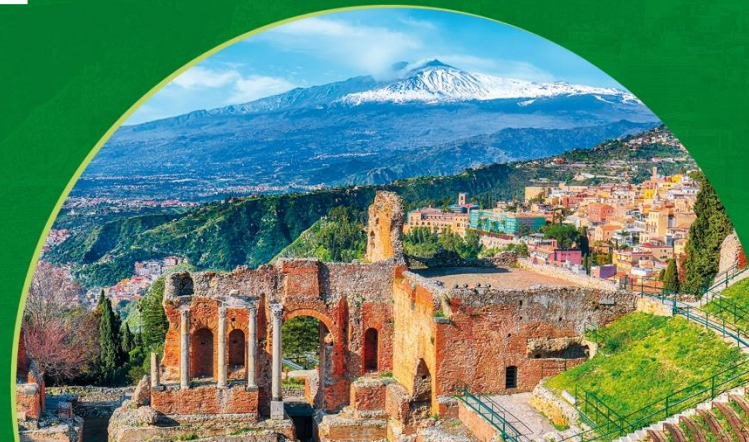


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17-18 aprile 2026



Il ruolo della radioterapia nei linfomi dell'anziano

Dr. Gabriele Simontacchi

SODc Radioterapia, DAI Oncologia, Azienda Ospedaliero Universitaria Careggi, Firenze

Disclosures of Name Surname

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KYOWA KIRIN					X	X	

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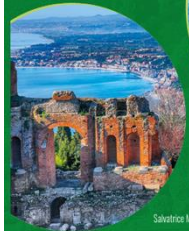
Giardini Naxos | 17-18 aprile 2026



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Marriott Delta Hotels
17-18 aprile 2026



RESPONSABILI SCIENTIFICI:
Annalisa Arcari, Francesco Di Raimondo, Giuseppe Longo

SEGRETARIA SCIENTIFICA:
Salvatrice Mancosi, Francesco Merli, Michela Sena, Alessandra Tucci



XII edizione

TORINO
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WEBINAR
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30.04.2021

Linee guida

TUMORI DELL'ANZIANO (parte generale)

Edizione 2022

G.I.O. Ger.
Gruppo Italiano di Oncologia Geriatrica

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di Oncologia
Geriatrica.**

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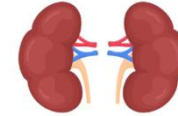


RADIOTERAPIA NEL PAZIENTE ANZIANO


1. Migliore tollerabilità
2. Adattabilità del trattamento
3. Controllo dei sintomi

MIGLIORE TOLLERABILITA'

- Minore tossicità sistemica:
 - Minore mielosoppressione
 - Minore tossicità cardiaca, renale, polmonare
 - Minori effetti su anoressia ed astenia
- Adatta a pazienti fragili (e superfragili!)
- Ridotte interazioni farmacologiche
- Conservazione qualità di vita

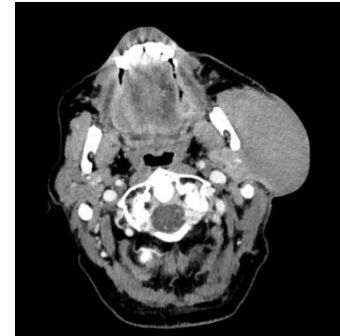


ADATTABILITA' DEL TRATTAMENTO

- Schemi ipofrazionati  $EQD_2 = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta}$
 - Trattamenti brevi
 - Ridotto impatto logistico
- Personalizzazione in base al paziente

CONTROLLO DEI SINTOMI

- Debulking di grosse masse
- Dolore (localizzazioni ossee)
- Sanguinamenti
- Compressioni

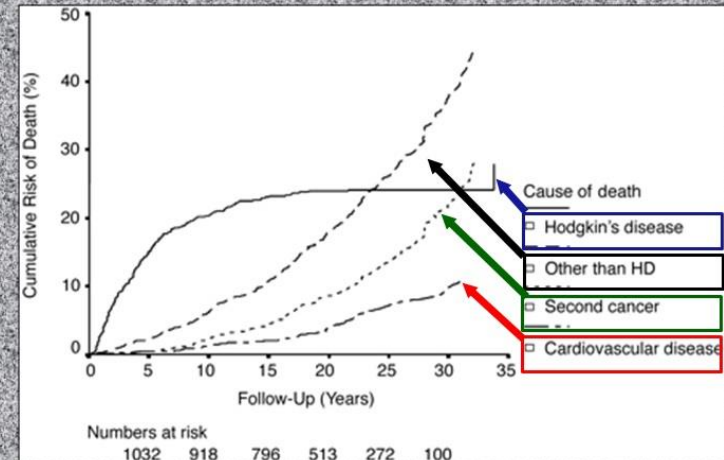


VANTAGGIO RISPETTO AI GIOVANI

- Minore rilevanza effetti tardivi
- Meno frequente (e meno rilevante!) sede mediastinica
- Miglior rapporto rischio/beneficio
- Obiettivi orientati alla qualità di vita

Importanza della tossicità tardiva

(from Aleman et al. JCO 21, 3431, 2003)

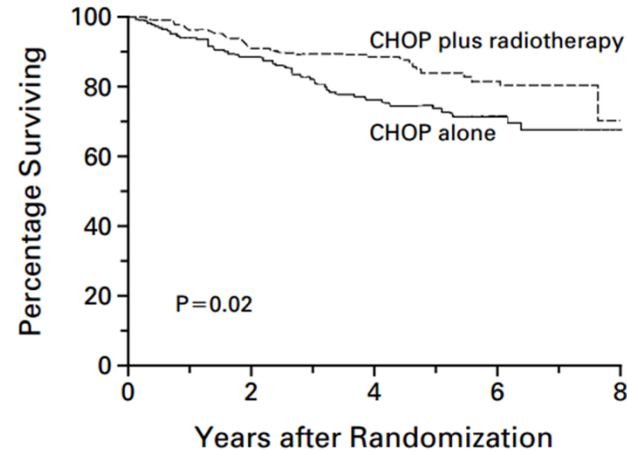


DIFFUSE LARGE B-CELL LYMPHOMA

SWOG 8736

➤ **CHOPx8 vs
CHOPx3+IFRT**

Miller, NEJM 1998



No. AT RISK

CHOP alone	201	187	120	61	14
CHOP plus radiotherapy	200	185	128	75	17

- stage I, stage IE (including bulky disease)
- stage II, stage IIE (nonbulky disease)

Table 2. Causes of Death for Patients in S8736

Cause of Death	CHOP8 (n = 92)	CHOP3RT (n = 89)	Total Deaths (n = 181)
Relapsed DLBCL	33	30	63
Cardiovascular	15	8	23
Congestive heart failure	7	1	8
Myocardial infarction	3	1	4
Stroke	4	3	7
Cardiac arrhythmia	1	1	2
Abdominal aortic aneurysm rupture	0	1	1
Pulmonary embolism	0	1	1
Second malignancy	4	10	14
Lung	1	5	6
GI	2	3	5
Breast	1	0	1
Prostate	0	1	1
Melanoma	0	1	1
Infection	8	7	15
Miscellaneous*	10	14	24
Unknown	22	20	42

Abbreviations: CHOP3RT, three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) plus radiotherapy; CHOP8, eight cycles of CHOP; DLBCL, diffuse large B-cell lymphoma.

*Amyotrophic lateral sclerosis (n = 1), Alzheimer's (n = 2), chronic obstructive pulmonary disease (n = 2), diabetes (n = 2), gastric outlet obstruction (n = 1), Lewy body dementia (n = 1), liver failure (n = 1), malnutrition (n = 2), Parkinson's (n = 2), renal failure (n = 2), respiratory failure (n = 3), suicide (n = 1), surgical complication (n = 1), and trauma (n = 3).

SWOG 8736

**Secondi tumori:
pari incidenza (11 vs 12% a 10y)**

RT ... IFRT to 40-55 Gy!

Miller, NEJM 1998



ELSEVIER



Phase III randomised trial

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

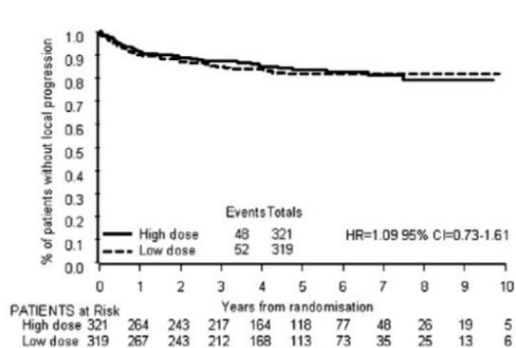
Lisa Lowry^a, Paul Smith^a, Wendi Qian^b, Stephen Falk^c, Kim Benstead^d, Tim Illidge^e, David Linch^f,
Martin Robinson^g, Andrew Jack^h, Peter Hoskin^{i,*}

RT 40-45Gy

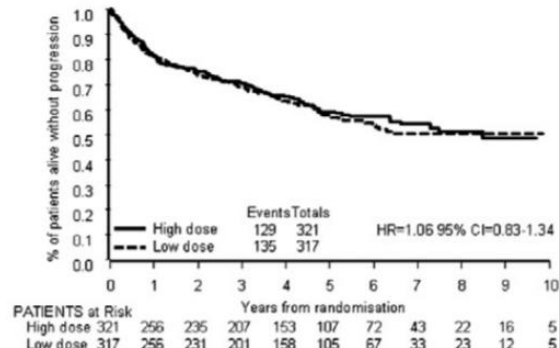
VS

RT 30Gy

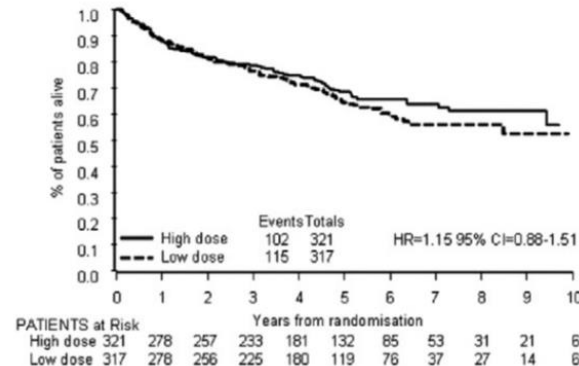
Freedom from local progression



Progression-free survival



Overall survival



CARDIAC MORTALITY IN PATIENTS WITH STAGE I AND II DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH AND WITHOUT RADIATION: A SURVEILLANCE, EPIDEMIOLOGY, AND END-RESULTS ANALYSIS

THOMAS J. PUGH, M.D., ARI BALLONOFF, M.D., KYLE E. RUSTHOVEN, M.D., ROBERT McCAMMON, M.D., BRIAN KAVANAGH, M.D., FRANCIS NEWMAN, M.S., AND RACHEL RABINOVITCH, M.D.

Cardiac Specific Mortality

Table 2. Univariate and multivariate analysis of risk factors for cardiac death in patients with early stage DLBCL*

Variable	Univariate analysis			Multivariate analysis		
	HR [†]	95% CI	p value	CHR	95% CI	p value
Age (≤60 vs. >60 yr)	5.26	4.54-6.09	<0.0001	9.91	7.72-12.7	<0.0001
Gender (female vs. male)	0.87	0.75-1.00	0.06	1.04	0.90-1.21	0.56
Race (white vs. nonwhite)	0.89	0.72-1.10	0.28	1.15	0.92-1.44	0.22
Stage (I vs. II)	0.92	0.78-1.06	0.24	0.94	0.80-1.10	0.42
Presence of extranodal disease (no extranodal vs. extranodal)	1.11	0.96-1.28	0.18	0.99	0.85-1.14	0.88
Radiation (RT vs. no RT)	1.35	1.16-1.56	<0.0001	1.32	1.13-1.54	0.0005

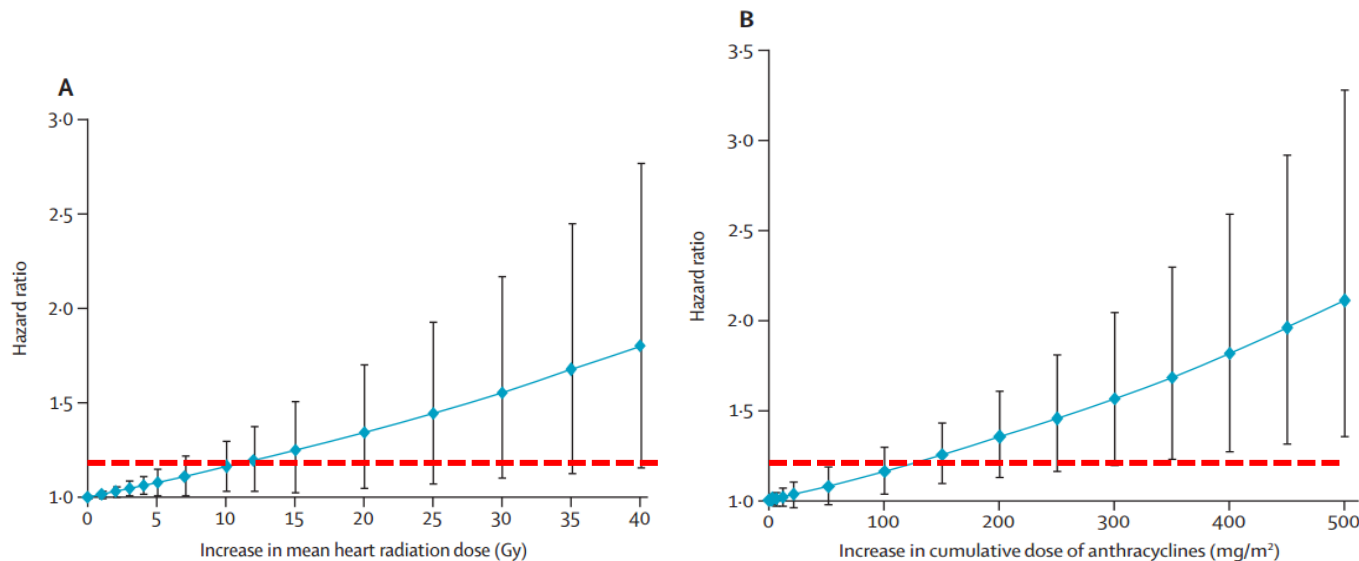
Months

No RT	9433	5129	2776	1697	1043	506	193
RT	6021	3928	2134	1189	632	321	123



Cardiovascular disease after treatment for Hodgkin's lymphoma: an analysis of nine collaborative EORTC-LYSA trials

Maja V Maraldo, Francesco Giusti, Ivan R Vogelius, Michael Lundemann, Marleen A E van der Kaaij, Safaa Ramadan, Bart Meulemans, Michel Henry-Amar, Berthe M P Aleman, John Raemaekers, Paul Meijnders, Elisabeth C Moser, Hanneke C Kluin-Nelemans, Pierre Feugier, Olivier Casasnovas, Catherine Fortpied*, Lena Specht*, on behalf of the European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group



5Gy Mean Heart Dose
=
50mg/m² anthracycline

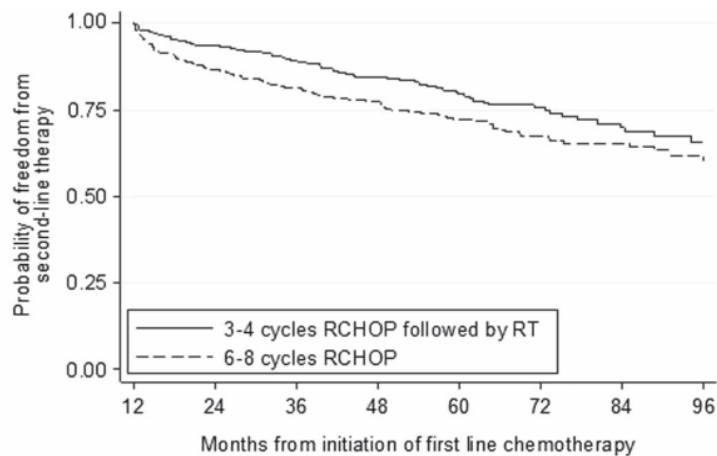
Maraldo, *LancetHaematol* 2015

Limited stage diffuse large B-cell lymphoma: comparative effectiveness of treatment strategies in a large cohort of elderly patients

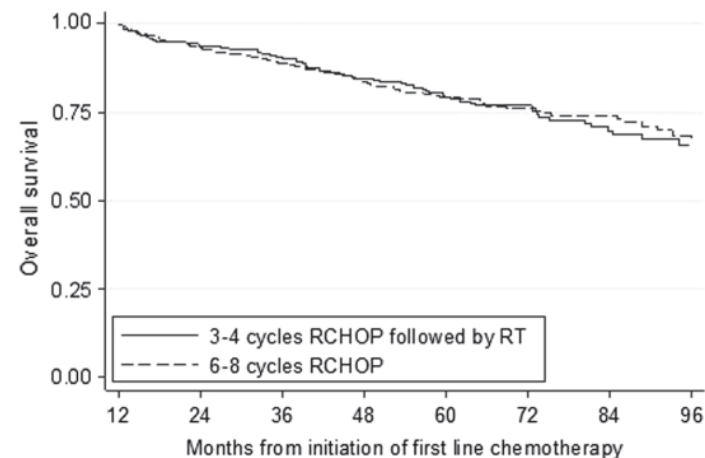
Oreofe O. Odejide^{1,3}, Angel M. Cronin¹, Amy J. Davidoff², Ann S. LaCasce³ & Gregory A. Abel^{1,4}

¹Division of Population Sciences, ³Center for Lymphoma and ⁴Center for Leukemia, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA and ²Agency for Healthcare Research and Quality, Rockville, MD, USA

- **874 pts**
- **Stage I-II**
- **>66y**



Number at risk		12	24	36	48	60	72	84	96
3-4 cycles + RT	345	275	217	177	133	95	59	33	
6-8 cycles	475	357	285	218	159	104	72	35	



Number at risk		12	24	36	48	60	72	84	96
3-4 cycles + RT	359	287	229	183	138	101	63	34	
6-8 cycles	515	418	339	259	185	124	84	38	

Table III. Association between treatment and adverse outcomes in the year following initiation of first-line therapy.

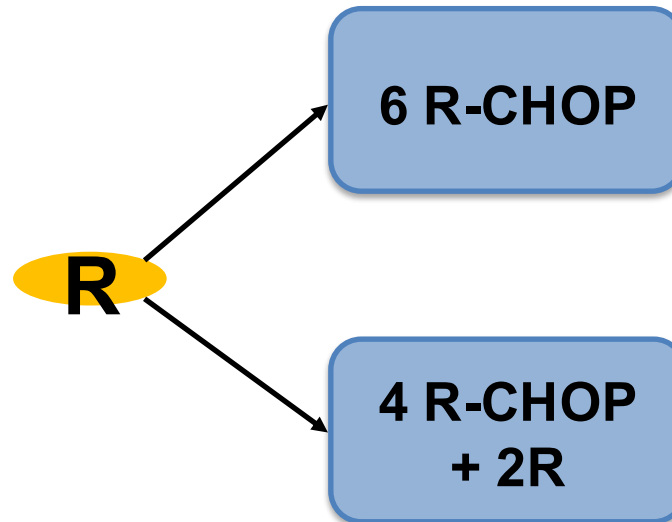
Outcome	Unadjusted % with event		Unadjusted			Propensity score adjusted, using inverse probability weights		
	3-4 cycles of RCHOP + RT	6-8 cycles of RCHOP	Odds ratio [‡]	95% CI	<i>p</i> -Value	Odds ratio [‡]	95% CI	<i>p</i> -Value
Hospitalization	42.1	47.2	0.81	0.62, 1.07	0.13	0.83	0.63, 1.09	0.17
Fever	21.2	30.9	0.60	0.44, 0.82	0.002	0.60	0.44, 0.82	0.002
Neutropenia	64.1	74.2	0.62	0.46, 0.83	0.001	0.63	0.47, 0.84	0.002
Fever & neutropenia	3.6	12.2	0.27	0.15, 0.50	<0.001	0.27	0.15, 0.50	<0.001
Infections	39.3	39.4	0.99	0.75, 1.31	0.97	0.98	0.74, 1.29	0.89
CHF*	8.8	9.1	0.97	0.59, 1.59	0.90	0.98	0.60, 1.62	0.95
Poor functional status [†]	17.5	15.5	1.16	0.78, 1.70	0.46	1.14	0.77, 1.68	0.50



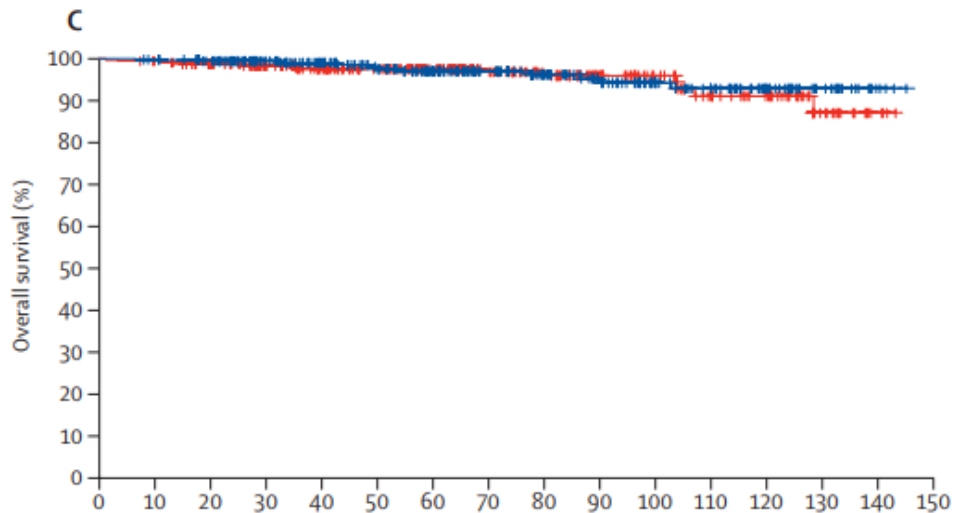
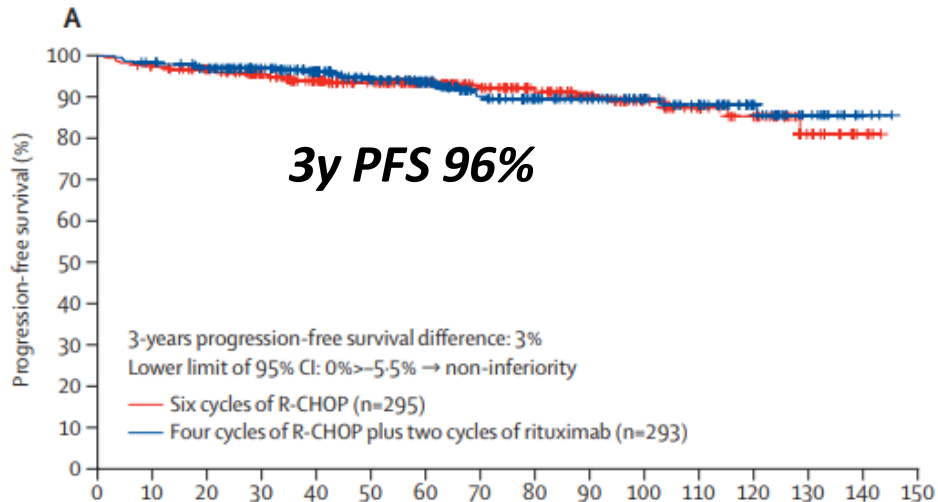
Four versus six cycles of CHOP chemotherapy in combination with six applications of rituximab in patients with aggressive B-cell lymphoma with favourable prognosis (FLYER): a randomised, phase 3, non-inferiority trial

Viola Poeschel*, Gerhard Held*, Marita Ziepert*, Mathias Witzens-Harig, Harald Holte, Lorenz Thurner, Peter Borchmann, Andreas Viardot, Martin Soekler, Ulrich Keller, Christian Schmidt, Lorenz Truemper, Rolf Mahlberg, Reinhard Marks, Heinz-Gert Hoeffkes, Bernd Metzner, Judith Dierlamm, Norbert Frickhofen, Mathias Haenel, Andreas Neubauer, Michael Kneba, Francesco Merli, Alessandra Tucci, Peter de Nully Brown, Massimo Federico, Eva Lengfelder, Alice di Rocco, Ralf Trappe, Andreas Rosenwald, Christian Berdel, Martin Maisenhoelder, Ofer Shpilberg, Josif Amam, Konstantinos Christofyllakis, Frank Hartmann, Niels Murawski, Stephan Stilgenbauer, Maik Nickelsen, Gerald Wulf, Bertram Glass, Norbert Schmitz, Bettina Altmann, Markus Loeffler†, Michael Pfreundschuh†, for the FLYER Trial Investigators†, on behalf of the German Lymphoma Alliance

- 592 pts aged 18–60 years
- stage I–II disease
- aalPI 0
- no bulky disease (7,5cm)



- No RT planned (except testicle)



... new standard for Early Stage, IPI 0, no Bulky DLBCL

...but not for older patients!

Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60) ➔ @ +

Michael Pfreundschuh, Joerg Schubert, Marita Ziepert, Rudolf Schmits, Martin Mohren, Eva Lengfelder, Marcel Reiser, Christina Nickenig, Michael Clemens, Norma Peter, Carsten Bokemeyer, Hartmut Eimermacher, Anthony Ho, Martin Hoffmann, Roland Mertelsmann, Lorenz Trümper, Leopold Balleisen, Ruediger Liersch, Bernd Metzner, Frank Hartmann, Bertram Glass, Viola Poeschel, Norbert Schmitz, Christian Ruebe, Alfred C Feller, Markus Loeffler, for the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL)

- 1222 pts >60y, any IPI
- RT to all sites of bulky disease

-Arm I: CHOP 14 x 6

-Arm II: R-CHOP 14 x 6

-Arm III: CHOP 14 x 8

-Arm IV: R-CHOP 14 x 8

Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60) ➔ @ +

Michael Pfreundschuh, Joerg Schubert, Marita Ziepert, Rudolf Schmits, Martin Mohren, Eva Lengfelder, Marcel Reiser, Christina Nickenig, Michael Clemens, Norma Peter, Carsten Bokemeyer, Hartmut Eimermacher, Anthony Ho, Martin Hoffmann, Roland Mertelsmann, Lorenz Trümper, Leopold Balleisen, Ruediger Liersch, Bernd Metzner, Frank Hartmann, Bertram Glass, Viola Poeschel, Norbert Schmitz, Christian Ruebe, Alfred C Feller, Markus Loeffler, for the German High-Grade Non-Hodgkin Lymphoma Study Group (DSHNHL)

	EFS			PFS			Death		
	RR	95% CI	p	RR	95% CI	p	RR	95% CI	p
8xCHOP-14	0.76	0.60-0.95	0.0172*	0.92	0.72-1.18	0.4906*	0.98	0.74-1.30	0.8969*
6xR-CHOP-14	0.51	0.40-0.65	<0.0001*	0.50	0.38-0.67	<0.0001*	0.63	0.46-0.85	0.0031*
8xR-CHOP-14	0.54	0.43-0.69	<0.0001*	0.59	0.45-0.77	0.0001*	0.78	0.58-1.05	0.1015*
LDH >UNV	1.53	1.26-1.86	<0.0001	1.75	1.41-2.17	<0.0001	1.77	1.39-2.27	<0.0001
ECOG >1	1.70	1.36-2.13	<0.0001	1.59	1.24-2.03	0.0002	1.67	1.29-2.16	<0.0001
Extranodal involvement >1	1.27	1.01-1.59	0.0402	1.45	1.14-1.85	0.0024	1.44	1.10-1.87	0.0074
Stage III or IV	1.57	1.28-1.93	<0.0001	1.76	1.39-2.22	<0.0001	1.59	1.23-2.06	0.0004
Bulky disease	0.96	0.80-1.16	0.7032	0.91	0.74-1.12	0.3526	1.14	0.91-1.43	0.2616
Age >70 years	1.34	1.12-1.60	0.0014	1.43	1.17-1.73	0.0004	1.77	1.43-2.20	<0.0001

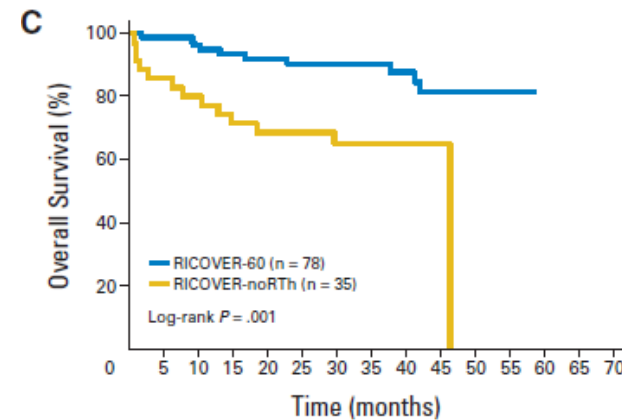
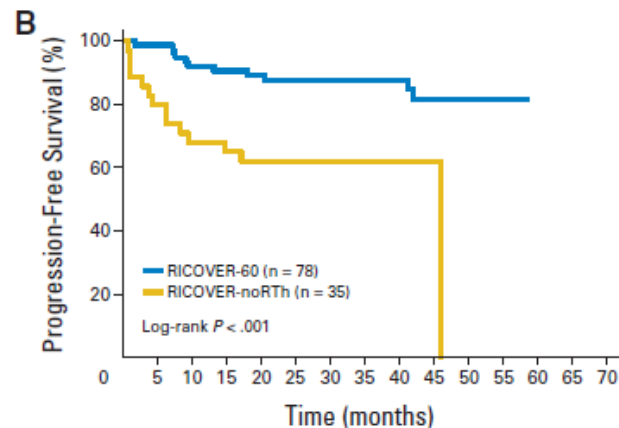
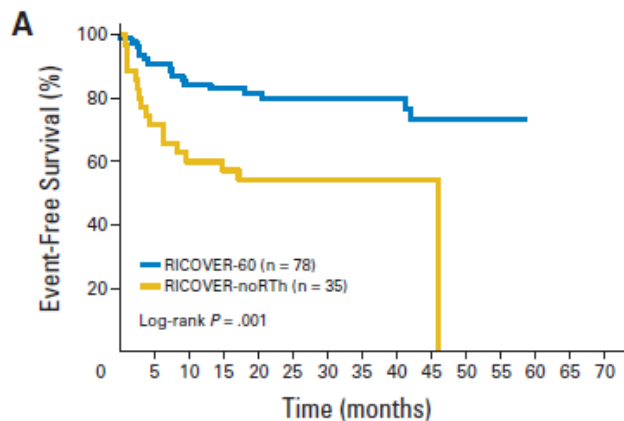
EFS=event-free survival. PFS=progression-free survival. *p value derived from comparison with 6xCHOP-14 treatment.

Table 3: Multivariate analysis of outcome adjusted for strata

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

Gerhard Held, Niels Murawski, Marita Ziepert, Jochen Fleckenstein, Viola Pöschel, Carsten Zwick, Jörg Bittenbring, Mathias Hänel, Sibylla Wilhelm, Jörg Schubert, Norbert Schmitz, Markus Löffler, Christian Rübe, and Michael Pfreundschuh

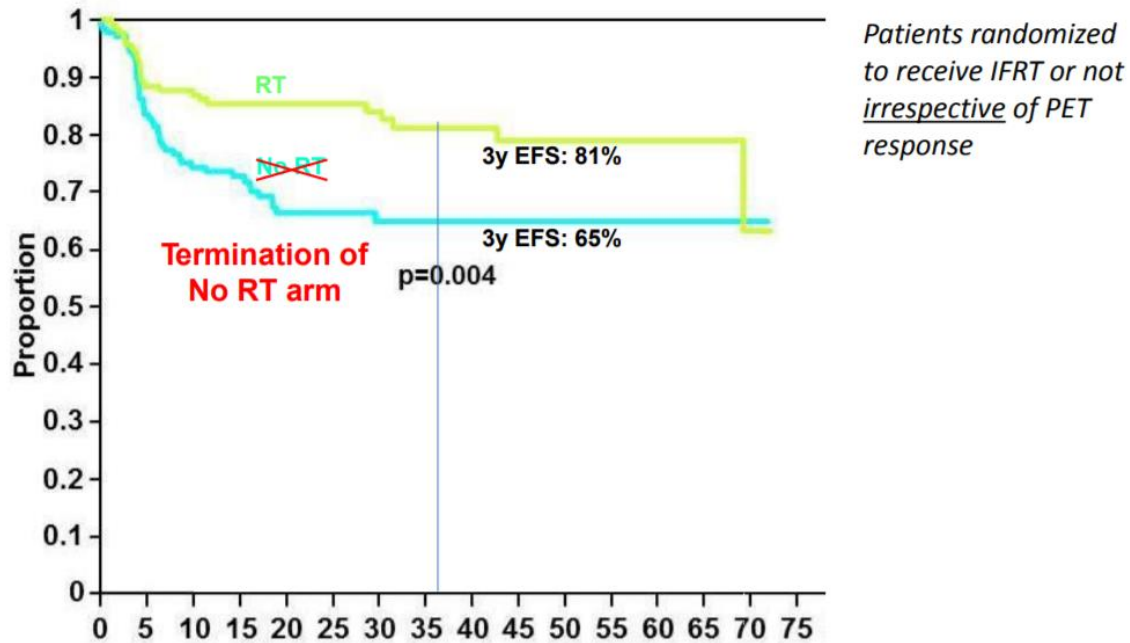
RICOVER 60-noRTh



UNFOLDER Trial

- ❖ Eligibility: early-stage DLBCL, aged 18-60, aa-IPI=1 or IPI=0 with bulky disease (≥ 7.5 cm)
- ❖ Pts with bulky and/or extranodal disease randomized to 1 of 4 arms (n=285):
 - Arm I: R-CHOP 21 x 6 alone
 - Arm II: R-CHOP 21 x 6; if CR \rightarrow IFRT
 - Arm III: R-CHOP 14 x 6 alone
 - Arm IV: R-CHOP 14 x 6; if CR \rightarrow IFRT

UNFOLDER Trial



Pfreundschuh, ASCO 2018

OPTIMAL>60 trial

Pfreundschuh et al. (2017)
(updated Thurner EHA 2025)

- 61 to 80 y-old pts.
- 2x2 factorial design:
-6xCHOP-14 or 6xCHLIP-14
-plus 8R vs 12R
- PET-based strategy for bulky patients:
-No RT if PET negative

- 187/505 (37%) had bulky disease and were compared to 117/306 (38%) RICOVER-60 pts.
- PET was performed in 166/187
- 80/166 (48%) bulks remained PET-positive after 6 cycles of chemotherapy and 62/80 (78%) were irradiated
- reducing RT from 67/117 (57%) in RICOVER-60 by 42% to 62/187 (33%) in OPTIMAL>60
- outcome of the 187 bulk pts. in OPTIMAL>60 was non-inferior to RICOVER-60
(2y PFS and OS 79% and 88% vs 75% and 78%)



Attenuated immunochemotherapy regimen (R-miniCHOP) in elderly patients older than 80 years with diffuse large B-cell lymphoma: a multicentre, single-arm, phase 2 trial

*Frédéric Peyrade, Fabrice Jardin, Catherine Thieblemont, Antoine Thyss, Jean-François Emile, Sylvie Castaigne, Bertrand Coiffier, Corinne Haioun, Serge Bologna, Olivier Fitoussi, Gérard Lepeu, Christophe Fruchart, Dominique Bordessoule, Michel Blanc, Richard Delarue, Maud Janvier, Bruno Salles, Marc André, Marion Fournier, Philippe Gaulard, Hervé Tilly, for the Groupe d'Etude des Lymphomes de l'Adulte (GELA) investigators**

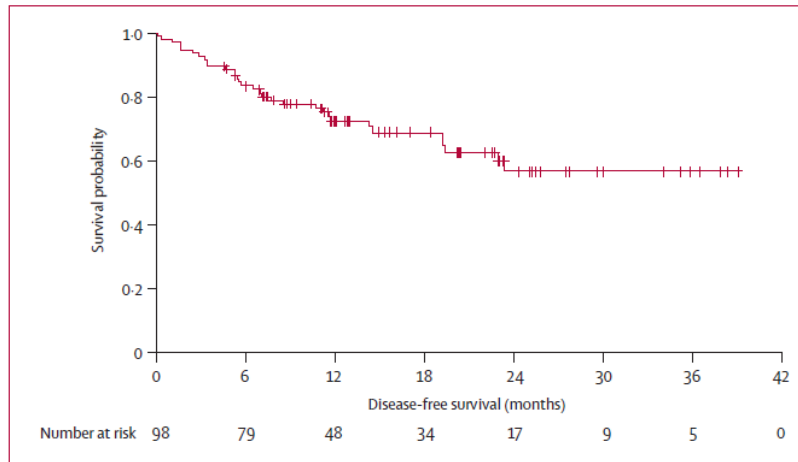





Figure 5: Disease-free survival

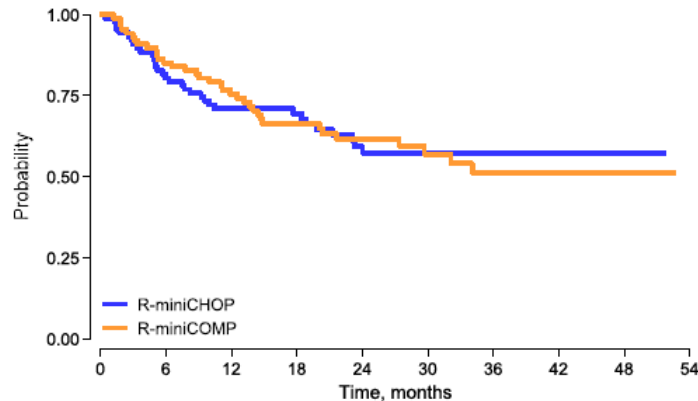
Only patients who attained a complete response or an unconfirmed complete response during treatment are included.

62% complete response and unconfirmed complete response rate.

These results compare unfavourably with those from patients aged 60–80 years who were treated with full-dose CHOP and rituximab, in whom the complete remission rate was 76% and median survival was more than 8 years

Comparative Effectiveness of R-miniCOMP Versus R-miniCHOP in Older Non-Fit Patients With Diffuse Large B-Cell Lymphoma: Insights From a “Fondazione Italiana Linfomi” Cohort Study

Alberto Bavieri^{1,2}  | Sara Veronica Usai³ | Michele Merli⁴ | Alice Di Rocco⁵ | Federica Cavallo⁶ | Vittorio Ruggero Zilioli⁷  | Manuela Zanni⁸ | Flenghi Leonardo⁹ | Dario Marino¹⁰ | Annalisa Arcari¹¹ | Emanuele Cencini¹² | Guido Gini¹³ | Barbara Botto¹⁴ | Alessandra Tucci¹⁵ | Clara Deambrogi¹⁶ | Plenteda Caterina¹⁷ | Bianchi Maria Paola¹⁸ | Stefan Hohaus¹⁹ | Manuel Gotti²⁰ | Benedetta Puccini²¹ | Daniela Dessì³ | Coscia Marta⁴ | Luigi Petrucci²² | Simone Ragaini⁶ | Emanuela Chimienti²³ | Luigi Marcheselli²⁴ | Caterina Mammi²⁵ | Stefano Luminari^{2,26} | Michele Spina²³ | Francesco Merli² 



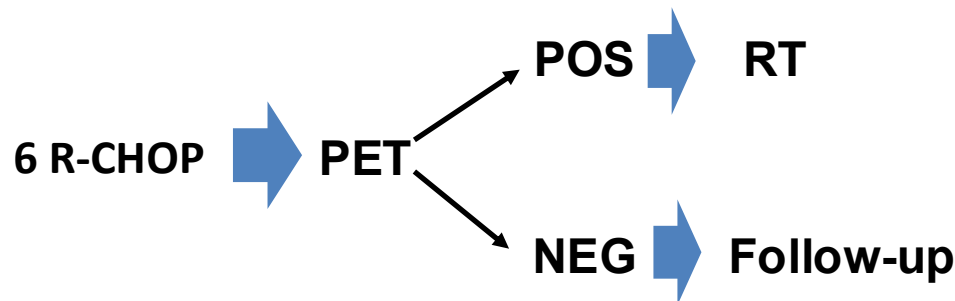
at risk (fall)	0	6	12	18	24	30	36	42	48	54									
RmCHOP	89	(17)	69	(8)	54	(1)	44	(6)	31	(1)	21	(0)	7	(0)	3	(0)	1	(0)	0
RmCOMP	87	(13)	74	(8)	60	(7)	46	(3)	33	(2)	22	(2)	12	(0)	5	(0)	4	(0)	0

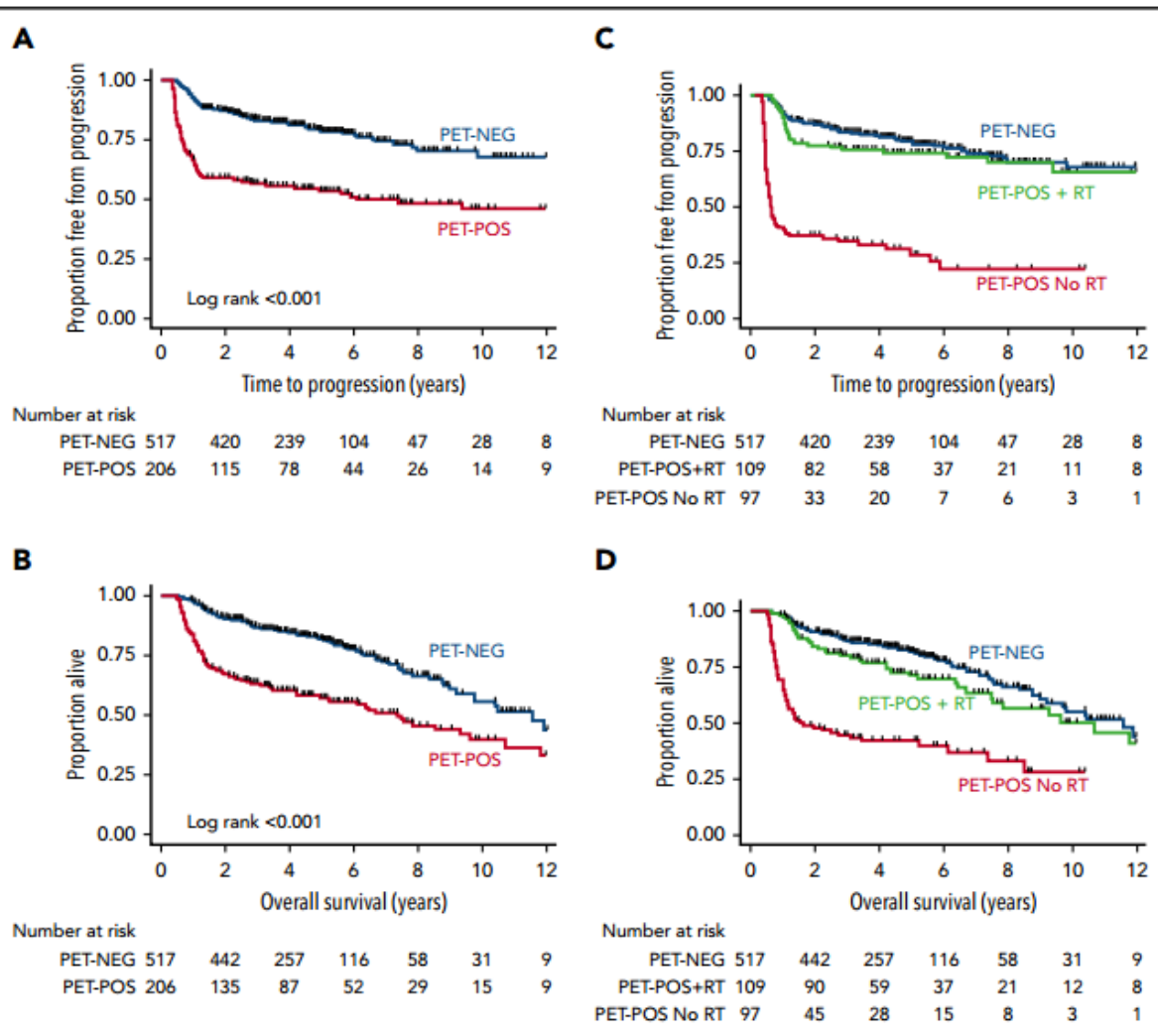
Long-term results of PET-guided radiation in patients with advanced-stage diffuse large B-cell lymphoma treated with R-CHOP

Ciara L. Freeman,^{1,2} Kerry J. Savage,^{1,2} Diego R. Villa,^{1,2} David W. Scott,^{1,2} Line Srour,³ Alina S. Gerrie,^{1,2} Maura J. Brown,⁴ Graham W. Slack,⁵ Pedro Farinha,⁵ Brian Skinnider,⁵ James Morris,⁶ François Bénard,⁷ Christina Aquino-Parsons,⁶ Andrea Lo,⁶ Tom Pickles,⁶ Don C. Wilson,⁷ Petter Tonseth,⁷ Joseph M. Connors,^{1,2} and Laurie H. Sehn^{1,2}

Blood 2021

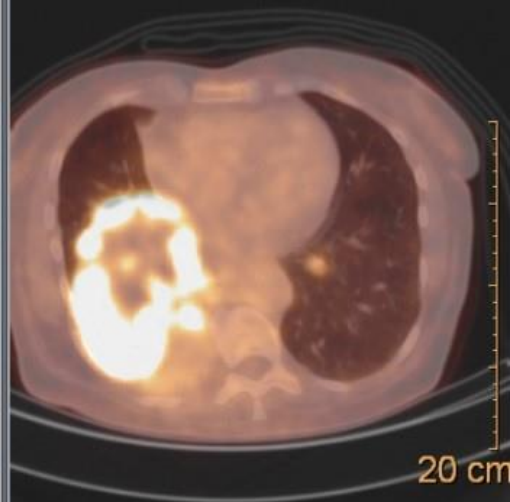
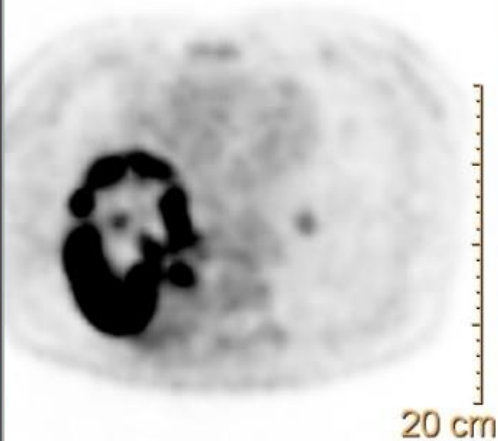
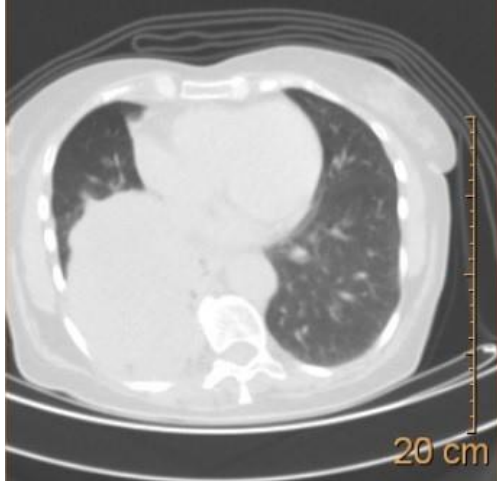
- 723 pts
- stage III-IV disease
- Any IPI
- Bulky 39%

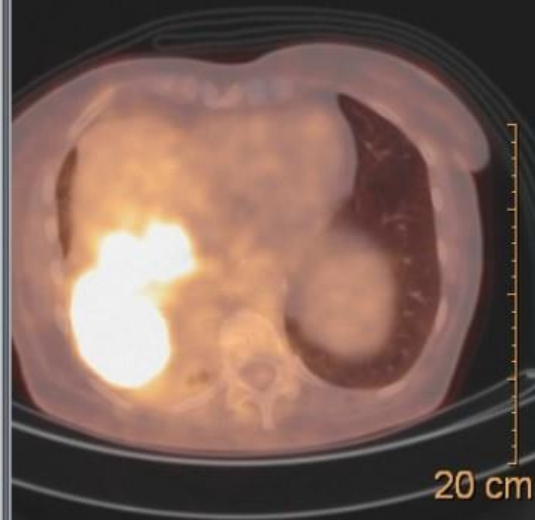
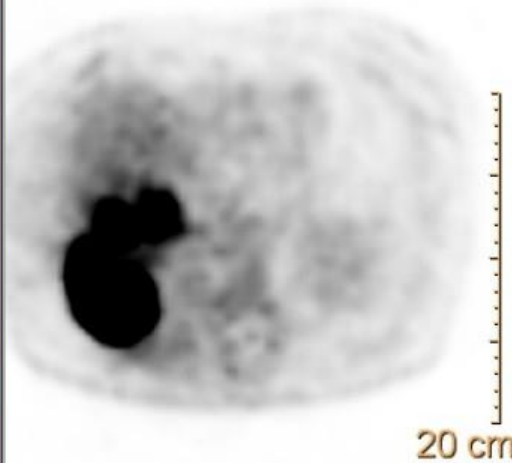


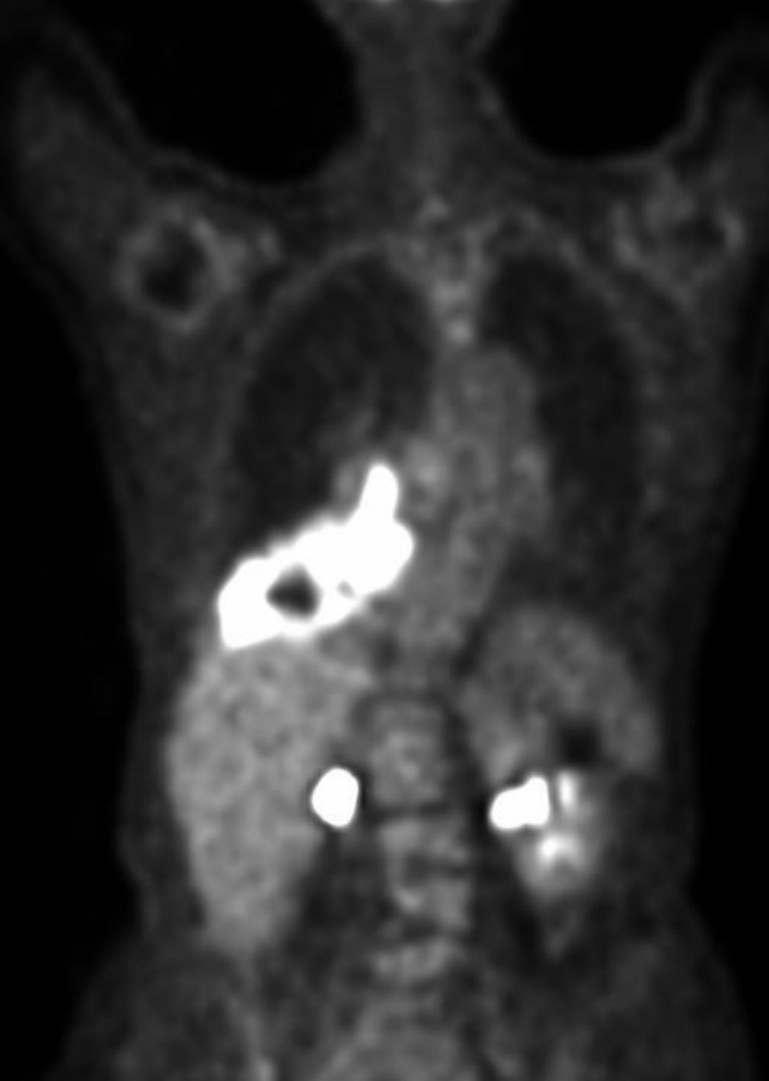


➤ «RESCUE» DI POSITIVITA' PET RESIDUA LIMITATA

- **G.P. (F, 71 anni)**
- Non comorbidità in anamnesi. PS 0
- Comparsa di tosse ed astenia
- TC (10/2020): a livello del L12 irregolare tessuto solido che raggiunge la pleura sovradiaframmatica con diametri maggiori sul piano assiale di circa 10cm (AP) x 8 cm (LL) per una estensione cranio-caudale complessiva di circa 13 cm (dal bronco subsegmentario allo sfondato costo frenico)
- Biopsia TC guidata: Linfoma diffuso a grandi cellule B, non-GCB (CD20+, Bcl-2+, c-Myc+ 30%, Ki67 80%)



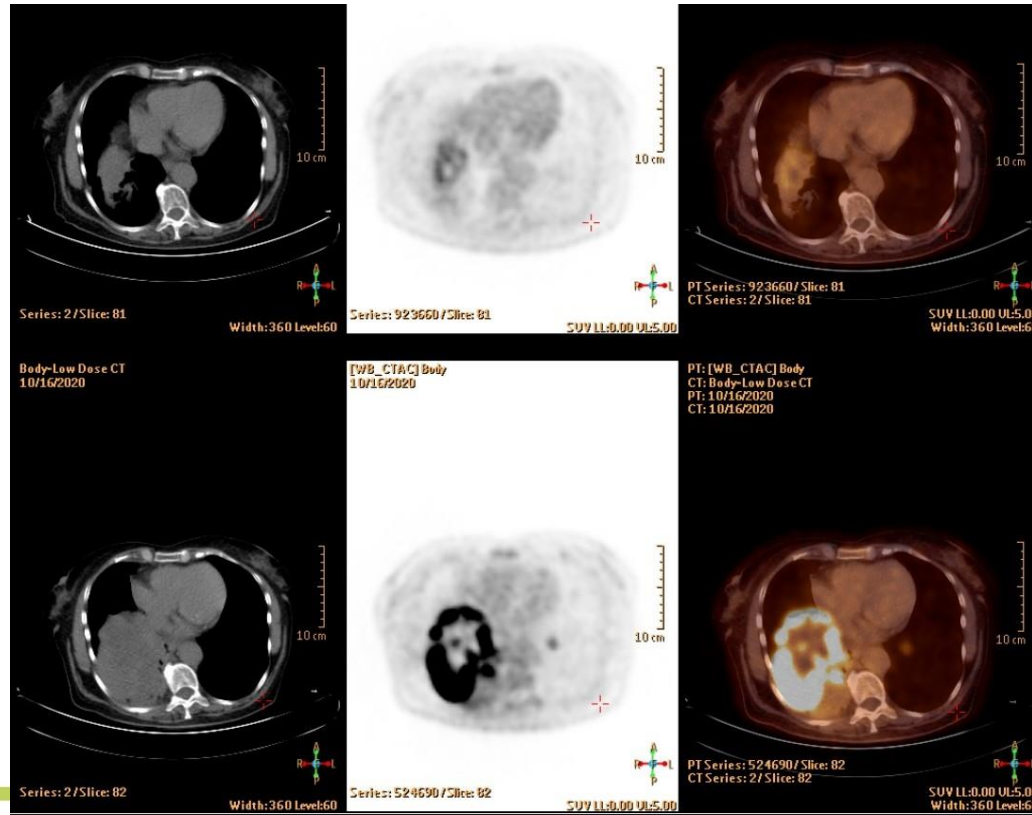




- Stadio IIE, IPI 1, bulky
- Effettua chemioterapia secondo schema R-CHOP per 6 cicli (terminati a marzo 2021)

PET (30/04/2021):

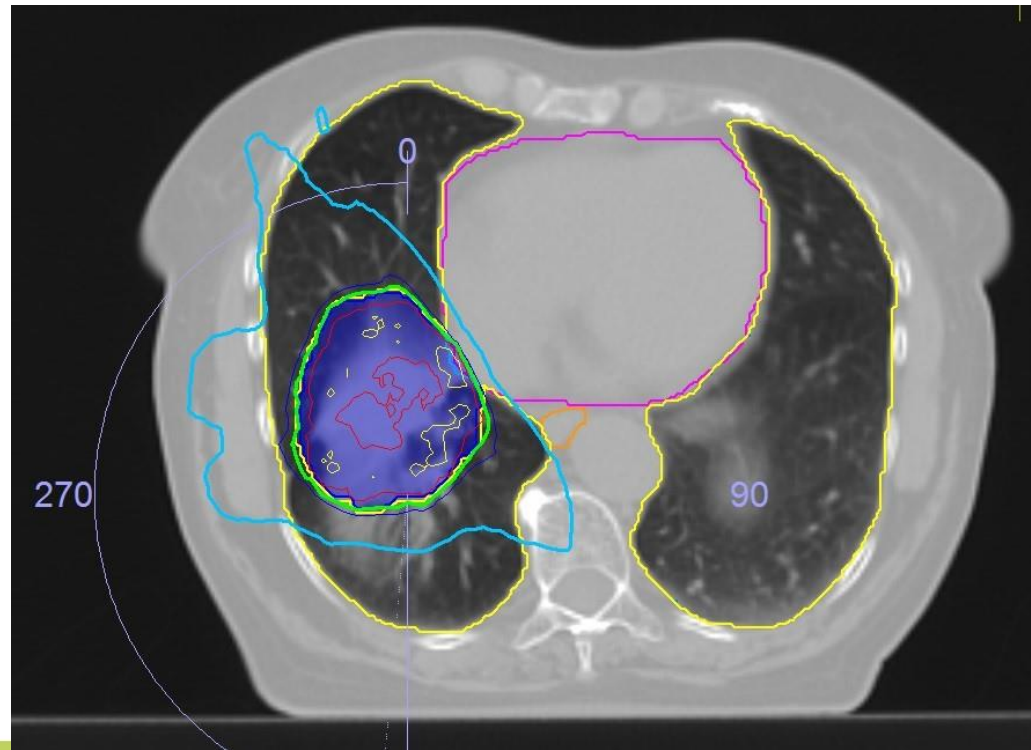
Persistenza solo di una disomogenea area di accumulo, tutt'ora ad intenso ipermetabolismo glucidico (SUV max 3.3 vs 2.4 SUV epatico), localizzata nel LID, ancorché ridotta per estensione ed attività, rispetto al precedente controllo (DS4)

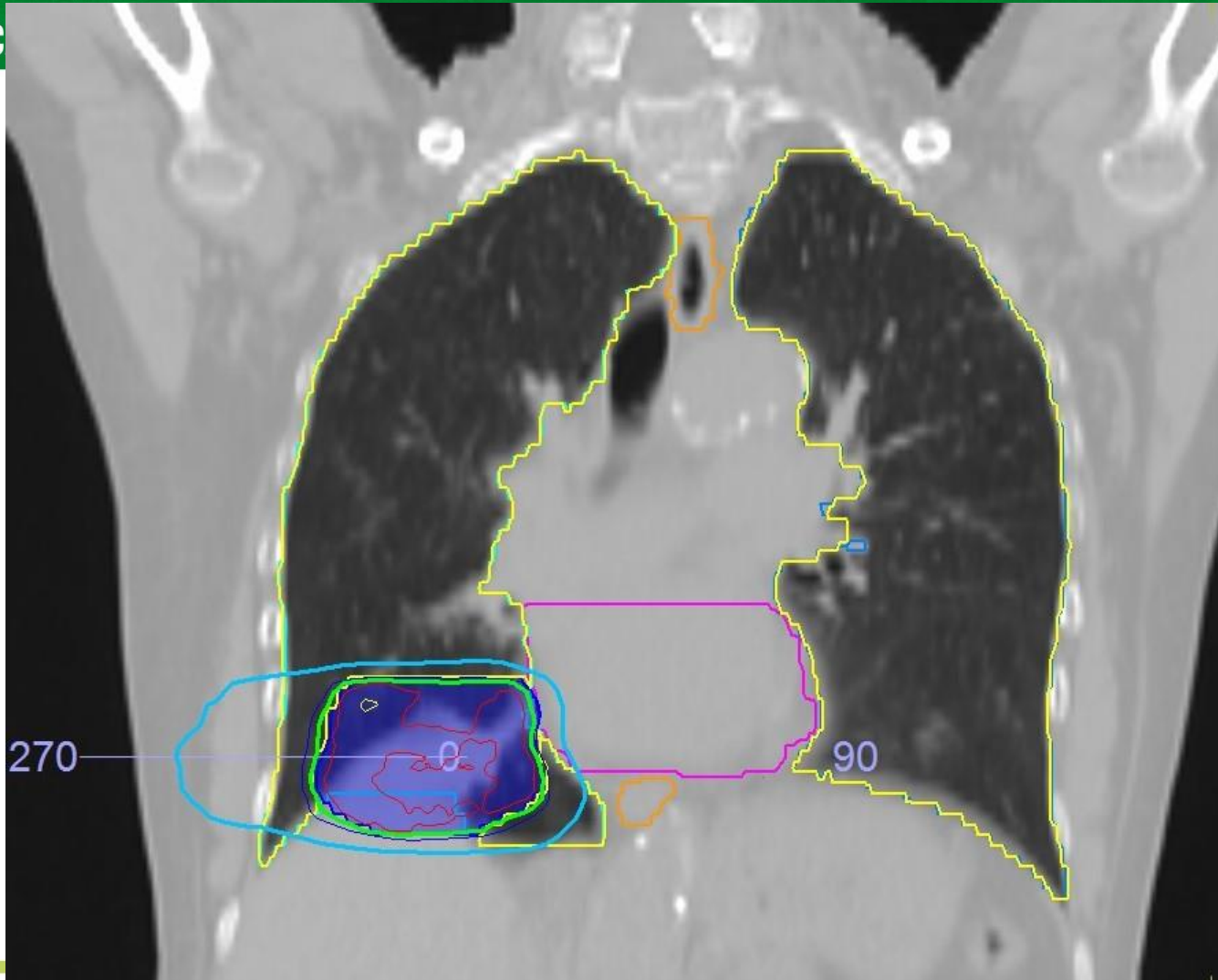


Dopo discussione collegiale la paziente è stata sottoposta a trattamento radioterapico a livello della sede bulky con residuo

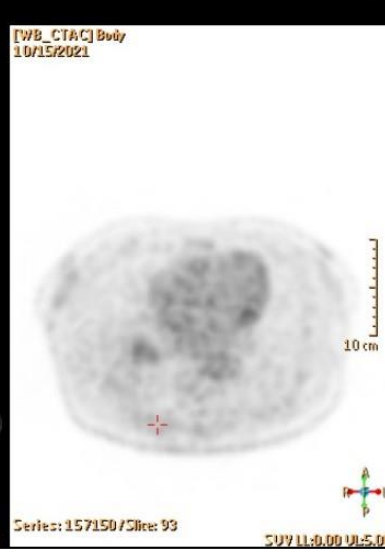
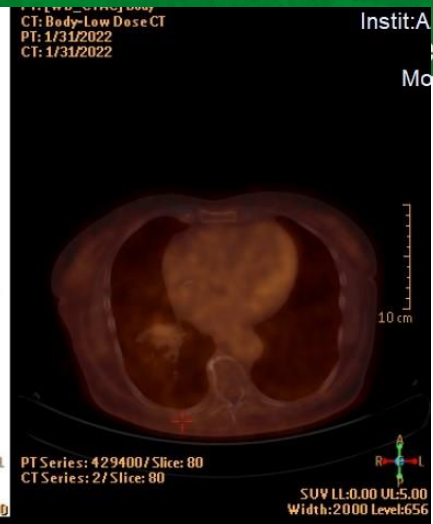
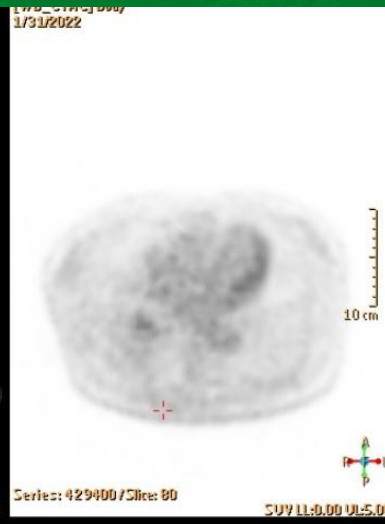
PET+

- TC 4D
- Tecnica VMAT
- 36Gy in 18 frazioni



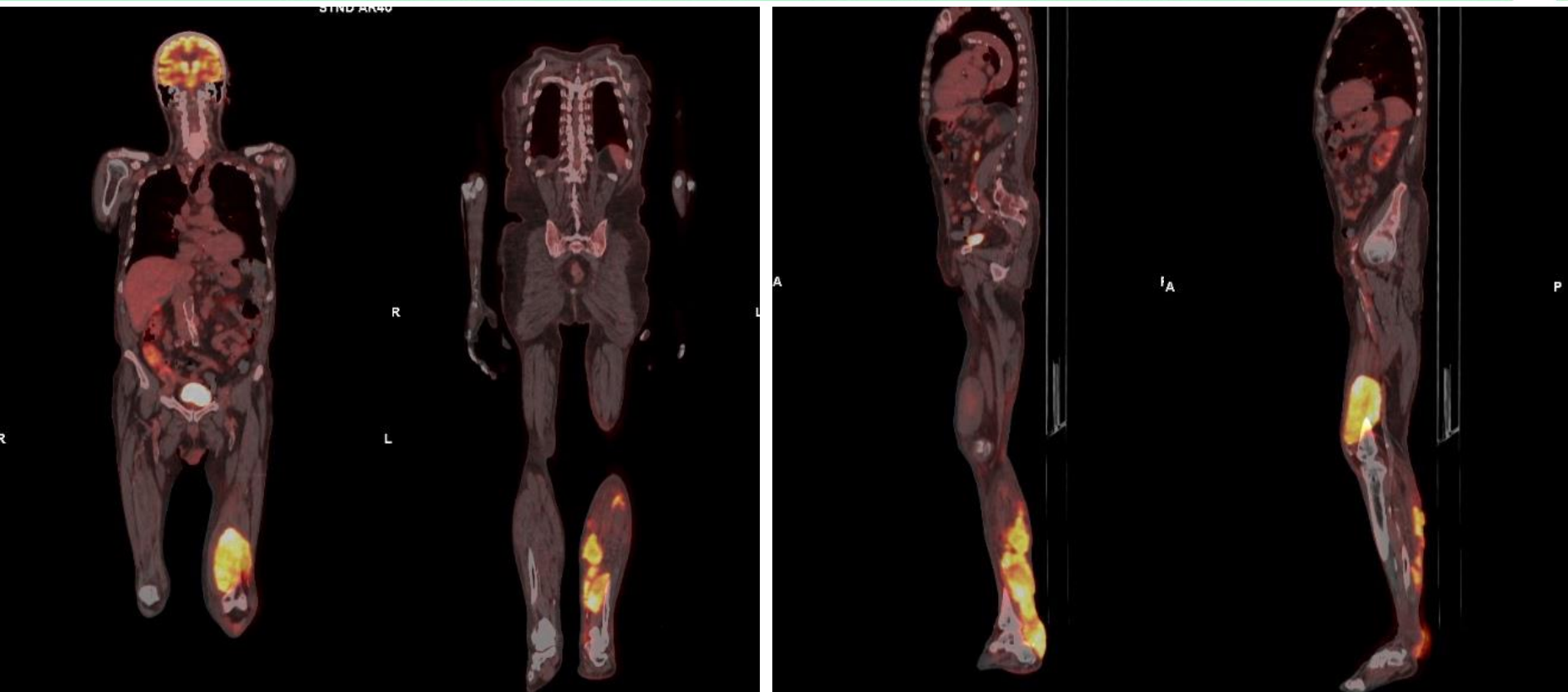


PET
 (31/01/2022)
 Ulteriore riduzione di uptake in corrispondenza dell'area intensamente ipermetabolica descritta a livello basale del LID



➤ RUOLO «RADICALE» NEI SUPER FRAIL

- L.P., 94 anni, buon PS con modesto decadimento cognitivo
- Paziente di 94 anni con diagnosi di linfoma diffuso a grandi cellule B, COO non GCB secondo Hans, CD20+, Ki-67 90%. Stadio IIAE.
- PET/FDG Gennaio 2025: la presenza di una **macroarea intensamente ipermetabolica nel piede e gamba sinistra**, estesa dalla **sede pericalcaneara**, lungo la regione **perimalleolare** fino ai **tessuti molli e muscolari della gamba sinistra**, in particolare in sede posteriore (SUVmax 11.72). Si associa altra **macroarea nel terzo distale della coscia sinistra**, a sede antero-mediale, nel contesto del muscolo quadricipite (SUVmax 11.86). Si rilevano anche piccole focalità intensamente ipermetaboliche lungo il decorso dei vasi femorali di sinistra.
- All'EO: tumefazione anteromediale della coscia sx dura non eritematosa con estensione longitudinale di circa 15 cm, gamba sx non valuabile per fasciatura. P presenza di nodularità a livello della regione malleolare-achillea sn, con ulteriori nodularità a livello della gamba sn; tumefazione dei tessuti molli del muscolo quadricipite sn.

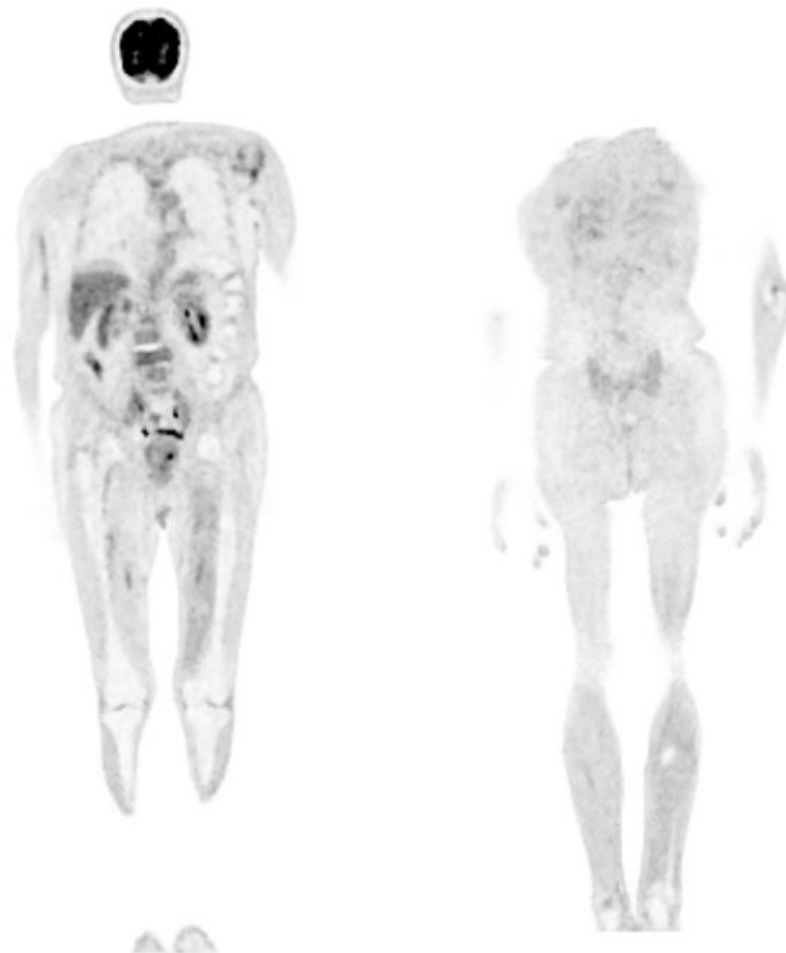


2 R-miniCOMP con omissione vincristina con riduzione del dolore e dell'edema





m



RT per una dose totale di 36Gy in 12 frazioni

Schema	Dose nominale totale	Dose/fraz.	Dose biologica equivalente	
Convenzionale	30 Gy	2 Gy × 15	30 Gy	

$$EQD_2 = D \cdot \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

Esperimento di Regaud

- ▶ Sperimentava come sterilizzare i montoni irradiando i testicoli, come modello di tessuto in rapida proliferazione
- ▶ Si accorse che:
 - Con **singola dose** – sterilizzazione possibile ma la dose richiesta portava ad un danno cutaneo
 - Con **dose frazionata** – si otteneva la sterilizzazione senza particolare danno dello scroto



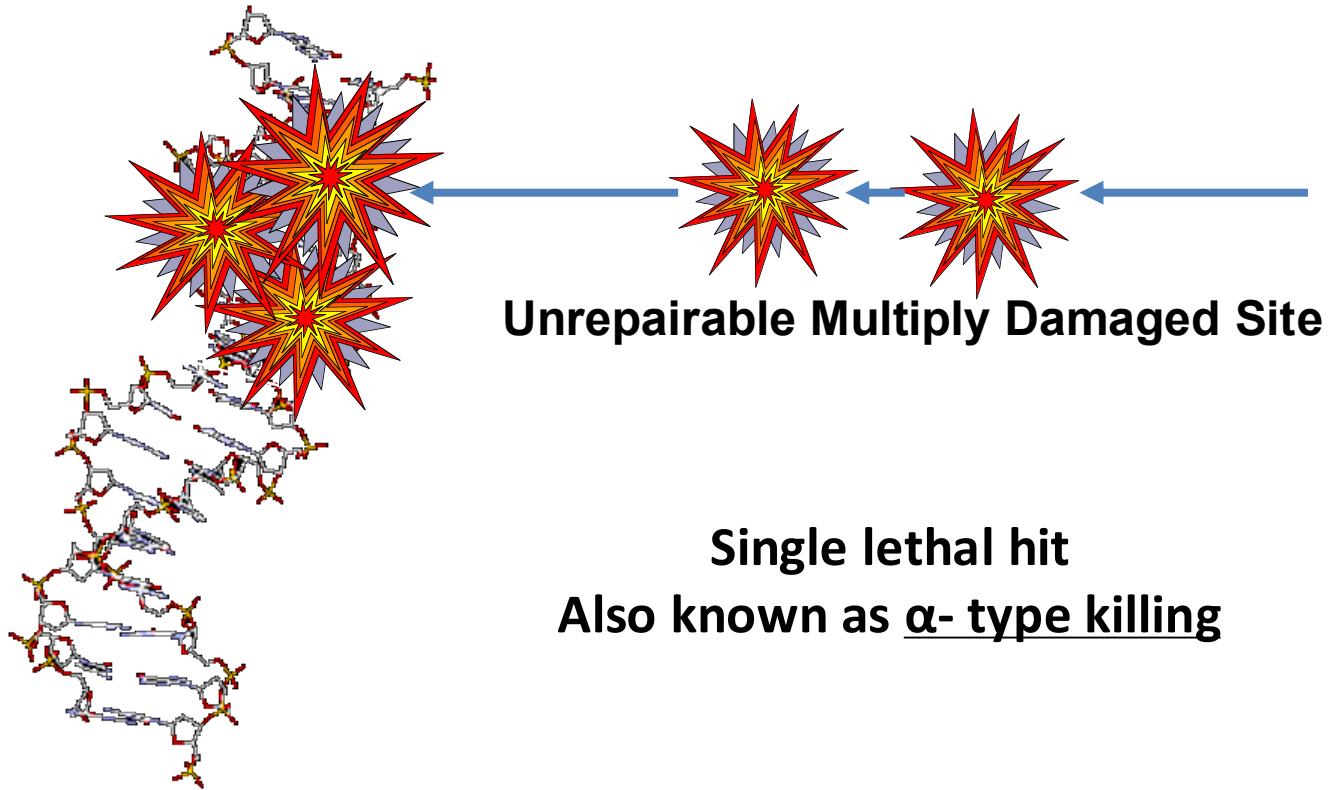
Jean Alban BERGONIE
(1857-1925)

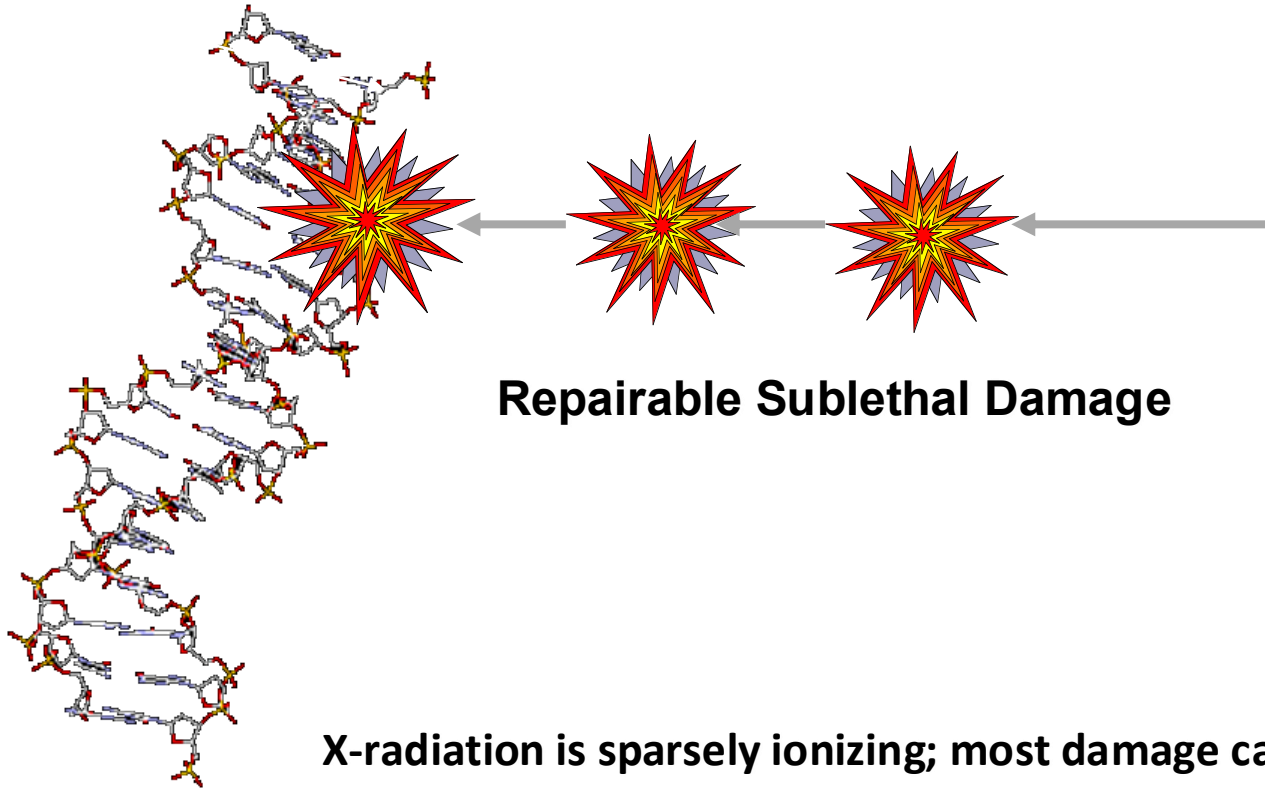


Louis TRIBONDEAU
(1872-1918)

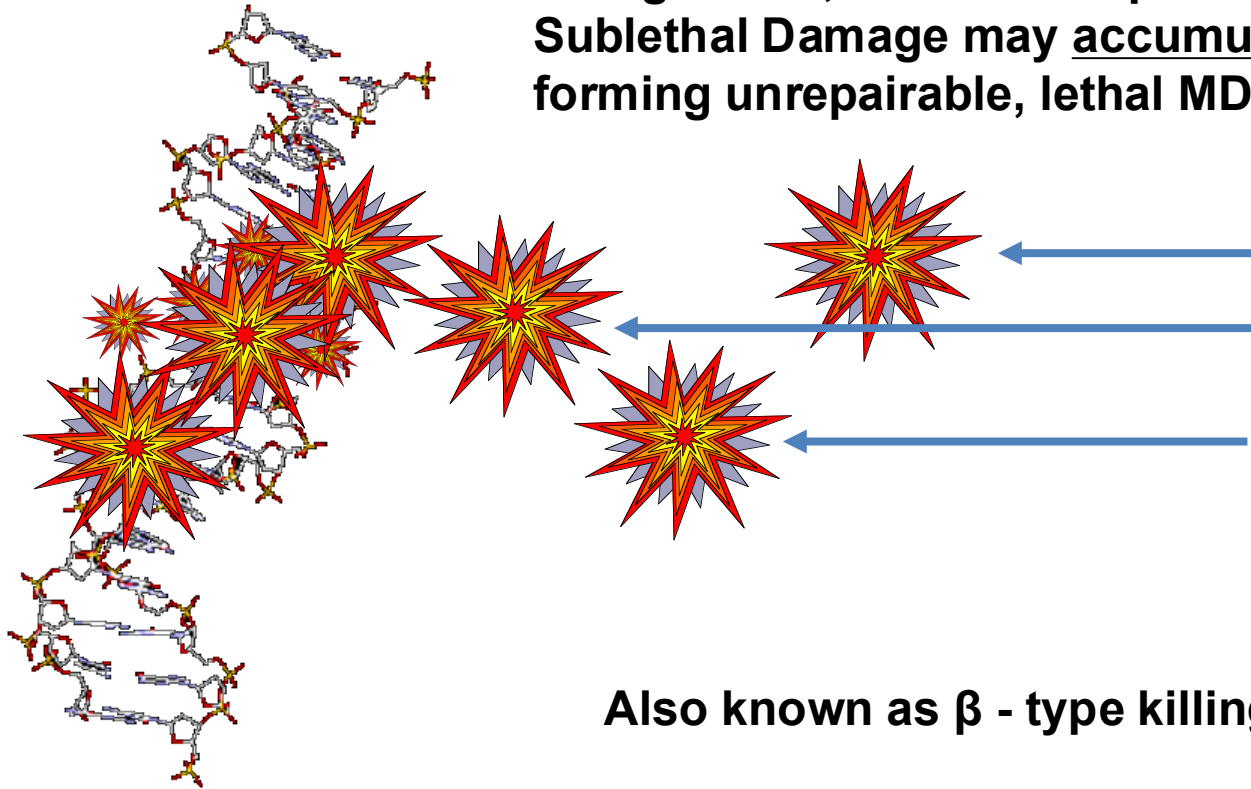


Claudius REGAUD
(1870-1940)



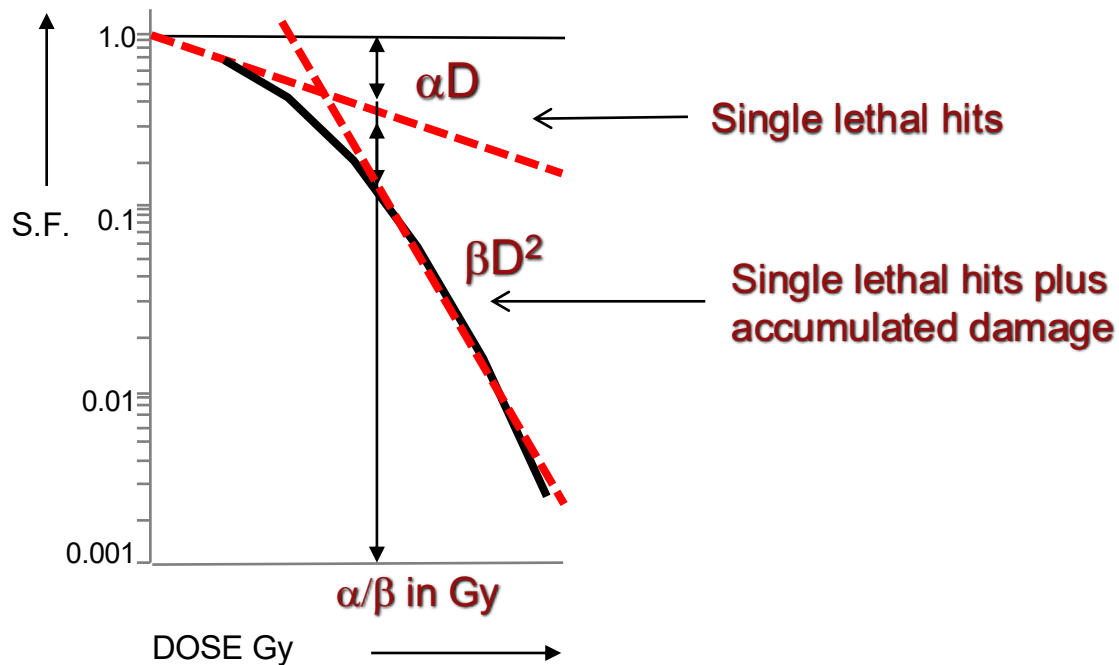


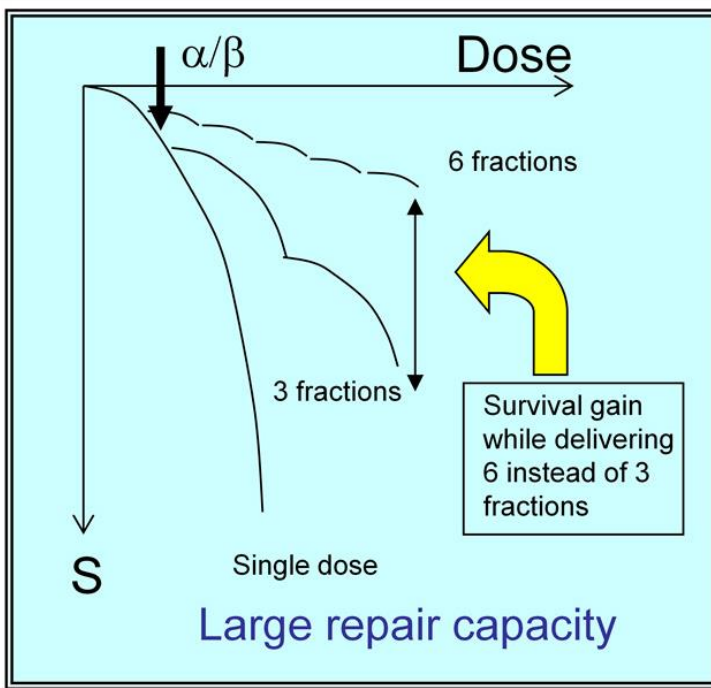
At high dose, intertrack repairable
Sublethal Damage may accumulate
forming unreparable, lethal MDS



Also known as β - type killing

Linear Quadratic Model

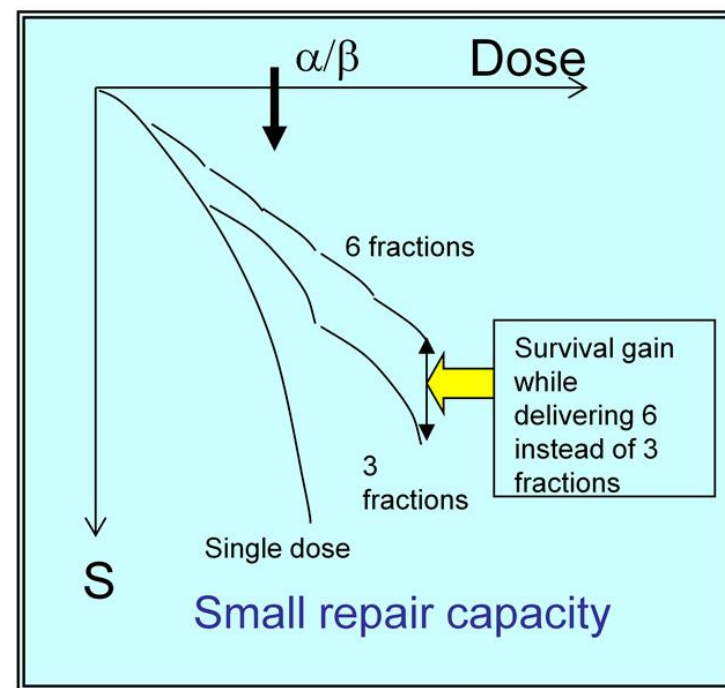




α/β BASSO

- Tessuti sani
- Elevata capacità di riparazione

ZIONE



α/β ALTO

- Tessuto tumorale
- Minore capacità di riparazione

RAZIONALE DIETRO IL FRAZIONAMENTO DELLA DOSE IN RADIOTERAPIA

-Ci sono differenze nella cinetica cellulare e nell'effetto delle radiazioni tra tessuto sano e tessuto tumorale



- ✓ Massimizzare il danno al tessuto tumorale
- ✓ Minimizzare il danno ai tessuti sani

Il Frazionamento Convenzionale

Lo standard storico della radioterapia

1.8 – 2.0 Gy
dose per frazione

- ✓ **Massima tolleranza dei tessuti normali**
- ✓ **Ottimo controllo locale per la maggior parte dei tumori**
- ✓ **Permette repair del DNA nelle cellule sane tra le frazioni**
- ✗ **Trattamenti lunghi: problematico per pazienti anziani/fragili**
- ✗ **Logistica gravosa: spostamenti quotidiani per settimane**

Esempi:

-36Gy in 12# da 3Gy ciascuna... Equivale a dare quasi 40Gy in 20#

-12Gy in 2# da 6Gy ciascuna... Equivale a dare 16Gy in 8#

Schema	Dose nominale totale	Dose/fraz.	EQD2 tumore ($\alpha/\beta=10$)	
Convenzionale	30 Gy	2 Gy × 15	30 Gy	
Ipfraz. moderato	30 Gy	3 Gy × 10	32,5 Gy	
Ipfraz. spinto	30 Gy	6 Gy × 5	40 Gy	

✓ Vantaggi

Migliore compliance nel paziente anziano

Durata ridotta del trattamento (1–2 settimane vs 3–4). Meno frazioni = meno accessi = meno fatica da viaggio e meno reazioni acute cumulative (mucosite, dermatite). Per i linfomi localizzati, inoltre, i volumi irradiati sono spesso limitati.

Effetto tumoricida equivalente

I linfomi hanno α/β alto (~ 10 Gy): sono relativamente insensibili all'aumento della dose/frazione → utilizzare una EQD2 tumorale simile al convenzionale.

⚠️ Rischi

Tossicità tardiva aumentata

I tessuti a risposta tardiva hanno α/β basso ($\sim 2-3$ Gy): subiscono un danno biologico proporzionalmente maggiore con frazioni alte. EQD2 tardiva può superare notevolmente lo schema convenzionale.

Organi critici a maggior rischio

Midollo spinale, cuore, polmone, rene, cavo orale (mucosite, xerostomia): tolleranze ridefinite per l'ipofrazionamento. La pianificazione dosimetrica deve essere particolarmente accurata, e lo schema deve essere personalizzato

FOLLICULAR LYMPHOMA

Definitive radiotherapy for localized follicular lymphoma staged by ^{18}F -FDG PET-CT: a collaborative study by ILROG

Jessica L. Brady,^{1,*} Michael S. Binkley,^{2,3,*} Carla Hajj,⁴ Monica Chelius,⁴ Karen Chau,⁴ Alex Balogh,⁵ Mario Levis,⁶ Andrea Riccardo Filippi,⁶ Michael Jones,⁷ Michael Mac Manus,^{8,9} Andrew Wirth,⁸ Masahiko Oguchi,¹⁰ Anders Krog Vistisen,¹¹ Therese Youssef Andraos,¹² Andrea K. Ng,^{13,14} Berthe M. P. Aleman,¹⁵ Seo Hee Choi,¹⁶ Youlia Kirova,¹⁷ Sara Hardy,¹⁸ Gabriele Reinartz,¹⁹ Hans T. Eich,¹⁹ Scott V. Bratman,^{2,3} Louis S. Constine,¹⁸ Chang-Ok Suh,¹⁶ Bouthaina Dabaja,¹² Tarec C. El-Galaly,¹¹ David C. Hodgson,⁷ Umberto Ricardi,⁶ Joachim Yahalom,⁴ Richard T. Hoppe,^{2,3} and N. George Mikhaeel¹

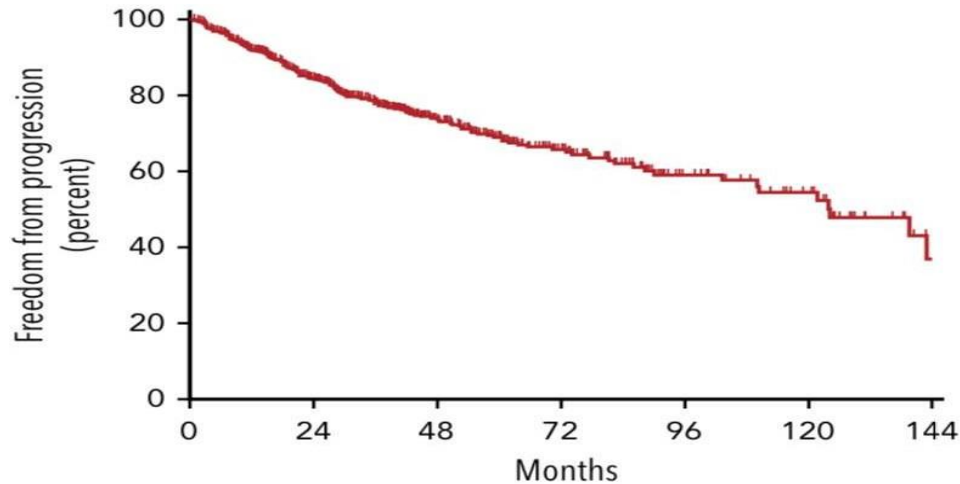
512 pts treated between 2000 and 2017 at 16 centers

- Multicentre retrospective analysis
- Stage I or II Follicular Lymphoma Grade 1-3a
- Staging by CT-PET
- RT dose $\geq 24\text{Gy}$

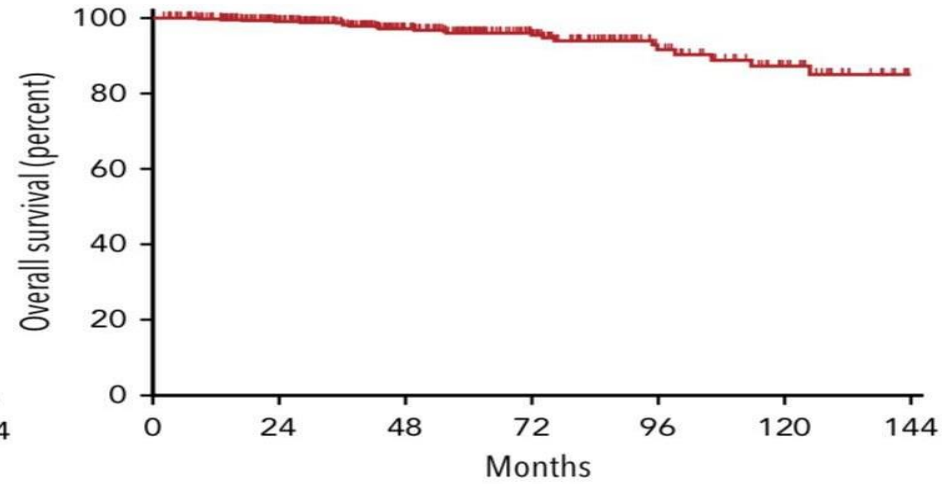
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5 year FFP - 68.9%
(74,9% for Stage I pts)

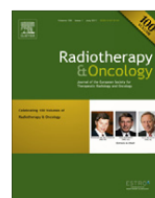


5 year OS 96%





ELSEVIER



RT 40-45Gy

VS

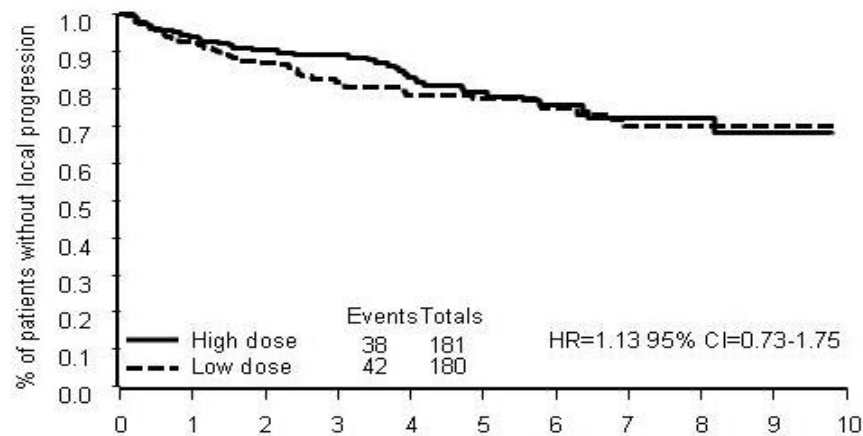
RT 24Gy

Phase III randomised trial

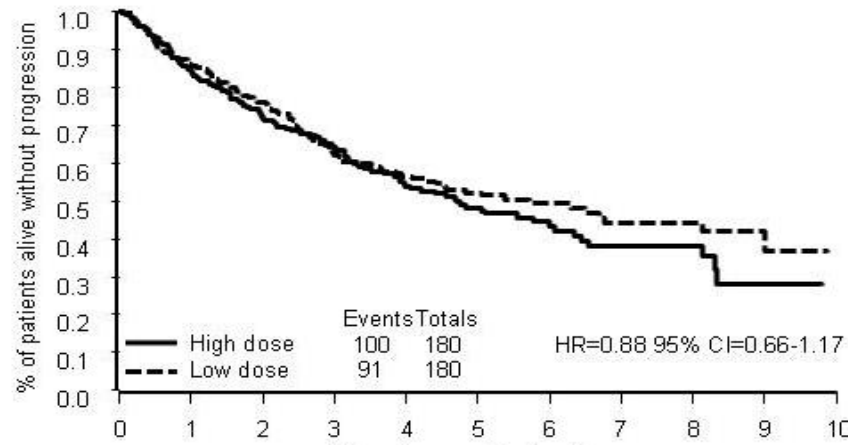
Reduced dose radiotherapy for local control in non-Hodgkin lymphoma:

A randomised phase III trial ☆☆☆

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



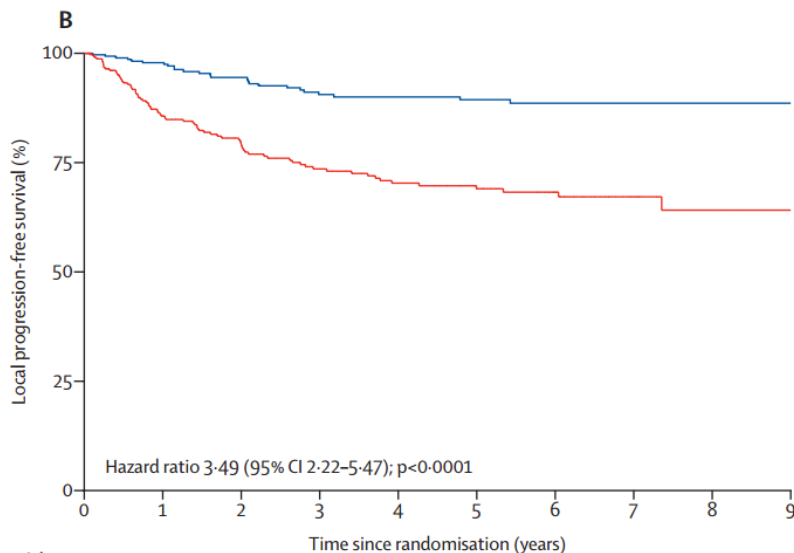
	PATIENTS at Risk										
	0	1	2	3	4	5	6	7	8	9	10
High dose	181	160	150	131	107	79	52	37	23	9	3
Low dose	180	159	147	119	101	83	54	38	24	10	1



	PATIENTS at Risk										
	0	1	2	3	4	5	6	7	8	9	10
High dose	180	150	127	109	82	63	38	24	14	4	1
Low dose	180	154	136	104	84	67	43	32	20	8	0

4 Gy versus 24 Gy radiotherapy for follicular and marginal zone lymphoma (FoRT): long-term follow-up of a multicentre, randomised, phase 3, non-inferiority trial

Peter Hoskin, Biliana Popova, Oliver Schofield, Caroline Brammer, Martin Robinson, A Murray Brunt, Krishnaswamy Madhavan, Tim Illidge, Eve Gallop-Evans, Isabel Syndikus, Laura Clifton-Hadley, Amy A Kirkwood



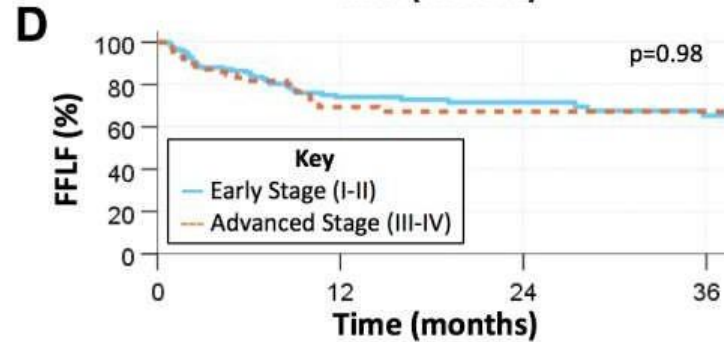
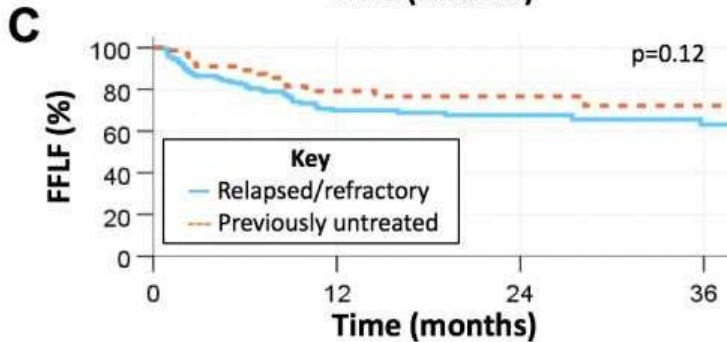
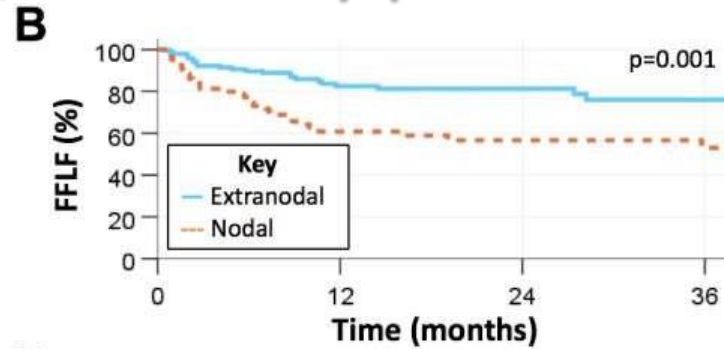
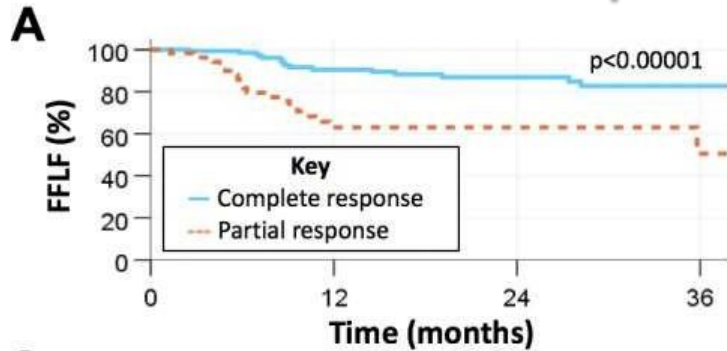
	24 Gy	4 Gy
All patients*		
Complete regression	176 (68%)	137 (49%)
Partial regression (>30%)	60 (23%)	90 (32%)
Stable disease (including <30% regression)	22 (8%)	44 (16%)
Progression	2 (<1%)	10 (4%)
Total	260	281

➤ **CR+PR 81%**

➤ **LPFS 70,4% at 5y**

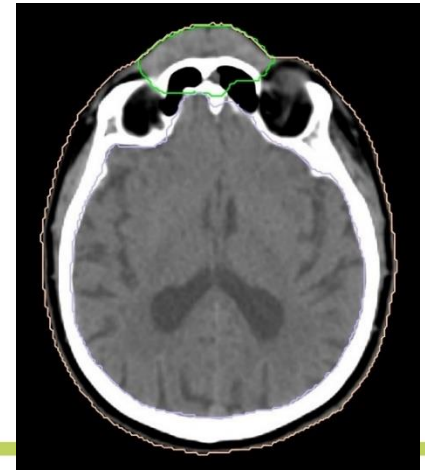
- **Conclusions:** 24 Gy in 12 fractions is the more effective radiation schedule for indolent lymphoma and should be regarded as the standard of care.
- *However, 4 Gy remains a useful alternative for palliative treatment.*

Low dose RT also works in advanced-stage and relapsed/refractory patients

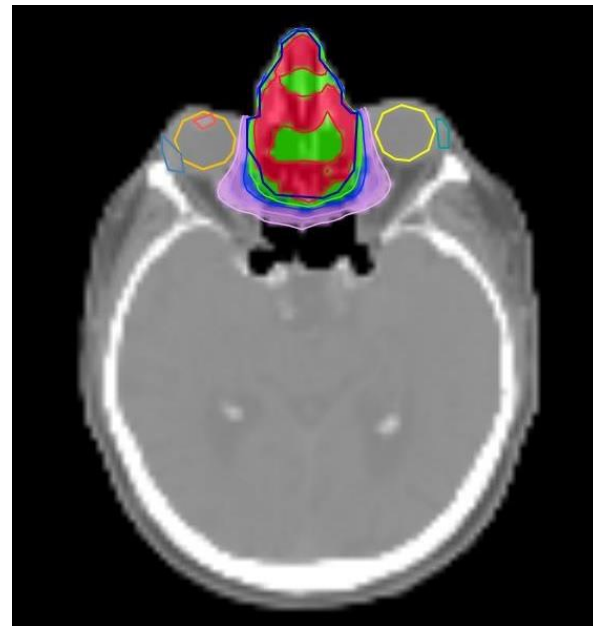
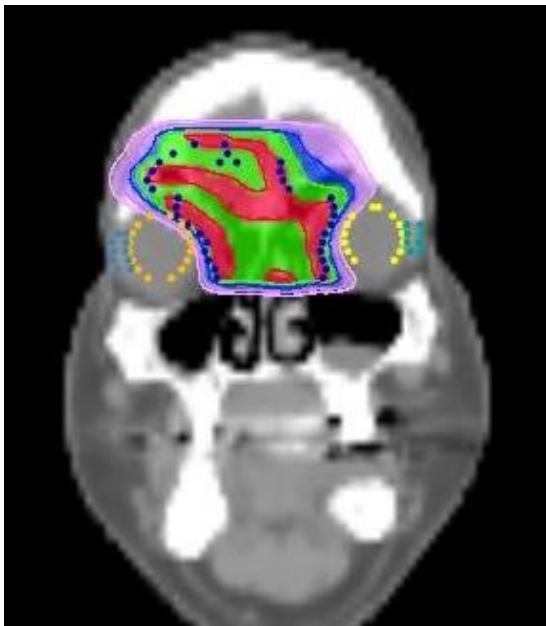


➤ STADIO I IN SEDE CRITICA

- P.G., uomo, 79 anni
- A Luglio 2020 tumefazione in sede glabellare, esegue TC e biopsia con diagnosi di Linfoma follicolare Grado 2
- PET-FDG: fissazione in sede sottocutanea glabellare frontale e di alcune cellette etmoidali antero-superiori
- Stadio IE

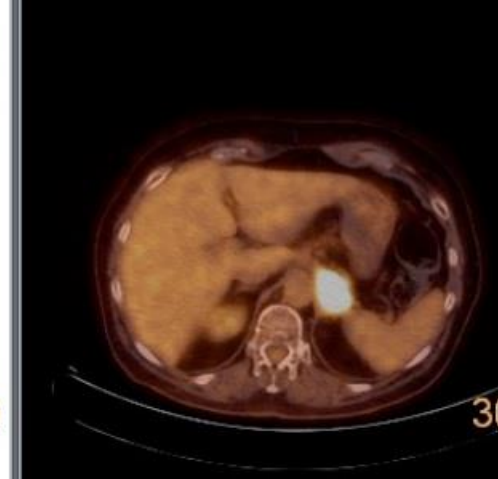
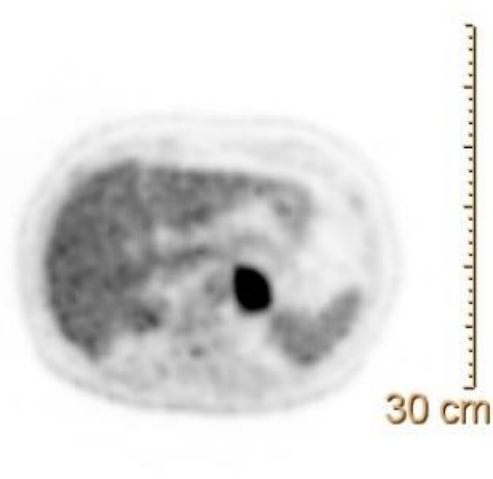
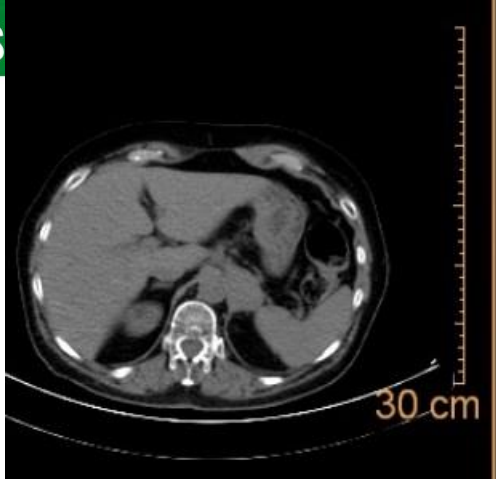


- RT radicale, 24Gy in 12# con Tomotherapy
- RC, nessuna tossicità oculare, paziente NED



➤ **RECIDIVA ISOLATA DOPO TERAPIA SISTEMICA IN PAZIENTE FIT**

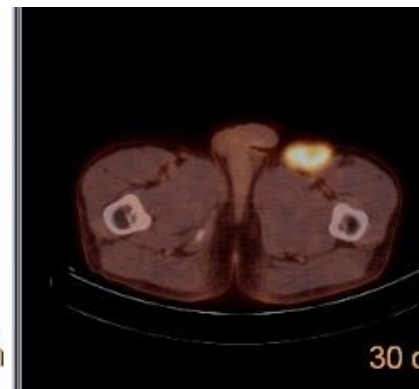
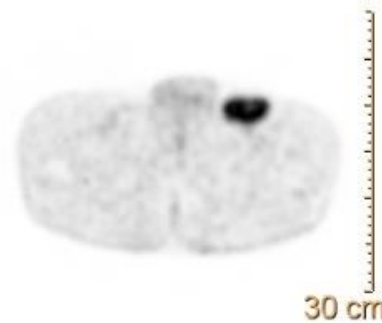
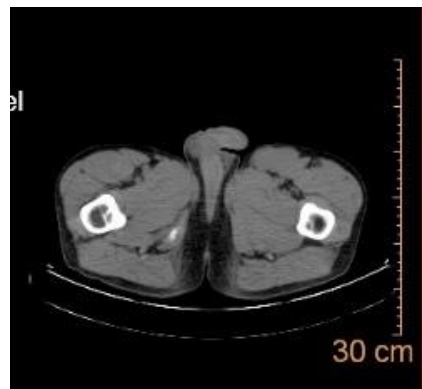
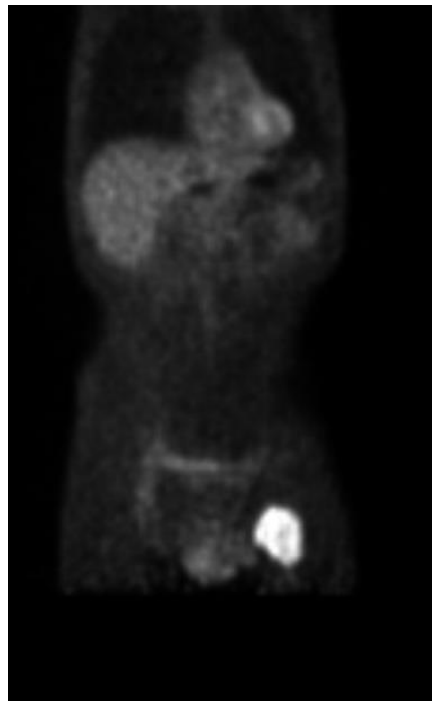
- T.C., donna 72 aa.
- 2017 FL Ki67 25% localizzazioni lomboaortiche, peripancreatiche, iliaco otturatorie dx, stadio IIA
- 6 cicli R-Benda terminato a Gennaio 2018 con RC
- Febbraio 2020 comparsa di recidiva unica 40mm a sede celiaca indissociabile da pilastro diaframmatico mediale sinistro
- Maggio 2020 PET-FDG conferma unica localizzazione, leggermente incrementata



- Luglio 2020 RT 24Gy in 12#
- NED ad oggi

➤ RECIDIVA MULTIPLA DOPO TERAPIA SISTEMICA IN PAZIENTE FRAIL

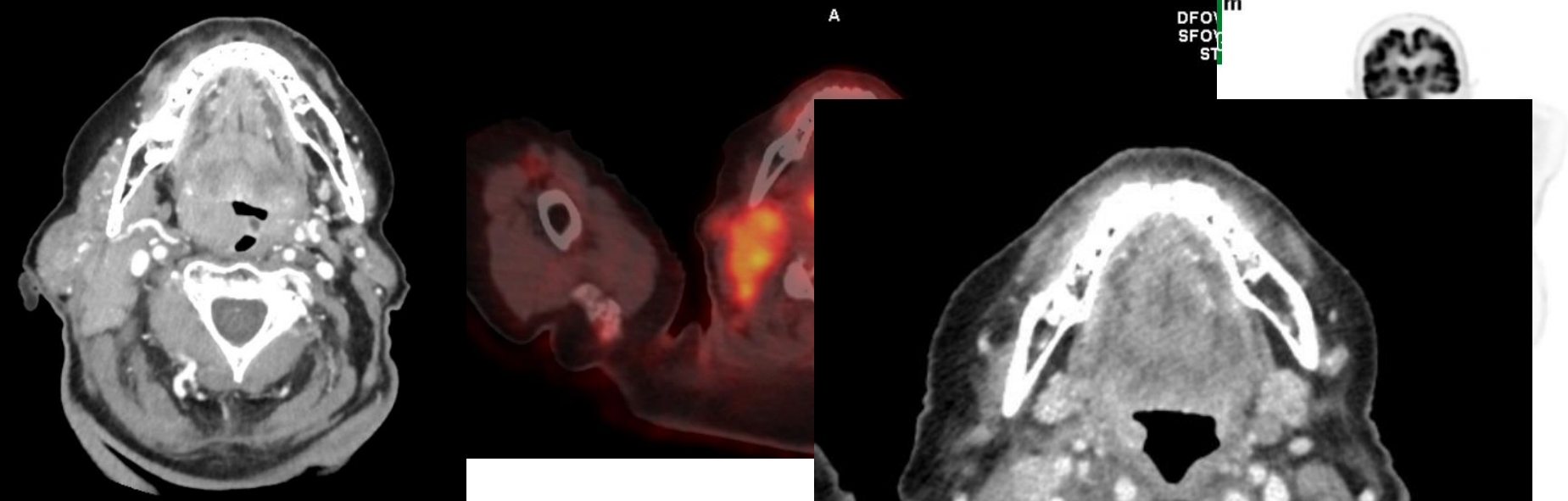
- G.M., uomo 77 aa.
- FL diagnosi nel 2009 trattato con R-Leukeran nel 2009
- Recidiva 2015 R-bendamustina + mantenimento con rituximab terminato nel settembre 2016.
- Nov 2016 recidiva con conferma istologica di linfoma follicolare G2 per cui inizialmente ha eseguito WW, seguito da R-CHOP
- 2022 recidiva multipla (3 sedi di piccole dimensioni) con massa inguinale sinistra di 6x8cm



- Luglio 2022 RT 4Gy in 2#
- RC su inguine, ancora in WW su altre sedi

➤ LOCALIZZAZIONE SINTOMATICA IN PAZIENTE SUPER-FRAIL

- P.E., donna, 90 anni. Paziente in mediocri condizioni generali, in carrozzina, ECOG 2. Riesce nonostante la difficoltà a deglutire ad alimentarsi correttamente, peso stabile.
- TC: ingrandimento della tonsilla orofaringea destra (diametro massimo di 3 cm) con riduzione dell'ampiezza del lume orofaringeo. Invariati i linfonodi ingranditi e parzialmente confluenti nei livelli II, III e IV di destra, i maggiori con diametro trasverso massimo di 3,5-4 cm, determinanti compressione sulla vena giugulare interna.
- Biopsia linfonodale: linfoma follicolare a basso grado 1/2 CD20+, Ki-67 5-10%



- RT su tumefazione tonsillare destra e LAP laterocervicali, 8Gy in due frazioni da 4Gy

Are all GELF criteria created equal? utility of individual GELF criteria as guidance for treatment initiation in patients with advanced stage FL

Clare Grieve¹, Esther Drill¹, Michelle Okwali¹, Ahmet Dogan¹, Jasmine Zain¹, Andrew Zelenetz¹, Pallawi Torka¹, Robert Stuver¹, Raphael Steiner¹, Lia Palomba¹, Ariela Noy¹, Colette Owens¹, Alison Moskowitz¹, Efrat Luttwak¹, Jennifer Lue¹, Anita Kumar¹, William Johnson¹, Steven Horwitz¹, Paul Hamlin¹, Paola Ghione¹, Zachary Epstein-Peterson¹, Kevin David¹, Philip Caron¹, Alexander Boardman¹, Pallavi Kanwar Galera¹, Katherine Lopez¹, Gilles Salles¹, Lorenzo Falchi¹

¹Memorial Sloan Kettering Cancer Center, New York, United States

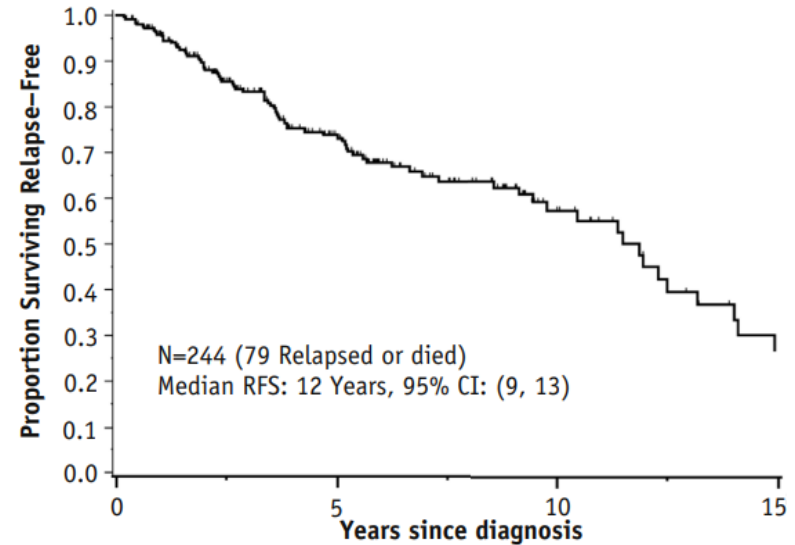
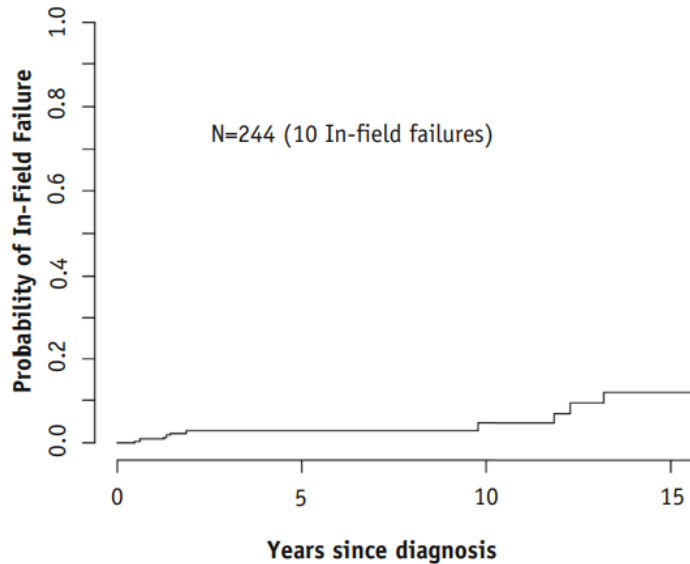
- 3 nodal sites, each ≥ 3 cm
- lymphoma lesion(s) ≥ 7 cm
- symptomatic splenomegaly
- FL related serous effusions
- constitutional symptom
- ≥ 1 cytopenia (i.e., platelets $< 100 \times 10^9/uL$, neutrophils $< 1 \times 10^9/uL$, hemoglobin $< 10g/dl$)
- malignant lymphocytosis (absolute lymphocyte count $> 5k/uL$)

MARGINAL ZONE LYMPHOMA

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

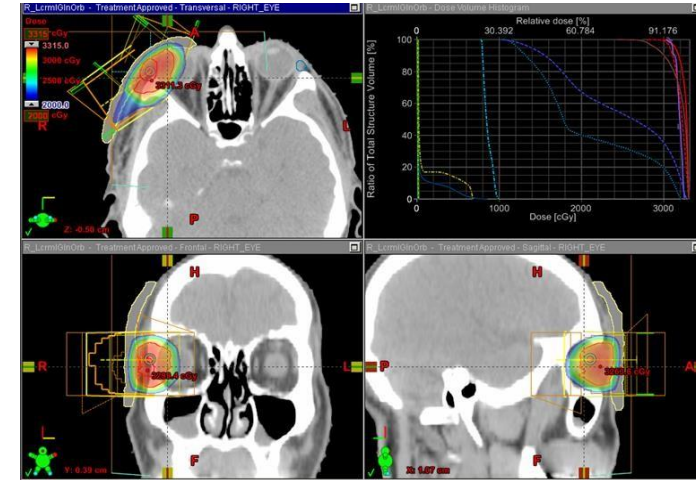
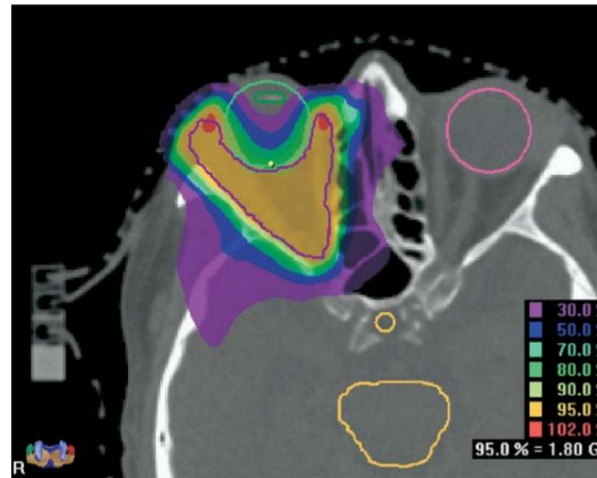
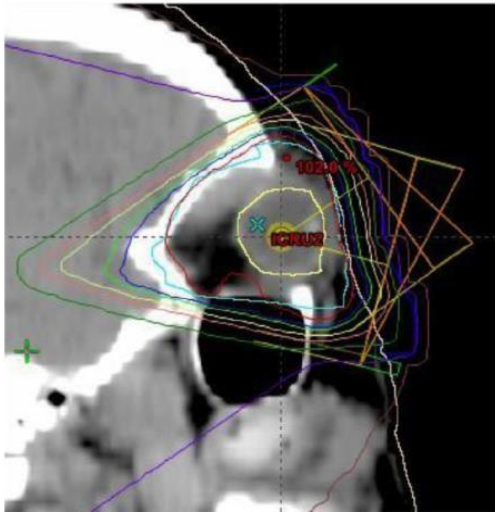
Sewit Teckie, MD,* Shunan Qi, MD,* Shona Lovie, MPH,*
Scott Navarrett, BS,‡ Meier Hsu, MS,§ Ariela Noy, MD,||
Carol Portlock, MD,|| and Joachim Yahalom, MD*

- 490 pts with I-IIe MZL treated with RT
- Local Relapse rate 4,6% at 10y
- PFS 57% at 10y
- Stomach, orbit, skin, breast, parotid...



• Orbit Marginal Zone Lymphomas

- CTV: for most cases of indolent NHL, the entire bony orbit including definite or suspected extraorbital extensions
- Lacrimal gland – treat the entire gland



Low dose RT provides excellent outcomes in MZL (with NO toxicity...!)

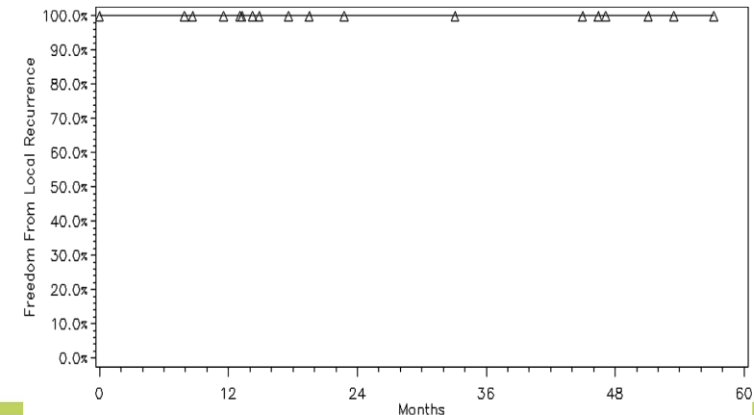
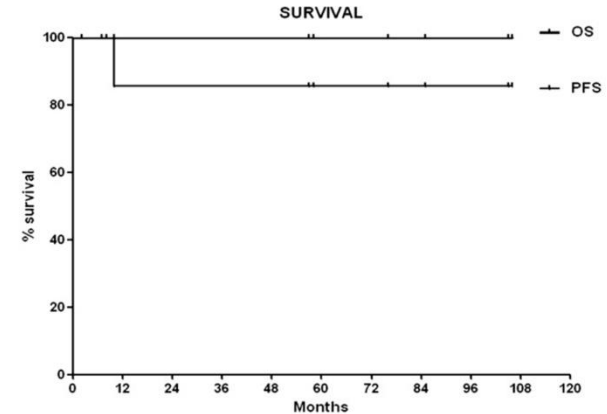
Low-Dose Radiation Treatment in Pulmonary Mucosa-Associated Lymphoid Tissue Lymphoma: A Plausible Approach? A Single-Institution Experience in 10 Patients

Theodore Girinsky, M.D.,* Amaury Paumier, M.D.,* Christophe Ferme, M.D.,†
 Colette Hanna, M.D.,† Vincent Ribrag, M.D.,† François Leroy-Ladurie,‡
 and Mithra Ghalibafian, M.D.*

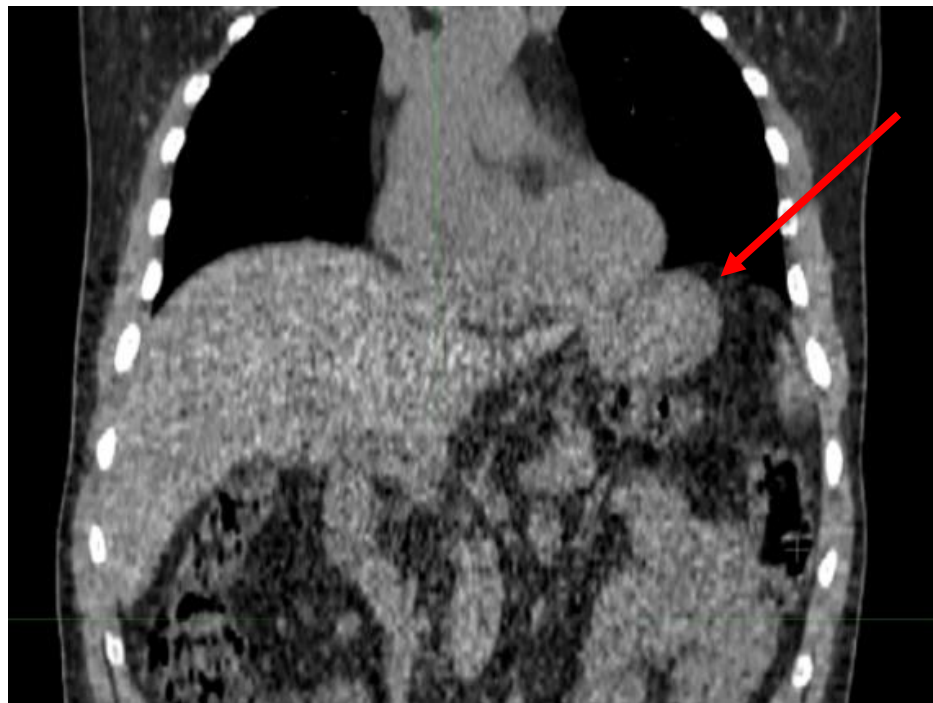
Clinical Investigation: Lymphoma

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*

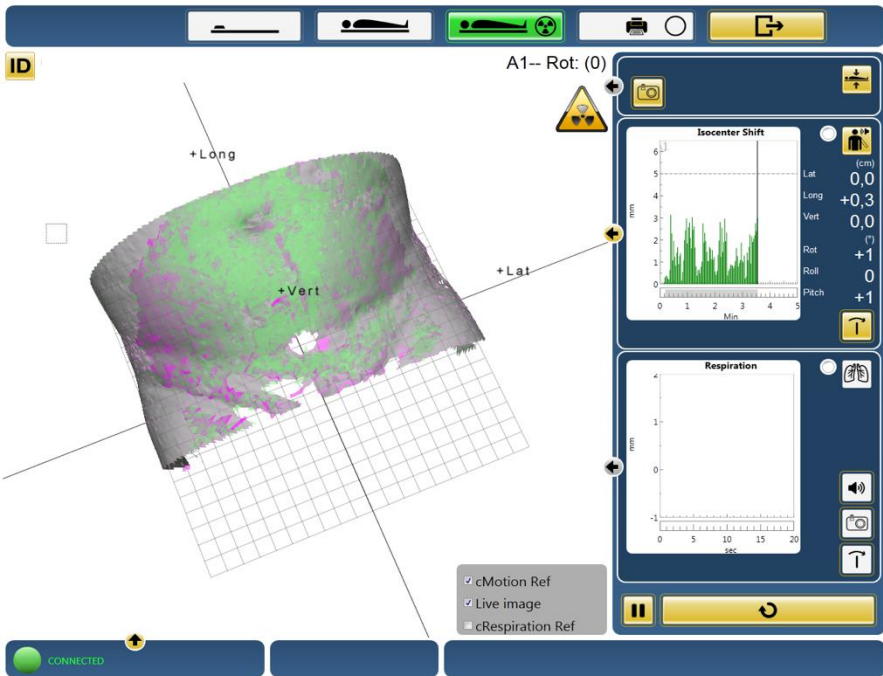


-AD, 72 y, gastric MALT HP-positive, stage IE, no response to antibiotic therapy

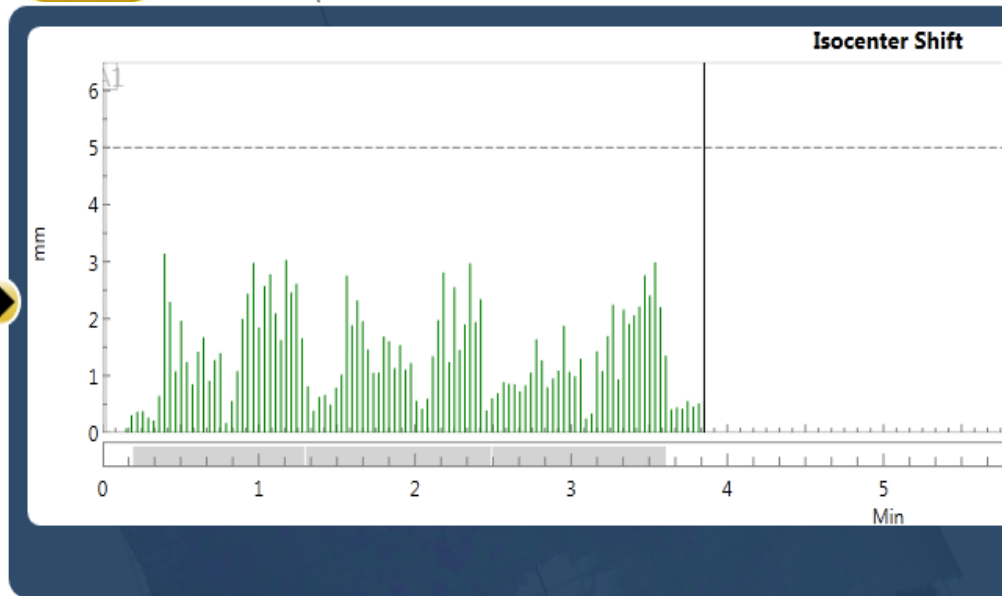


Scanner 3D a Luce Strutturata

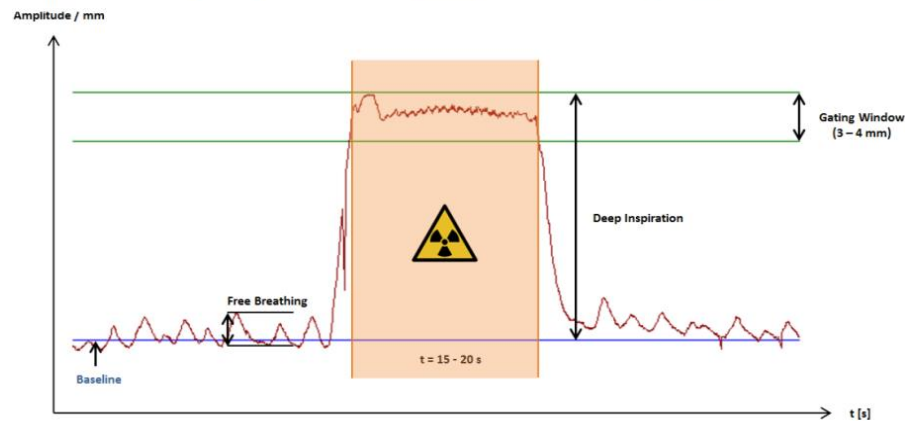
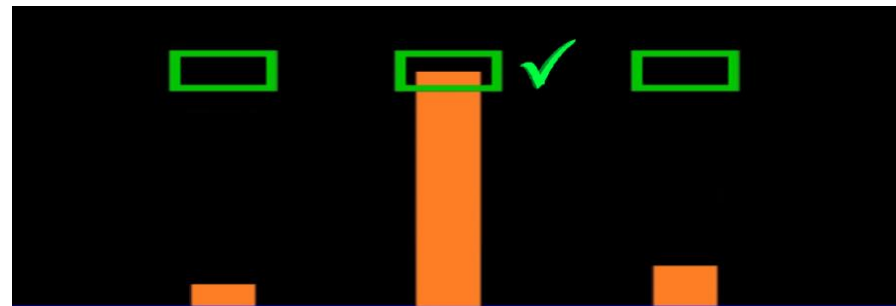
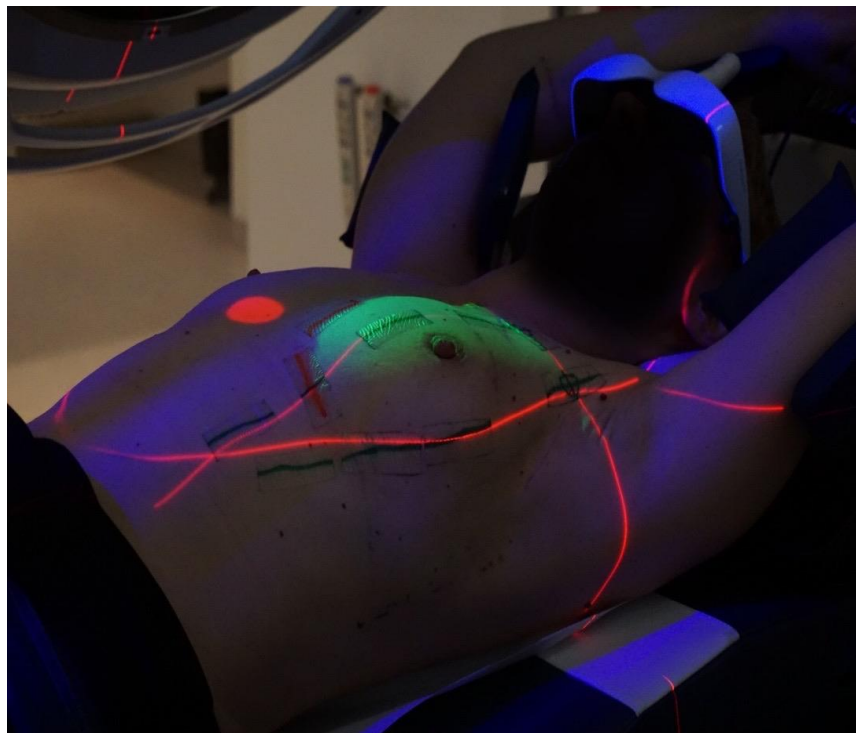




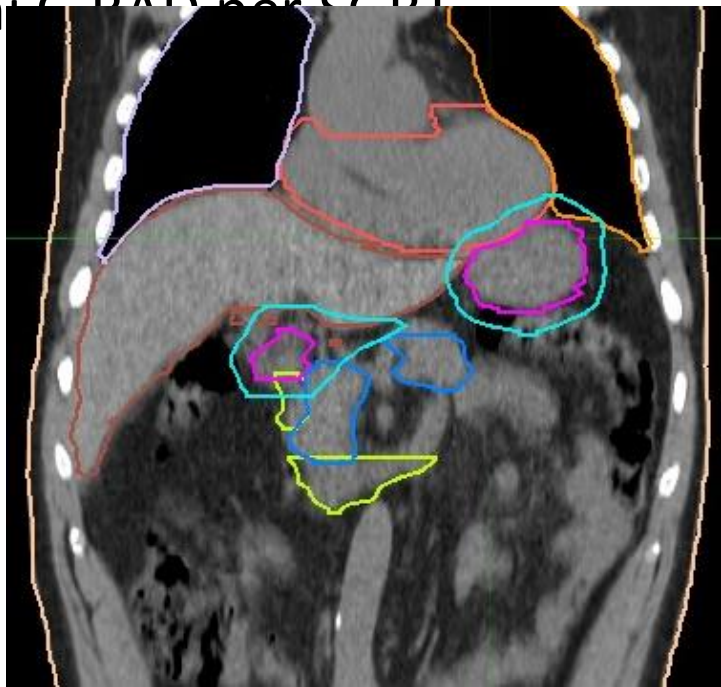
MONITORAGGIO IN REAL-TIME



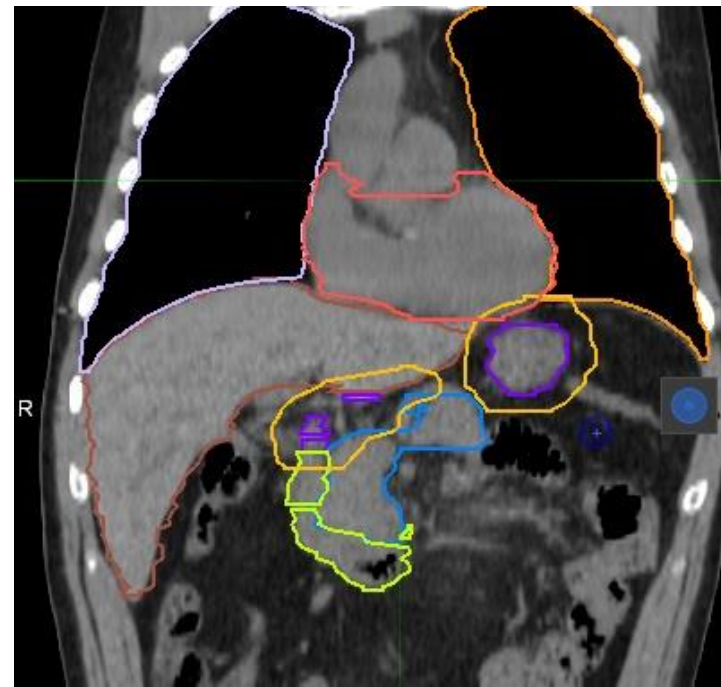
CONTROLLO MOVIMENTO RESPIRATORIO



sistemi C-PAID per SCBT



4D-CT

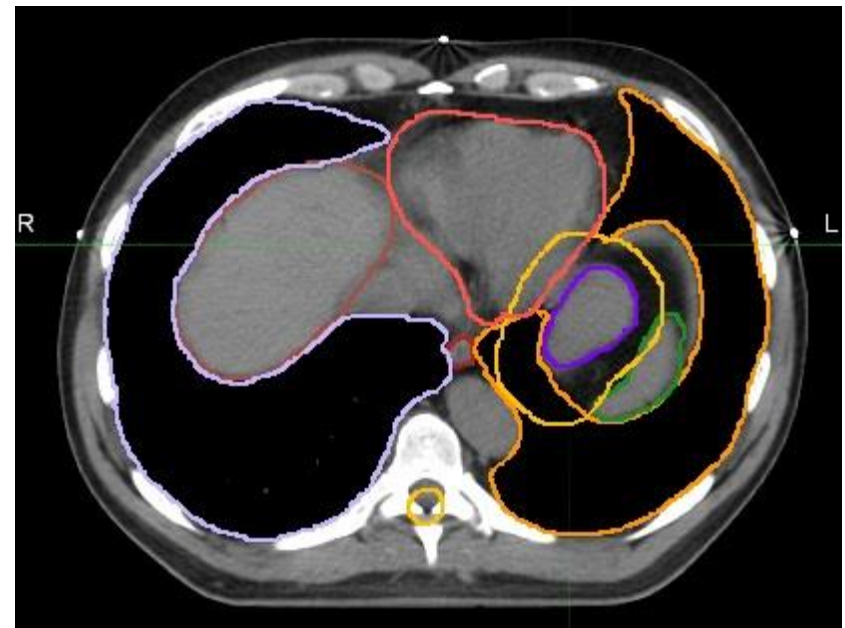


DIBH

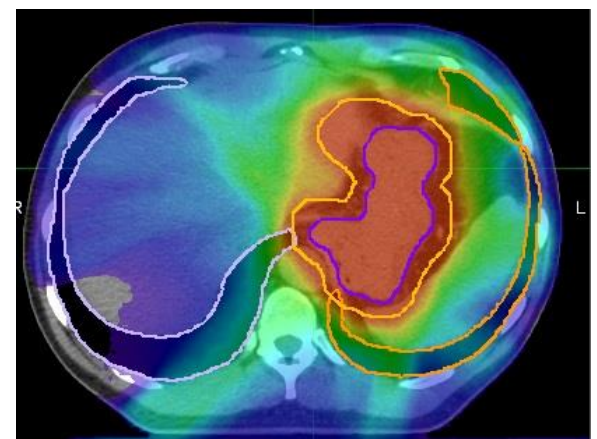
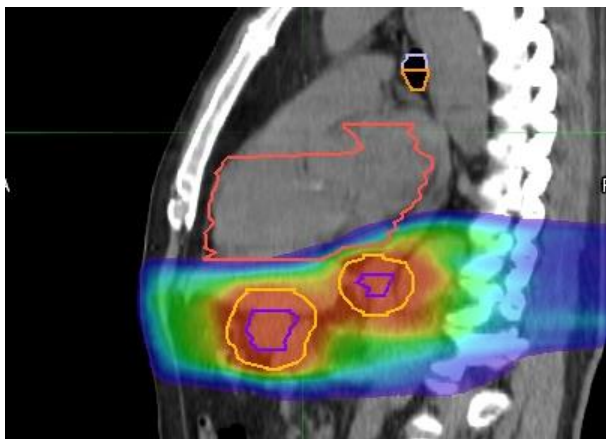
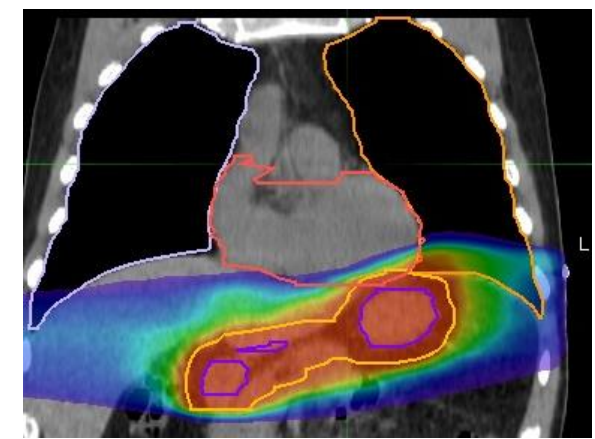
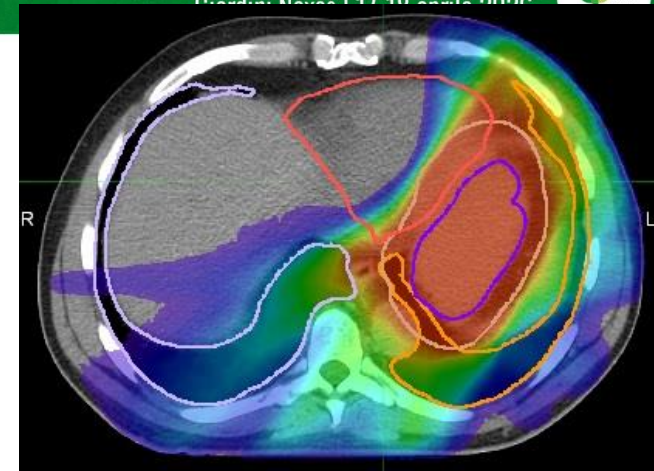
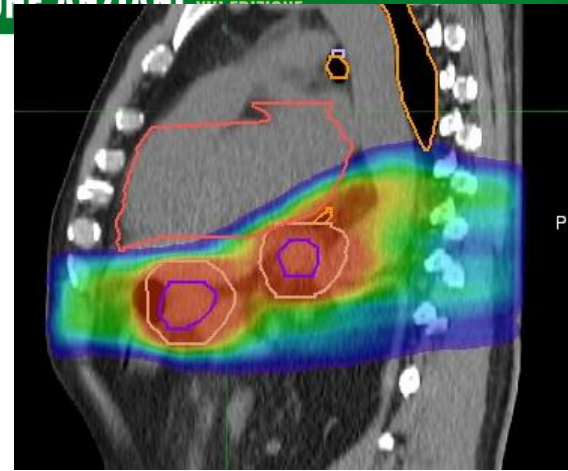
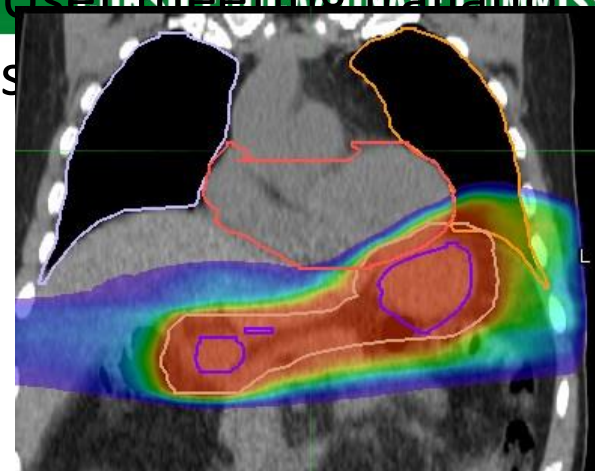
Uso di sistemi C-RAD per SGRT



4D-CT

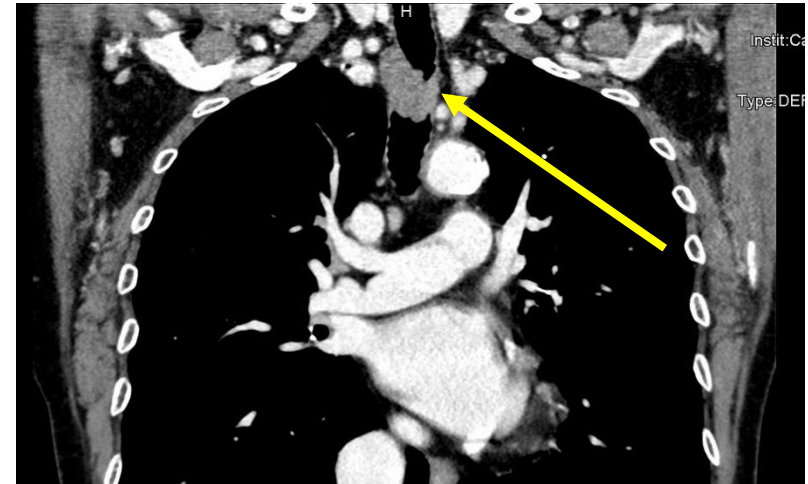
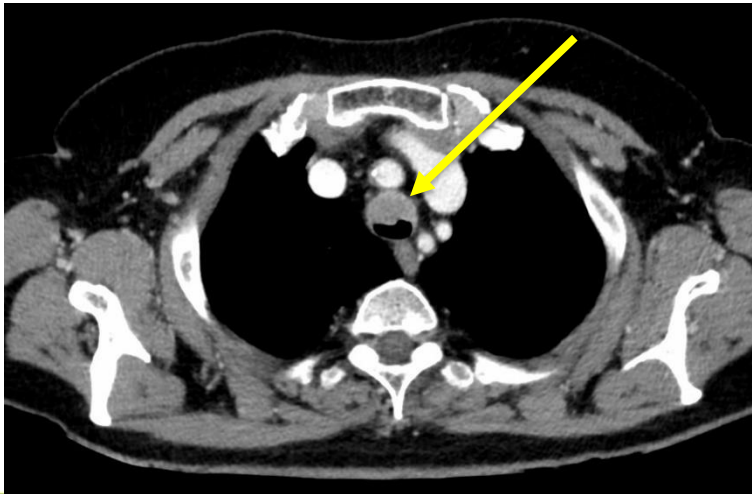


DIBH



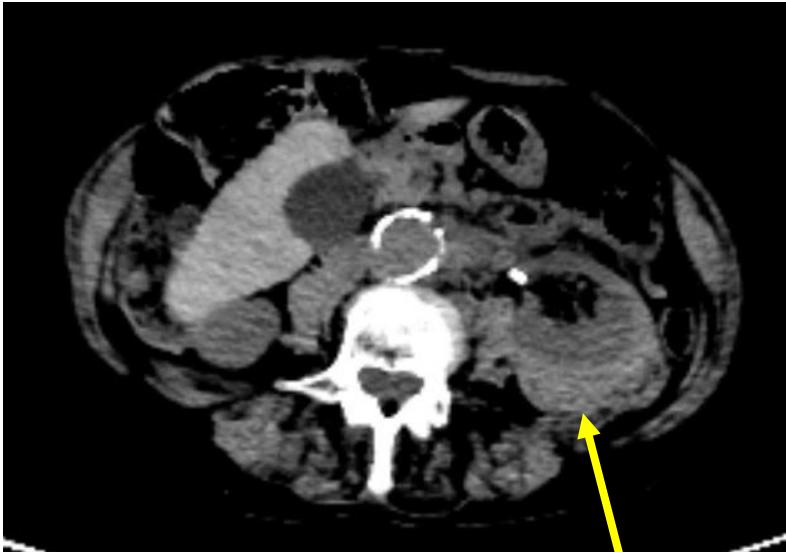
	4D-CT	DIBH
CTV/ITV volume	315 cm ³	247 cm ³
PTV volume	919 cm ³	707 cm ³
PTV V95%	97,4%	97,4%
Heart mean	3,9Gy	2.9Gy
Heart V20Gy	5,5%	2,3%
Heart V15Gy	8,5%	4,8%
Heart V10Gy	11,8%	7,9%
Kidney V5Gy	18,1%	10,1%
Pancreas mean dose	14,4Gy	13,7Gy

- F.M., donna 81 aa
- Giugno 2017 Tosse e dispnea, TC con tumefazione parete anteriore trachea
- Broncoscopia e biopsia: linfoma marginale con parziale differenziazione plasmacitica (Ki67 10-20%)
- Disostruzione laser in broncoscopia
- RT 24GY in 12#.
- Esofagite G1 risolta in una settimana
- NED 2025

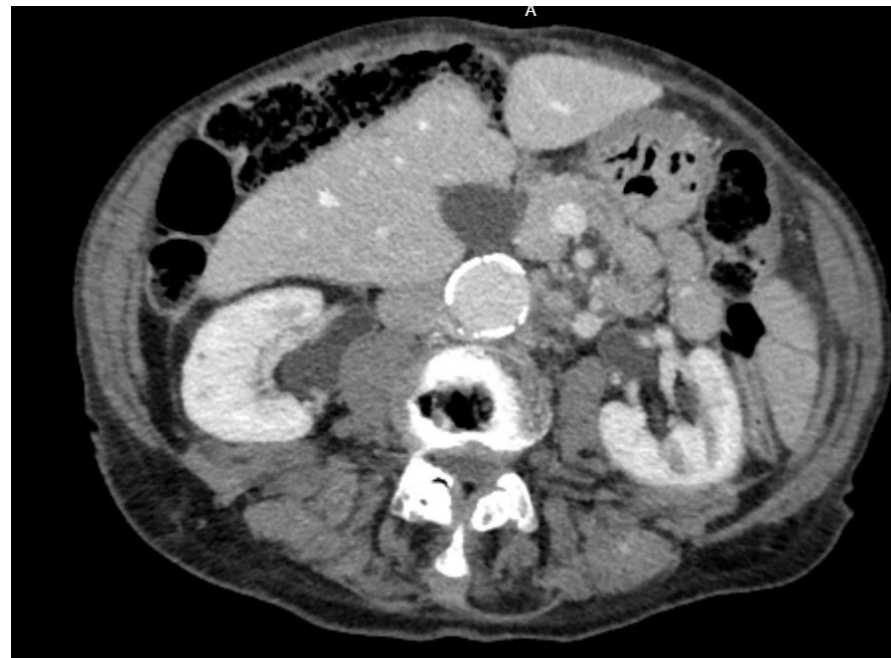


➤ LOCALIZZAZIONE SINTOMATICA IN PAZIENTE FRAIL

- G.G.P, donna 87 anni.
- TC Addome con mdc: a sinistra tessuto solido impregnato di mdc localizzato a sede paraortica infra-sottorenale e attorno al rene, ad avvolgere completamente l'organo con estensione sopra e sotto renale (sopra per 3.5cm e sotto per 2.5cm). Inglobati l'arteria renale, porzione della vena renale, la vena ovarica (che appare ectasica) e l'uretere. Scarsi/assenti piani di clivaggio con la parete sinistra dell'aorta e porzioni di muscolo psoas. Il tessuto ha spessore massimo di circa 2 cm attorno al rene.
- Posizionamento di stent ureterale sn a J con biopsia e con diagnosi di linfoma della zona marginale

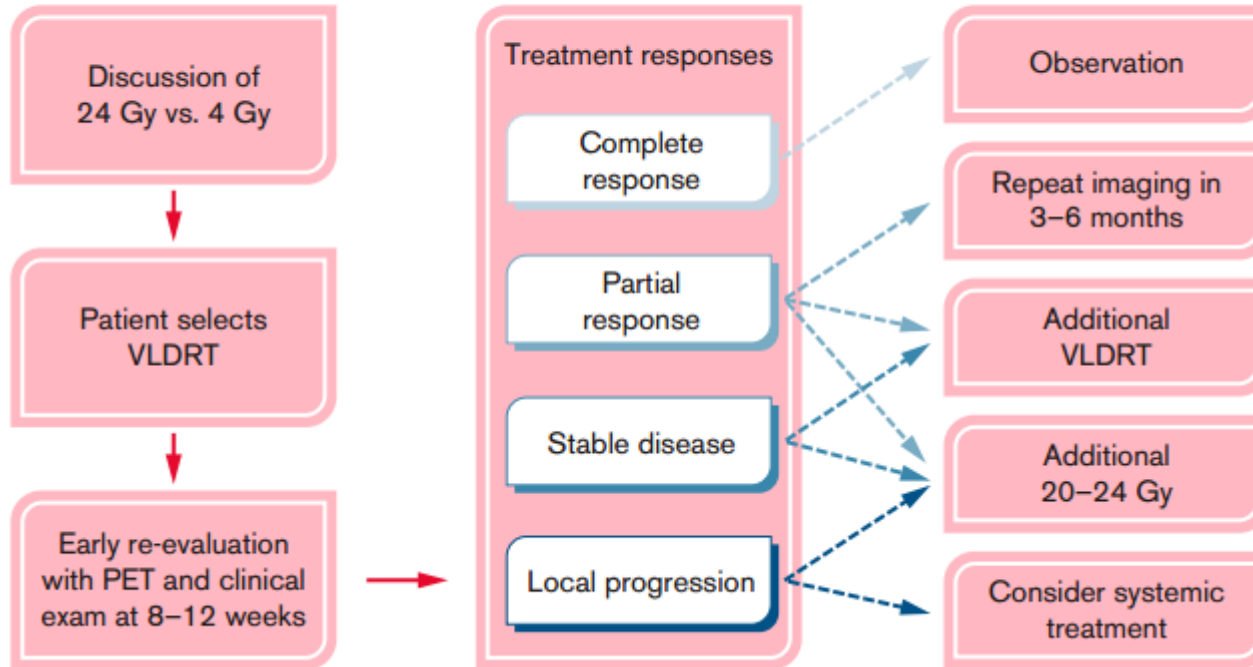


- RT 4Gy in 2 frazioni
- TC post-RT: Ridotto il tessuto solido a sede perirenale e para-aortico sinistro, dello spessore massimo di 1,3 vs 2,2 cm poco al di sotto dell'origine dell'a. renale.
- Rimosso il pig-tail ureterale a sinistra.
- Creatinina 1.01

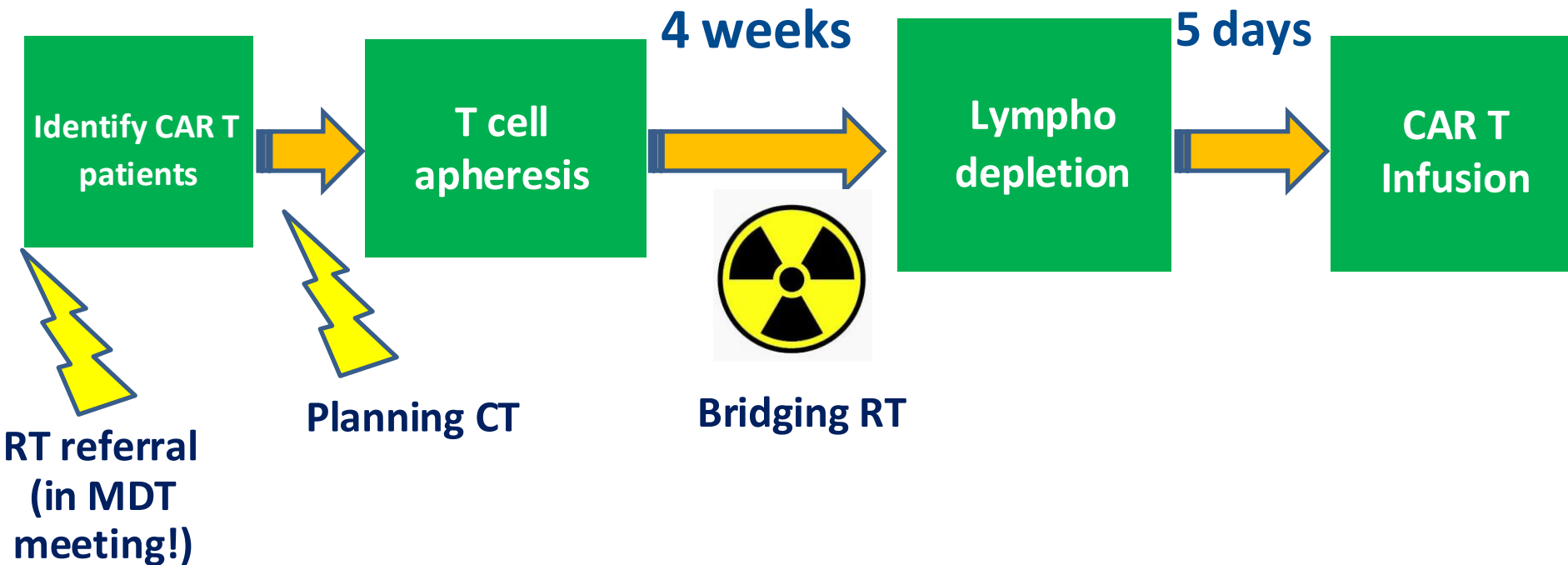


MSKCC framework for indolent NHL

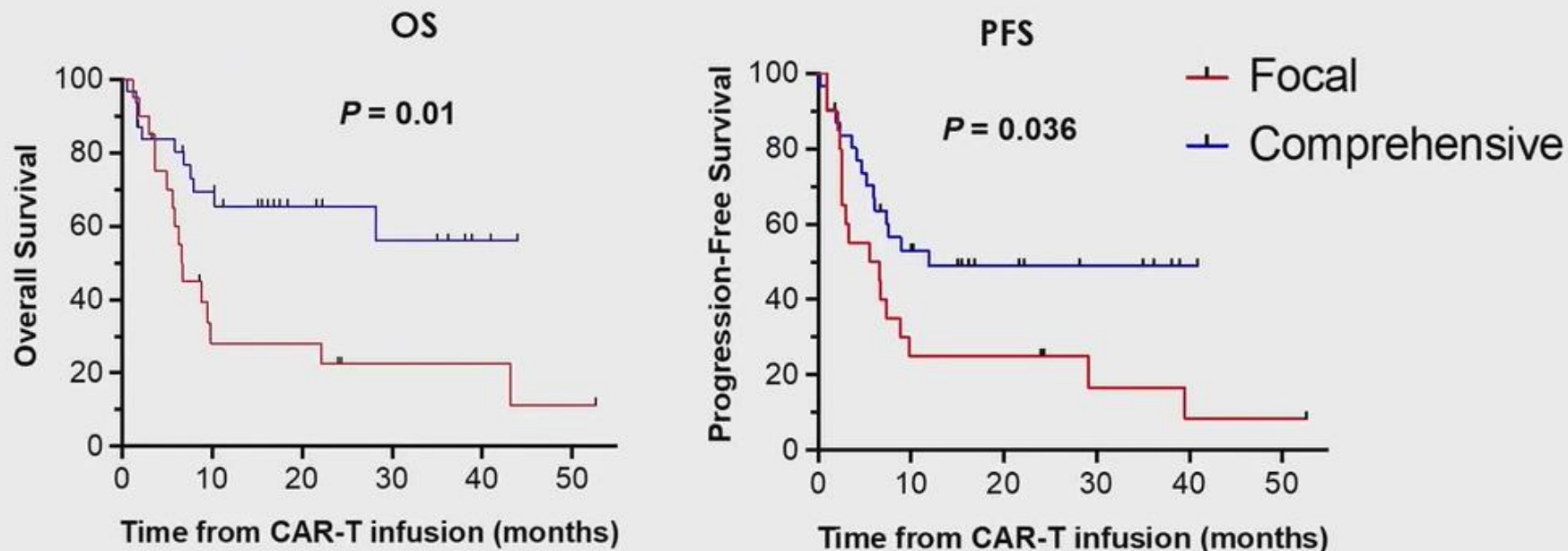
Adaptive, incremental radiotherapy program



RADIOTHERAPY AND CAR-T

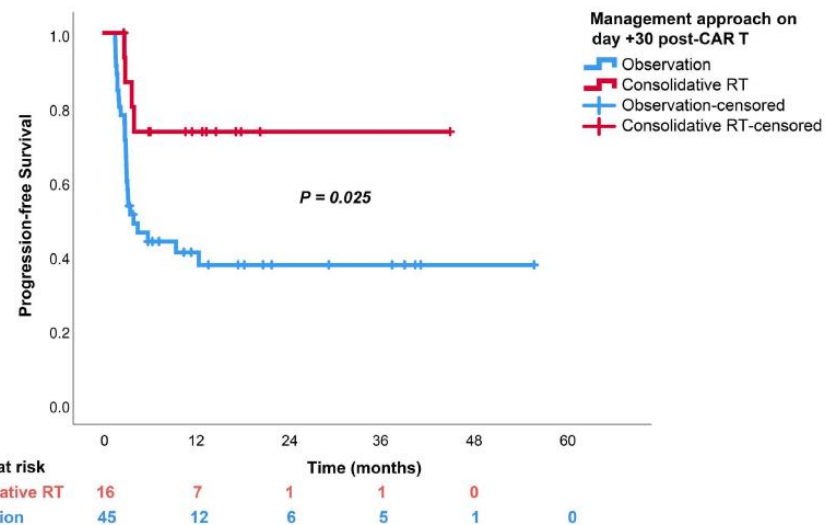
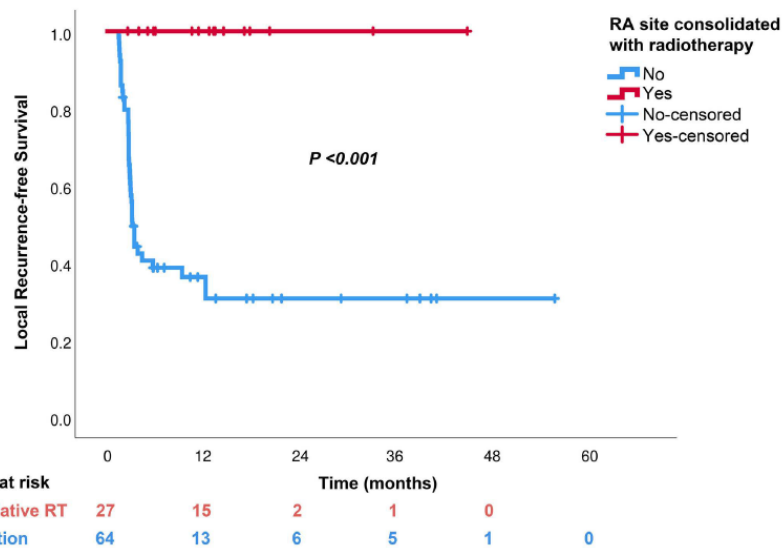


OS & PFS ↑ with **comprehensive** bRT to all disease sites



1 yr OS: 72% [52-85] vs. 45% [23-65], $p=0.01$

Consolidative radiotherapy for residual fluorodeoxyglucose activity on day +30 post CAR T-cell therapy in non-Hodgkin lymphoma

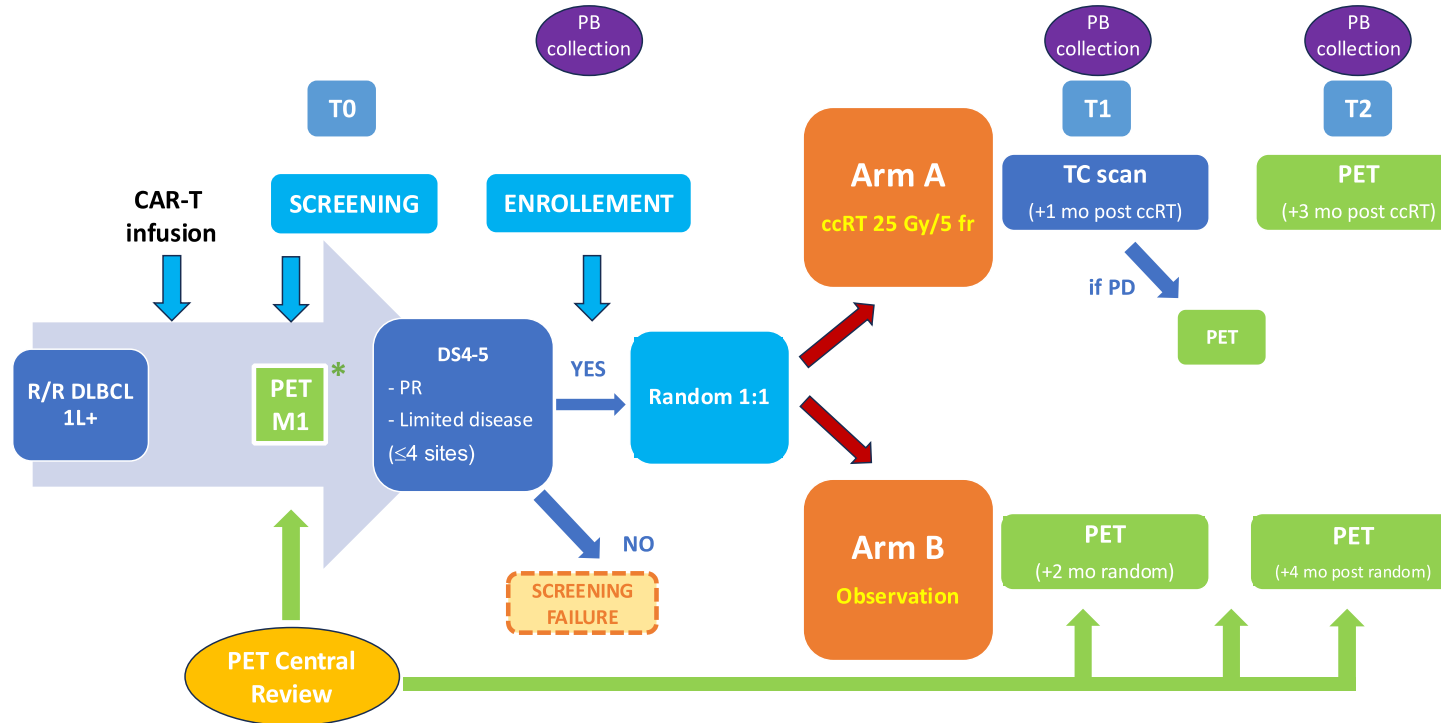


CompreheNsive CosolidativE RadioTherapy for relapsed-refractory diffuse large B-cell lymphoma with incomplete response and limited disease at 1 month post CAR-T: a multicentric phase II randomized CONCERT study

- **PRINCIPAL INVESTIGATOR:** Mattia Novo, Torino
- **CO-PI:** Mario Levis, Torino
- **WRITING COMMITTEE AND SCIENTIFIC SUPPORT:**
B Botto (Torino) A Castellino (Cuneo) A Chiappella (Milano), P Ciammella (Reggio Emilia), A Di Rocco (Roma), A Evangelista (Torino), L Guerra (Monza) M Levis (Torino), M Novo (Torino), S Ragaini (Torino), U Ricardi (Torino), G Simontacchi (Firenze), MC Tisi (Vicenza), VR Zilioli (Milano)

Study Flow Chart

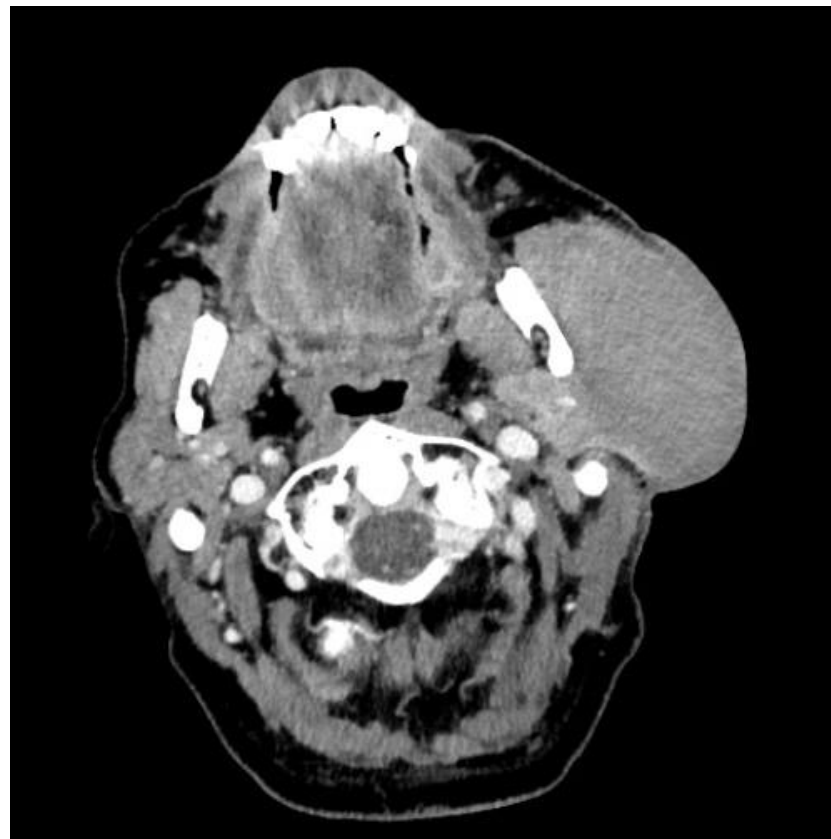
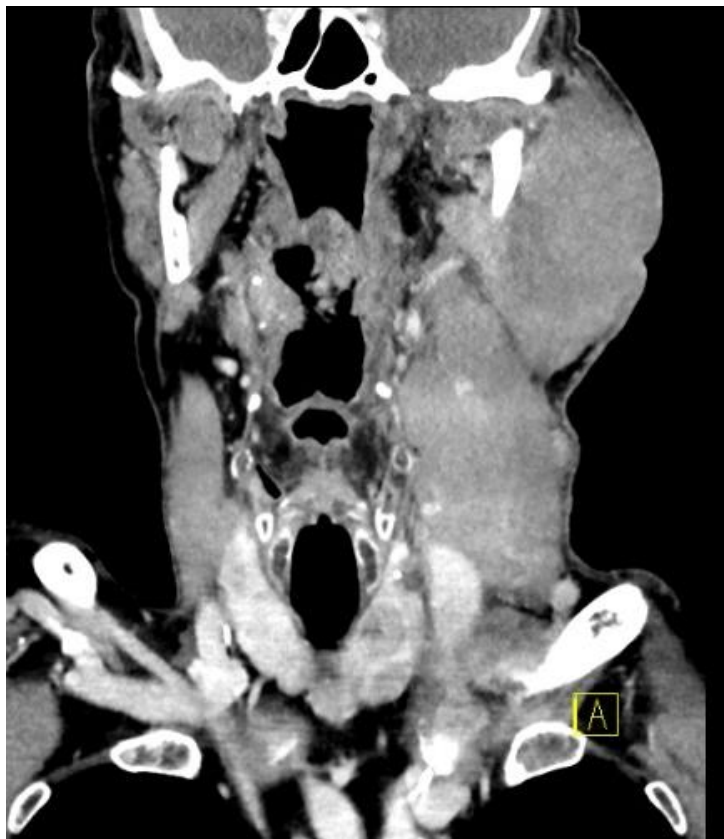
R/R DLBCL patients with PR at PET-M1 post CAR-T will be screened and PET central review at M1 will be performed



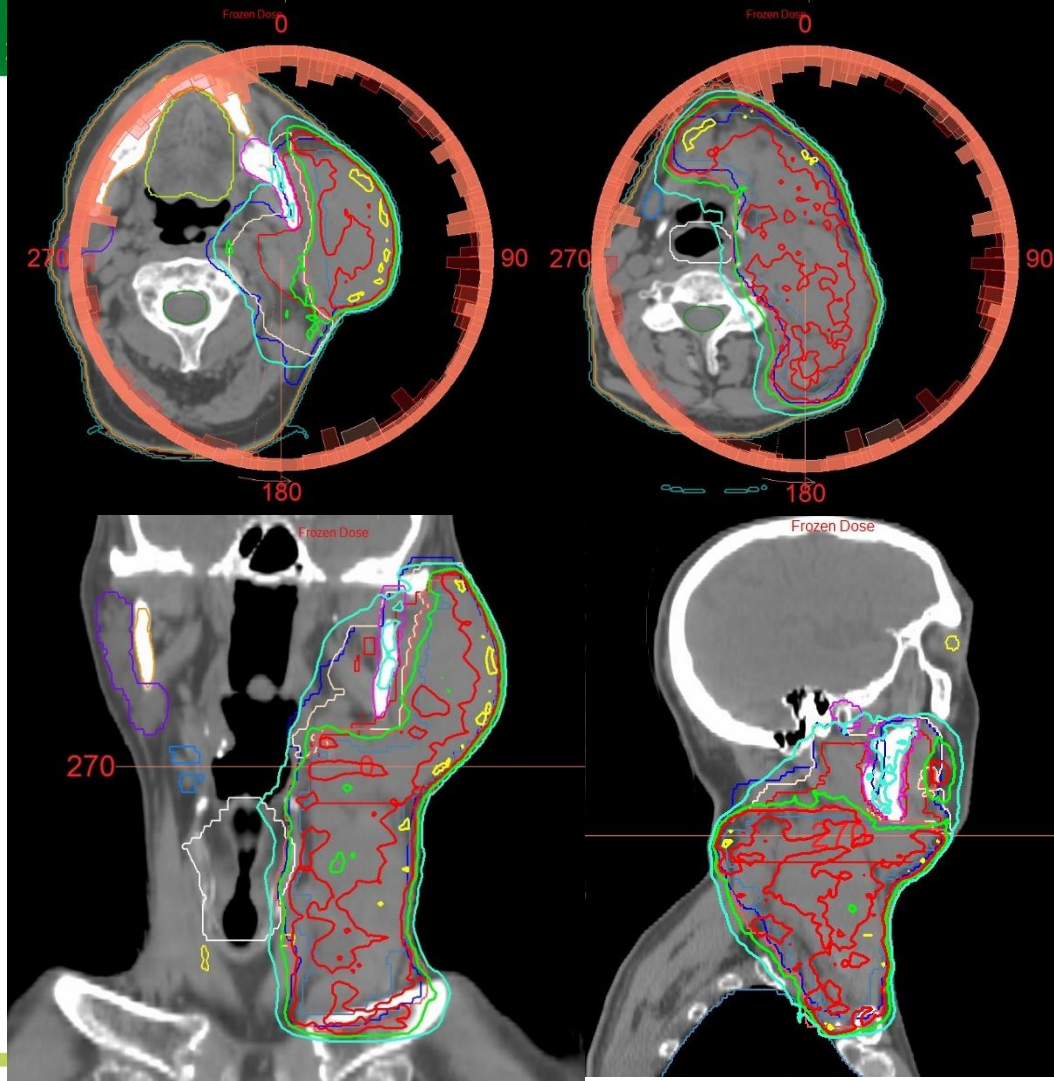
* In addition to PET scan a CT scan at M1 will be required (not central review required)

P.G., uomo, nato nel 1951

- Gennaio 2014 diagnosi di MCL stadio IV.
- RCHOP, poi ASCT Nov 2014 + Lenalidomide di mantenimento
- Dicembre 2016 recidiva, R-BAC, poi RT su regione laterocervicale sn per 36Gy in 18 frazioni, poi Rituximab di mantenimento
- A novembre 2019 recidiva di linfoadenopatia in sede parotidea sinistra, che si estendeva a livello laterocervicale e sottomentoniero omolaterale, inizia Ibrutinib
- Progressione di malattia, valutazione presso INT per protocollo CAR T compassionevole
- A settembre 2020 ulteriore radioterapia su tumefazione parotidea sn e LAP sottomentoniere e laterocervicali per una DTF di 36 Gy in 18#
- CAR-T Tecartus KTE-X19 secondo protocollo compassionevole in data 23.12.2020



- RT per una dose di 36 Gy in 18# da 2Gy con Simultaneous Integrated Boost (SIB)
- PTV 30Gy per risparmiare ATM, branca mandibolare e coclea sx)
- Remissione completa a 5 anni da CAR-T.



REVIEW

WILEY

Radiotherapy in mantle cell lymphoma: A literature review

Sharon Ben Barouch¹ | John Kuruvilla¹ | Richard W. Tsang¹ | Eva Yashphe² |
Nadav Sarid²





TABLE 2 Publications of radiotherapy for advanced-stage mantle cell lymphoma

Study	Year of Publication	Design	Patients, n	Radiation Dose, Gy	Symptoms Relief, %	Local RR, %	Local CR, %	Local PFS, mo	Systemic PFS, mo	OS
Rosenbluth et al ¹⁴	2006	Retro	21	30	94	100	64	10	N/A	1 y, 55%
Haque et al ¹⁵	2014	Retro	39	30	95	94	69	7	N/A	73 mo
White et al ¹⁶	2016	Retro	14	4	94	88	68	10	10	N/A
Neville et al ¹⁷	2015	Retro	25	17	93	85	72	N/A	6.2	74.3 mo
Ning et al ¹⁸	2019	Retro	19	4	N/A	86	81	4 mo, 85%	7.9	1 y, 90%

Abbreviations: CR, complete response; N/A, not available; OS, overall survival; PFS, progression free survival; Retro, retrospective; RT, radiotherapy; RR, response rate.

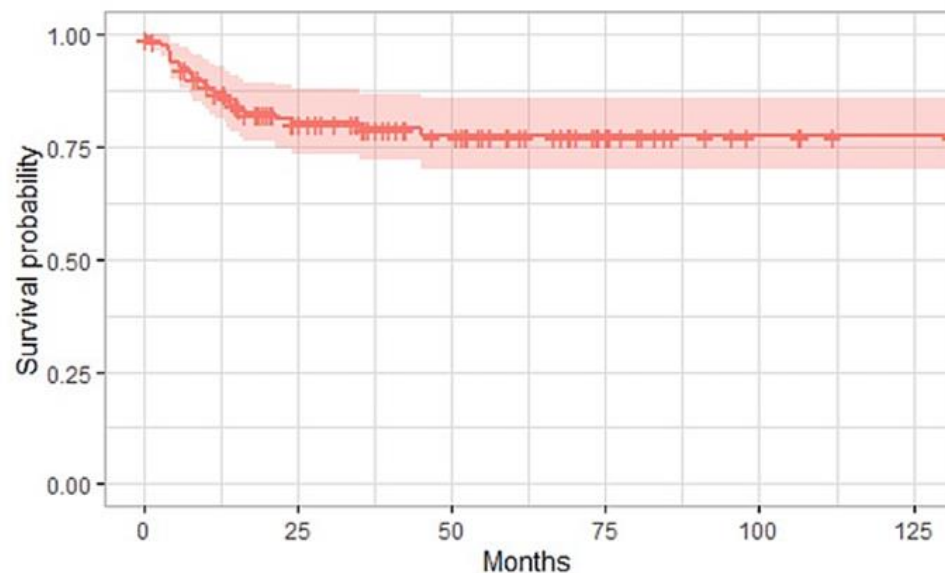
CUTANEOUS LYMPHOMA

Low-Dose Radiotherapy for Primary Cutaneous Indolent B-Cell Lymphomas: a Multicenter Retrospective Study

E Alì^a, G Simontacchi^b, M Levis^c , F Iori^a , S Gambarà^d, EM Cuffini^c, N Pimpinelli^e, V Grandi^f, A Botti^g, G Paolani^g , C Iotti^a , U Ricardi^c , P Ciammella^{a,*} 

Local Control

Strata  All



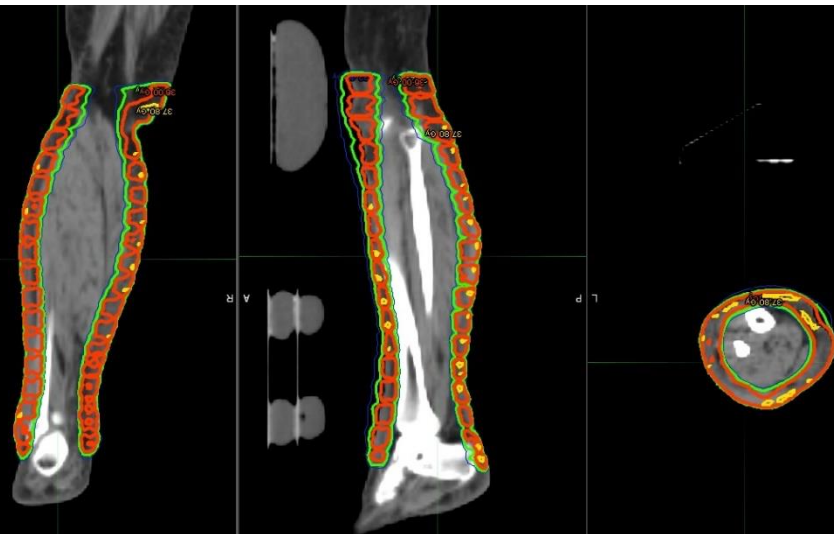
- 75pts, 137 lesioni trattate
(77 MZL, 55 FL, 5 other)
- 4Gy in 2 frazioni
- LC @3y 77%

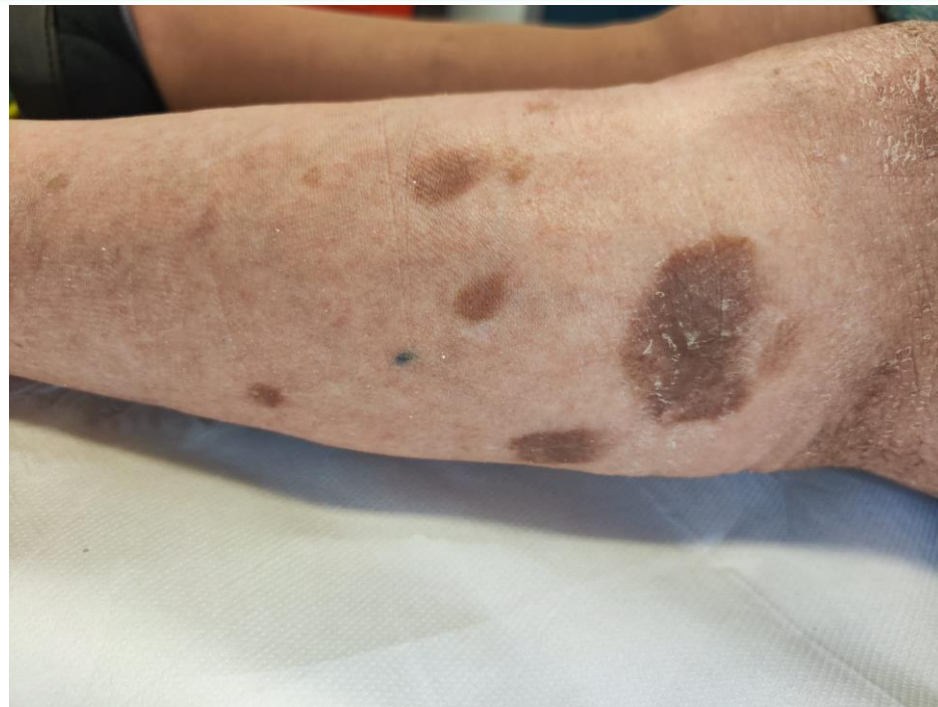
➤ TRATTAMENTO RADICALE IN DLBCL SUPER-FRAIL

- D.D., donna, 98 anni
- Comparsa a livello della gamba sinistra aree di malattia rilevate non ulcerate "legermente abrase" di dimensioni da subcentimetriche a 6-7 cm, in particolare a livello della faccia posteriore, non sanguinanti, non dolore.
- Reperti morfo-fenotipici coerenti con linfoma B diffuso a grandi cellule [profilo immunofenotipico sec. Hans: Non Germinal Center B-Cell-like (non GCB)], possibile leg-type.



- RT per una dose di 36 Gy in 12# da 3Gy





➤ RC a 12 mesi dal trattamento

Ultrahypofractionated Low-Dose Total Skin Electron Beam in Advanced-Stage Mycosis Fungoides and Sézary Syndrome

Khaled Elsayad, PhD,* Carsten Weishaupt, PhD,[†] Christos Moustakis, PhD,* Moritz Fabian Danzer, MSc,[‡] Elisa Christina Müller, MD,* Daniel Rolf, MD,* Rene Stranzenbach, PhD,[§] Elisabeth Livingstone, PhD,^{||} Nina Booken, PhD,[¶] Rudolf Stadler, PhD,[#] and Hans Theodor Eich, PhD*

- 18 pts
- TSEBT 4Gyx2

- OS 88.9% (CR 16,9%, PR 72,2%)
- Median TTNT 12m
- Median PFS 8m

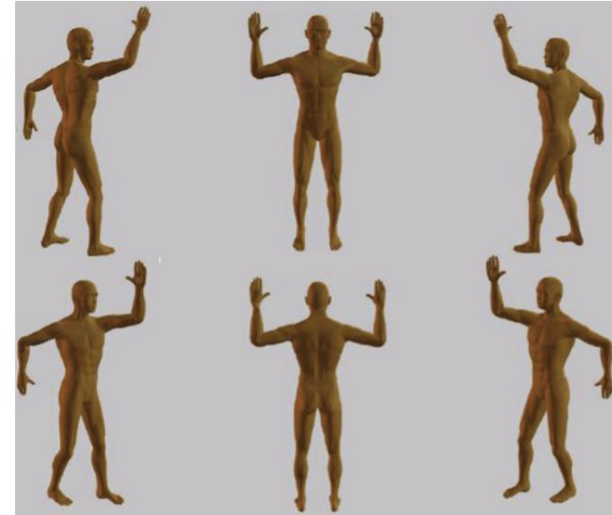
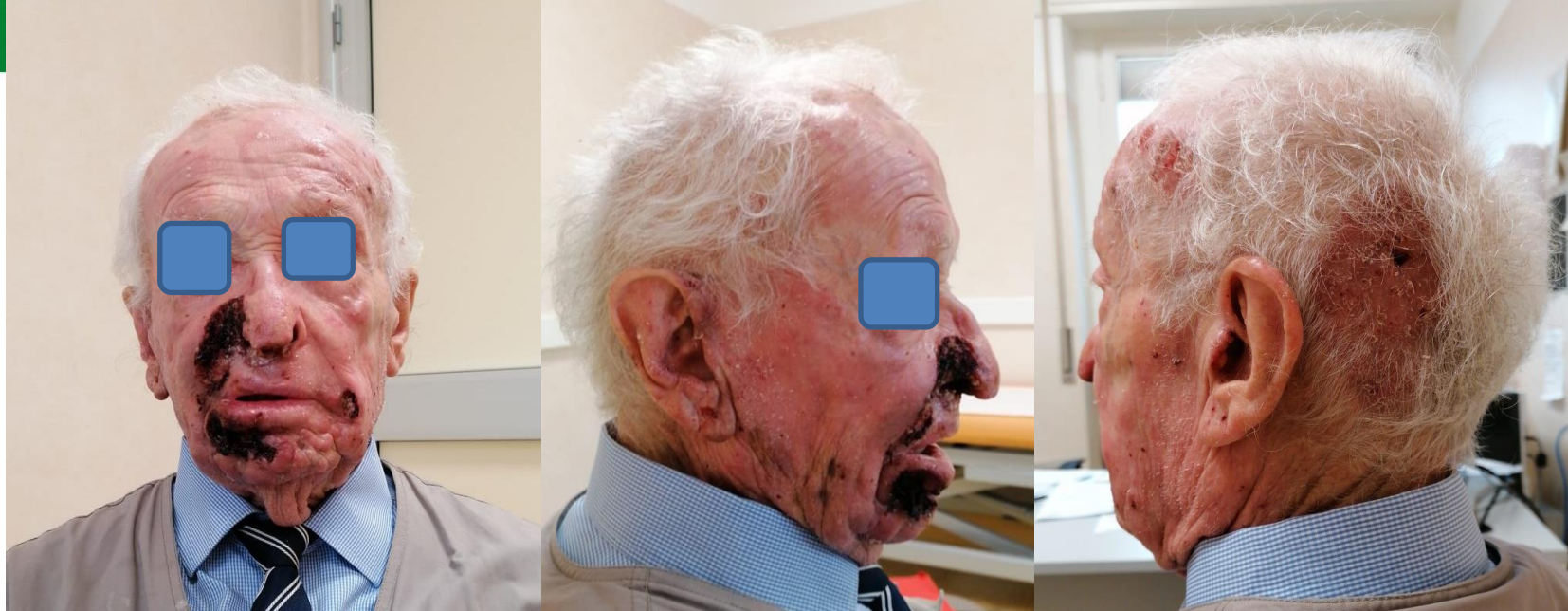
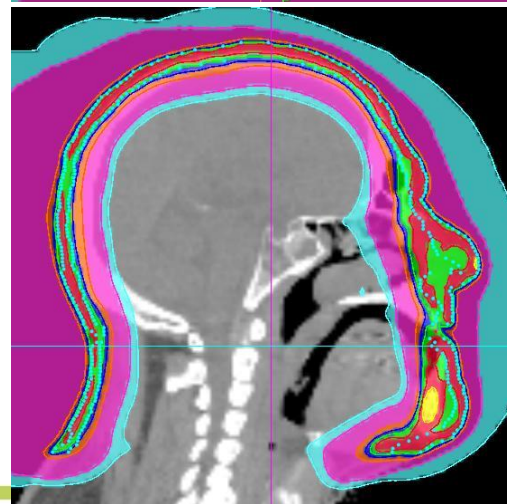
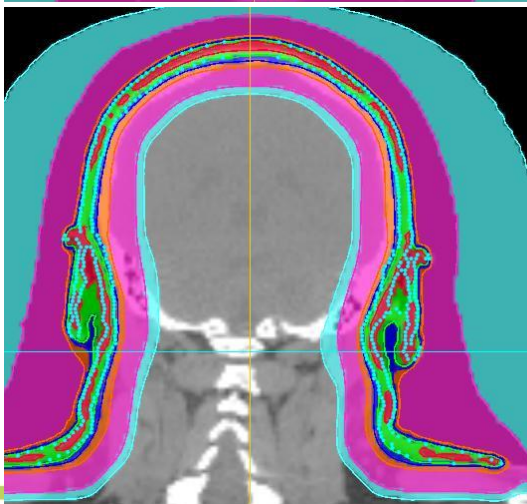
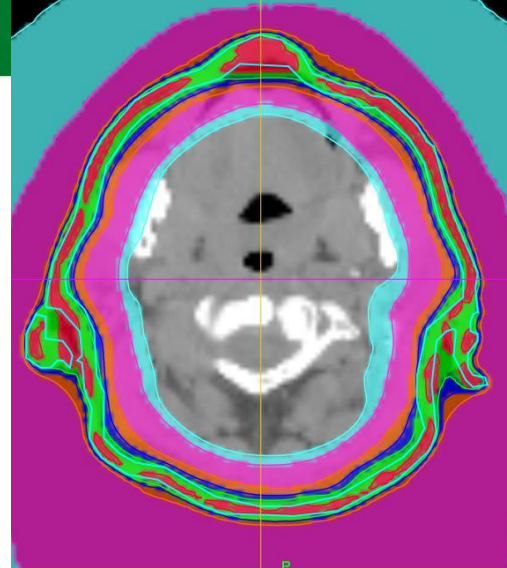
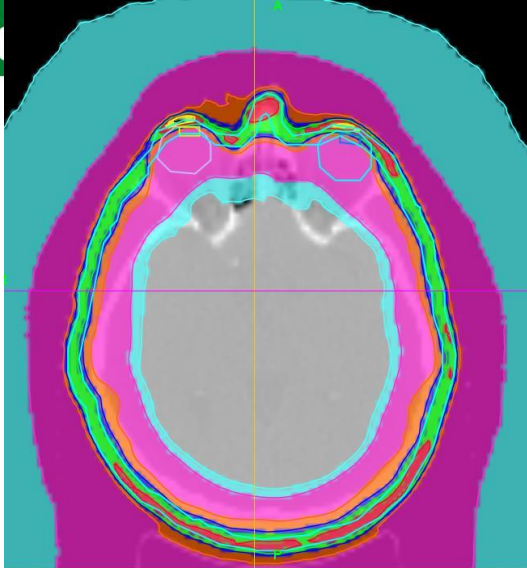


Fig. 10. Patient positions for total skin electron beam therapy, 6-field technique. The straight anterior, right posterior oblique, and left posterior oblique fields are treated on one day. The straight posterior, right anterior oblique, and left anterior oblique fields are treated the next day.



- A.G., 91 anni, Micosi Fungoide con modesti aspetti follicolotropismo, comorbidità cardiologica rilevante
- Precedenti trattamenti con RT locale
- Terapia con Gemcitabina interrotta dopo due cicli per scarsa tolleranza
- Trattamento di «Total scalp+face irradiation», 20Gy in 10 sedute con Tomotherapy







***... ASK YOUR
RADIATION
ONCOLOGIST!!***