Gy	100	5 years 100	5-year OS 100
Koch et al. 2005 [42]	144	Whole abdominal RT: 30 Gy ± 10 Gy boost	ND	42-month FFP 88	42-month OS 93
Avilés et al. 2005 [5]	78	Whole abdominal RT : 30 Gy ± 10 Gy boost	CR 100	10-year FFP 52	10-year OS 75
Vrieling et al. 2008 [87]	56	Stomach + whole abdominal RT : 20 Gy + 20 Gy boost	CR 95	ND	5-year OS 74 10-year OS 63 10-year CSS 94
Wirth et al. 2013 [89]	102	RT to the stomach and involved nodes (61 pts) or whole abdominal RT (41 pts): median 40 Gy	CR 96	10-year FFTF 88	10-year OS 70

RR response rate, *EFS* event-free survival rate, *ND* not determined, *OS* overall survival rate, *CR* complete remission, *FFTF* freedom from treatment failure, *CSS* cancer-specific survival rate, *FFP* freedom from progression

Orbital (ocular/adnexae) MALT lymphoma

- ✓ 1-2% of all NHL
- ✓ 7-8% of extranodal lymphomas
- ✓ Most cases of extraocular orbital lymphoma are MALT lymphomas



Treatment of Orbital MALT lymphomas (antibiotics)

Chlamydophila Psittaci Eradication With Doxycycline As First-Line Targeted Therapy for Ocular Adnexae Lymphoma: Final Results of an International Phase II Trial

Andrés J.M. Ferreri, Silvia Govi, Elisa Pasini, Silvia Mappa, Francesco Bertoni, Francesco Zaja, Carlos Montalbán, Caterina Stelitano, Maria Elena Cabrera, Antonio Giordano Resti, Letterio Salvatore Politi, Claudio Doglioni, Franco Cavalli, Emanuele Zucca, Maurilio Ponzoni, and Riccardo Dolcetti



48% Chlamydial eradication,
15% complete lymphoma regression,
41% partial regression.

ONGOING



Cp-eradicating antibiotic therapy



IELSG 39

International prospective phase 2 trial addressing the efficacy of first-line *Chlamydophila psittaci*-eradicating therapy with protracted administration of doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed Ocular Adnexal Marginal Zone Lymphoma (OAMZL)

44 patients (accrual completed)

([A. Ferreri](#), [E. Zucca](#), [S. Govi](#))

Aim of the study is to establish in a prospective, multicentre phase 2 trial, the efficacy of an upfront targeted therapy consisting of Cp-eradicating therapy with prolonged administration of doxycycline followed by eradication monitoring and antibiotic re-treatment at infection re-occurrence in patients with newly diagnosed OAMZL.

Treatment of Orbital MALT lymphomas (systemic therapy)

Chemotherapy

- ☐ Limited data
- ☐ Different chemotherapy regimens



Complete response: 70-100%

BUT

Local recurrence: >29%

Immunotherapy



- ☐ response rates 50-87%
- ☐ median time to disease progression <1y

Treatment of Orbital MALT lymphomas (radiotherapy)

Reference, year	No. of patients	Stage I, %	Gy	CR, %	LR, %	DR, %	Survival, %	LRM, %
Stafford et al. 2001	40	85	15-54	98	2	25	5-y RFS 88 5-y OS 74 5-y DSS 100	0
Le et al. 2002	31	100	30-40	100	0	16	10-y PFS 71 10-y OS 73	3
Fung et al. 2003	48	81	30.6	100	8	25	10-y OS 81 10-y DSS 100	0
Hasegawa et al. 2003	20	95	30	100	5	20	10-y PFS 70 10-y DSS 100	0
Tsang et al. 2003	30	97	25	97	17	10	5-y DFS 74 5-y OS 97	ND
Uno et al. 2003	50	100	20-46	98	6	6	5-y OS 91	2
Lee et al. 2005	29	100	30-45	100	3	0	3-y EFS 93 3-y OS 100	0
Ejima et al. 2006	42	100	30-36	84	10	10	5-y PFS 77 5-y DSS 100	0
Suh et al. 2006	48	96	30.6	96	6	0	10-y DFS 93 10-y DSS 98	2
Tanimoto et al. 2007	58	94	30-40	83	9	2	10-y PFS 72 10-y OS 92	0
Nam et al. 2009	66	100	20-45	97	3	7.5	5-y RFS 92 5-y OS 96.4	ND
Goda et al. 2011	89	100	25	99	2	22.5	7-y OS 91 7-y DSS 96% 7-y RFS 64%	4
Tran et al. 2013	25	92	24-25	100	4	8	5-y PFS 81 5-y OS 100	0

Primary RT is considered to be
the treatment of choice

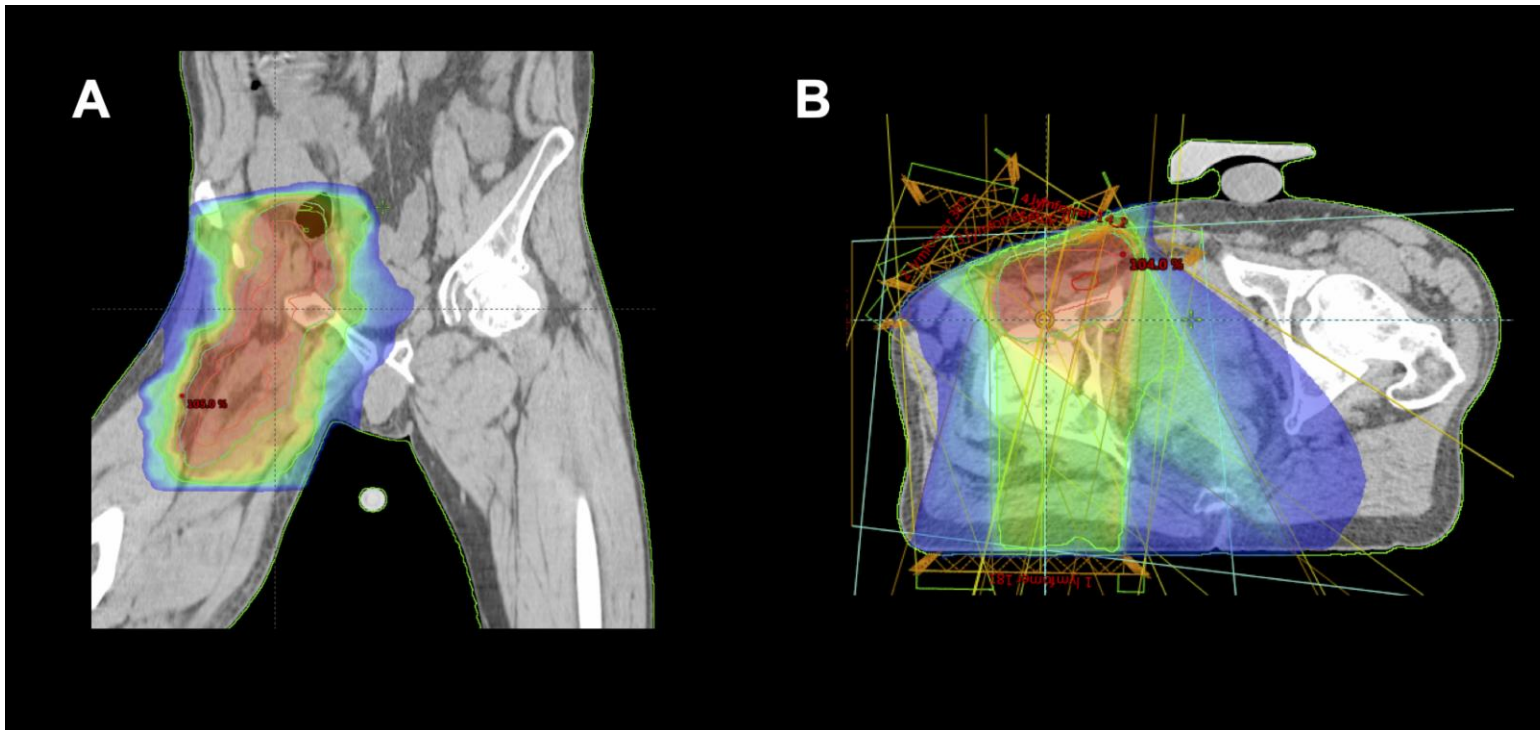


Local control 85-100%

Distant recurrence: 10-25%

Long-term RFS or DFS 70-90%

Technical issues for Radiation Oncologists

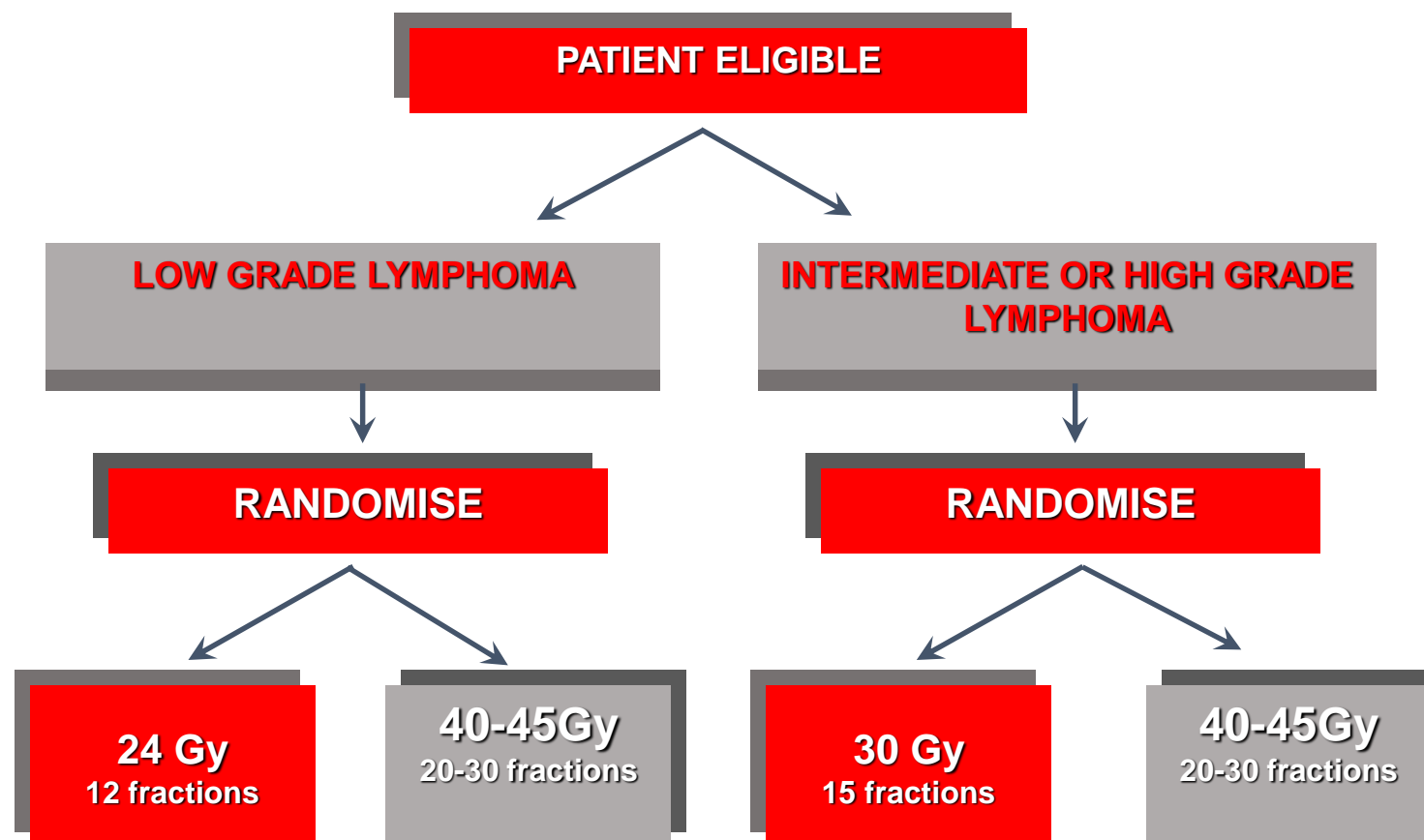


- ✓ **Doses**
- ✓ **Volumes**
- ✓ **Technique**

1 – Doses (24 vs 45 Gy)

Reduced dose radiotherapy for NHL : A randomised phase III trial

360 indolent NHL (mostly follicular and MZL) randomized



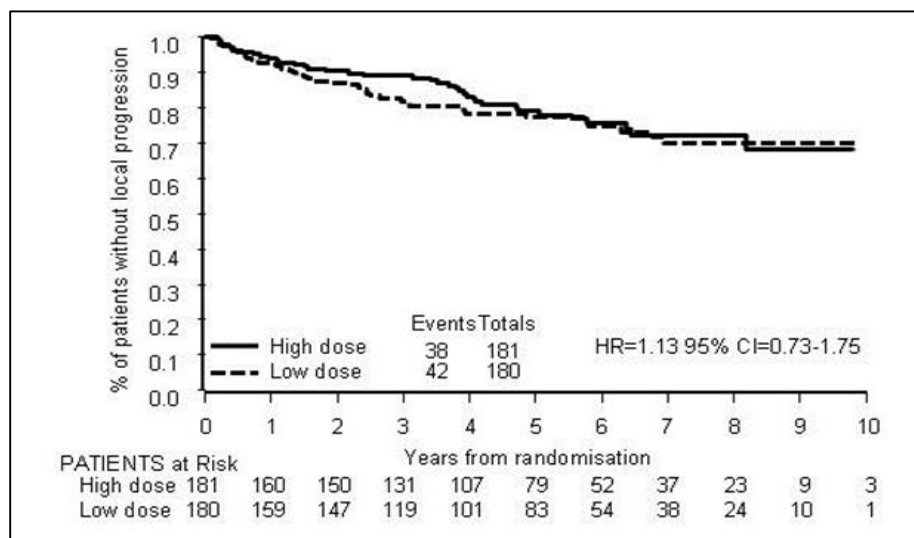
1 – Doses (24 vs 45 Gy)

Phase III randomised trial

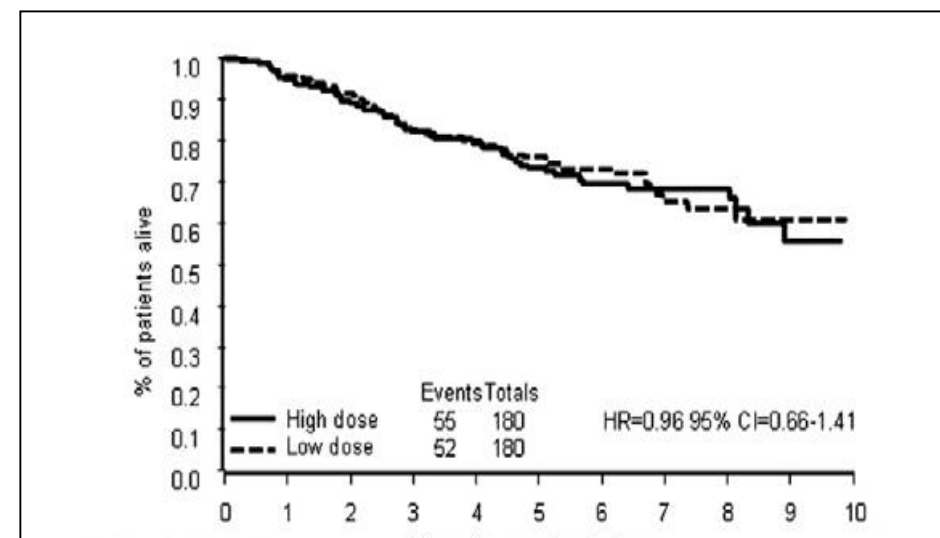
Reduced dose radiotherapy for local control in non-Hodgkin lymphoma:
A randomised phase III trial ☆,☆☆



Local Control



Overall Survival



No loss of efficacy associated with radiotherapy doses of 24 Gy in indolent NHL

2 – Volumes (IFRT vs ISRT)

**What Volume should be treated
with radiotherapy ?**

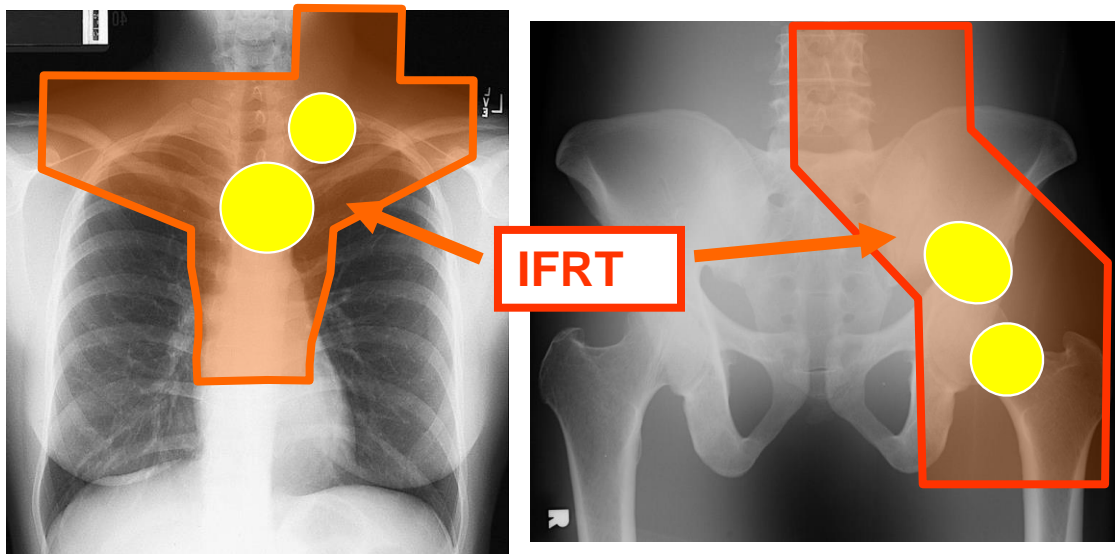
2 – Volumes (IFRT vs ISRT)

www.filinf.it



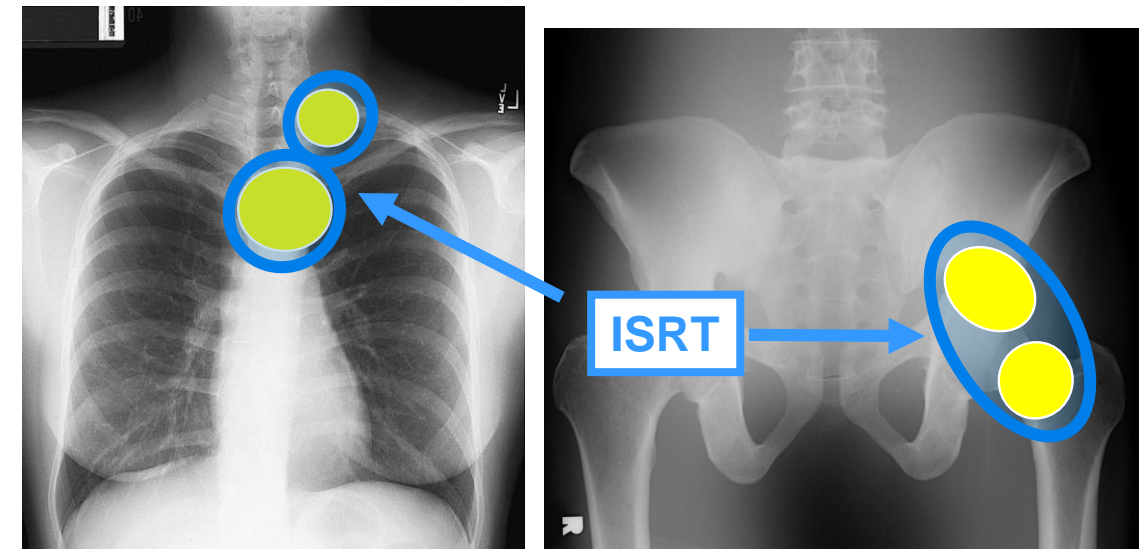
Involved Field (IFRT)

2D planning, based on bony landmark



Involved Site (ISRT)

3D planning, based on lymphoma volume



Long-Term Outcomes for Patients With Limited Stage Follicular Lymphoma

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Involved Regional Radiotherapy Versus Involved Node Radiotherapy

Table 2. Patterns of Failure

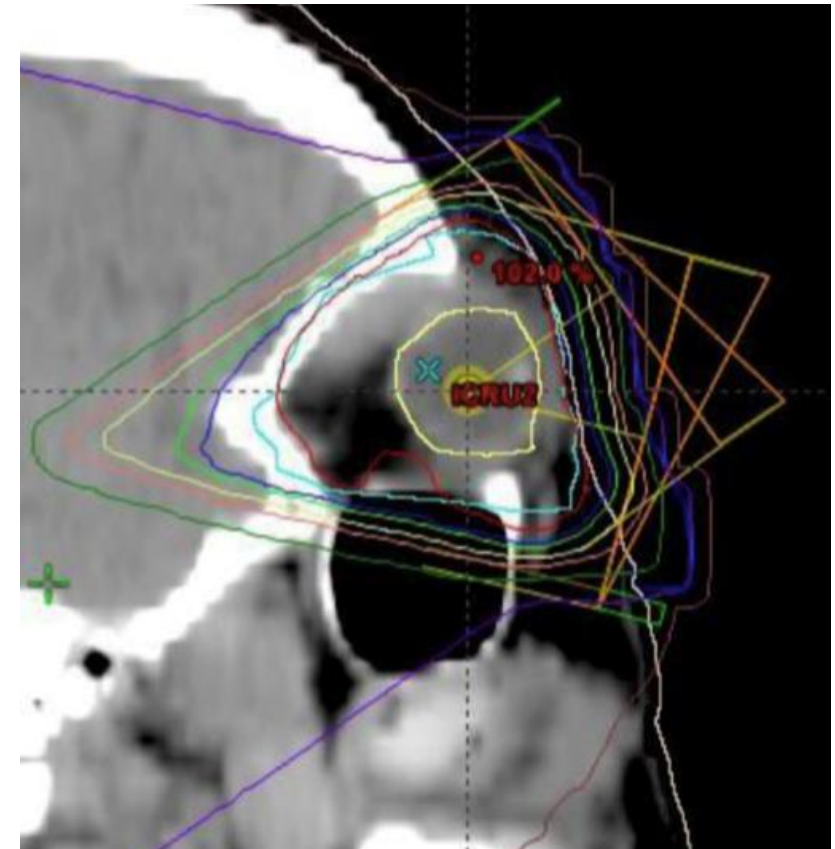
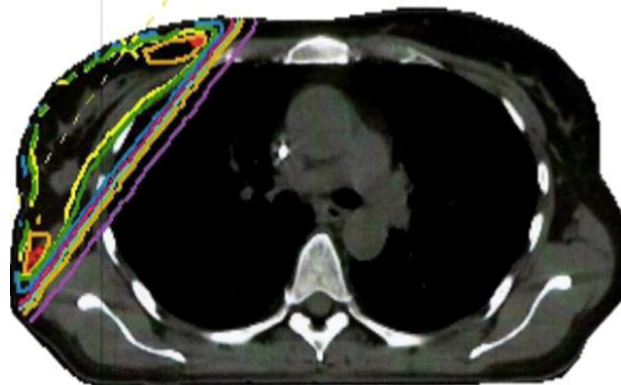
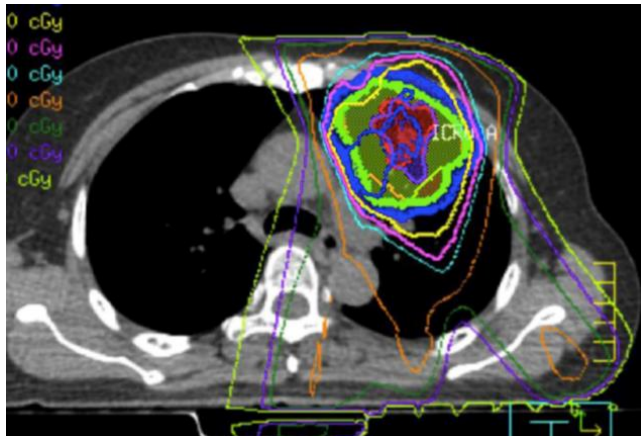
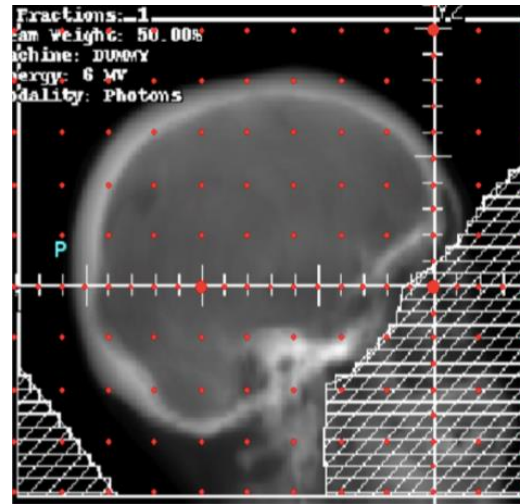
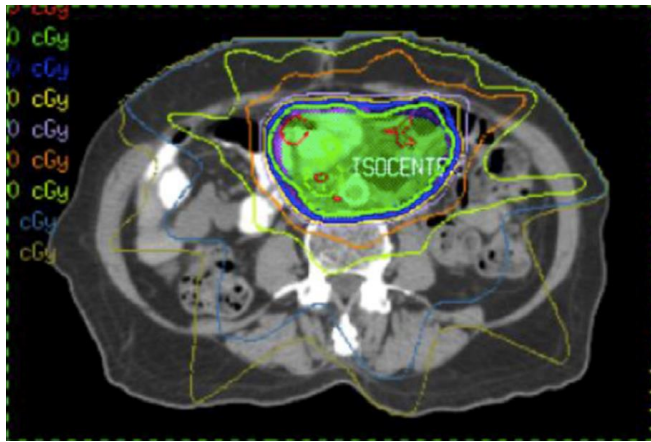
	No. of Patients (%)		
	Total, n=237	IRRT, n=142	INRT≤5 cm, n=95
Total no. of recurrences	98 (41)	65 (45)	32 (35)
Infield relapse only	3 (1)	2 (1)	1 (1)
Distant relapse without infield relapse	84 (35)	54 (38)	30 (32)
Distant only	82	54	26
Regional only	1	—	1
Regional and distant	1	—	1
Distant and infield recurrence	11 (5)	9 (6)	2 (2)

IRRT indicates involved regional radiotherapy; INRT≤5 cm, involved node radiotherapy with margins up to 5 cm.

INRT/ISRT < 5 cm appears to be a safe alternative to IRRT/IFRT and is associated with a very low rate of regional-only recurrence

Modern Radiation Therapy for Extranodal Lymphomas: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group

Yahalom J et al. IJROBP 2015;92:11-31



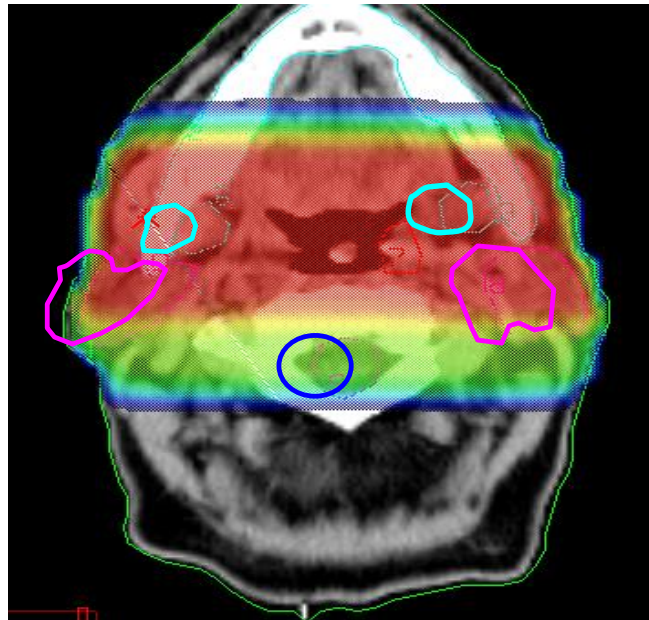
3 – Technique (3DCRT vs IMRT)

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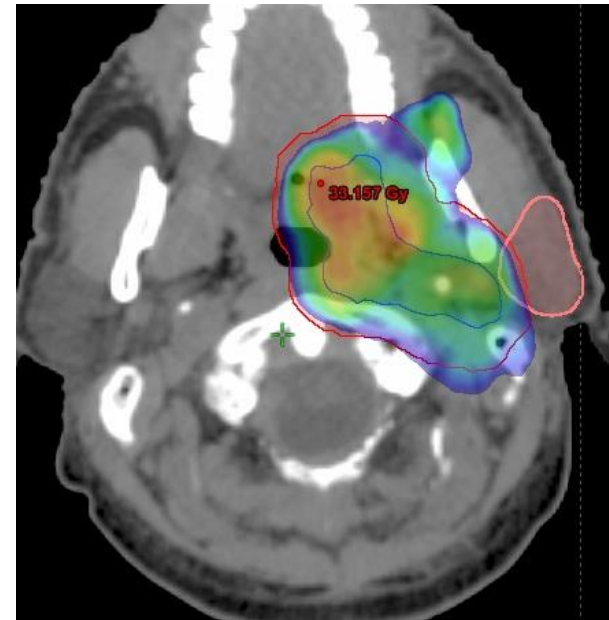


Conformal planning and precise delivery

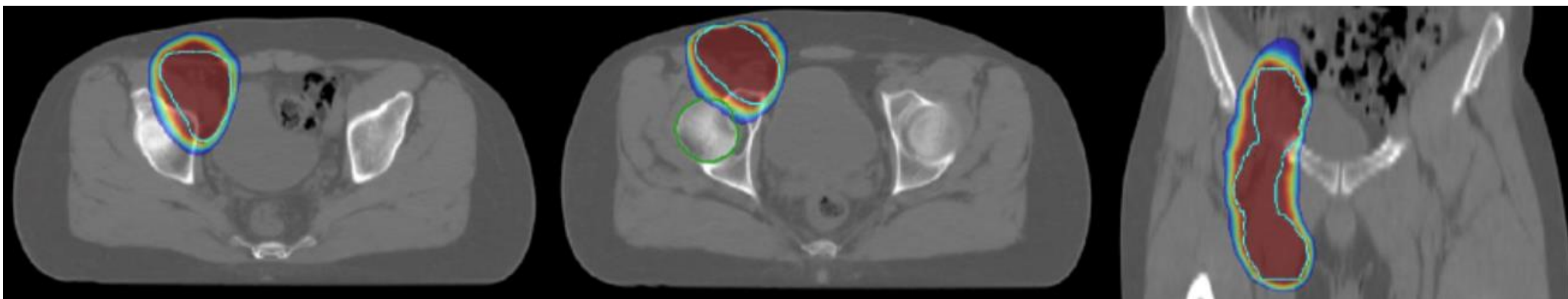
Conventional RT
3DCRT



Intensity modulated RT
IMRT

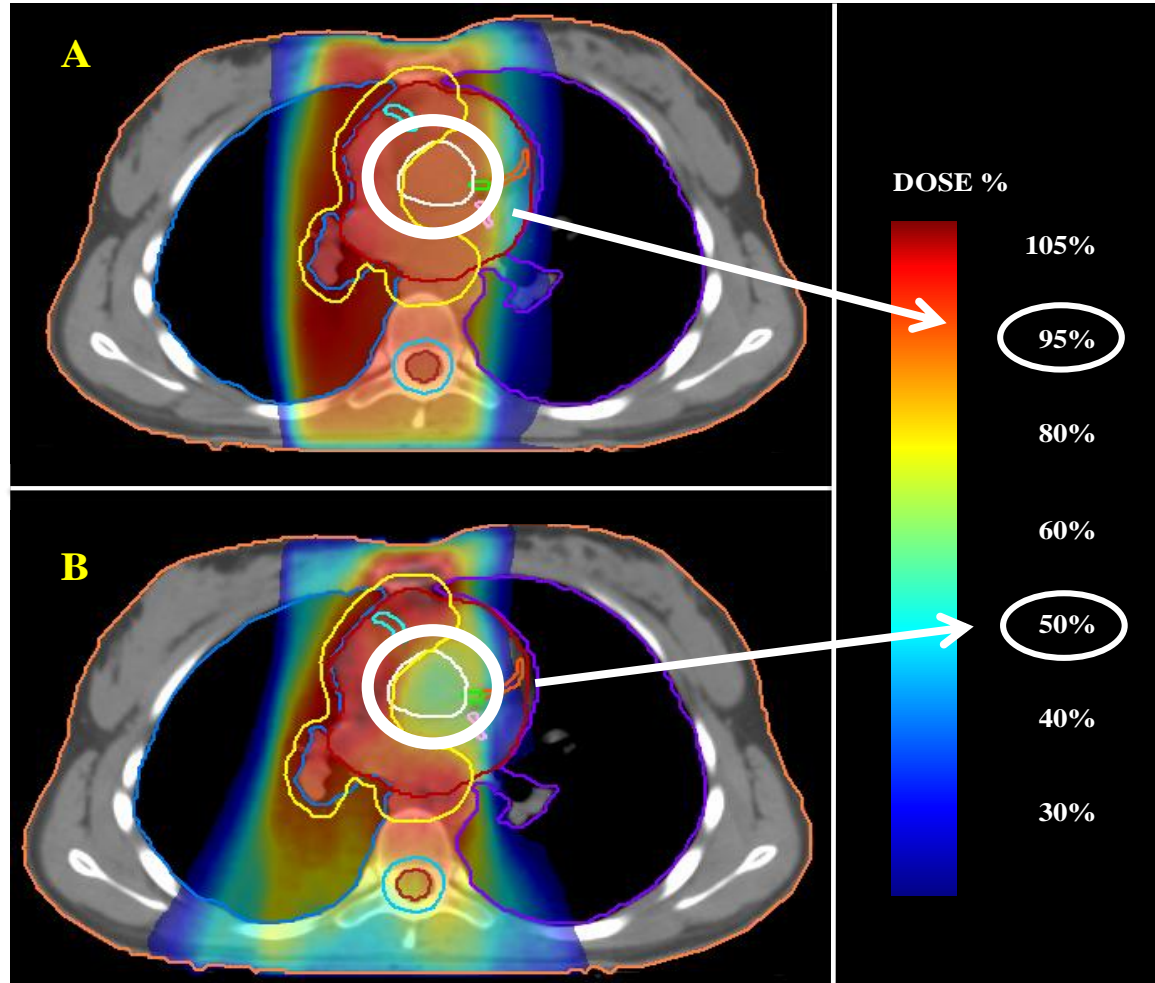


IMRT better spares organs at risk



3 – Technique (3DCRT vs IMRT)

Conventional RT
3DCRT



Intensity Modulated RT
IMRT

*IMRT better spares organs at risk
from “high doses” of radiation*

Critical issues #1: PLANNING

(GASTRIC MALT LYMPHOMA)

Technical issues of radiotherapy planning

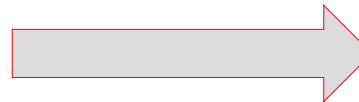
Proposed solutions

✓ *Gastric filling*



✓ *Fasting 6 hours before RT fractions*

✓ *Gastric motion (intra- and inter-fraction)*



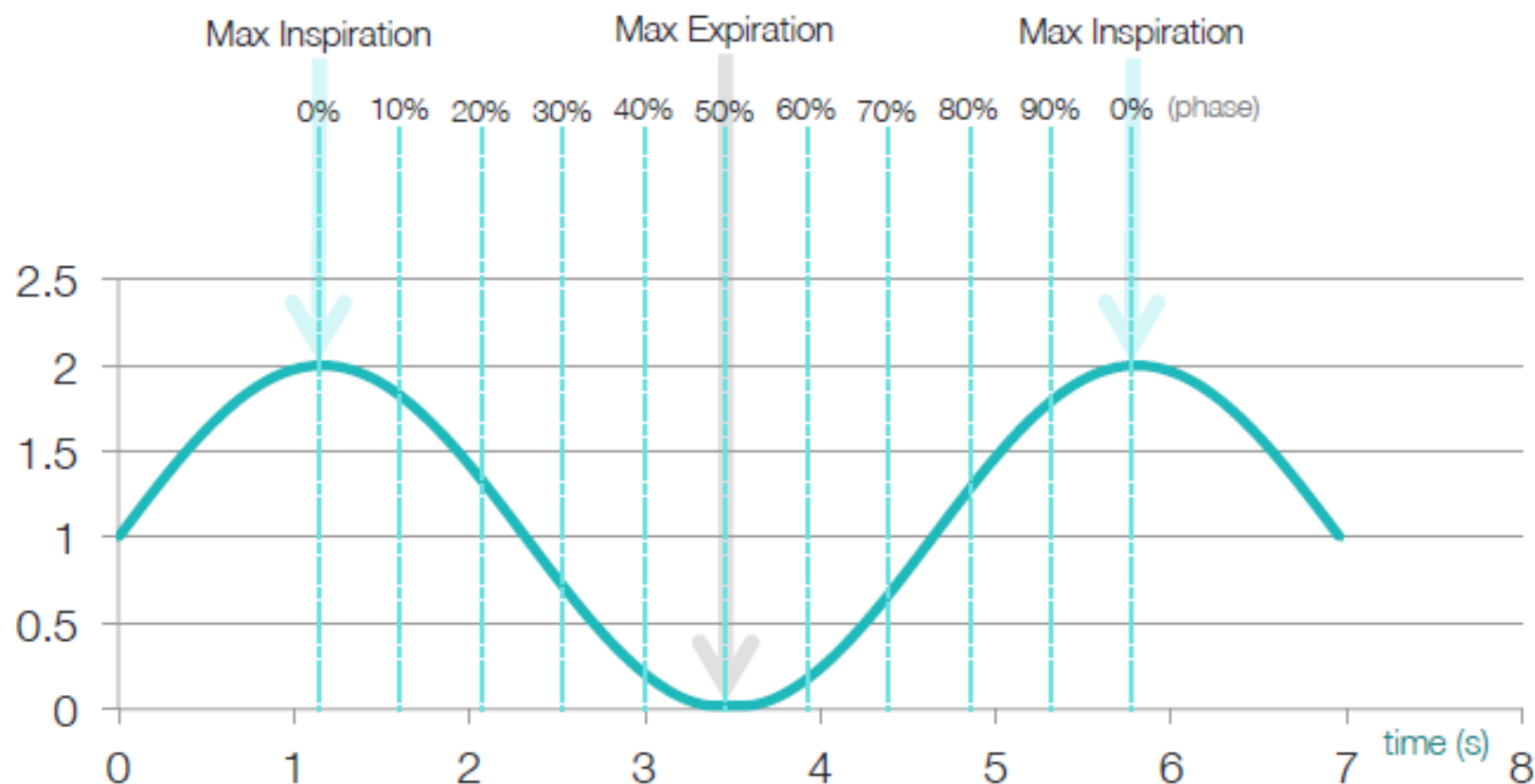
✓ *4D-CT planning (ITV definition)*

✓ *Large radiated volume*

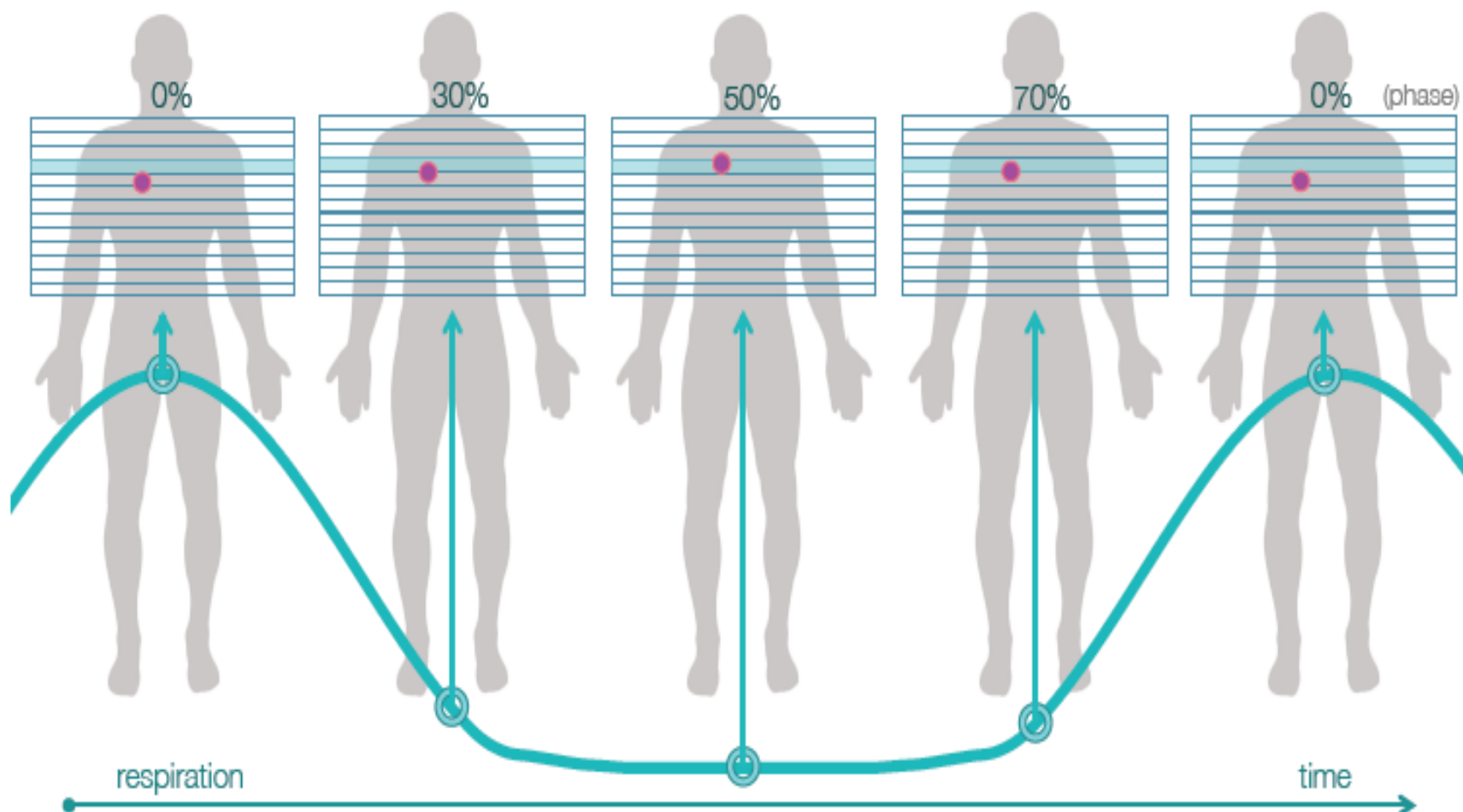


✓ *IMRT planning*

GASTRIC MALT LYMPHOMA (4D-CT planning)

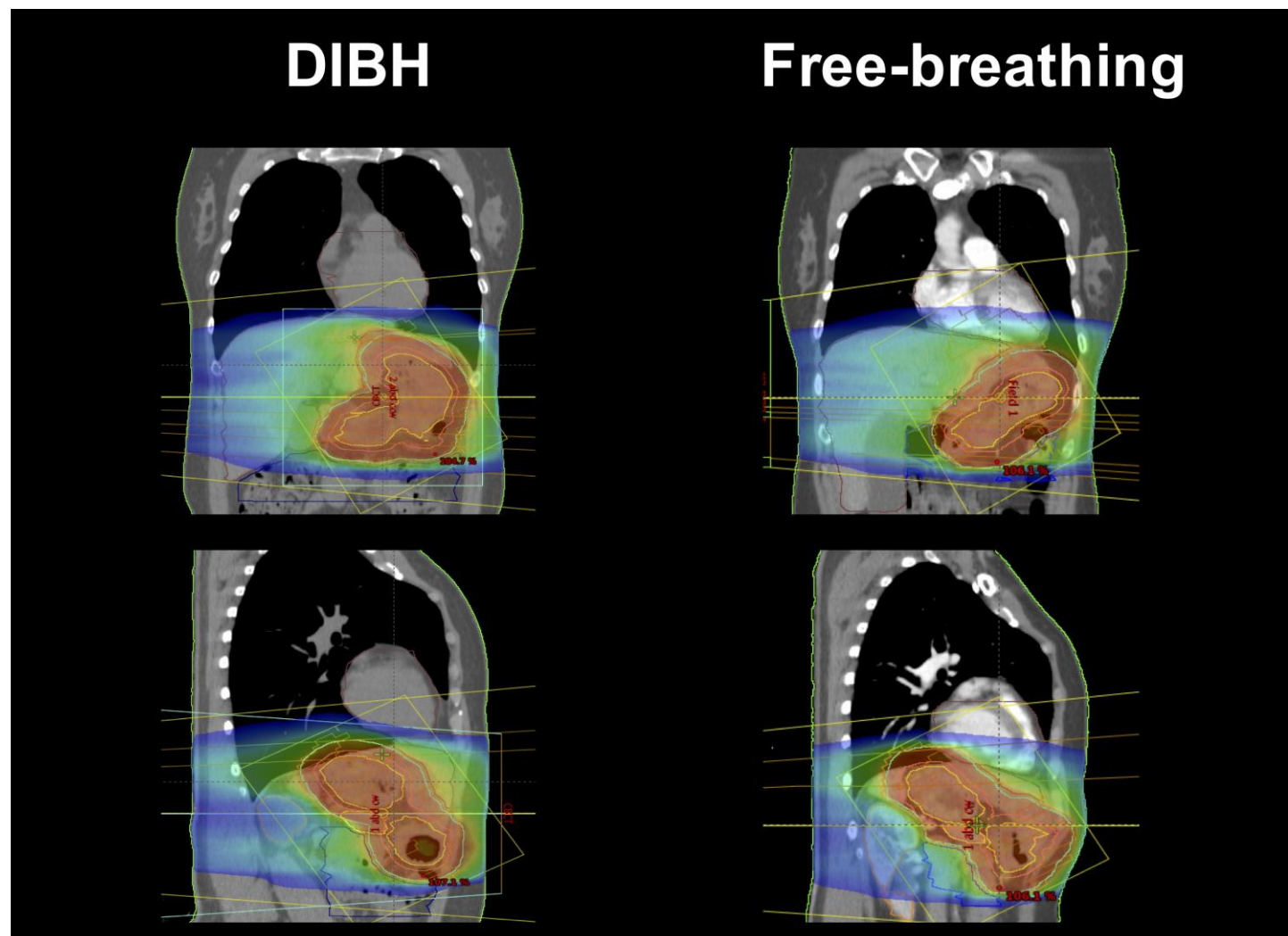


GASTRIC MALT LYMPHOMA (4D-CT planning)

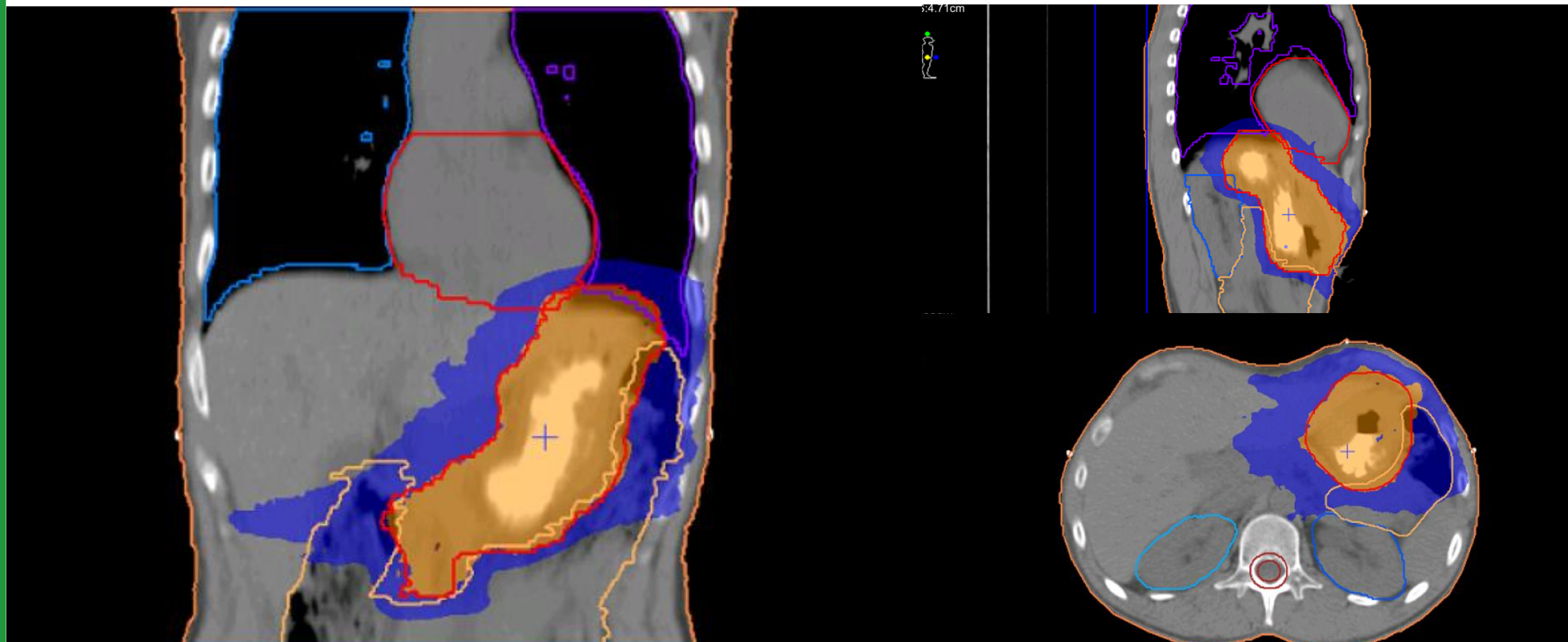


GASTRIC MALT LYMPHOMA

(DIBH is alternative to 4D-CT planning)



Optimal dose distribution with IMRT/VMAT



Critical issues #2: RT DOSES

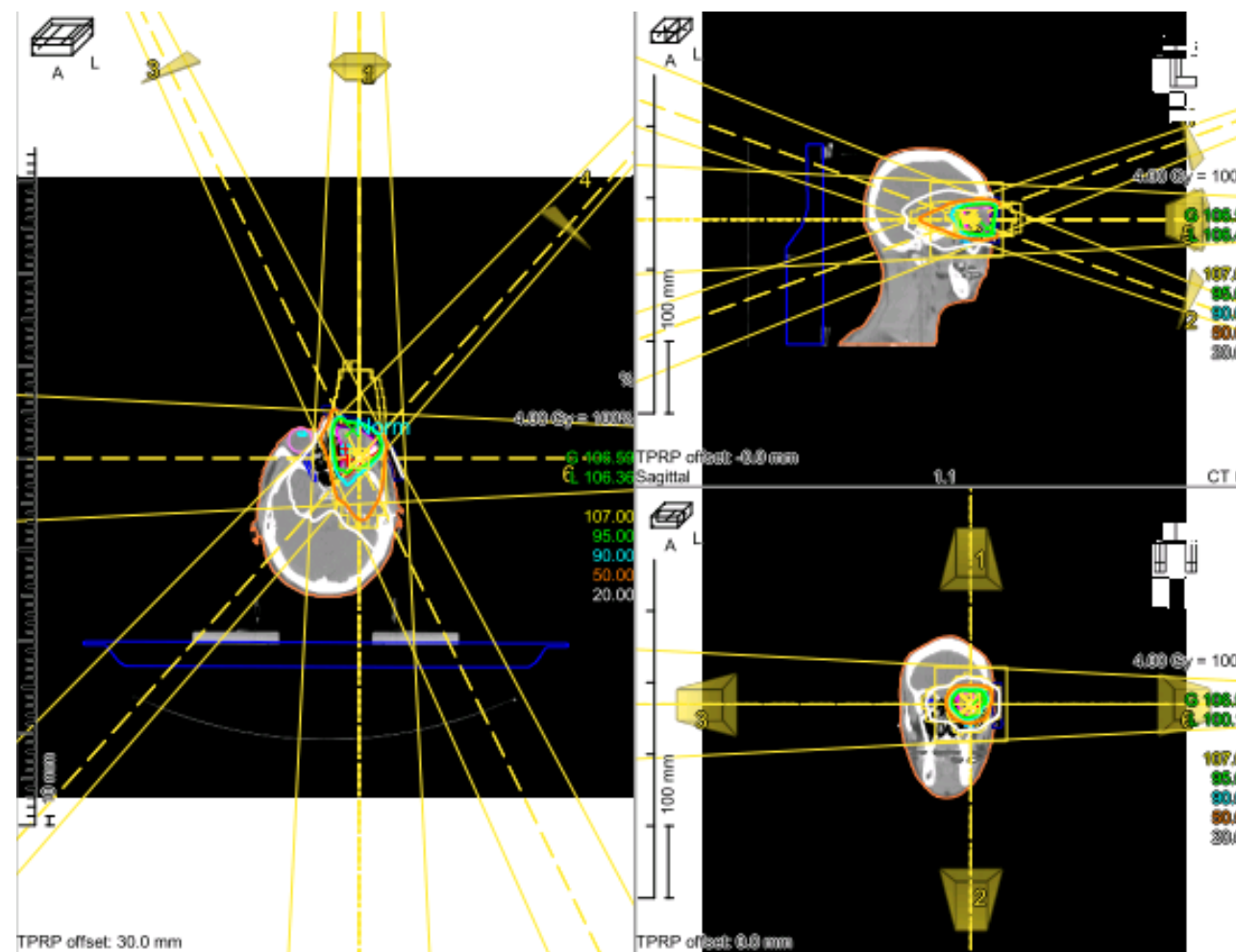
(ORBITAL MALT LYMPHOMA)

Main Complication of Ocular RT:

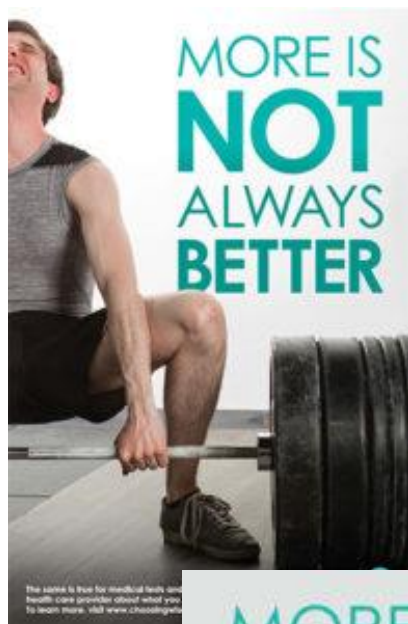
Cataract

Max RT dose tolerated by lens:

5 Gy



Can we further reduce RT dose ?



***Sometimes
more is just more...!***

Low Dose Radiotherapy

BOOM

BOOM



Basis for “Boom-Boom” Palliation

The discovery that small doses of radiotherapy could eradicate low-grade lymphomas was purely due to “serendipity”

Institute Gustave Roussy (IGR): patient refused additional palliative WAI after receiving 4 Gy

At follow-up found to be in CR



“Boom-Boom” palliation of Recurrent/Refractory NHL

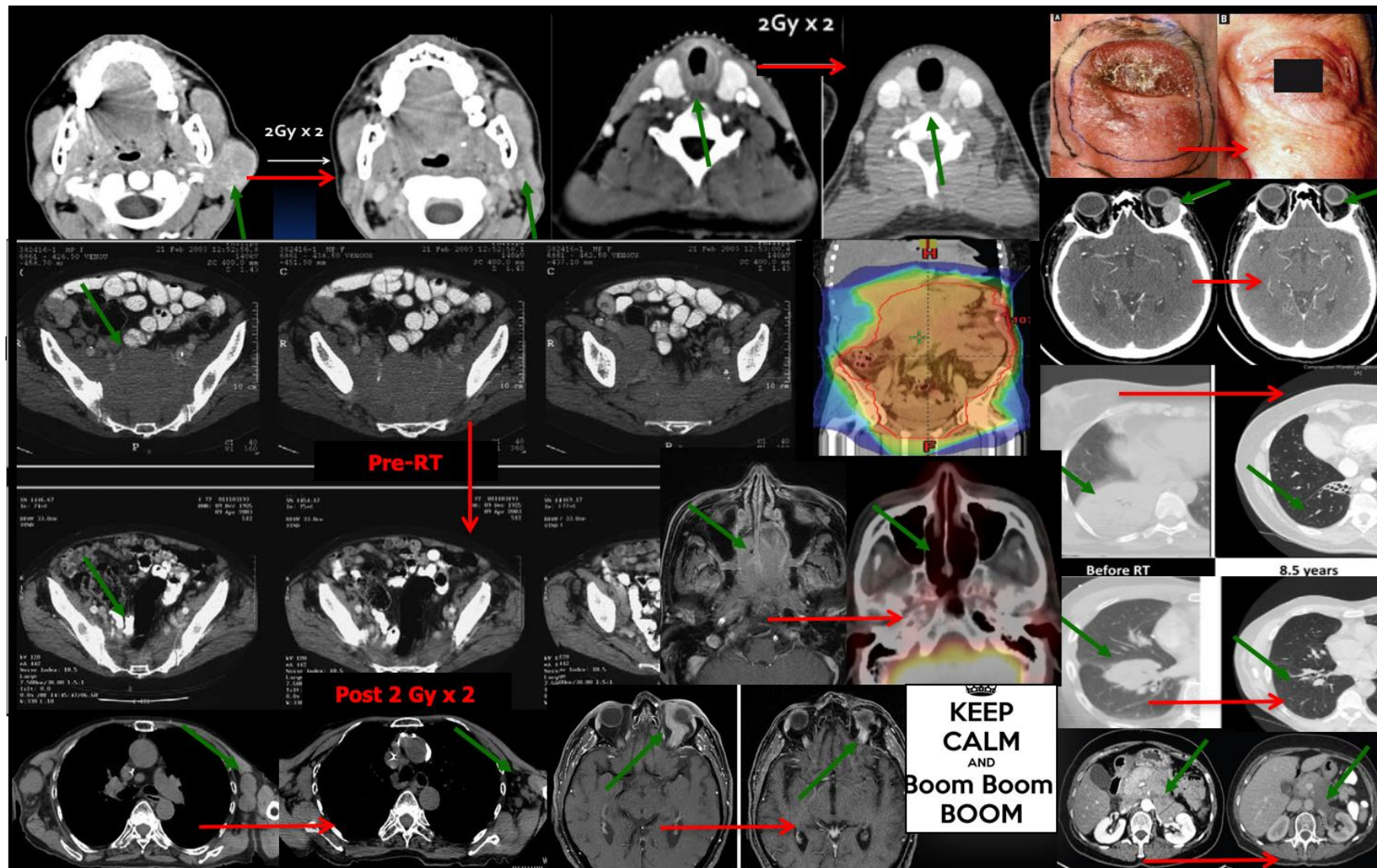
Study	N (pts)	N (sites)	PR	CR	Overall RR	Response duration	Comment
Ganem 1994	27	N/A	52%	37%	89%	Range: 4 – 35 mo	
Sawyer 1997	11	16	38%	56%	94%	Median: 7 mo	
Girinsky 2001	48	135	24%	57%	81%	2 yr actuarial: 56%	
Johannsson 2002	22	31	22%	65%	87%	Median: 22 mo	Prospective Phase II
Haas 2003	109	304	31%	61%	92%	Median: 25 mo	Prospective Phase II
Haas 2005 [†]	71	177	39%	48%	87%	Median: 22 mo	Prospective Phase II
Summary			34%	54%	88%	Median: 19 mo	

[†]Includes 30 patients (42%) with aggressive NHL.

Advantages of “Boom-Boom”

- Short treatment duration.
- Minimal morbidity. No myelosuppression.
- High response rate similar to that obtained with primary therapy.
- Effective and simple re-treatment
- Rapid response onset.
- Significant LPFS interval.

Clinical Applications



Whom to “Boom-Boom” ?

- ✓ Follicular
- ✓ Mantle-cell
- ✓ CLL/SLL
- ✓ Marginal zone

**Relapsed, refractory to systemic therapy?
As an alternative adequate first-line ?**

FoRT: A randomised trial of low dose radiotherapy for indolent lymphomas

Histologically proven follicular NHL requiring radiotherapy for definitive treatment of stage IA or IIA disease or for palliation by virtue of tumour bulk or anatomical position

Randomisation

Arm A (Control)

24Gy in 12 fractions

Arm B (Experimental)

4Gy in 2 fractions

Follow up for 5 years

(4 weeks, 12 weeks, 6 months, 12 months, 18 months, 24 months and annually thereafter)

4 Gy versus 24 Gy radiotherapy for patients with indolent lymphoma (FORT): a randomised phase 3 non-inferiority trial



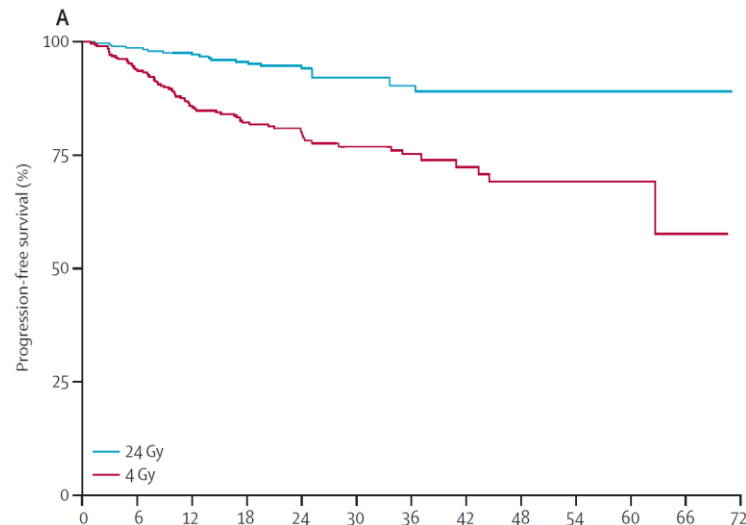
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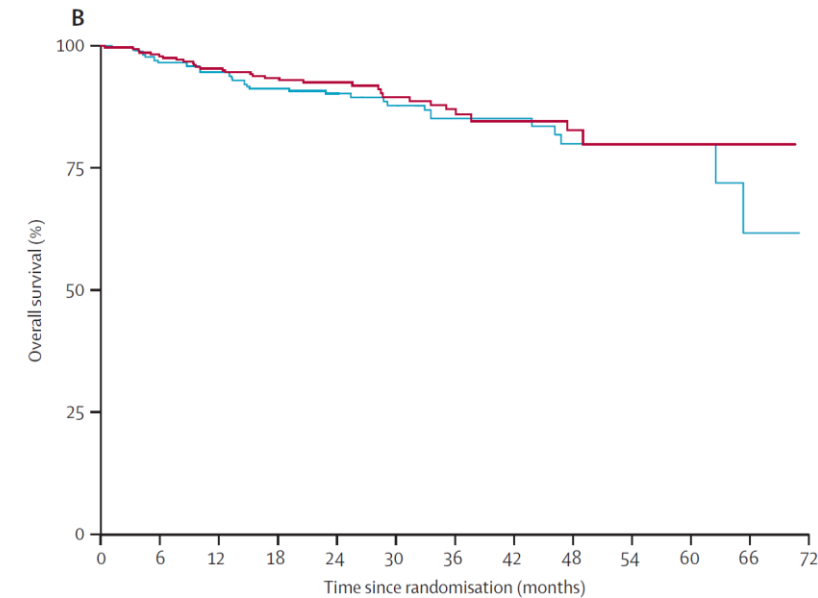
Peter J Hoskin, Amy A Kirkwood, Bilyana Popova, Paul Smith, Martin Robinson, Eve Gallop-Evans, Stewart Coltart, Timothy Illidge, Krishnaswamy Madhavan, Caroline Brammer, Patricia Diez, Andrew Jack, Isabel Syndikus

Lancet Oncol 2014

Progression Free Survival



Overall Survival



24 Gy in 12 fractions is more effective and remains the standard of treatment. “Boom boom” RT (2 Gy x 2) achieves high response rates (ORR 74%) and is a feasible option for palliation or retreatment

FORT trial (UK) 4 Gy vs 24 Gy

Response rate according to histology

Hoskin et al. Lancet Oncol 2014

	24 Gy	4 Gy
All patients*		
Complete regression	176 (68%)	137 (49%)
Partial regression (>30%)	60 (23%)	90 (32%)
Stable disease (including <30% regression)	22 (8%)	44 (16%)
Progression	2 (<1%)	10 (4%)
Total	260	281
Follicular lymphoma		
Complete regression	152 (67%)	116 (48%)
Partial regression (>30%)	53 (23%)	78 (32%)
Stable disease (including <30% regression)	19 (8%)	40 (16%)
Progression	2 (<1%)	9 (4%)
Total	226	243
Marginal zone lymphoma		
Complete regression	24 (71%)	21 (55%)
Partial regression (>30%)	7 (21%)	12 (32%)
Stable disease	3 (1%)	4 (11%)
Progression	0	1 (3%)
Total	34	38



ORR: 90% vs 80%, $p < 0.01$



ORR: 92% vs 87%, $p = 0.71$

Boom Boom RT in Orbital MALT Lymphoma

Clinical Investigation: Lymphoma

Low-Dose Radiation Therapy (2 Gy × 2) in the Treatment of Orbital Lymphoma

Carolina E. Fasola, MD, MPH,* Jennifer C. Jones, MD, PhD,[†] Derek D. Huang, MD,[‡]
Quynh-Thu Le, MD,* Richard T. Hoppe, MD,* and Sarah S. Donaldson, MD*

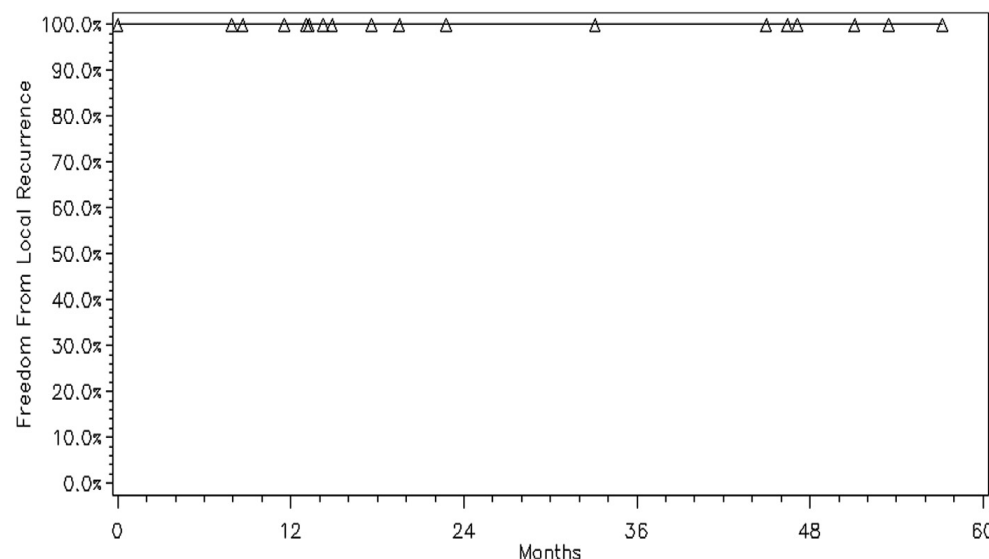
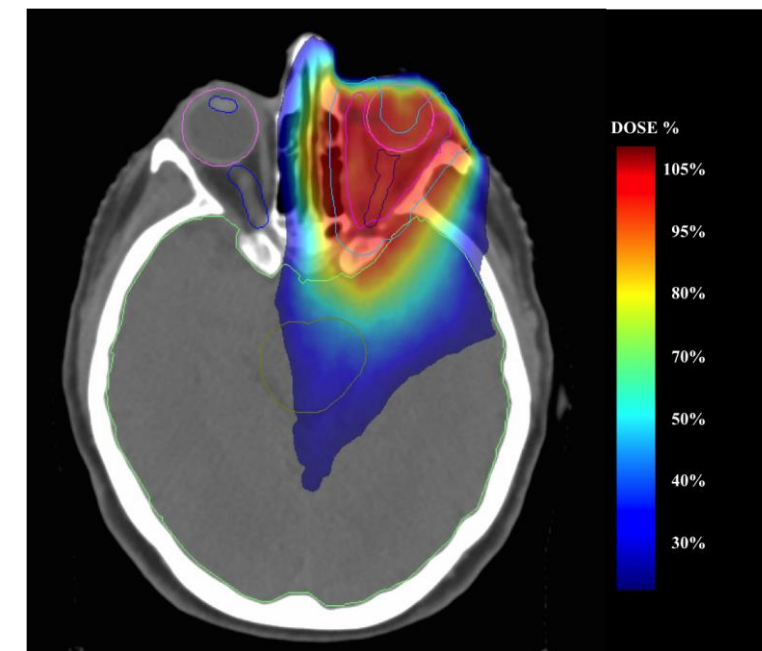


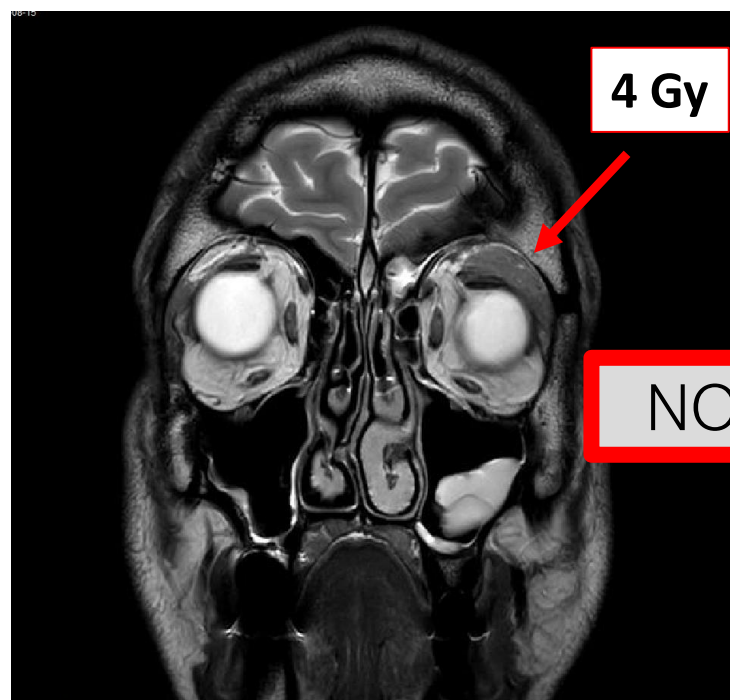
Fig. 1. Freedom from local relapse for all sites with complete response treated with low-dose radiation therapy (N=23).



LOCAL CONTROL: 100%

Efficacy of Boom Boom RT in Orbital MALT Lymphoma

Radiological response:



At diagnosis



1st FU (2 months after RT)



3rd FU (6 months after RT)

NO ACUTE and CHRONIC TOXICITIES!!!

Previous Experiences investigating LDRT in MALT lymphomas

www.filinf.it



First author, year	No. of Patients	Site of disease	Treatment	Results
	MALT/total			
Ganem, 1994 ⁶⁹	7/27	Nodal & Extranodal	2 Gy x 2 in 3 days	37% CR
Sawyer, 1997 ⁶⁶	5/11	Nodal & Extranodal	2 Gy x 2 in 3 days	38% CR, 56% PR
Haas, 2003 ⁶⁰	9/109	Nodal & Extranodal	2 Gy x 2 / 4 Gy x 1	61% CR, 31% PR, 8% non-responders
Haas, 2005 ⁶¹	25/71	Nodal & Extranodal	2 Gy x 2 / 4 Gy x 1	Median OS 67 months
Ng, 2006 ⁶⁵	2/10	Nodal & Extranodal	2 Gy x 2	90% CR
Luthy, 2008 ⁶³	2/23	Nodal & Extranodal	2 Gy x 2	88% CR, 12% PR
Rossier, 2011 ⁷⁰	13/43	Nodal & Extranodal	2 Gy x 2	28% CR, 15% PR, 26% SD, 11% PD; median OS 41 months
Chan, 2011 ⁷¹	5/54	Nodal & Extranodal	2 Gy x 2	71% CR, 17% PR, 8% SD, 2% PD, median TTLP 1.62 years
Girinsky, 2012 ⁵⁰	10/10	Lung	2 Gy x 2	5-years OS 100%, 5-years PFS 87.5%
Russo, 2013 ⁷²	18/187	Nodal & Extranodal	2 Gy x 2	TTFT-L 2.82 HR
Fasola, 2013 ⁴⁷	20/20	Orbit	2 Gy x 2	85% CR, 11% PR; 2-years FFLR 100%
Hoskin, 2014 ³⁴	72/548	Nodal & Extranodal	2 Gy x 2 vs. 24 Gy x 12	55% CR
Pinnix, 2017 ⁴⁸	14/22	Ocular adnexa	2 Gy x 2	86% CR, 14% PR; ORR 100%
Konig, 2018 ⁷³	20/47	Nodal & Extranodal	2 Gy x 2	90% CR, 3% PR; ORR 93%
Goyal, 2018 ⁷⁴	34/54	Skin	2 Gy x 2 / 4 Gy x 2	94% CR, 1-year failure rate: 6.7%
Ludmir, 2019 ⁷⁵	11/11	Breast	2 Gy x 2 vs 30 Gy x 15	Time from initial treatment to progression: 45.6 months; 5-years PFS 100%
Total	267/1247			

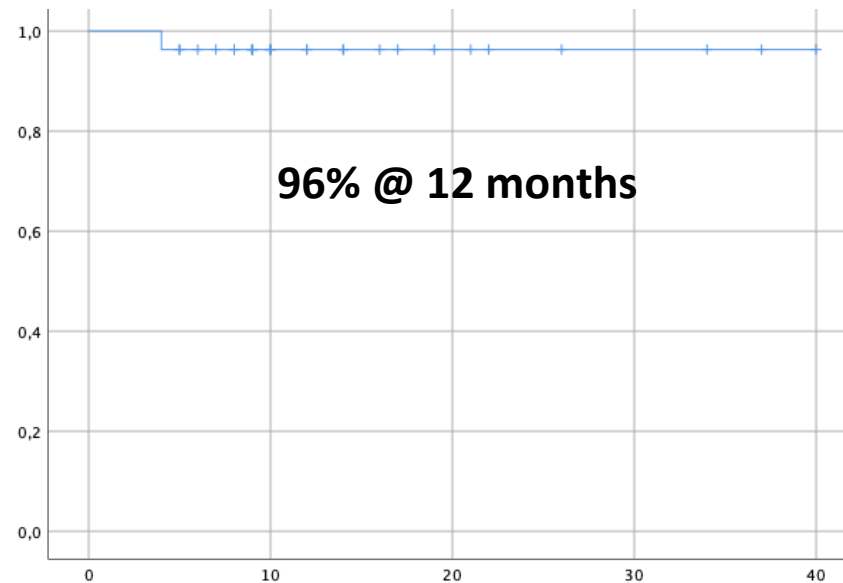
LDRT Experience in MZLs and MALT lymphomas @ UniTo

□ 27 patients

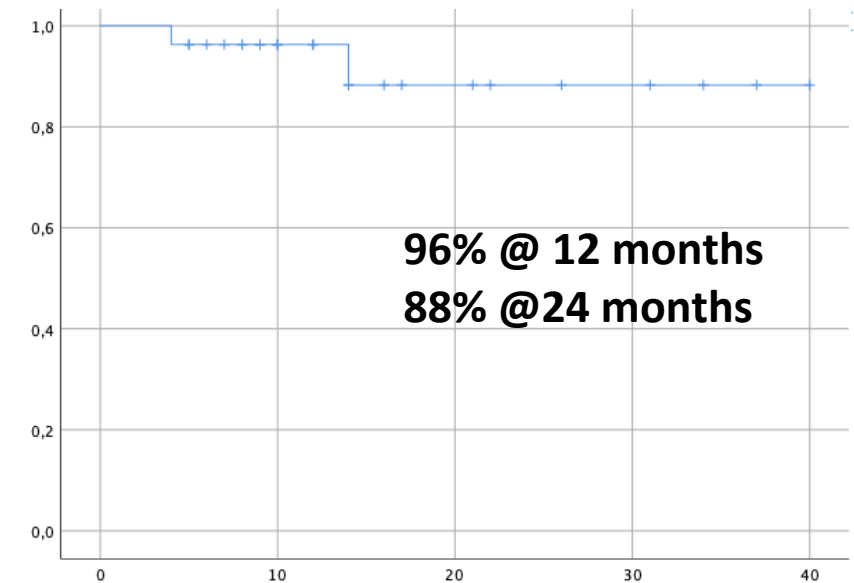
□ Sites of disease:

- Nodal
- Gastric
- Orbit
- Lung
- Breast
- Salivary glands

Local Control



Progression Free Survival

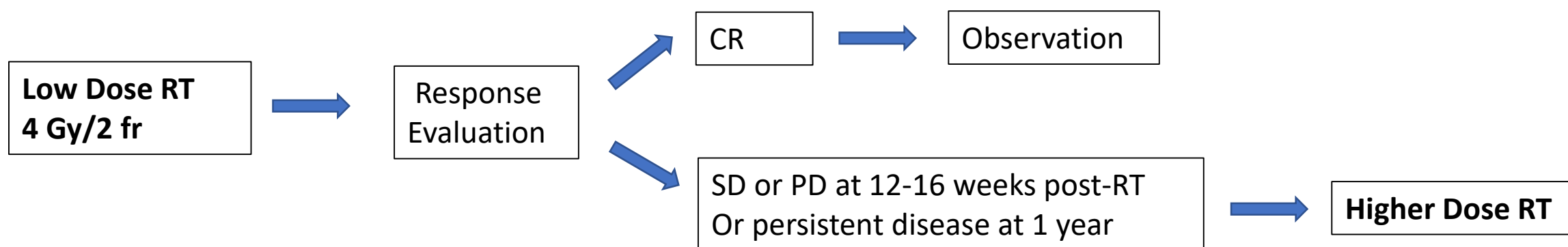


Low-Dose Radiation Therapy in Treating Patients With Stage I-IV Stomach MALT Lymphoma

Ongoing study

M.D. Anderson Cancer Center

Jillian Gunther



Primary outcome: Complete gastric response [Time Frame: Up to 1 year]

**Estimated Primary Completion
Date**

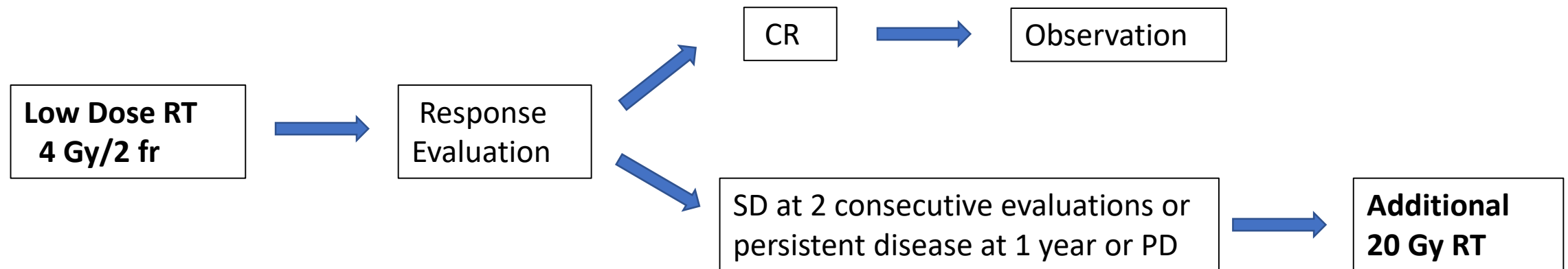
May 8, 2021 (Final data collection date for primary outcome measure)

Ultra Low Dose 4 Gy Orbital Radiation for Definitive Therapy of Indolent B Cell Lymphoma

M.D. Anderson Cancer Center

Chelsea C. Pinnix, MD

Ongoing study



Primary outcome: Local Orbital Control [Time Frame: 12 weeks]

Estimated Primary Completion
Date

July 1, 2019 (Final data collection date for primary outcome measure)

***Low dose radiotherapy (2 x 2 Gy) in early stage nodal
and extra-nodal Marginal Zone Lymphoma: a
prospective multicenter phase II study.***

PI: Mario Levis

Department of Oncology, Radiation Oncology

University of Torino

Obiettivo dello Studio

Obiettivo principale dello studio è indagare se il trattamento radiante a bassa dose **(2 x 2 Gy) sia efficace quanto quello a dose standard**, per quanto riguarda il controllo locale di malattia (LC) e la sopravvivenza libera da progressione sistemica (PFS).

Disegno dello studio

Si tratta di uno **studio prospettico interventistico a singolo braccio di fase II**, per pazienti affetti da Linfoma non Hodgkin ad istologia marginale in stadio iniziale, a localizzazione nodale ed extranodale, candidati a **trattamento radioterapico esclusivo**.

Considerazioni Statistiche

ENDPOINT PRIMARIO:

Controllo locale di malattia a 2 anni

ENDPOINT SECONDARI:

Sopravvivenza globale a 2 anni

Sopravvivenza libera da malattia a 2 anni

Considerazioni Statistiche

- ❑ In base ai dati di letteratura ci si attende un dato di controllo locale (LC) di malattia di circa 95% a 2 anni con trattamento a dose standard (24 Gy/12 frazioni)
- ❑ Assumendo un follow-up minimo di almeno 2 anni per ogni singolo paziente arruolato nello studio, sarà necessario arruolare **93 pazienti** per raggiungere un obiettivo di non inferiorità del 10% (**dato attuariale minimo per rispettare tale obiettivo: 91%**) in termini di LC a 2 anni, con un errore alpha del 5% ed una potenza statistica del 95%.
- ❑ I costi stimati per la conduzione di tale studio (incluse le spese di assicurazione), in un numero massimo di 20 centri FIL, ammonterebbe a circa 75.000 Euro

Conclusions

- ❑ RT remains treatment of choice for majority of stage I/II₁ non follicular indolent lymphomas, resulting in long term progression free survival and possible “cure” achievable with very low morbidity
- ❑ LDRT seems to be a safe and interesting solution, particularly for MALT lymphomas.
Prospective studies are ongoing to confirm this assumption