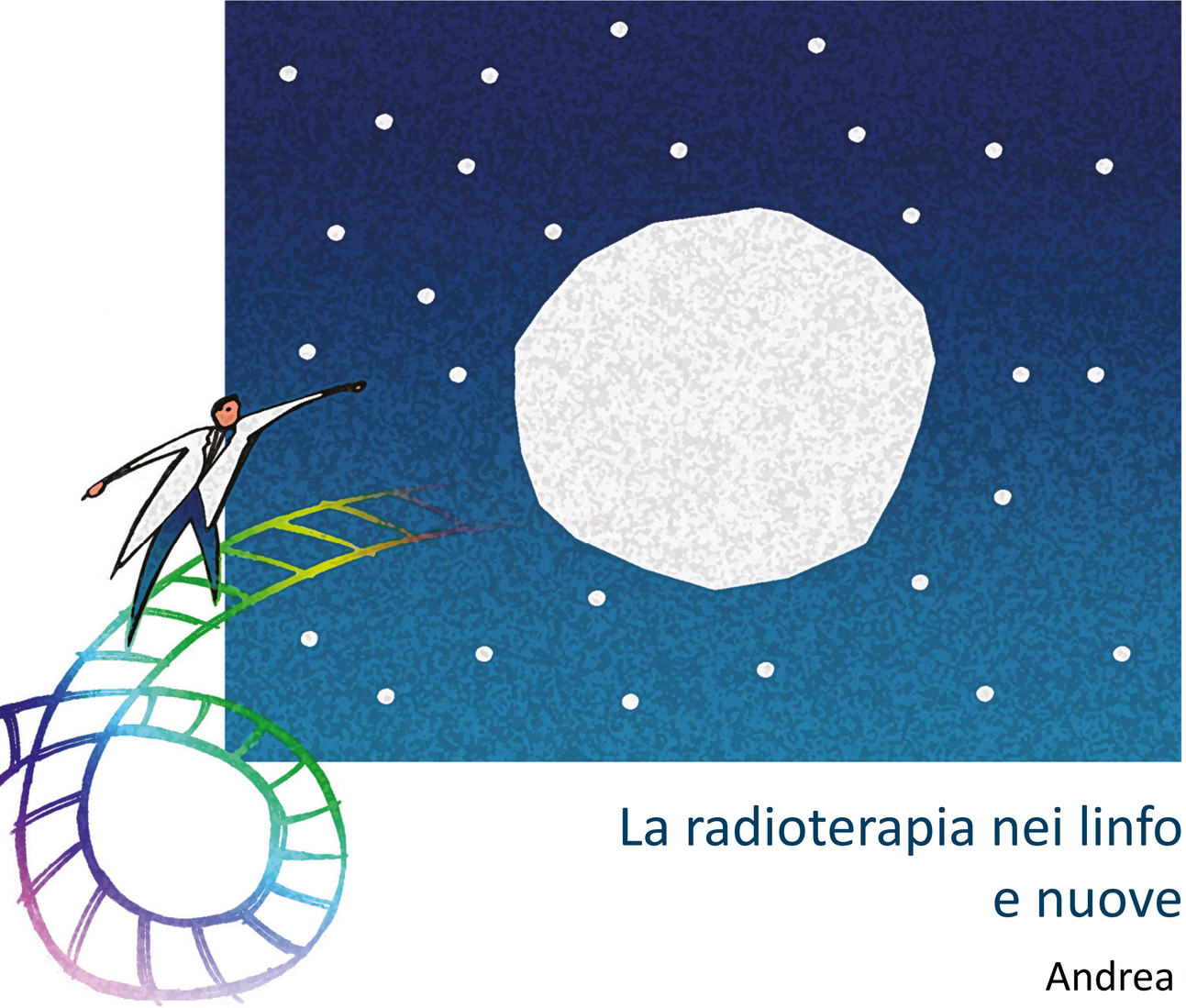


The young side of
LYMPHOMA

gli under 40 a confronto

Verona, Centro Congressi Camera di Commercio
26-27 settembre 2025

La radioterapia nei linfomi indolenti: nuovi approcci e nuove integrazioni

Andrea Guerini

Università degli Studi di Brescia

Disclosures of Andrea Guerini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Background

- Mature B cell neoplasms or indolent non-Hodgkin lymphomas (iNHLs): heterogeneous group of malignancies sharing similar disease courses and treatment paradigms.

- most common i-NHL subtypes follicular lymphoma (FL), marginal zone lymphoma (MZL), lymphoplasmacytic lymphoma (LL), small lymphocytic lymphoma (SLL), and a subset of mantle cell lymphoma (MCL).

- Taken together, all i-NHLs incidence close to that of DLBCL

- generally incurable, most patients lifespan similar to that of the age-matched population, with the exception of those who are young at diagnosis and those who progress rapidly or experience transformation into aggressive lymphomas (8–10% risk at 5 years)
~50% asymptomatic
transformation after 5–10 years of 10-15% > poor prognosis

- 75–85% of patients diagnosed in the advanced stage (III-IV), 15–25% present with limited disease (I-II) > curable?

- localized presentation by chance (i.e., incidental early identification) or inherent biological property/ genetic profile? > curable?

- Advanced-stage FL incurable and the therapeutic approach focuses on long remission duration.

- with the introduction of rituximab 10-y OS 75-85%

Background

- Following RT >90% ORR, few in-field recurrences > ~50% 10y PFS

LIMITED DISEASE

- RT suggested by current guidelines > potential "curability"

- Upfront RT: why not?
Fear of SMN risk
Fear of toxicity
Good results with WW and potential spontaneous remission (up to 20%)

- patients with a localized major site and minimal systemic involvement > no curative intent
FL 40-70% MALT 10% other MZL 30-60% MCL 50-90% BM involvement

-minimal residual disease (MRD), defined as detectable circulating BCL2/IGH + cells, at diagnosis despite negative molecular BM assessment > negativization after RT ~ 50%

Background

ADVANCED DISEASE

- early treatment of asymptomatic patients with low-burden iNHL does not prolong OS or reduce the rate of histologic transformation (HT) compared to WW

Typically, treatment is indicated for patients with symptomatic or high-burden (mass > 7 cm; involvement of ≥ 3 nodal sites each ≥ 3 cm; splenomegaly, > 5.0 k/mcl circulating lymphoma cells) disease and those with end-organ compromission or rapid progression over 3mo

criteria are based on data from the pre-rituximab era, still valid

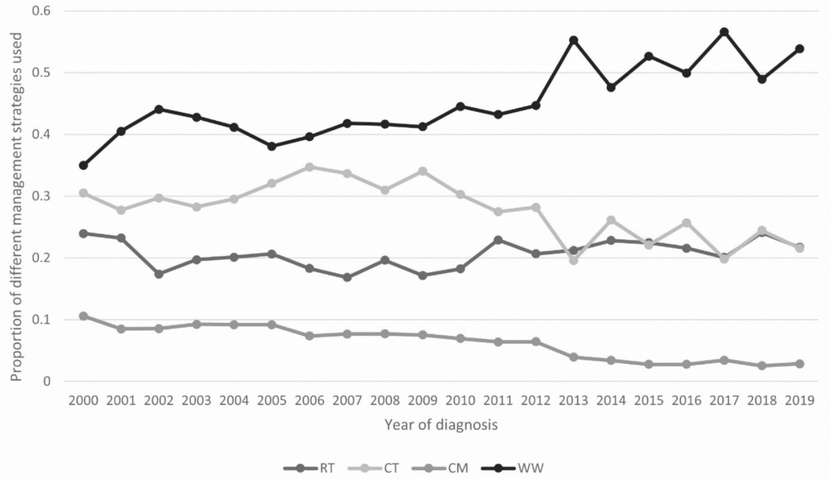
Lack of survival advantage = lack of benefit? QoL!
- prolong the chemotherapy-free interval
- cosmetical burden
- anxiety

Versus
lack of survival benefit
20–30% of patients will not meet treatment criteria for at least 10 years

RT impact on OS and SMNs

Zengh W et al Ann Hematol. 2024 Nov;103(11):4589-4598. doi: 10.1007/s00277-024-06025-1.

SEER database. 10,900 patients (62% St I) 930 cases developed SPMs. 2000-2020
- RT use low (20%)
- rituximab era, multivariate analysis RT significantly superior OS
and did not increase SPMs risk in comparison with ST and WW.



ST (HR, 1.414; P < 0.001) or WW (HR, 1.315; P < 0.001) poorer OS vs RT

ST (RR, 0.900; P = 0.288), WW (RR, 0.869; P = 0.107) or CM (RR, 1.123; P = 0.417)
similar SPMs risk vs RT.

Rtx era significantly superior survival and lower SPMs risk for all pts and RT pts > smaller fields, lower dose

pre-RTX, the SPMs risk of patients receiving RT was significantly higher in comparison with patients receiving ST > extended fields and higher dose.

Nie et al Ann Hematol. 2025 Jan;104(1):691-700. doi: 10.1007/s00277-025-06209-0. Epub 2025 Jan 24.

SEER database 2003-2014, 7551 FL patients 60-month follow-up
RT associated with better OS (P < 0.001) and CSS (P = 0.002) and no significant association with second primary cancer (SPC) risk

▪Pugh TJ Cancer. 2010;116:3843–3851. doi: 10.1002/cncr.25149.

SEER analysis 6568 pts 1973-2004 localized grade 1–2 FL upfront RT improved disease-specific survival (DSS) and overall survival (OS) (10 y and 20 y DSS 79% and 63% for RT vs. 66% and 51% for no RT)

RT impact on OS and SMNs

Friedberg JW et al. J Clin Oncol. 2012 Sep 20;30(27):3368-75. doi: 10.1200/JCO.2011.40.6546. Epub 2012 Aug 20.

LymphoCare Study 471 pts StI FL (enrolled form 2004), 206 staging (CT or PET) > 56 pts RT

PFS significantly improved with either R-chemo or systemic therapy + RT compared with patients receiving RT alone

limited follow-up (45 months), study was not intention-to-treat.

Zhong Q et al Leuk Lymphoma. 2024 Mar;65(3):312-322. Doi: 10.1080/10428194.2023.2283296. Epub 2023 Nov 21.

5305 pts early-stage grade I-II FL in the SEER database (2000-2015)
Primary therapy RT alone (RT, 20.7%), chemotherapy alone (CT, 27.6%), combined modality therapy (CMT, 5.9%), and observation (45.8%).
RT +/- CT significantly higher 10-year OS (78%) and relative survival (>95%)
RT was an independent predictor of better OS and RS in multivariate analyses ($p < .001$).

Relatively small pre-RTX retrospective series of iNHL treated with RT > no SMNs increase

Int J Radiat Oncol. 2006;64:928–934. doi: 10.1016/j.ijrobp.2005.08.010.
Ann Oncol Off J Eur Soc Med Oncol. 1999;10:317–321. doi: 10.1023/A:1008328226599.
Cancer. 2010;116:3815–3824. doi: 10.1002/cncr.25226.

Leuk Lymphoma. 2024 Mar;65(3):312-322. doi: 10.1080/10428194.2023.2283296. Epub 2023 Nov 21.

5-year risk of SHM was 1·1% associated with multiple lines of treatment (P = 0·016)
0·5% after the first-line treatment 1·6% after the second-line.

RT impact on OS and SMNs

Tian Y et al PLoS One. 2025 May 28;20(5):e0324532. doi: 10.1371/journal.pone.0324532.

2000-2020, 33104 pts FL from SEER

Univariate and multivariateanalysis revealed that radiotherapy (HR: 1.13, P = 0.002) risk of developing SPMs.

11.5% SPMs, incidence 5.8% at 5 years, 9.4% at 10 years

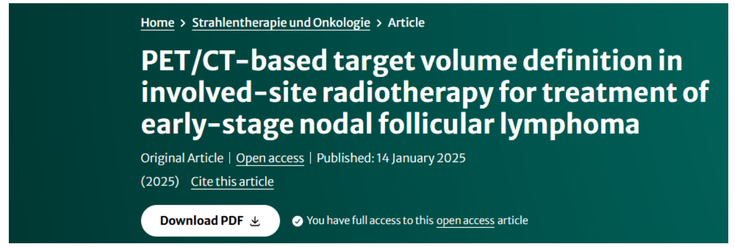
A greater percentage of individuals with SPMs underwent RT (21.4% vs. 18.9%, P < 0.001) or surgery (52.7% vs. 44.4%, P < 0.001)

In contrast, both RT and surgery significant associations with reduced all-cause mortality and better OS. Notably, among patients developing SPMs, initial radiotherapy maintained protective effects for both OS and lymphoma-specific survival (LSS)

Wang Y et al Discov Oncol. 2025 Mar 26;16(1):397. doi: 10.1007/s12672-025-02149-3.

SEER database, 19,326 FL patients, 9539 patients
Initial chemotherapy and radiotherapy in patients with grade I-II FL were associated with increased risk of certain subtypes of MNs, such as MDS and AML > incidence 0.01%

Modern treatment of iNHL



Do these results apply to current clincal practice?

1. PET-CT STAGING

Modern staging for indolent NHL is PET-based, which can upstage 10–60% compared to CT.

PET-CT staging of clinical stage I FL may contribute to the improved prognosis

Leuk Lymphoma. 2018 May;59(5):1163-1171. doi: 10.1080/10428194.2017.1375102.

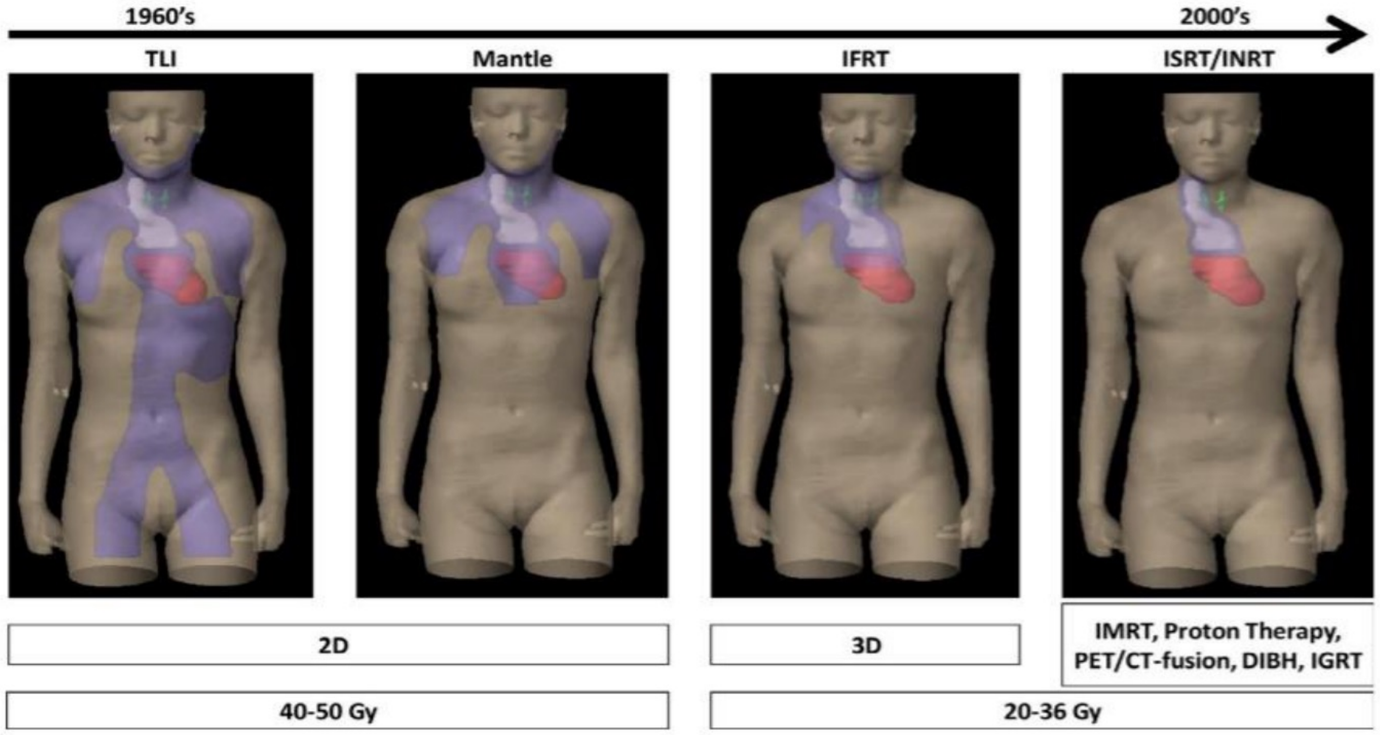
GAZAI 170 involved lymph nodes FDG-PET/CT identified additionally involved lymph nodes not detected by CT in 61% of the patients, leading to a significant change in radiation treatment fields for 30%

2. Anti-CD20 BASED SYSTEMIC THERAPY

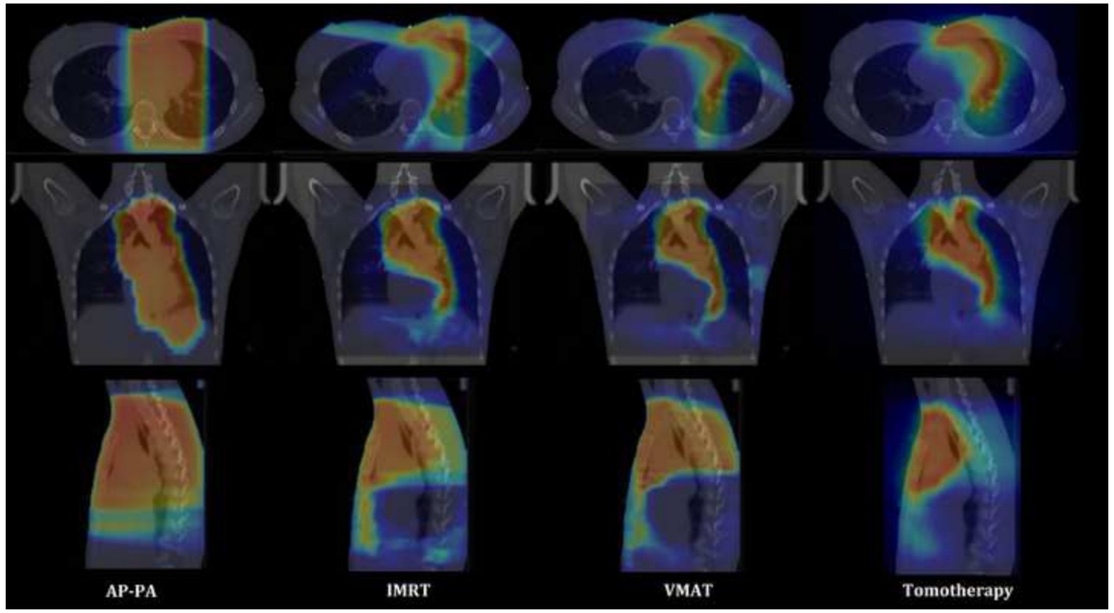
3. REDUCED RT DOSE AND VOLUMES

4. MODERN RT TECHNIQUES

Modern radiotherapy



Int J Radiation Oncol Biol Phys, Vol. 111, No. 4, pp. 841–850, 2021



Case 1

Female 32 yo, no comorbidities, IK100

Due to swelling in the left inguinal region, investigations were carried out:

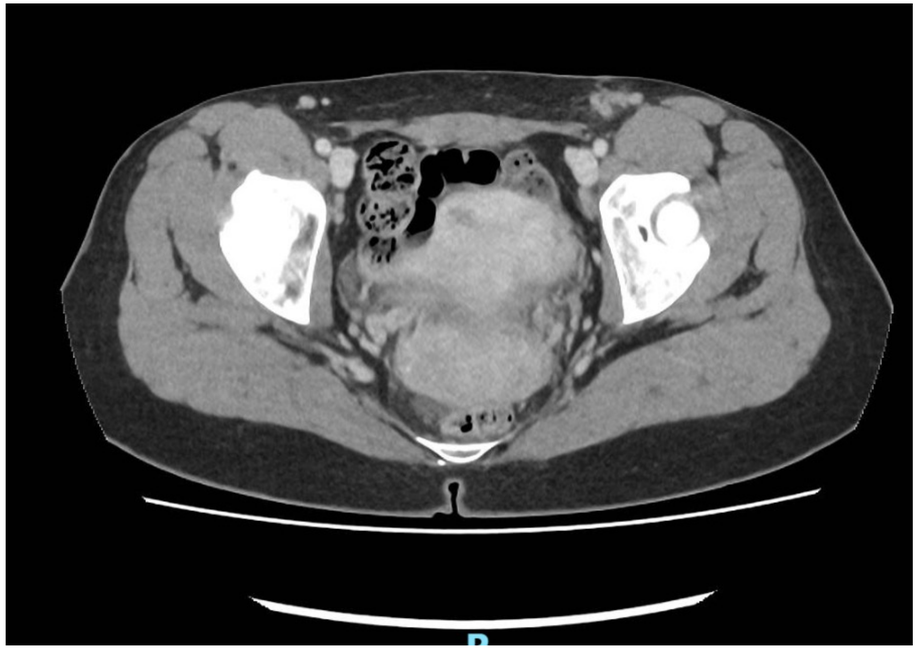
17/10/2024 – ultrasound: lymphadenopathy in the left inguinal region, with a maximum diameter of 25 mm.

28/11/2024 – Excisional biopsy of the left inguinal lymphadenopathy; pathology report: low-grade follicular B-cell non-Hodgkin lymphoma.

9/1/2025 – Total body CT scan: negative for residual disease.

14/1/2025 – PET CT: post-excisional biopsy changes in the left inguinal region; caudal to this site, a millimetric lymphadenopathy with moderate radiotracer uptake, compatible with disease involvement.

29/1/2025 – Bone marrow biopsy: negative



Case 1

Therapeutic options

1. **Watchful waiting**
2. **RT alone**
3. **Chemotherapy**
4. **Rituximab/Obinutuzumab**
5. **RT + R/O**

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#3546 320

RT dose

Reference	Year	Design	RT fields	Pathology summary	No. of patients	No. of sites	Median follow-up (mo)	ORR (%)	CR (%)	PR (%)	Results
This study	2021	Retrospective	ISRT	66% FL, 27% MZL, and 7% low-grade NOS	250	299	26	90	68	22	2-y cumulative incidence of LP for overall, 25%; non-curable, 29%; potentially curable, 9%
24,25	2014, 2021	Randomized, phase 3, noninferiority of 4 Gy vs 24 Gy (FoRT)	IFRT	56% FL, 7% MZL, 6% other (ie, CLL, DLBCL, HL), 12% no diagnosis possible, 21% with no central review	281	315	74	81	49	32	LPFS at 5 y: 89.9% after 24 Gy and 74.4% after 4 Gy ($P < .001$)
21	2008	Phase 2	IFRT	62% indolent (mostly FL) and 36% aggressive lymphoma	36	47	5	86*	48*	38*	Median time to LP for the entire group, 15 mo
19	2005	Phase 2	IFRT	SLL and CLL (n = 23), MZL (n = 18), MCL (n = 17), DLBCL (n = 13)	71	177	9	93*	56	37	Median time to LP for iNHL, 23 mo
18	2003	Phase 2 (HORA-1)	IFRT	FL 90%, MZL 8%, lymphoplasmacytoid lymphoma 2%	109	304	7	92	61	31	Median time to LP, 25 mo
17	2002	Phase 2	IFRT	68% iNHL, 32% CLL	22	31	8	87*	74*	13*	Median time to LP for full group, 22 mo

Reference	Year	Design	RT fields	Pathology summary	No. of patients	No. of sites	Median follow-up (mo)	ORR (%)	CR (%)	PR (%)	Results
35	2018	Retrospective		57% FL, 43% MZL	47	50	21	90			LPFS at 2 y for all patients, 91.1%; curative, 96.7%; palliative, 83.8%
34	2013	Retrospective	IFRT	66% FL, 9% CLL or SLL, 10% MZL, 6% MCL, 8% other	127	187	23	82	57	25	Median time to first recurrence, 13.6 mo
22	2011	Retrospective		56% indolent, 28% CLL, 13% aggressive, 2% of sites were other	54	85	16	88*	71	17	LPFS at 2 years, 50%
20	2008	Retrospective	IFRT	FL 85%, MZL 6%, MCL 6%, CLL 3%	33	43	14	95	84	12	Median time to LP, 9 mo
15	2001	Retrospective	IFRT	100% low-grade lymphomas	48	135	54	81	57	24	LPFS at 2 y, 56%

RT dose

large single-institution VLDRT for FL or MZL 2005-2018

299 lesions; 250 patients

Positron emission tomography staging and involved site radiotherapy

ORR 90% CR 68% median FU 2.4y 2y LP 25% (9% in first line localized, n=52)

Lesion size >6 cm was associated with lower odds of attaining a CR and greater risk of LP.

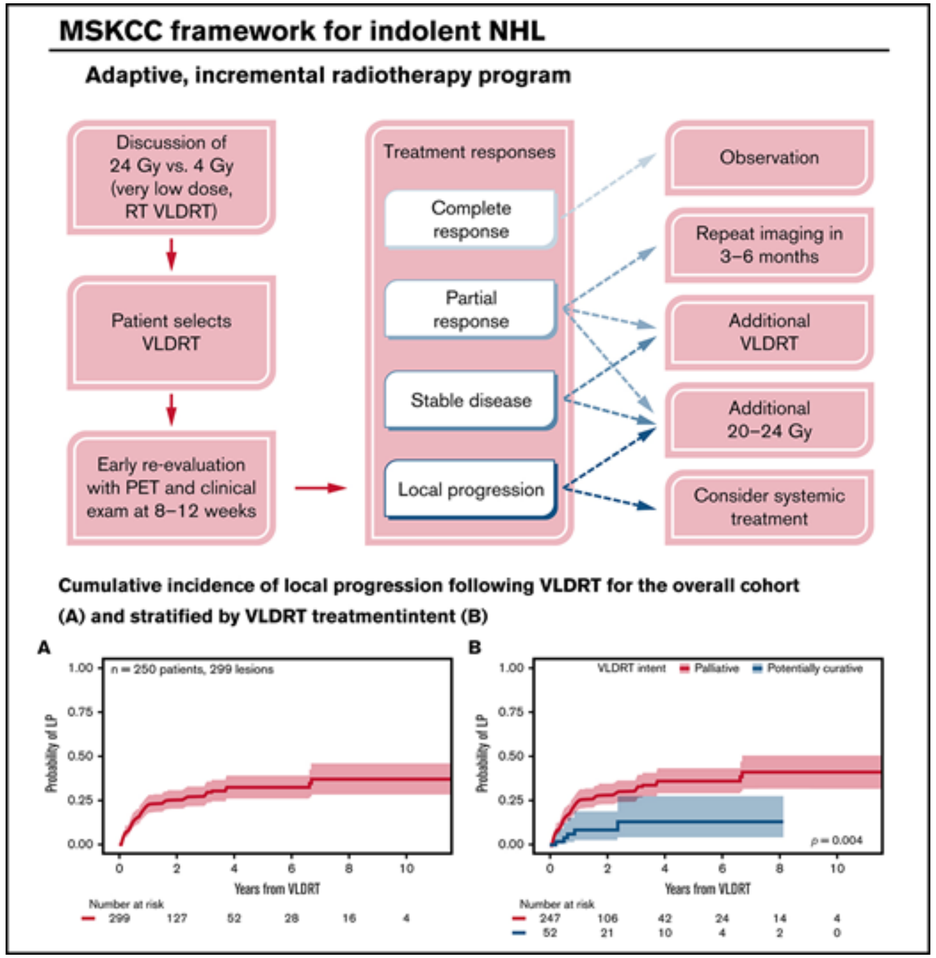
Additional RT to 45 lesions (12 subopt resp, 30 salvage, 4-30 Gy) > 68% CR 18% PR, 2y LP 15%

blood advances LYMPHOID NEOPLASIA | OCTOBER 22, 2021

Excellent response to very-low-dose radiation (4 Gy) for indolent B-cell lymphomas: is 4 Gy suitable for curable patients?

Clinical Trials & Observations

Brandon S. Imber, Karen W. Chau, Jasme Lee, Jisun Lee, Dana L. Casey, Joanna C. Yang, N. Ari Wijentunga, Annemarie Shepherd, Carla Hajj,



RT dose

randomised, multicentre, phase 3, non-inferiority trial at 43 study centres in the UK
indolent NHL (FL 86% , MZL)
randomized 2/24 Gy vs 2/4 Gy

primary endpoint 2y LC, non-inferiority threshold 10%

614 target sites in 548 patients, median FU 74 mo,
CR at 3mo 91% vs 81% 2y LPFS 94.1% vs 79.8%, 5y LPFS 89.9% vs 70.4% (p<0·0001)

Tox G1–2 acute 57% vs 25% late 37% vs 23%

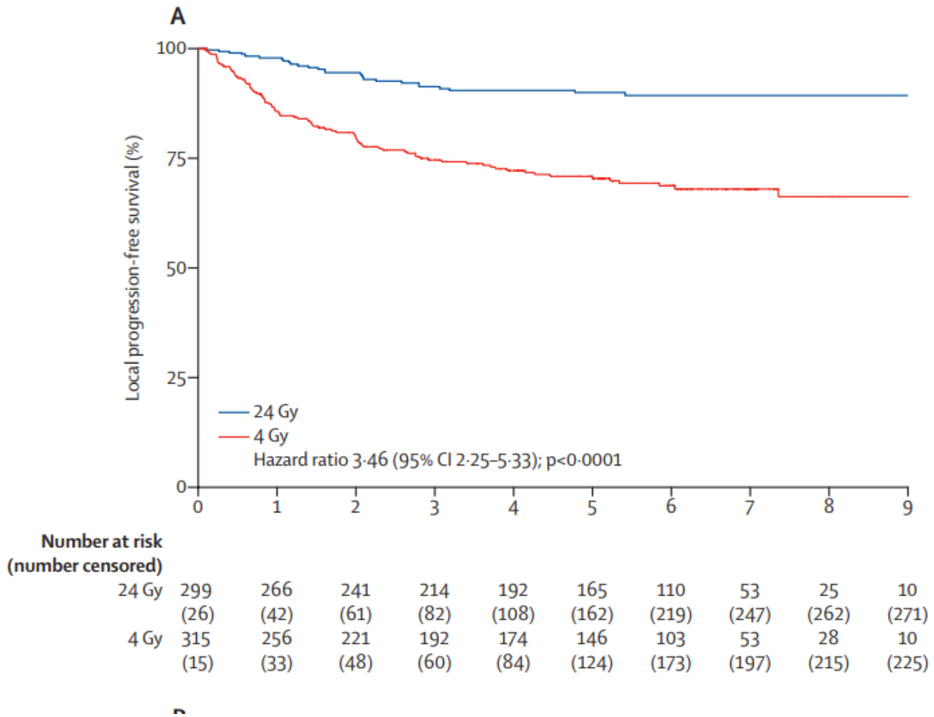
optimal RT dose 24 Gy in 12 fractions when durable local control is the aim

4 Gy > closer surveillance, increases anxiety for patients

Lancet Oncol 2021; 22: 332–40

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



RT dose

phase 2 prospective nonrandomized stage I to IV indolent B-cell lymphoma of the ocular adnexa

50 pts (62% StI) 2015-2021
response-adapted strategy > response at 3 mo intervals > additional 20 Gy
median FU 37 mo > 90% CR 2y LCR 89.4% 2y OS 98%
22 newly diagnosed > 2y LCR 90.7%
6% G1 dry eye, 2% G2 dry eye

55-patient retrospective 2013-2021
2y LCR 96.3% 2y OS 98%
1 pt (4+20 Gy) cataracts

JAMA Oncol
Published Online: July 11, 2024
2024;10;(9):1195-1203.
doi:10.1001/jamaoncol.2024.2112

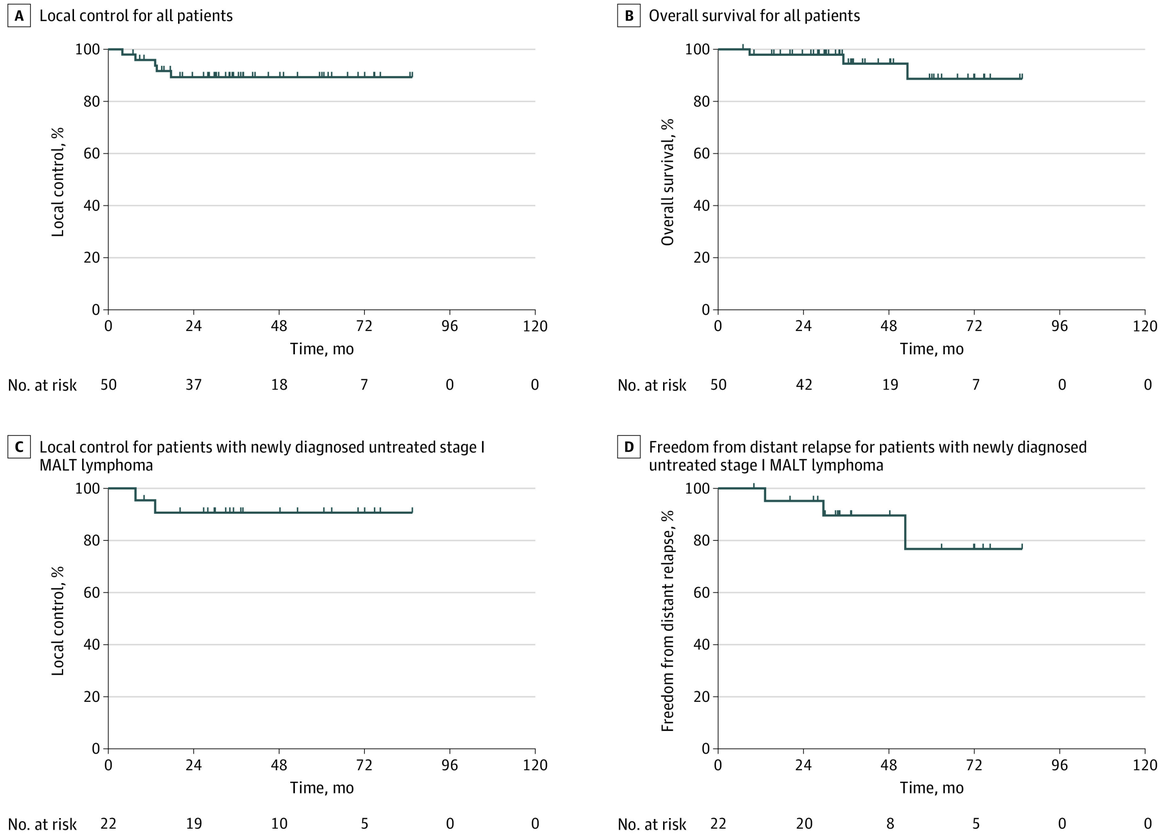
Original Investigation

JAMA Oncology

Response-Adapted Ultralow-Dose Radiation Therapy for Orbital Indolent B-Cell Lymphoma

A Phase 2 Nonrandomized Controlled Trial

Chelsea C. Pinnix, MD, PhD[1]; Bouthaina S. Dabaja, MD[1]; Jillian R. Gunther, MD, PhD[1] ; et al



RT dose

COVID-19 ILROG emergency GL > replace boom-boom with Big-boom 4 Gy x 1

471 lesions, 386 patients, 172 lesions (37%) treated with 4 Gy x 1 and 299 lesions (63%) treated with 2 Gy x 2.

ORR similar (Big B = 86%, BB = 87%) at first post-RT evaluation (median of 2.23 mo),similar CR and toxicity

1206 · Volume 117, Issue 2, Supplement , S160, October 01, 2023

INTERNATIONAL JOURNAL OF RADIATION ONCOLOGY · BIOLOGY · PHYSICS ASTRO

Very Low Dose Radiation Therapy for Indolent Lymphomas: Comparing "Big Boom" (4 Gy x 1) vs. "Boom Boom" (2 Gy x 2)

C. Hajj [1] · J. Lee [2] · L.A. Boe [1] · ... · M.E. Freret [3] · B.S. Imber [3] · J. Yahalom [3] ... Show more

Characteristic	4 Gyx1	2 Gyx2	Overall variable p-value
Number of patients	136	250	
Number of treated lesions	172	299	
Age at Radiation	67 (24, 97)	68 (20, 94)	>0.9
Male Sex	54 (40%)	127 (51%)	0.034
Diagnosis			0.016
FL	93 (54%)	197 (66%)	
FL Gr1-2	86 (50%)	188 (63%)	
FL Gr3A	7 (4.1%)	7 (2.3%)	
FL, Gr3B	0 (0%)	2 (0.7%)	
Marginal Zone	54 (31%)	80 (27%)	
Other	25 (15%)	22 (7.4%)	

Characteristic	4 Gyx1	2 Gyx2	Overall variable p-value
Max axial diameter > 5 cm			<0.001
> 5 cm	15 (8.7%)	40 (13%)	
< = 5cm	96 (56%)	259 (87%)	
Unknown	61 (35%)	0 (0%)	
Time to first follow up (months)	2.37 (0.30, 4.40)	2.10 (0.70, 13.50)	0.001
Response			0.8
Complete Response	93 (62%)	190 (64%)	
Partial Response	35 (23%)	68 (23%)	
Progressive Disease	6 (4.0%)	16 (5.4%)	
Stable Disease	15 (10%)	24 (8.1%)	
Not assessed yet	23	1	

RT dose

low-dose RT (LDRT) + concurrent chemotherapy in relapsed, multiply refractory MCL.

2014-2018 19 pts r/r MCL, 98 sites
RT 2/4 Gy, median FU 15.4 mo, median 7 courses of CHT, 58% ibrutinib refractory

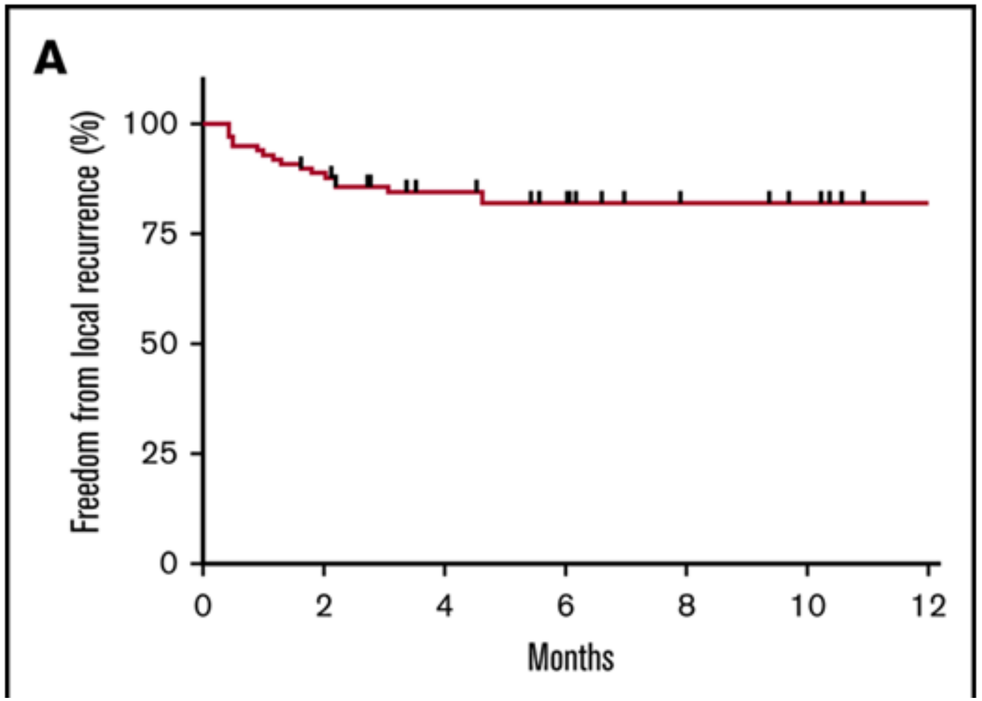
LDRT concurrent with CHT 76%
CR 81% 1y OS 90% 1Y pfs 55%

blood advances CLINICAL TRIALS AND OBSERVATIONS | JULY 9, 2019

Low-dose radiation (4 Gy) with/without concurrent chemotherapy is highly effective for relapsed, refractory mantle cell lymphoma

Clinical Trials & Observations

Matthew S. Ning, Chelsea C. Pinnix, Bhavana V. Chapman, Jillian R. Gunther, Sarah A. Milgrom, Joseph D. Khoury, Preetesh Jain, Wendy Y. Chen,



RT dose

Received: 9 December 2020 | Revised: 19 February 2021 | Accepted: 6 March 2021
DOI: 10.1002/hon.2865

WILEY

Low grade, indolent lymphomas of the head and neck: Comparative toxicity of standard versus very low dose radiation therapy

Monica Chelius[1,2] | Karen Chau[1] | Joanna Yang[1,3] | Carla Hajj[1] | Brandon Imber[1] | Joachim Yahalom[1]

Retrospectively analysis 266 pts with HN iNHL receiving RT from 1994 to 2017.

Total cohort (n=266) 4 Gy (n=62) >4 Gy(median 30 Gy) (n=204)
CR 73% vs 89%, in field failure 8% vs 4%

	Early toxicity				Late toxicity			
	4 Gy		>4 Gy		4 Gy		>4 Gy	
Site irradiated	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Orbit	(*n* = 12)		(*n* = 69)		(*n* = 10)		(*n* = 68)	
	5	(41.7)	66	(95.7)	2	(20)	48	(70.6)
Nonorbital head[a]	(*n* = 17)		(*n* = 51)		(*n* = 17)		(*n* = 50)	
	4	(23.5)	49	(96.1)	1	(5.9)	33	(66.0)
Neck	(*n* = 18)		(*n* = 80)		(*n* = 18)		(*n* = 79)	
	4	(22.2)	75	(93.8)	1	(5.6)	45	(57.0)
Skin	(*n* = 16)		(*n* = 15)		(*n* = 15)		(*n* = 13)	
	5	(31.3)	13	(86.7)	0	(0)	6	(46.2)

[a]Includes oral cavity, nasal cavity, salivary glands, sinuses, Waldeyer's ring, and nodal disease.

Tran K et al Int J Radiat Oncol Biol Phys. 2025 Aug 1;122(5):1207-1216. doi: 10.1016/j.ijrobp.2025.03.011.

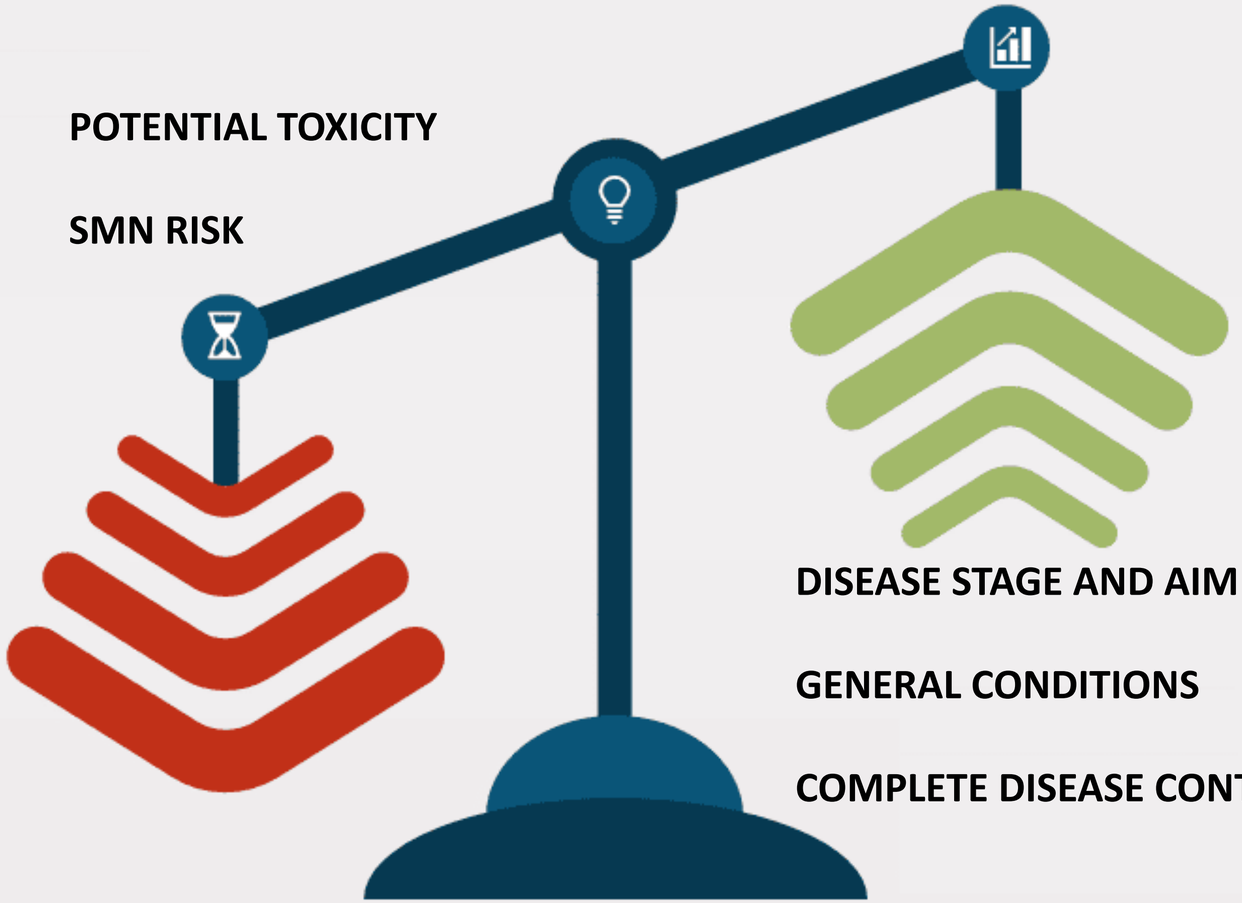
ILROG retrospective 184 patients IOAL from 16 centers.

Late toxicities included dry eye in 42% of patients (grade 1 in 86%) and cataract in 27%.

Panda G et al Clin Lymphoma Myeloma Leuk. 2022 Jul;22(7):513-522. doi: 10.1016/j.clml.2021.12.013. Epub 2021 Dec 25.

Retrospective 70 pts dose 36 - 45 Gy.
Cataract was the most common 44.3%
Xeropthalmia 31.8%

RT dose – PERSONALIZED TREATMENT



RT technique – MR Linac

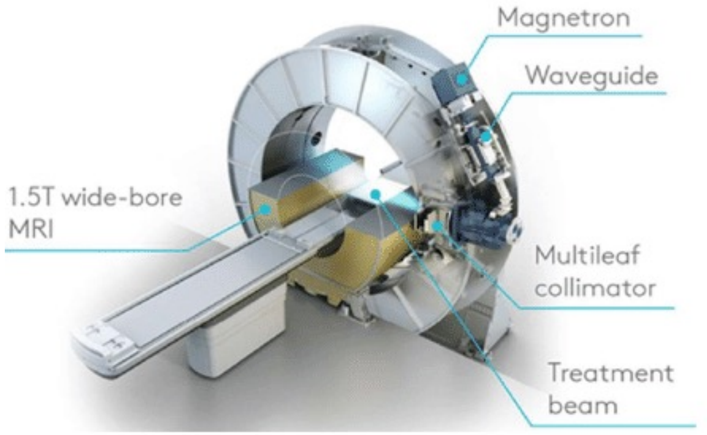
Elekta Unity® (Elekta Unity, Elekta AB, Stockholm, Sweden)
1.5 T scanner coupled with a single-energy 7-MV FFF linac
step-and-shoot IMRT through a 160 leaves MLC dose rate of 425 MU/min

two different workflows to generate treatment plans on the daily MRI for Unity®: Adapt-To-Position (ATP) or Adapt-To-Shape (ATS).

ATP the reference plan is re-optimized with an isocenter shift determined from rigid translation-only co-registration of the daily and reference images, maintaining the optimization parameters of the original plan and modifying the shape and weights of the original beams.

The ATS workflow allows for plan adaptation based on the new patient anatomy and the plan is optimized on the daily MRI. The contours registration can be rigid or deformable and volumes and OARs can be modified and the adaptive plan can be comprehensively optimized from fluence map and adjusting as well the dosimetric objectives.

During treatment cine-MRI can be acquired on the cardinal planes at 5 FPS



Case 2

Male, 56 years old, history of hypertension (IK80).

April 2024: Noticed swelling of the right upper eyelid. Underwent ultrasound and subsequent diagnostic investigations, including a biopsy in June, which resulted negative.

October 2024: Underwent MRI, which raised suspicion of a lymphoproliferative lesion.

November 2024: Biopsy confirmed diagnosis of marginal zone non-Hodgkin lymphoma (NHL).
Hematological evaluation revealed submucosal lesions also involving the left cheek and lower right lip. Biopsy confirmed marginal zone lymphoma involvement at these sites.

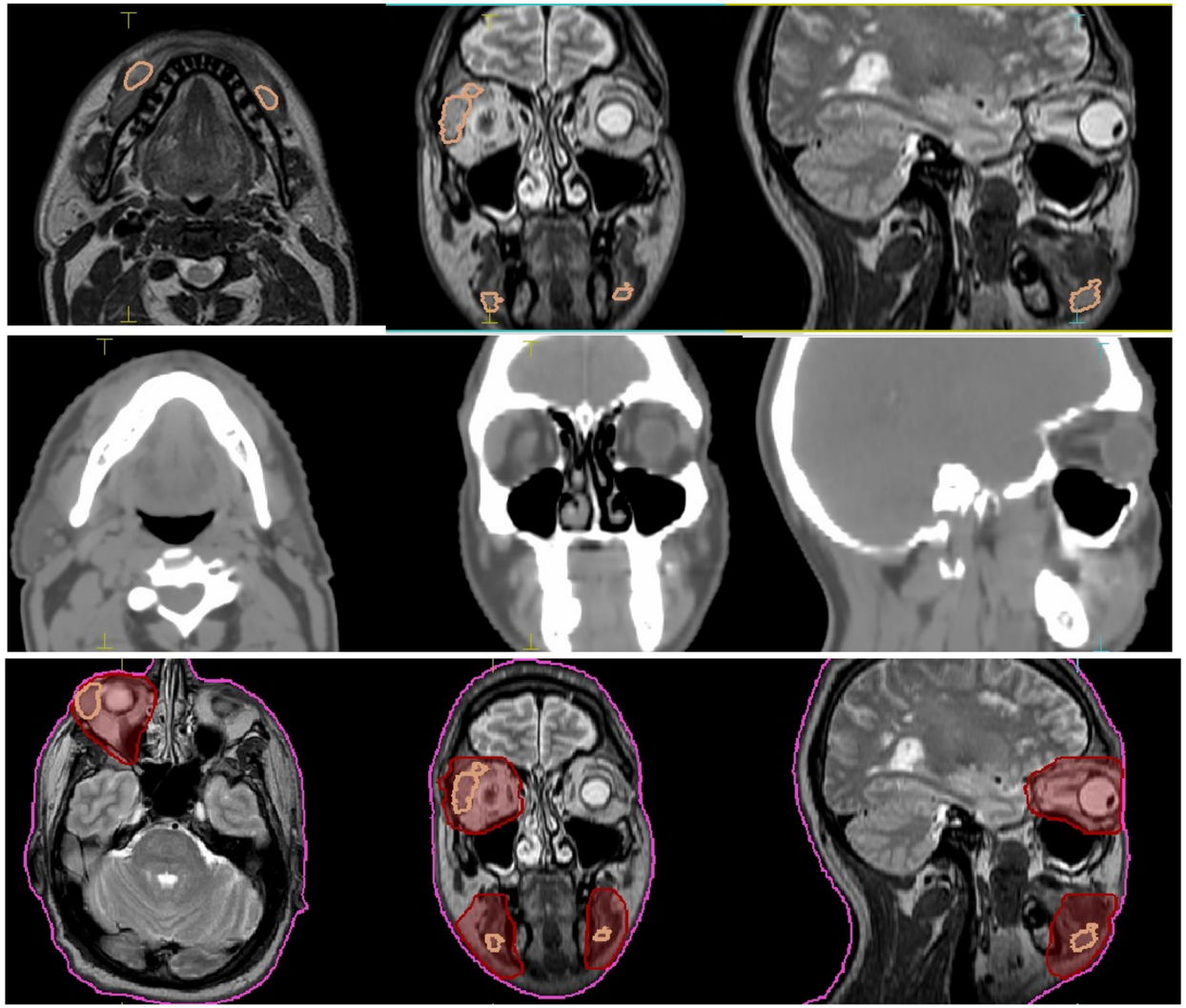
January 2025: PET scan showed no evidence of additional disease localizations. Bone marrow biopsy (BOM) was negative.

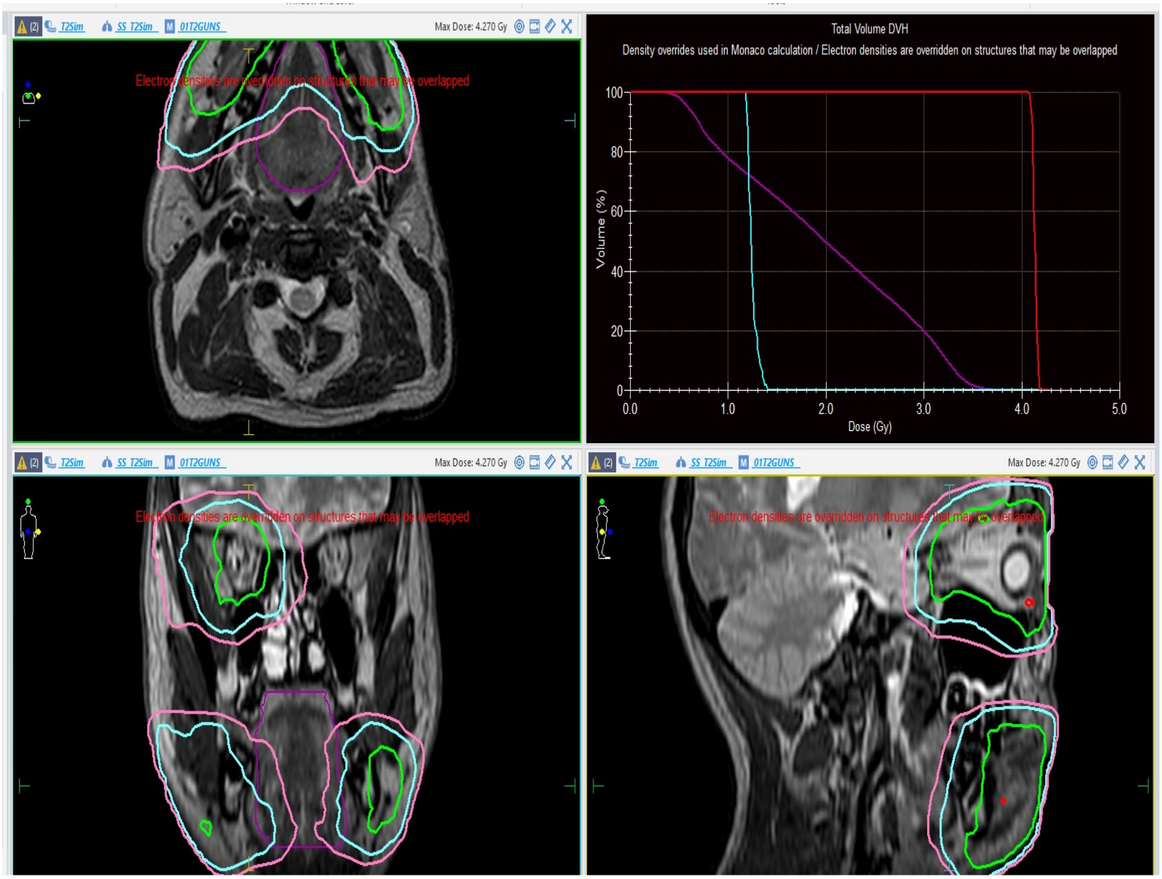
April 2025 boom-boom RT 4 Gy/ 2fr with MR-linac

22/08/25 MRI: complete response

Clinical complete response, no early or late toxicity

Case 2



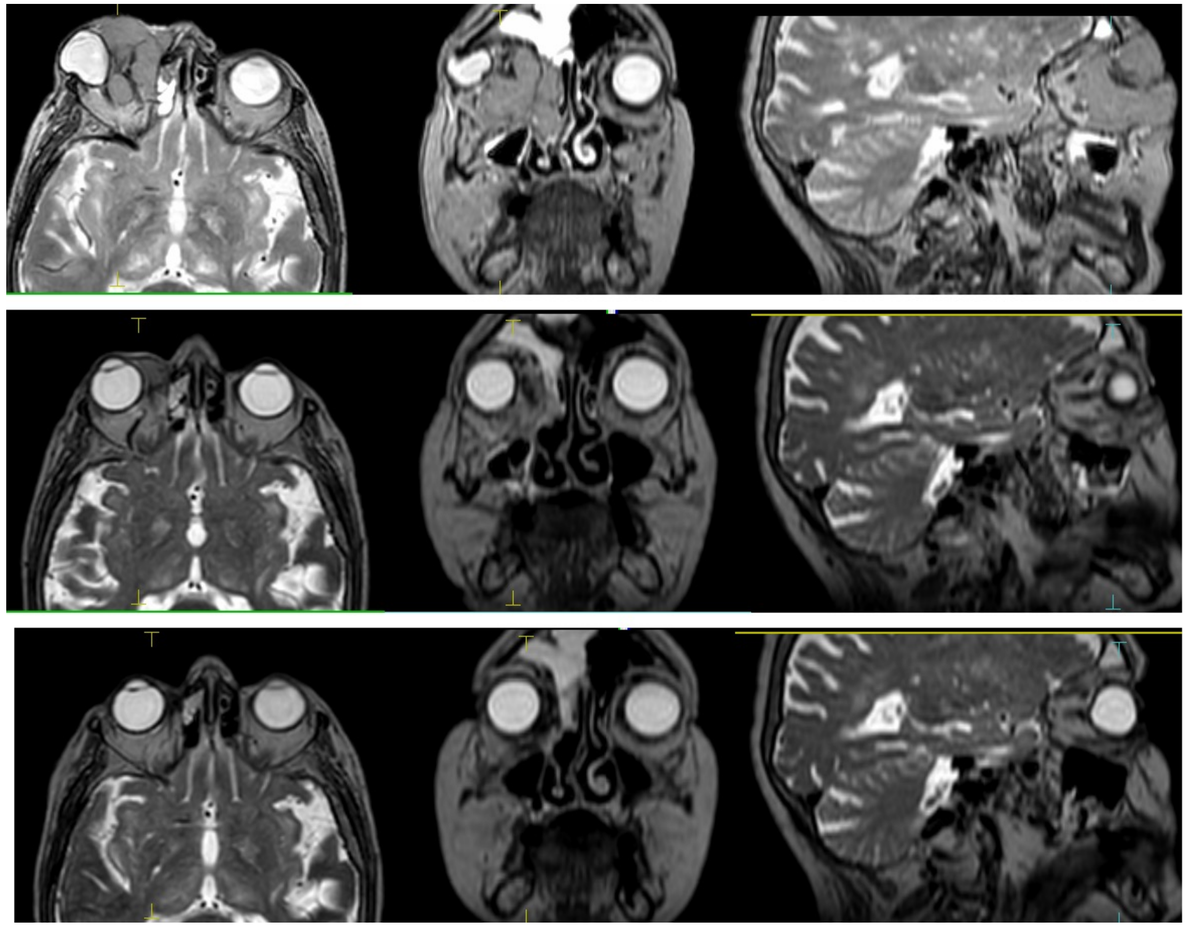

T2Sim
SS T2Sim
01T2GUNS
Max Dose: 4.270 Gy
Electron densities are overridden on structures that may be overlapped
Total Volume DVH
Density overrides used in Monaco calculation / Electron densities are overridden on structures that may be overlapped
Volume (%)
Dose (Gy)
0
20
40
60
80
100
0.0
1.0
2.0
3.0
4.0
5.0

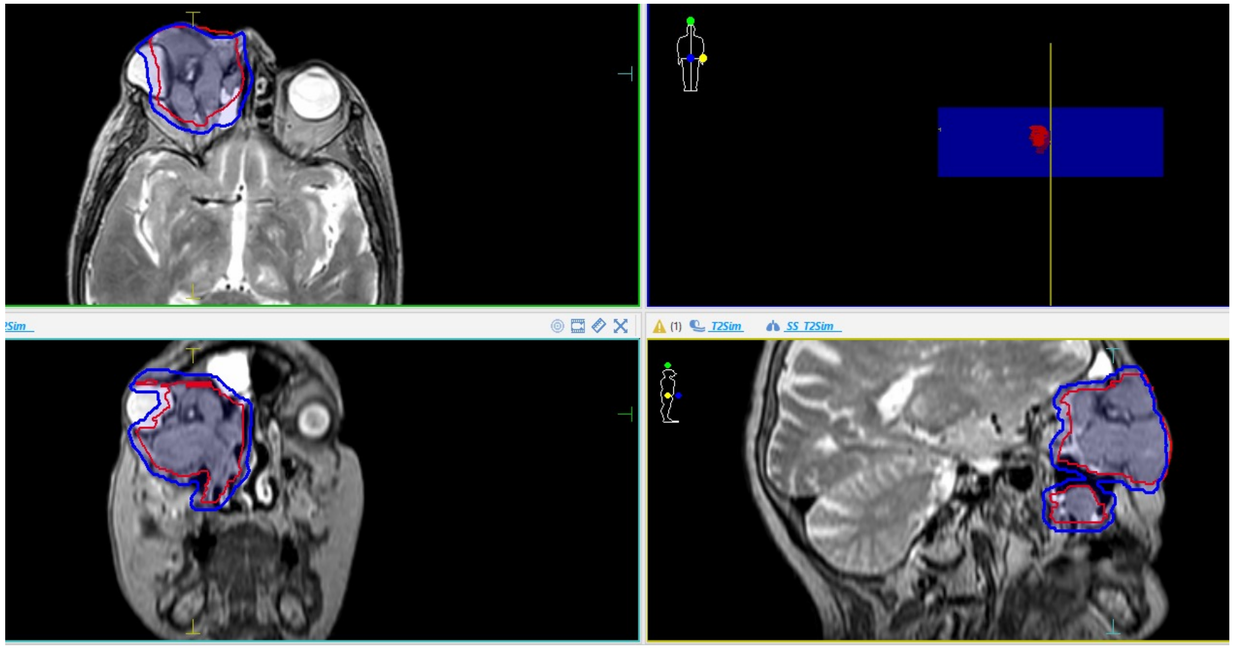
Case 3

Female, 89 years old, IK80.
In June 2025, the patient developed swelling and proptosis of the right eye, accompanied by a gradual and complete loss of vision. Ophthalmologic evaluations were performed.
19/06/2025 – CT scan showed a 25 x 27 x 30 mm lesion causing antero-lateral displacement of the eyeball.
14/07/2025 – Biopsy performed. Histological findings compatible with plasmablastic lymphoma.
31/07/2025 – Initiated steroid therapy.
03/08/2025 – Presented to the emergency department for worsening clinical condition with further ocular displacement. Admitted to the Hematology Unit; started dexamethasone 4 mg twice daily. Staging work-up initiated to assess candidacy for cytoreductive therapy with oral cyclophosphamide.
06/08/2025 – Staging contrast-enhanced CT: no suspicious lesions except for the orbital mass, which showed marked progression in size (45 x 41 mm), with compression and displacement of the eyeball.
08/08/2025 – Referred to our institution for further management.

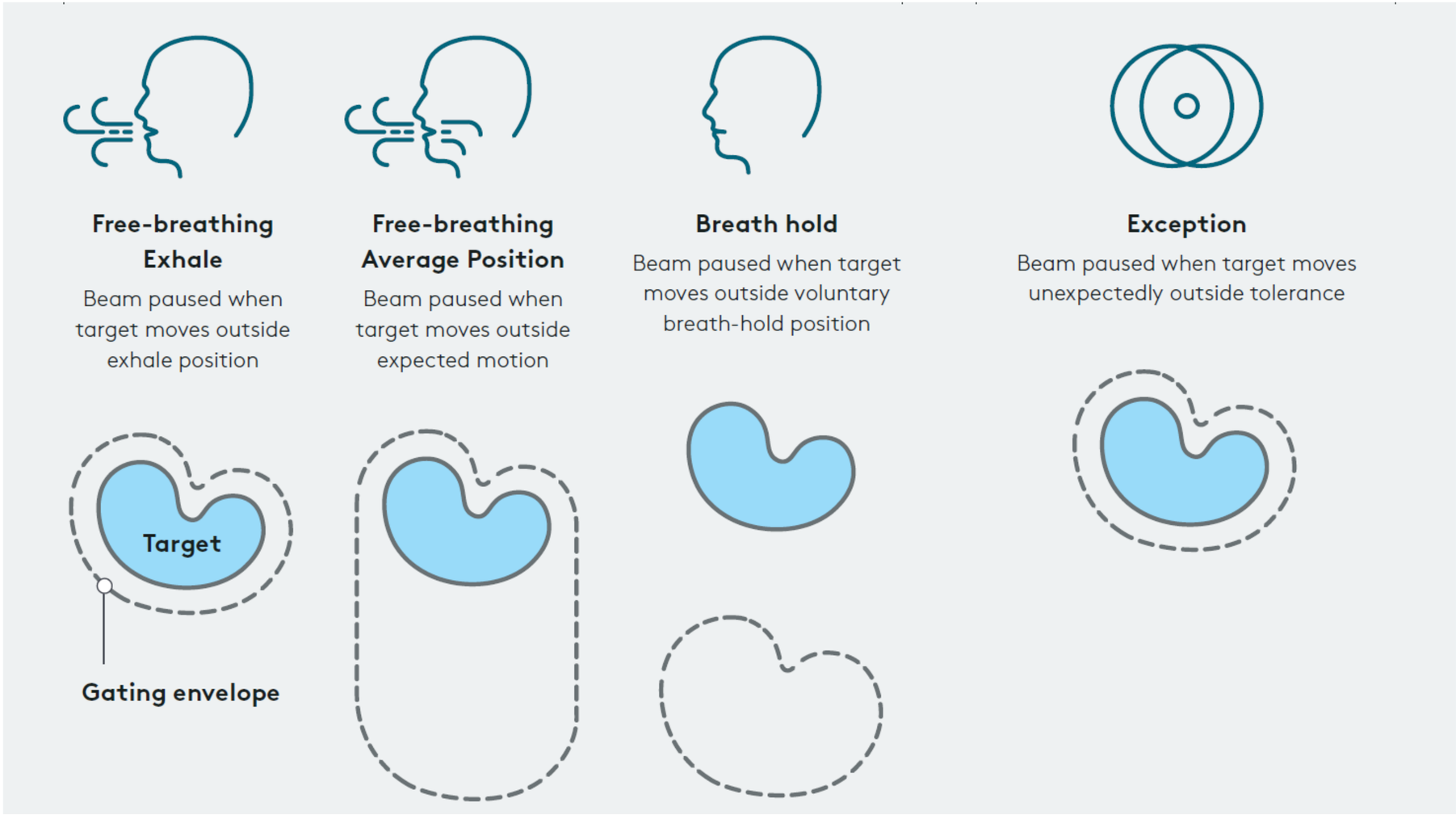
From 11/08/2025 to 29/08/2025, the patient underwent radiation therapy with MR-Linac, receiving 32.5 Gy in 13 fractions.
A marked reduction of the disease was observed, with partial recovery of vision at the end of treatment.

Case 3





RT technique - gating



Case 4

Male, 63 years old, history of hypertension (IK90), currently under treatment.
Recent pulmonary embolism (06/2025).

Complaints of dyspepsia led to upper endoscopy (EGD) in January 2025, which revealed gastric MALT lymphoma and chronic gastritis on histological examination.

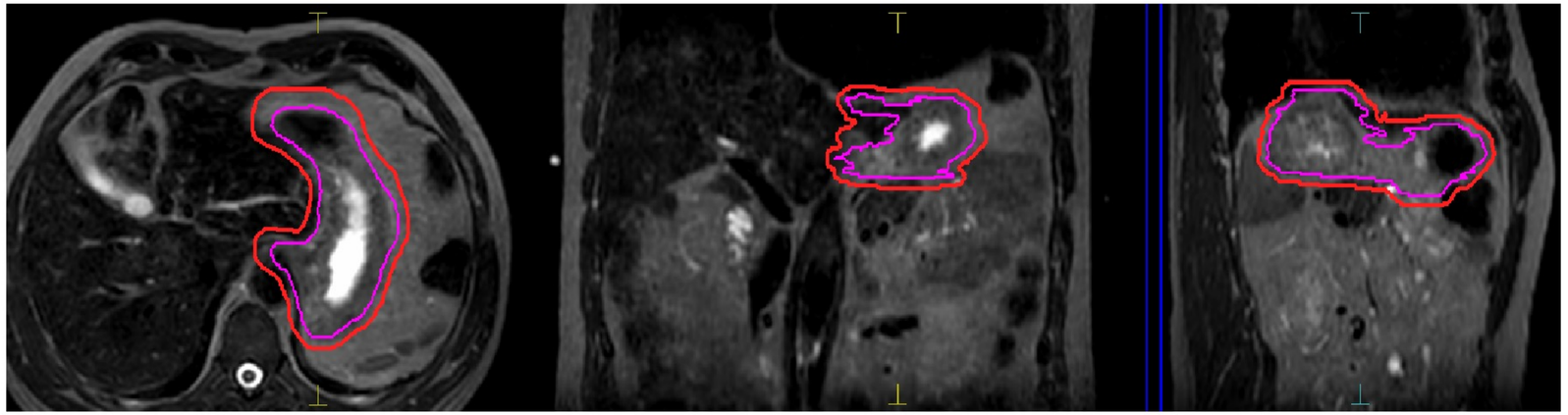
In February 2025, evaluated by hematologists; initiated antibiotic eradication therapy.

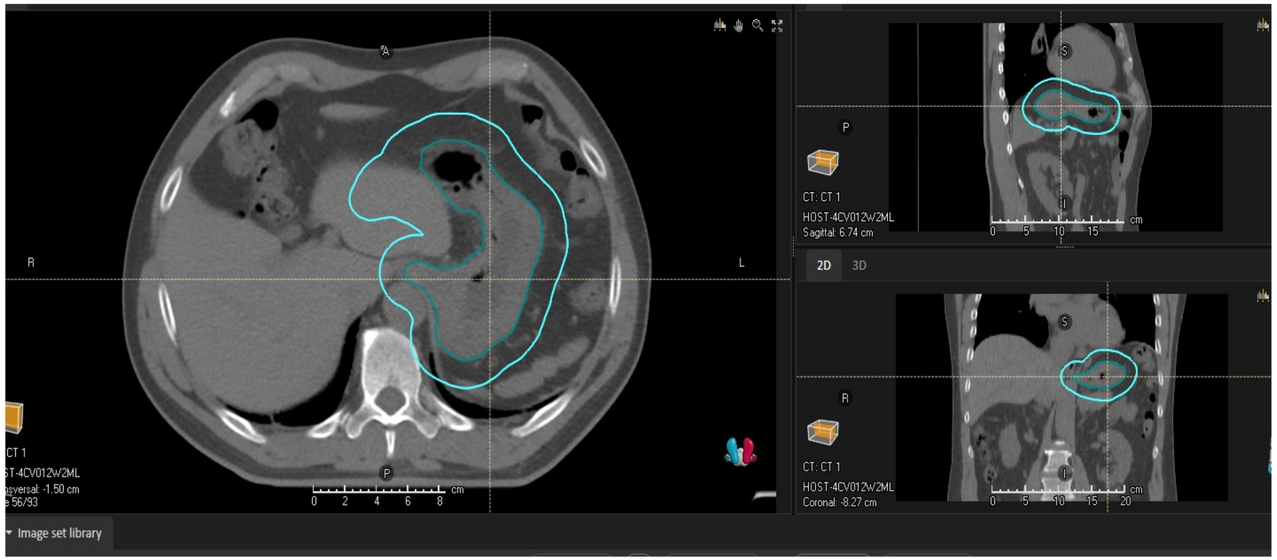
Follow-up EGD in July 2025 confirmed persistence of gastric MALT lymphoma.

Concurrently, an incidental renal mass was discovered and treated with nephrectomy in March 2025.
Histology: Renal oncocytoma.

28/08/2025: PET scan showed no additional disease localizations

Case 4




A
R
L
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CT: CT 1
HOST-4CV012W2ML
Sagittal: 6.74 cm
2D
3D
CT: CT 1
HOST-4CV012W2ML
Coronal: -8.27 cm
Image set library

Combination with systemic treatment

Leuk Lymphoma. 2015;56(8):2350-6. doi: 10.3109/10428194.2014.990010. Epub 2015 Jan 21.

Radiotherapy with rituximab may be better than radiotherapy alone in first-line treatment of early-stage follicular lymphoma: is it time to change the standard strategy?

Andrea Janikova [1], Zbynek Bortlicek [2], Vit Campr [3], Natasa Kopalova [1], Katerina Benesova [4],

93 patients with stage I-II indolent FL treated with RT (n=65) or RT+R (n=14) or R alone (n=14)

Median FU was 5.0 years, 2.8 years, 2.5 years

CRR 92%, 100% and 86% (not significant)

median PFS 3.3 years, not reached and 4.9 years (p=0.035)

No impact on overall survival

Anticancer Res. 2014 Nov;34(11):6701-4.

Radiotherapy for stage I/II follicular lymphoma (FL): is it time for a re-appraisal?

Patrizia Mondello [1], Normann Steiner [2], Ines Wasle [3], Vincenzo Pitini [4], Michael Mian [5]

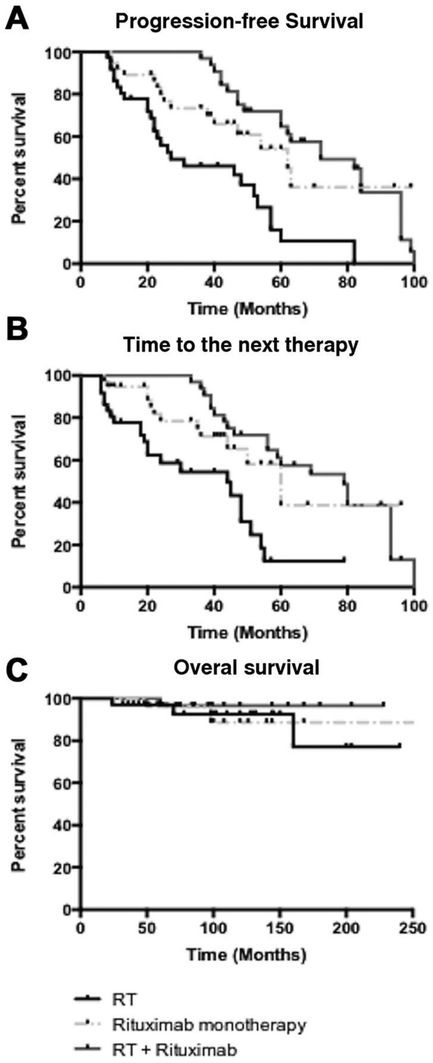
Retrospective, 2 institutions, stage I, II FL (grade 1-3A) 1995-2012

IFRT-alone vs RTX alone vs RT+RTX

108 early-stage FL: 36 IFRT, 38 R-alone and 34 R+IFRT.

CR 84% IFRT vs 87% RTX vs 97% R+IFRT, median

PFS higher in R groups vs IFRT alone: 2.3y vs 5y vs 6y (*p*<0.001)



Combination with systemic treatment

INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY · BIOLOGY · PHYSICS ASTRO

CLINICAL INVESTIGATION · Volume 94, Issue 4, P783-791, March 15, 2016

Addition of Rituximab to Involved-Field Radiation Therapy Prolongs Progression-free Survival in Stage I-II Follicular Lymphoma: Results of a Multicenter Study

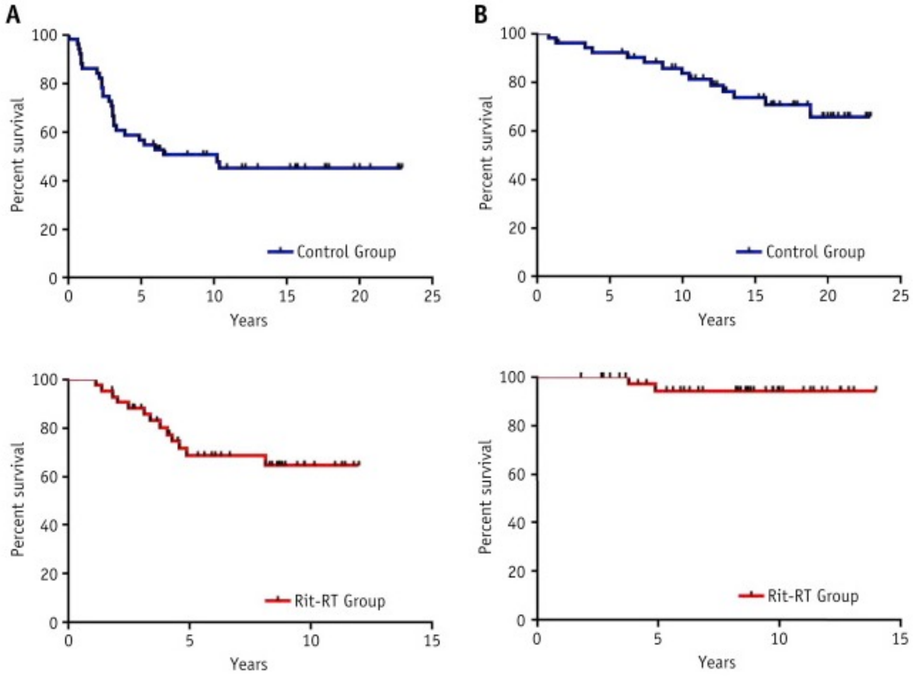
Marco Ruella, MD *,† · Andrea Riccardo Filippi, MD § · Riccardo Bruna, MD * · ... · Umberto Ricardi, MD § ·

retrospective multicenter study limited-stage grade 1-3a FL 94 pts 1985-2011
5 institutions

51 pts RT alone vs 43 pts 4 RTX weekly before RT
median FU of 10.9 years, 10y PFS RT 50.7% vs RT+RTX 64.6% (p<0.05)

10y OS similar

bivariate analysis controlling for stage, only a trend toward improved PFS for RTX-RT (HR, 0.55; P=.081).



Combination with systemic treatment

MacManus M et al EBioMedicine. 2024 Dec:110:105468. doi: 10.1016/j.ebiom.2024.105468.
MacManus M et al J Clin Oncol. 2018 Oct 10;36(29):2918-2925. doi: 10.1200/JCO.2018.77.9892.

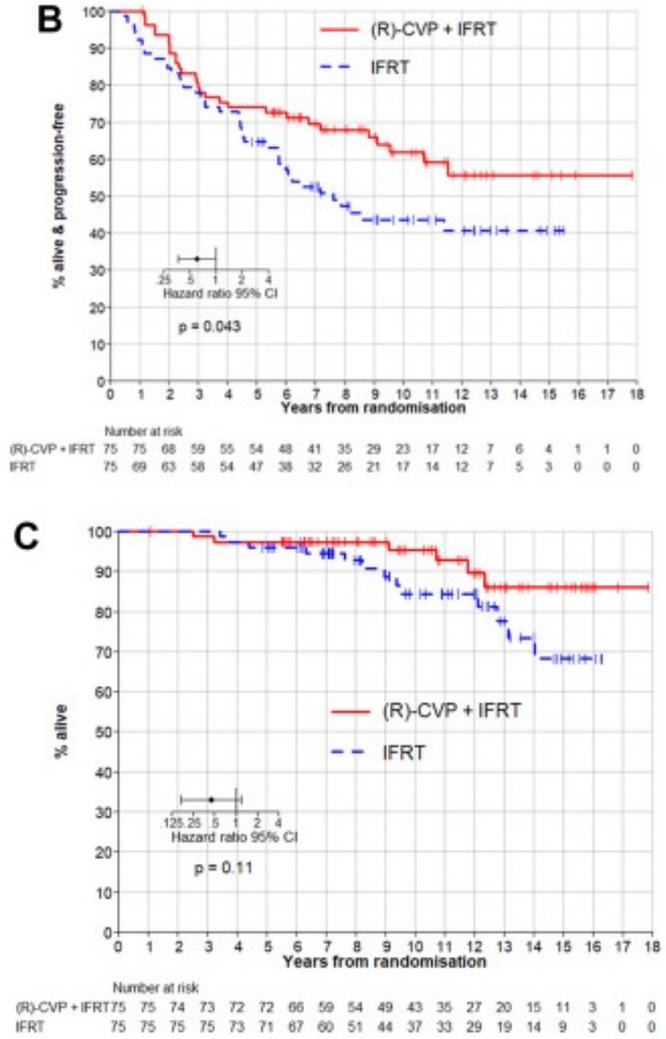
extended follow-up of TROG99.03, randomised phase III trial in early-stage follicular lymphoma (ESFL)

IFRT 30 Gy vs IFRT + 6-cycles cyclophosphamide/vincristine/prednisolone (IFRT + CVP) + RTX (from 2006)

median FU 11.3-years, PFS remained superior for IFRT+(R)CVP vs. IFRT (p = 0.043; 62% vs. 43%) No significant difference in OS (p = 0.11, 95% vs. 84%), patients receiving IFRT+(R)CVP experienced fewer composite (histological transformation and death) events (p = 0.045).

PET staging was associated with superior PFS (HR, 0.61; P = .056)

IFRT G3-4 tox 2% IFRT+CVP+RTX G3-4 tox 50.7%



Combination with systemic treatment

German Low-Grade Lymphoma Study Group (GLSG) MIR Study

16 centers 2008-2010
prospective, single-arm multicenter phase 2 design.

85 stage I–II FL 8 cycles of RTX + IFRT (30/40 Gy).

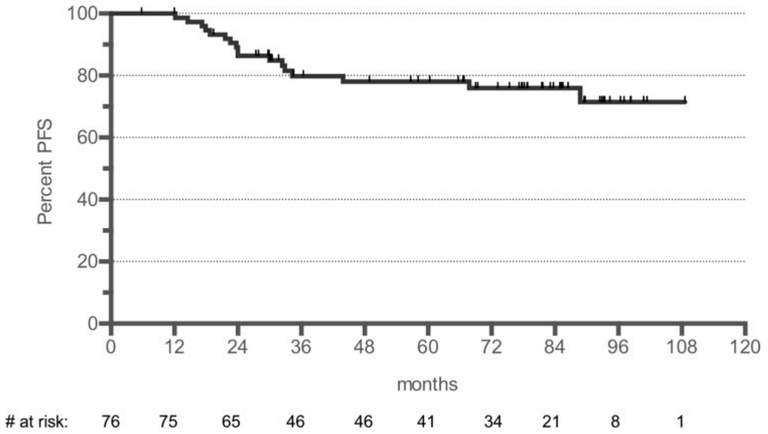
2y PFS 85% 5y PFS 78% 5Y os 96% (median FU 66 mo)
17 recurrences, 14 only out-of-field

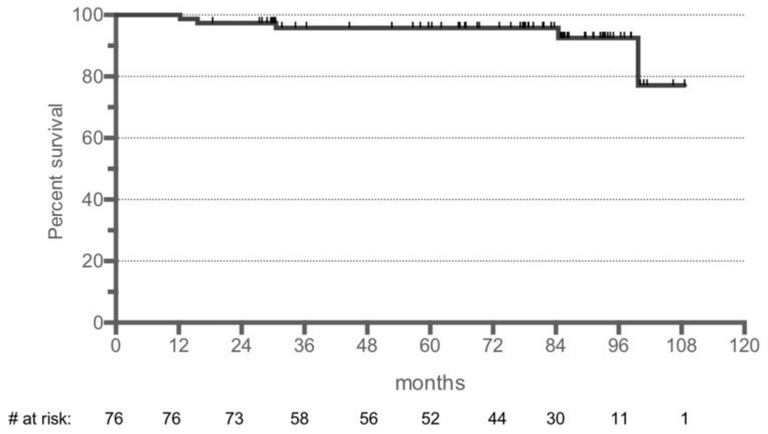
MRD+ 36% at diagnosis > all but one negative after treatment

CR 51% week 7 (after RTX) 73% week 18 85% 6mo

Tox G1 61% G2 31% G3 4%
No substantial influence on patients' quality of life.

Herfarth K et al. Hemasphere. 2018 Nov 30;2(6):e160. doi: 10.1097/HS9.0000000000000160





Combination with systemic treatment

Hematological ONCOLOGY

SUPPLEMENT ABSTRACTS | Free Access

First published: 09 June 2023 |

https://doi.org/10.1002/hon.3163_142

HIGH RATE OF METABOLIC COMPLETE RESPONSE AFTER LOW DOSE RADIOTHERAPY AND OBINUTUZUMAB IN EARLY STAGE FOLLICULAR LYMPHOMA: INITIAL RESULTS OF THE GAZAI STUDY (GLA 2018-3)

K. Herfarth, C. W. Scholz, K. Hübel, S. Wirths, C. Buske, J. Dürig, R. Forstpointner, S. Heidegger, G. Lenz,

Prospective, multicentric phase II GAZAI study of the German Lymphoma Alliance (GLA)

early stage nodal FL G1/2 11 German centers. Ann Arbor sta
MRD in peripheral blood was monitored at baseline and at week 18

Obinutuzumab weeks 1, 2, 3, 4, 8, 12 and 16

An interim CT scan performed at week 7 > RT ISRT 2x2 Gy week 9 > PET CT week 18

Preliminary results (abstract Lugano): 54 pts showing FDG-PET-positive lymph nodes.

At week 18, metabolic CR (DS<3) 87% PR (DS3) 6%

Morphologic (CT based): week 7 CR 39% PR 32% week 18 CR 91% PR 7%

13/54 patients (24%) were initially MRD positive. All but one patient converted to MRD negativity at week 18.

Combination with systemic treatment

ORIGINAL RESEARCH article
Front. Oncol., 31 July 2025
Sec. Radiation Oncology
Volume 15 - 2025 | https://doi.org/10.3389/fonc.2025.1617087
Frontiers in Oncology
Radiation Oncology

Single-agent rituximab and ultra-low-dose adaptive radiotherapy for the treatment of indolent B-cell non-Hodgkin lymphomas

Katherine E. Lake [1] Meredith Jackson [1] Samantha Hull [1]

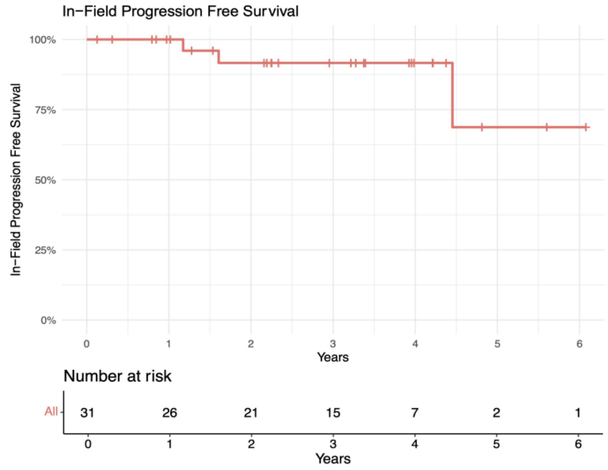
iNHLs (n=26) St I-IV

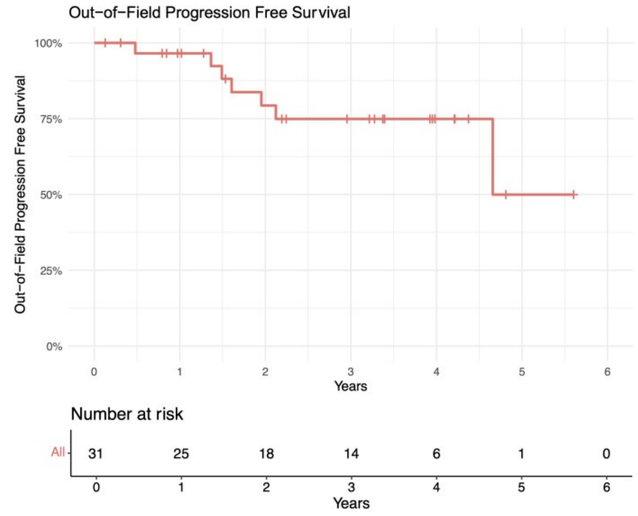
ULDRT + 4 weekly RTX concurrently or within 16 d 2017-2024

At 1st FU ORR 98% CR 61% 2y OS 92%

At 2y: in-field, out-of-field, and overall PFS rates were 91%, 78%, and 78%

TOX G1-2 7% no G3
65% symptomatic > 80% resolution of symptoms, 5% improvement, 15% stable





Combination with systemic treatment

Local radiotherapy and measurable residual disease-driven immunotherapy in patients with early-stage follicular lymphoma (FIL MIRO): final results of a prospective, multicentre, phase 2 trial

Alessandro Pulsoni, Simone Ferrero, Maria Elena Tosti, Stefano Luminari, Alessandra Dondi, Federica Cavallo, Francesco Merli,

I marrow

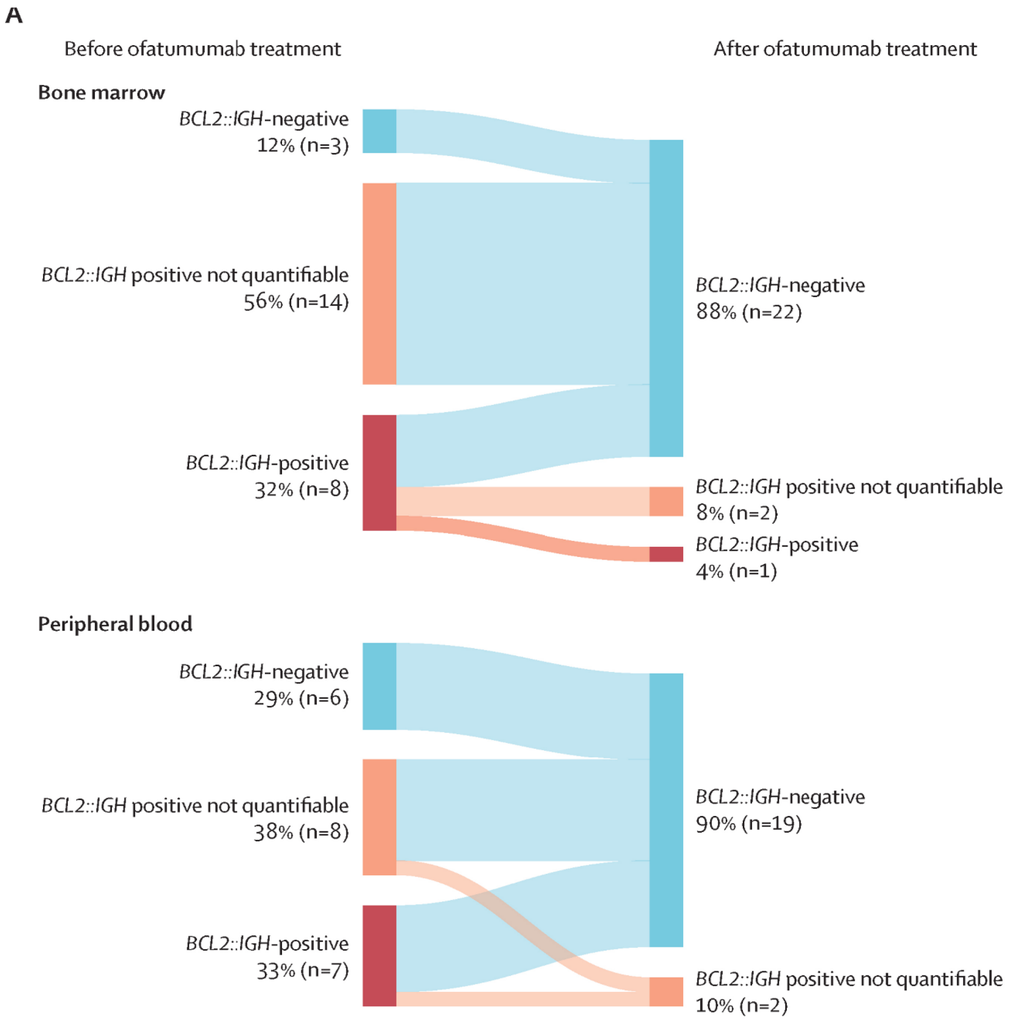
initially 24 Gy IFRT > if MRD positive after RT or during FU > weekly anti-CD20 mAb ofatumumab x 8

2015-2018 105 pts: 32 (30%) had a detectable BCL2::IGH rearrangement at baseline.

After RT, 12 (40%) of 30 MRD-negative, 3 (25%) long-lasting (>36 mo)

MRD-positive after RT > ofatumumab induced MRD-negativity in 23 (92%) of 25 evaluable. median FU 46 mo, 14 (61%) remain in CR and are MRD-negative.

most common G3–4 adverse events were infusion-related reactions, observed in four patients.



Combination with systemic treatment – Ongoing studies

FORTPLUS - GLA 2022-5

FORTplus - GLA 2022-5 -> Early Stage Follicular LymphOma and RadioTherapy PLUS Anti-CD20 Antibody

Early Stage Follicular Lymphoma WHO Grade 1/2 or 3a

Study arms:
Standard 12 x 2 Gy involved site radiotherapy plus Rituximab

Experimental 2 x2 Gy involved site radiotherapy plus Obinutuzumab

Primary outcomes
1. Morphologic complete response
Rate of morphologic complete response based on CT scan in patients with initially remaining lymphoma

Secondary outcomes
1. Metabolic complete response
Rate of metabolic complete response based on FDG PET in patients with initially remaining lymphoma
2. Morphologic response
Morphologic CR in patients with initially remaining lymphoma
3. PFS
Progression-free survival (PFS) of each treatment arm
4. Frequency and extent of Toxicity
Toxicity (NCI-CTC criteria, version 5) of all patients
5. Overall survival
Overall survival (OS) of each treatment arm

GAZEBO

- **An open-label, randomized phase III trial comparing local radiotherapy alone or combined with Obinutuzumab in early stage Follicular Lymphoma: the GAZEBO Trial from the Fondazione Italiana Linfomi**

Prospective, multicenter, open label, phase III randomized clinical trial in previously untreated Follicular Lymphoma in early stage. Patients will be randomized to receive Radiotherapy or Radiotherapy plus Obinutuzumab.
Prospective, multicenter, open label, phase III randomized clinical trial in previously untreated Follicular Lymphoma in early stage (I-II non-bulky).
Patients will be randomized to receive:
- Involved-Site Radiation Therapy at standard dose 24Gy - standard arm
OR
- Involved-Site Radiation Therapy at standard dose 24Gy followed by Obinutuzumab 4 infusions weekly + 4 infusions every 3 weeks (8 total doses) - experimental arm

Follicular Lymphoma grade I-IIIAAnn Arbor Stage IA or IIA (includible in one radiation field), or IE, non-bulky (<7 cm).
Primary outcome: To investigate the superiority in terms of Progression-Free Survival (PFS) for the combination of radiotherapy and obinutuzumab (experimental arm) vs. radiotherapy alone (standard arm).

Case 1

Therapeutic options

1. **Watchful waiting**
2. **RT alone 4 Gy**
3. **RT alone 24 Gy**
4. **Chemotherapy**
5. **Rituximab/Obinutuzumab**
6. **RT 4 Gy + R/O**
7. **RT 24 Gy + R/O**

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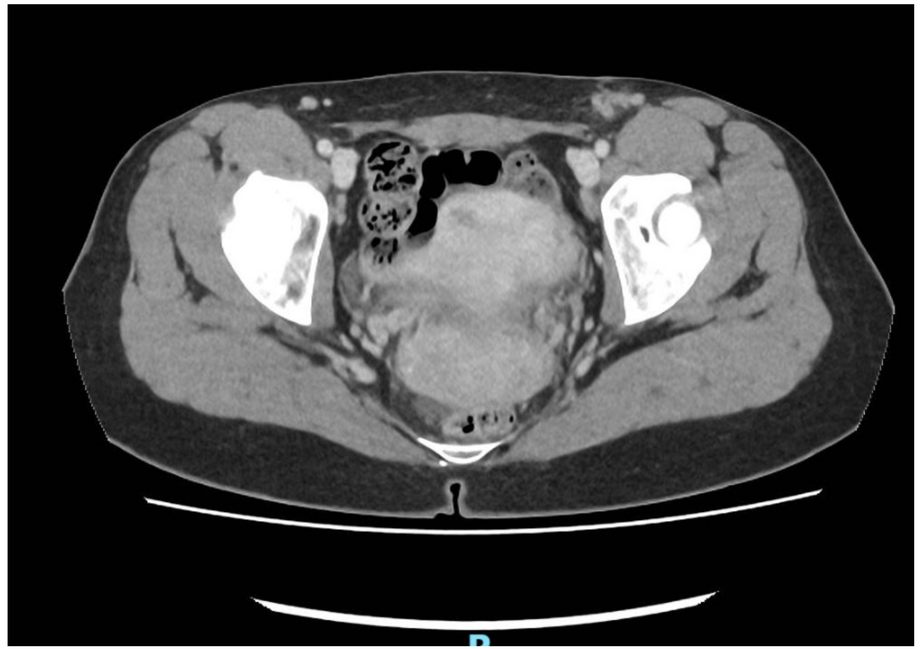

GRAZIE MILLE PER L'ATTENZIONE

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