Indolent Lymphomas and RT

Joachim Yahalom, MD
Member and Professor, Memorial Sloan Kettering Cancer Center
New York

Chairman, ILROG

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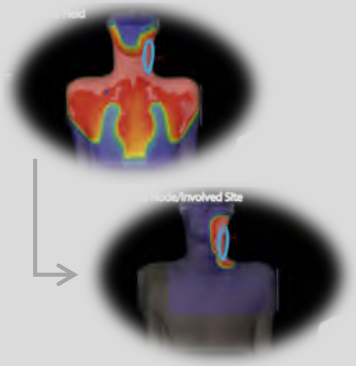
Memorial Sloan Kettering
Cancer Center

Recent and current trends: Dose ↓ Fractions ↓ Duration ↓

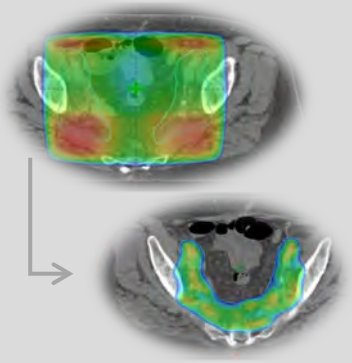
1. Transition to smaller RT fields



- Mantle to EFRT to IFRT
- **ISRT** is now standard
- Possible future evolution to CVRT?

Modern radiotherapy is delivered in a highly precise manner using less toxic doses resulting in overall improved tolerability

2. Improvements in RT delivery

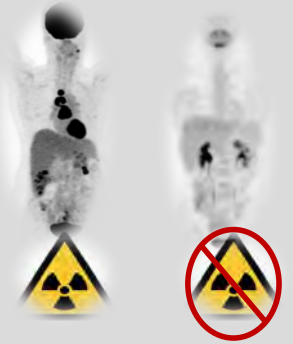


- RT is delivered using highly conformal techniques
  - **IMRT**
  - **Protons** in selected situations

3. Reductions in RT doses

- Phase III BNLI study reduced standard NHL doses from 45-50 Gy to:
  - Indolent: **24 Gy**
  - Aggressive: **30 Gy**

4. Risk and PET-adapted strategies



- Reductions in RT consolidation guided by
  - **Interim PET** (e.g., OPTIMAL>60)
  - **Lower clinical risk** (e.g., FLYER study)

Maraldo and Specht, IJROBP 2014
Lowry et al. Rad Onc. 2011
Pfreundschuh et al. ASCO 2017
Poeschel et al. Lancet 2019

Indolent lymphomas: More with less?

- Follicular lymphomas Grade 1-3A
- Marginal zone lymphoma
- CLL/SLL
- Mantle cell

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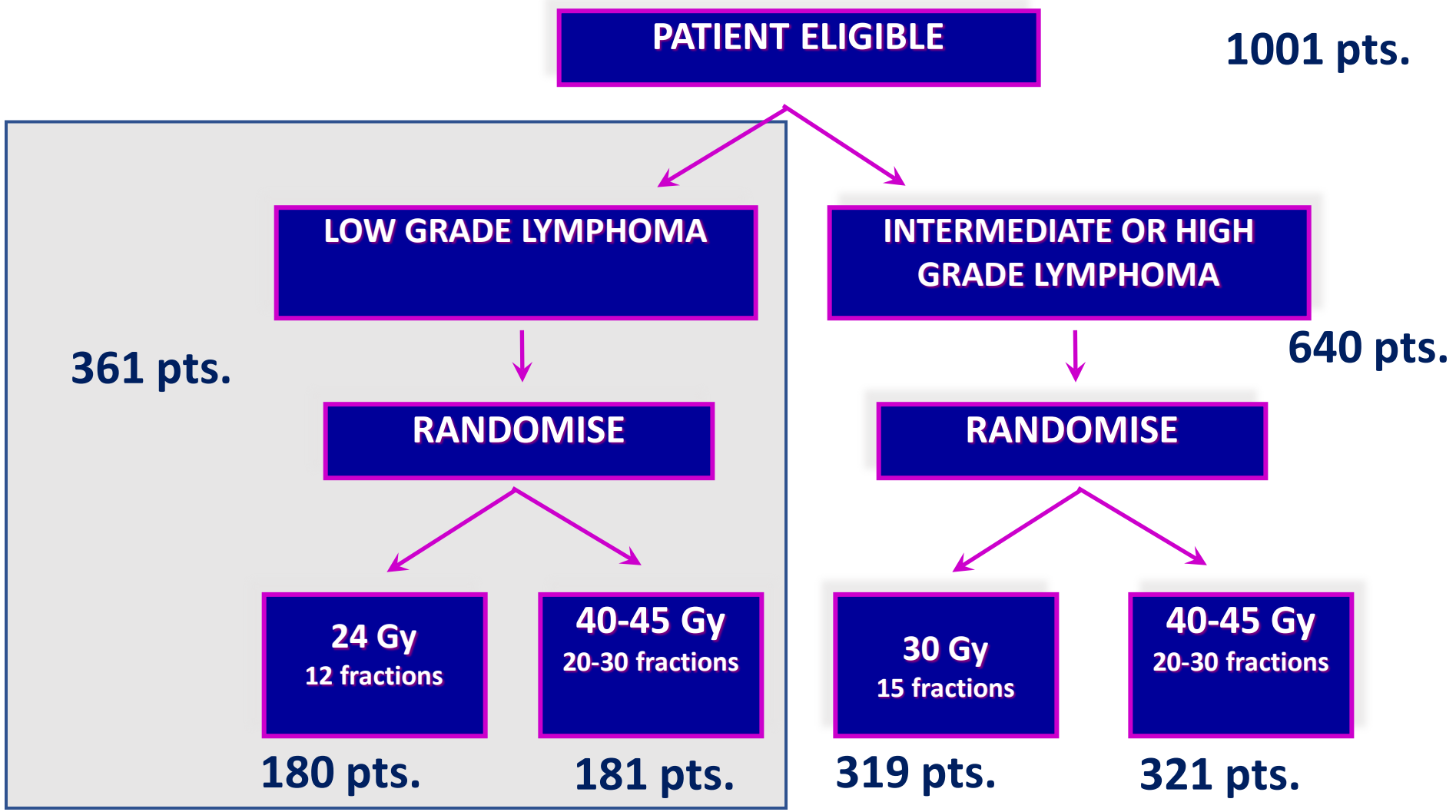
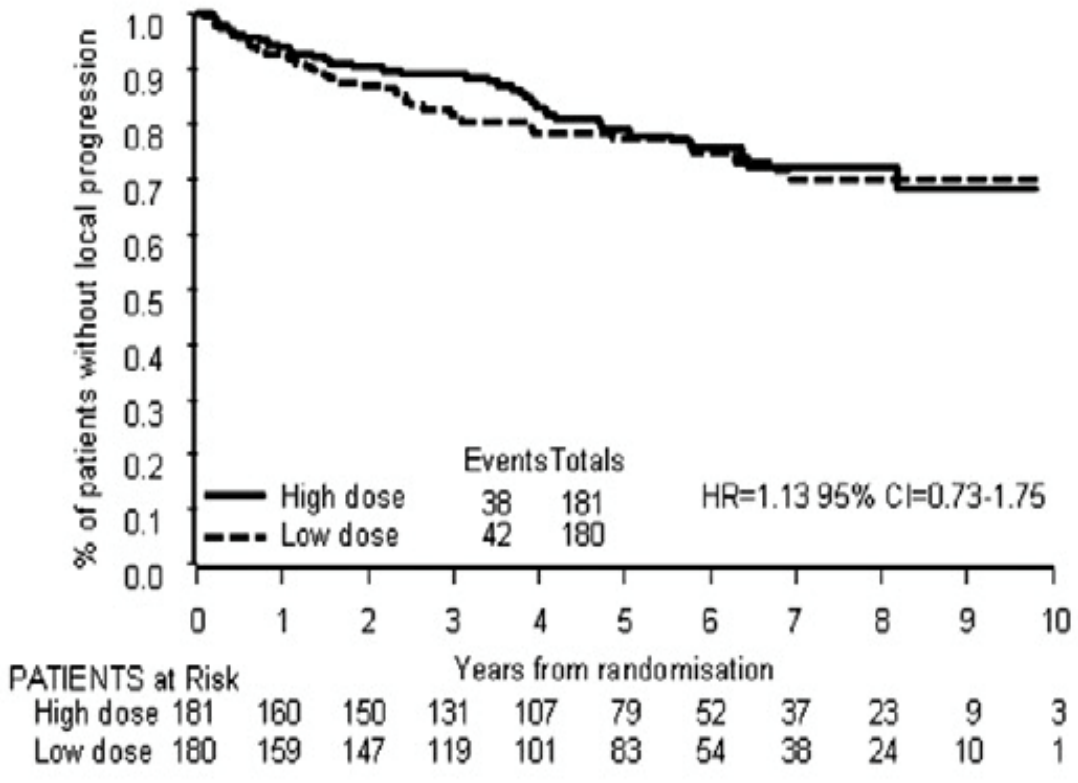
The Phase III BNLI study was the first major effort at RT dose deintensification



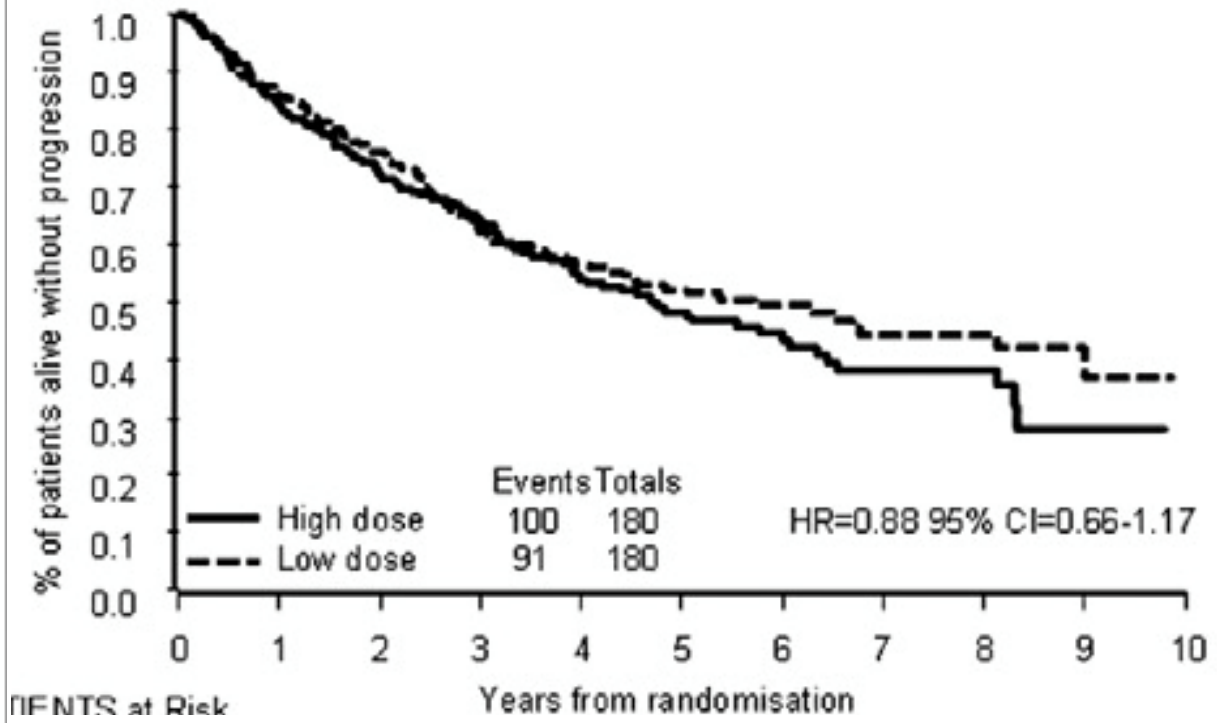
Lowry et al. 2011

Low(er) dose of RT shown to be equivalent for indolent lymphomas

Local control



Progression free survival



Lowry et al. 2011

What are the outcomes of definitive RT in modern era?

ILROG Multicenter FL series
Inclusion Criteria

- **Received RT alone for untreated localized FL (stage I-II)**
- **FL grade 1-3A**
- **RT dose equivalent of at least 24 Gy**
- **Staged by PET/CT**
- **Follow-up at least 3 months**

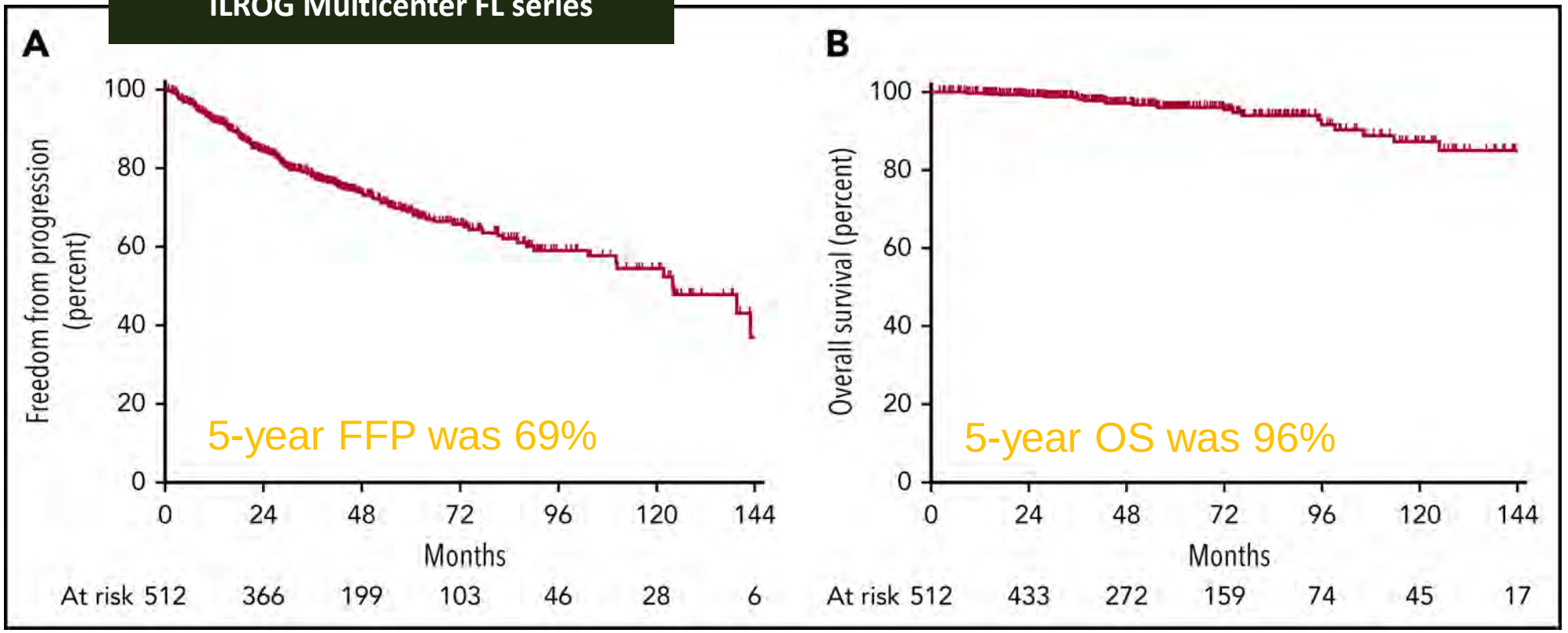
Patient and treatment characteristics

- 512 patients treated 2000-2017
- 80% stage I, 20% stage II
- Stage I 72% nodal, 28% extranodal
- 90% FL grade 1-2, 10% grade 3A or 3 NOS
- Median lesion size = 2.8 cm (range 0.2-10)
- Median RT dose = 30 Gy (67% 24-30 Gy)
- 50% IFRT, 29% ISRT, 21% unknown

Source: Brady et al. Blood 2019

Modern, PET staged ISRT has excellent local control outcomes

ILROG Multicenter FL series



- Only 8 patients relapsed in RT field (1.6%), and 4 had marginal recurrences (0.8%), resulting in a local control rate of 98%

Median follow-up = 52 months

- 137 (92%) relapses occurred outside of the irradiated sites

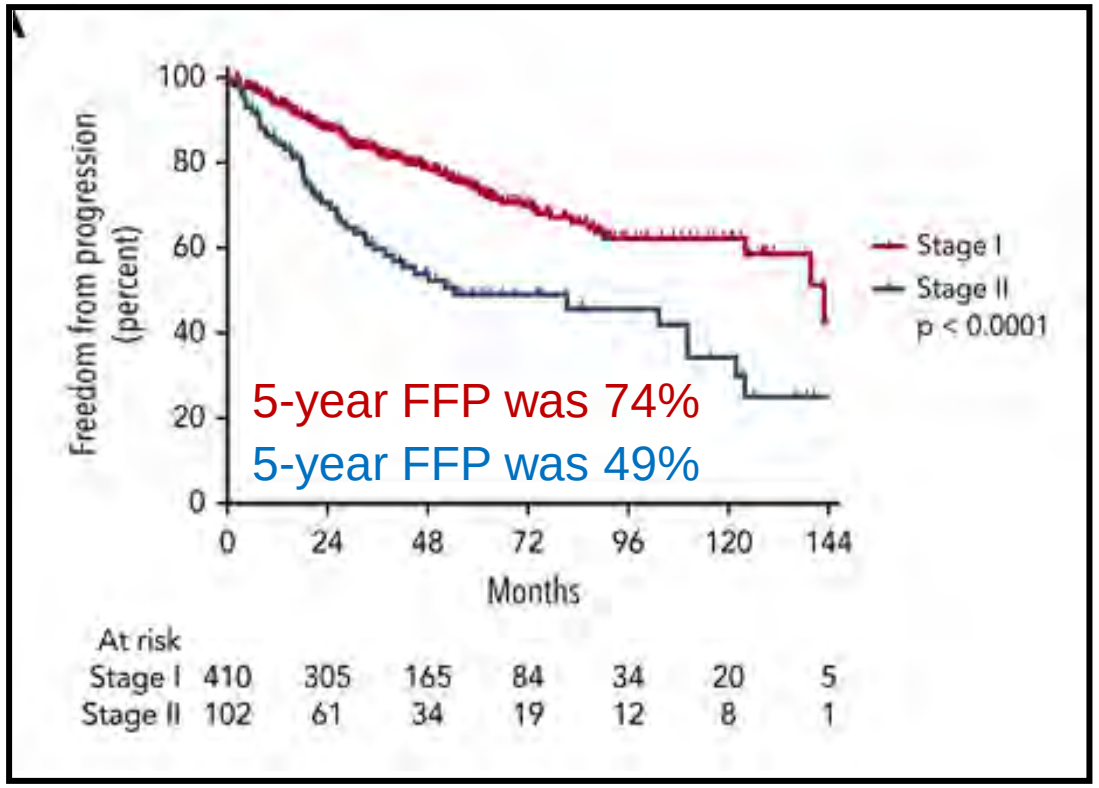
- Toxicity data available for 73%; Overall 23% of patients had grade 1-2 acute toxicities; grade 3 and late toxicities were rare

Source: Brady et al. Blood 2019

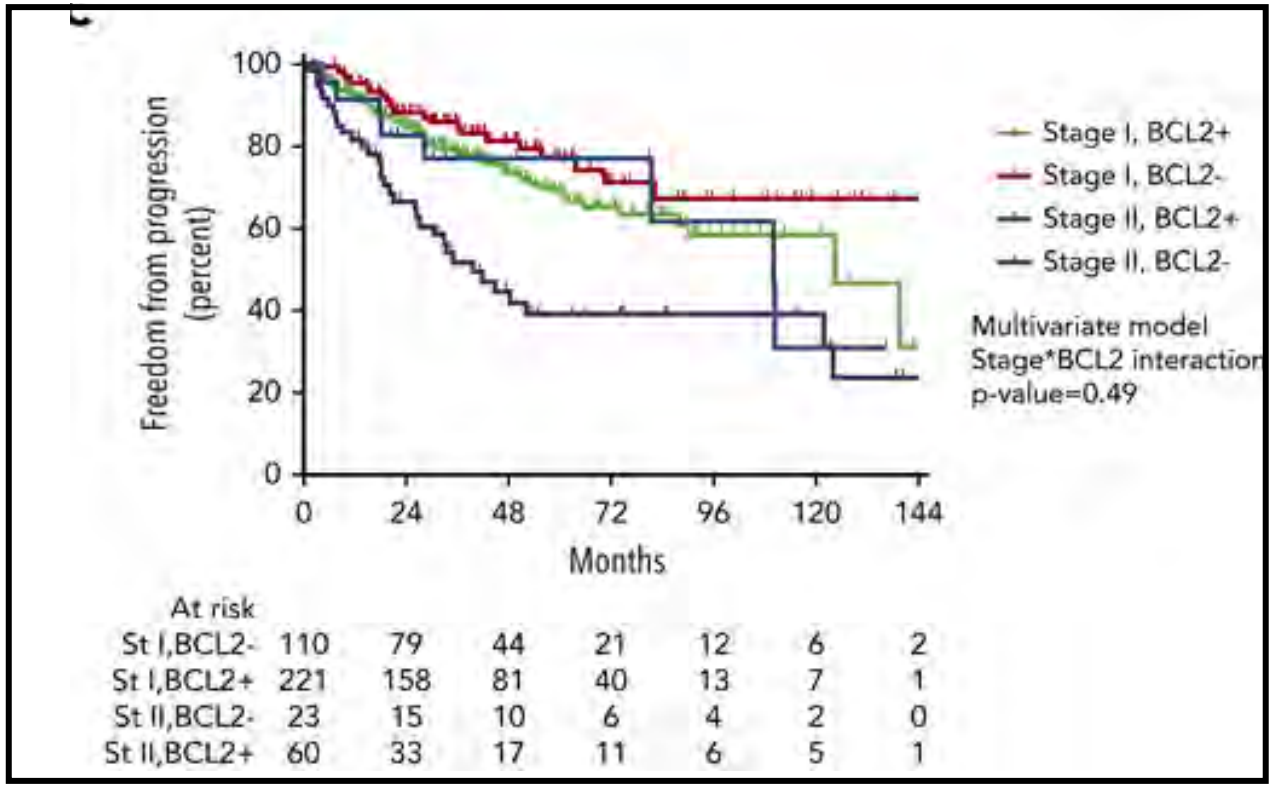
Stage is most strongly associated with post-RT outcomes

Factors prognostic for FFP following definitive RT for localized FL

A. Stage at treatment



B. BCL2 expression status



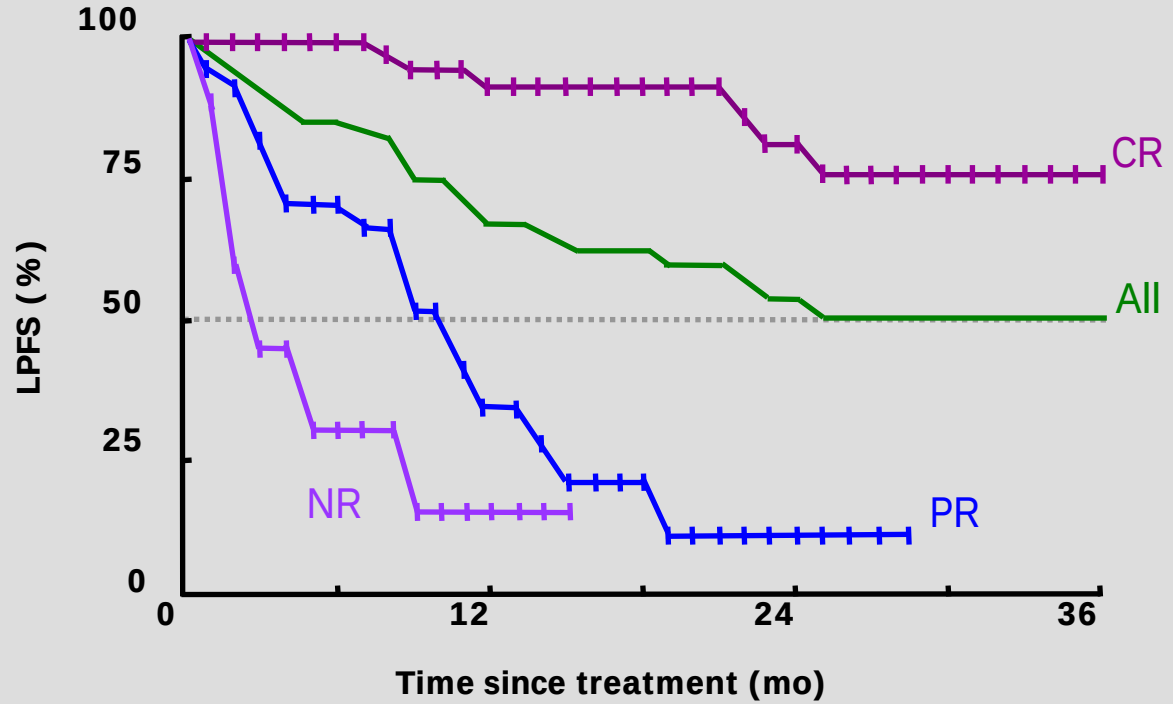
C. Post-RT imaging response:
Failure to achieve CMR (n = 23; 14%) was associated with higher risk of progression (p=0.001)

Source: Brady et al. Blood 2019

High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

Journal of Clinical Oncology, Vol 21, No 13 (July 1), 2003: pp 2474-2480

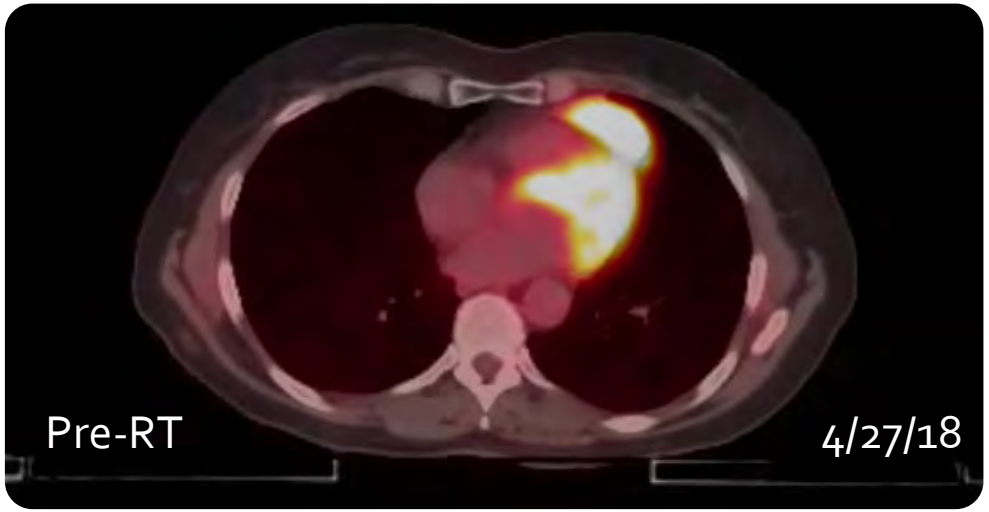
By R.L.M. Haas, Ph. Poortmans, D. de Jong, B.M.P. Aleman, L.G.H. Dewit, M. Verheij, A.A.M. Hart, M.H.J. van Oers, M. van der Hulst, J.W. Baars, and H. Bartelink



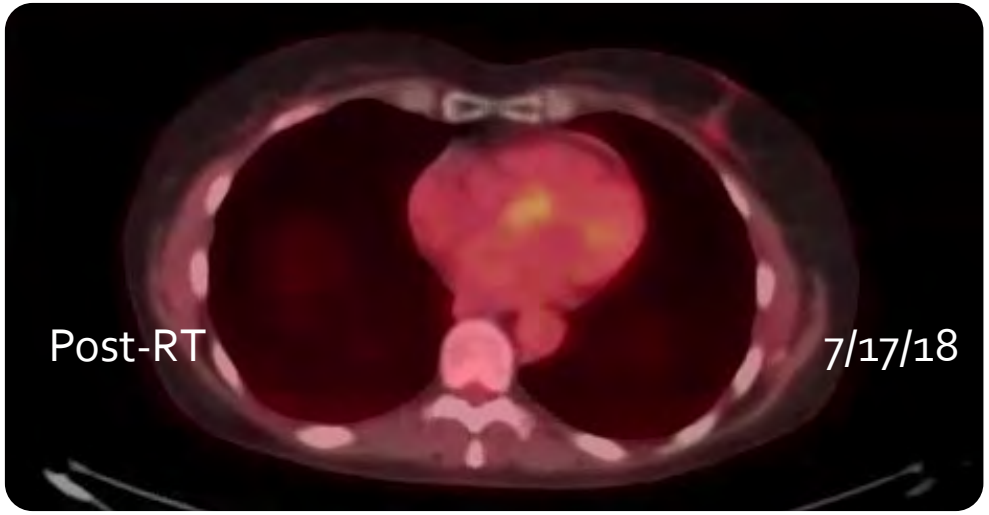
Advantages of “Boom-Boom”

- Short treatment duration.
- Minimal morbidity. No myelosuppression.
- Rapid response onset – high and lasting
- Effective and simple re-treatment

LR - 62F stage IIIA FL with pericardial node



- **L anterior mediastinal mass**
  - SUV: 8.0
  - 5.0 x 2.0 cm



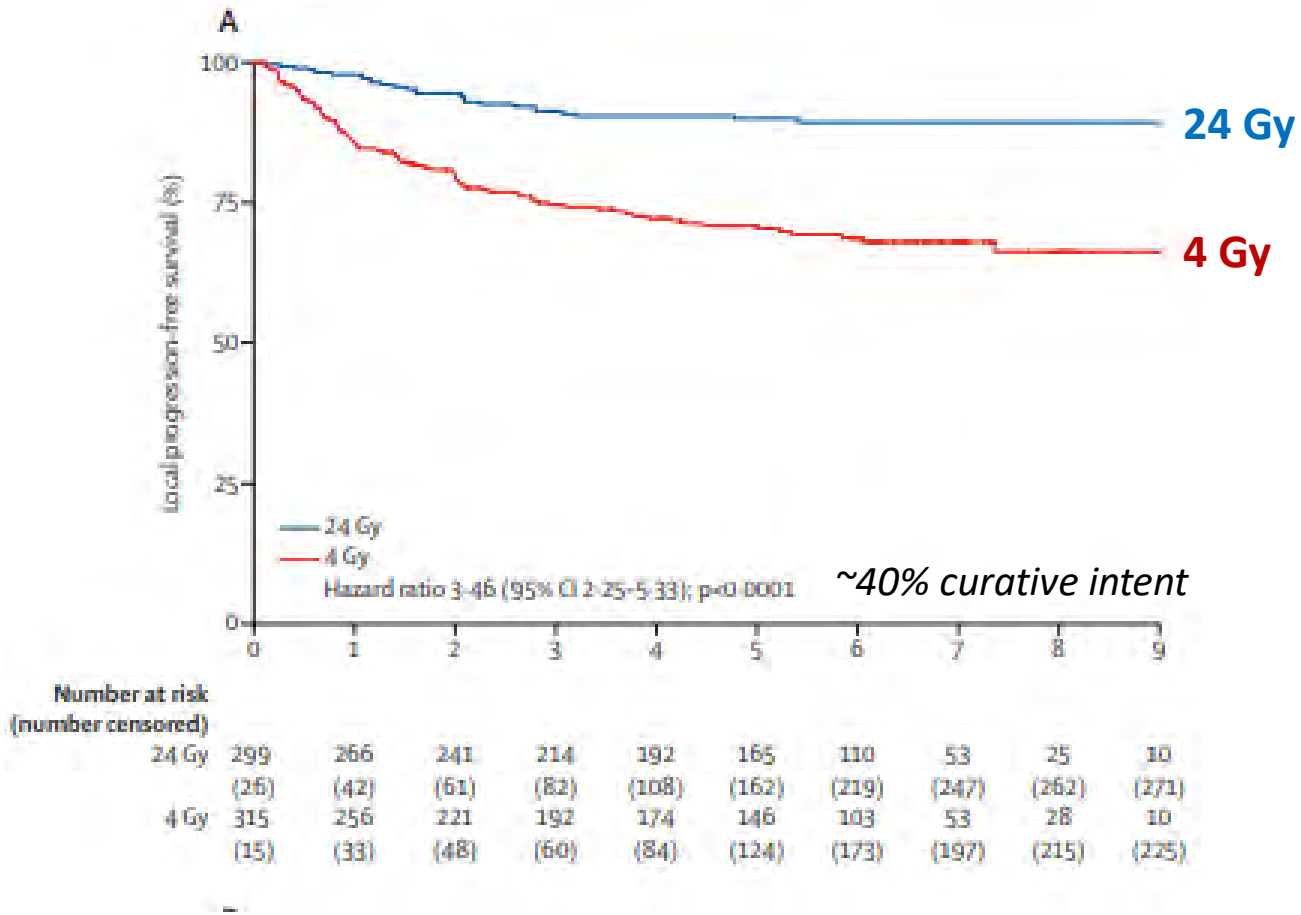
- **L anterior mediastinal mass**
  - Non-hypermetabolic
  - 3.2 x 0.6 cm

FoRT: A phase III multi-centre randomised controlled trial of low dose radiotherapy for follicular and marginal zone lymphoma

Hoskin P, Kirkwood A, Popova B, Brammer C, Diez P, Gallop-Evans E, Jack A, Madhavan K, Robinson M, Syndikus I, Smith P

FoRT has defined 24 Gy as the current standard of care dose for mature B-cell lymphomas

FoRT study update (median f/u: 74 mos)



24 Gy

4 Gy

~40% curative intent

Study population:

- Total of 614 treatment sites (indolent NHL) in 548 patients were randomized

Design and Endpoints:

- Primary - **local PFS**
- Secondary – response using RECIST 1.1
- Non-inferiority design, excluding 4Gy has **>10% worse** local PFS at 2 years

Results:

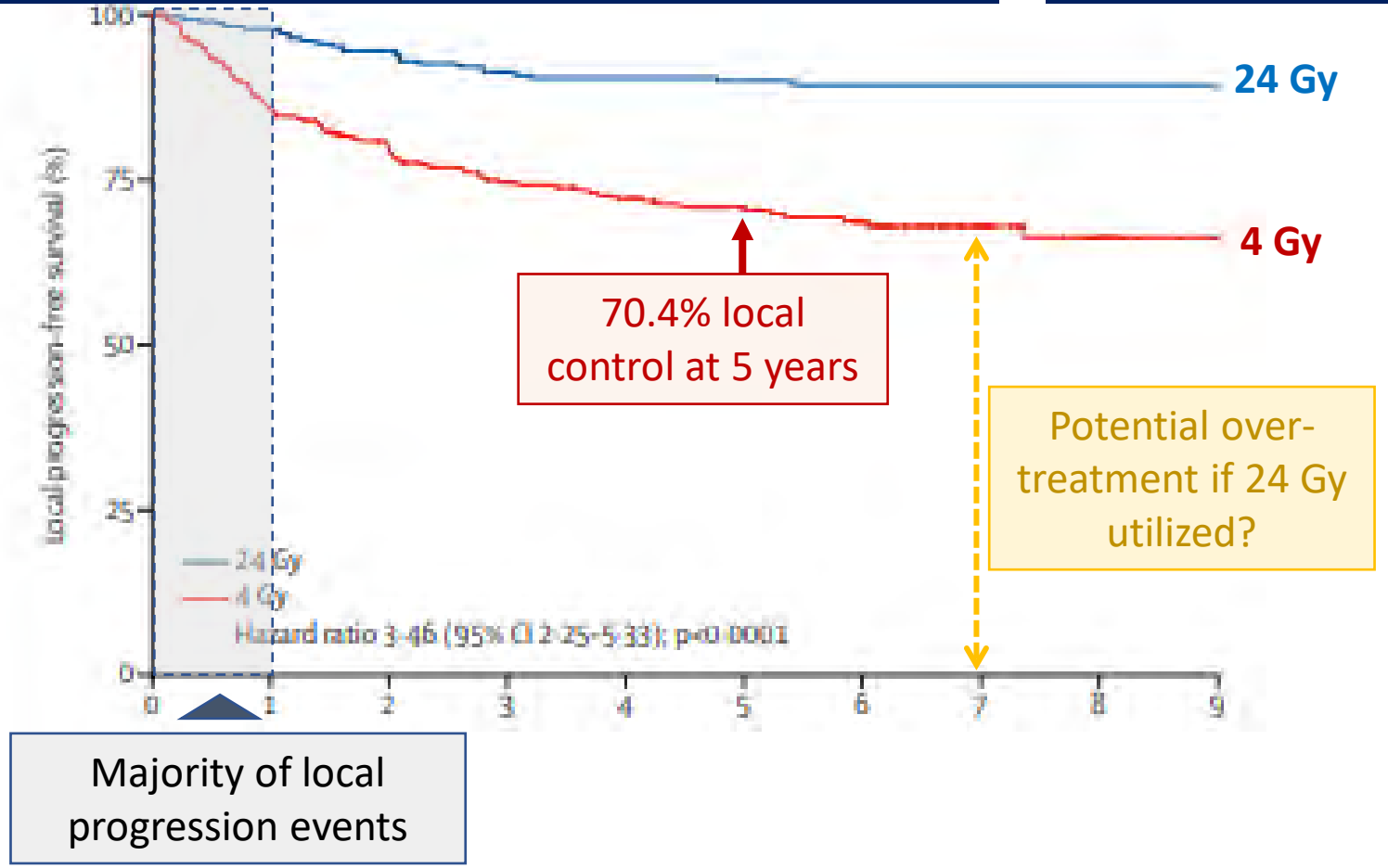
- Local PFS at 5 years
  - 89.9% after 24Gy
  - 70.4% after 4Gy (p<0.001)
- For curative intent subgroup (248 sites, 34 events)
  - 4Gy remained inferior (HR 5.8,, p<0·001).
- **No difference in OS**

Hoskin et al Lancet Oncology 2021

Two “schools of thought” emerge when interpreting FoRT data for potentially curable patients

School 1: “Glass 30% empty” – 4 Gy has clearly inferior local PFS and cannot become a standard of care

School 2: “Glass 70% full” – 4 Gy is clearly enough for most, and we should do more with less

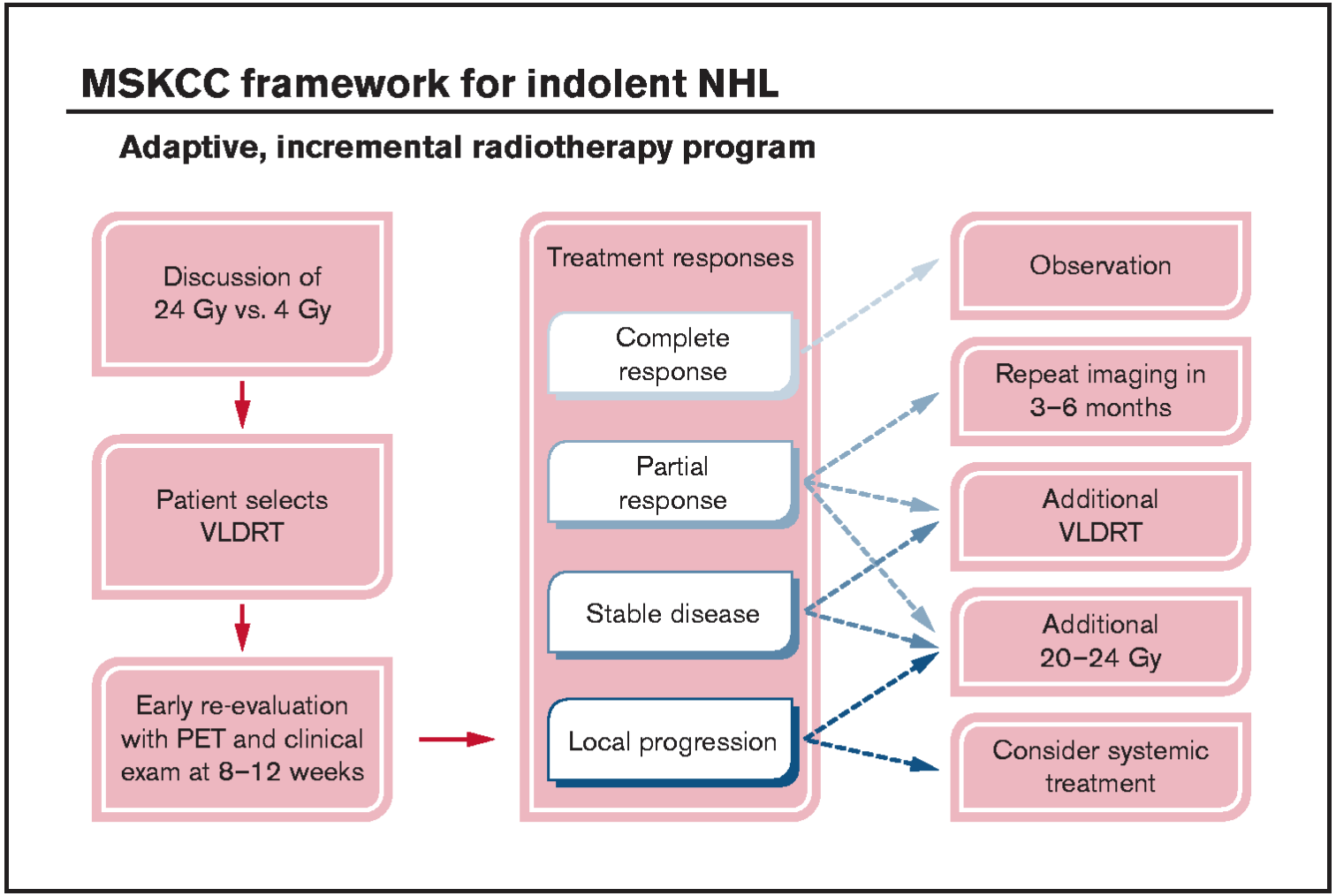


Median time to local progression has not been reached, but for sites that had local progression these occurred at a median time of

- 19.3 months (IQR 12.0–31.0) for sites treated with 24 Gy
- **12.3 months (7·1–27·5) for sites treated with 4 Gy**

Hoskin et al Lancet Oncology 2021

At MSKCC, VLDRT is considered more broadly as part of an adaptive program



It is well-established that very low doses of RT (VLDRT) can be exquisitely powerful for NHL

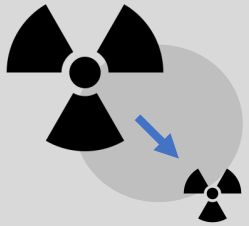
VLDRT mechanisms of action are both local within irradiated tumors and systemic

- **Local (intratumoral) effects**
  - Induction of apoptosis overcoming anti-apoptotic Bcl-2 overexpression
  - Stimulation of intrinsic/extrinsic apoptotic pathways (TRAIL-R2, FAS mediated)
  - Triggers altered expression of several pathways: p53, immune response, cell cycle

- **Systemic effects**
  - Enhanced tumor-specific immunity (*in situ* vaccines, abscopal effects)
  - Improved T-cell trafficking to irradiated sites
  - Antigen spreading and T-cell expansion

Mechanistic differences between VLDRT and standard “cytotoxic” doses remain poorly understood

Potential opportunities to optimize the RT treatment outcomes for localized FL



Refine our understanding of whether **very low dose radiotherapy (4 Gy)** has broader applicability outside palliation

Explore **rational integration of novel (non-chemotherapy) systemic therapies** for highest risk disease

Broader utilization of **personalized genomic and radiomic insights** to inform RT decision making

Methods

Inclusion criteria

- Biopsy-confirmed indolent B-cell lymphomas
- Lesions completely excised without residual measurable disease were excluded

Study endpoints/statistical methods

- Primary: incidence of local progression (LP) using competing risk of death
- Secondary:
  - Best clinical/radiographic response in 1.5-6 months following VLDRT using Lugano criteria
  - Distant POD (outside VLDRT field)
  - Overall POD (LP, Distant POD, additional in field or out of field RT, start of systemic therapy)
  - Overall survival
  - Time to subsequent therapy
  - Histologic transformation to DLBCL

Subgroup analysis

- Lesions were stratified based on VLDRT treatment intent
  - **Potentially curable intent** – newly diagnosed, Ann Arbor stage I-II disease with no history of any lymphoma-directed therapy
  - **Non-curable intent** – non PCI patients including all advanced stage patients or those with any prior lymphoma-directed treatments

VLDRT has an ORR of 90% for indolent NHL

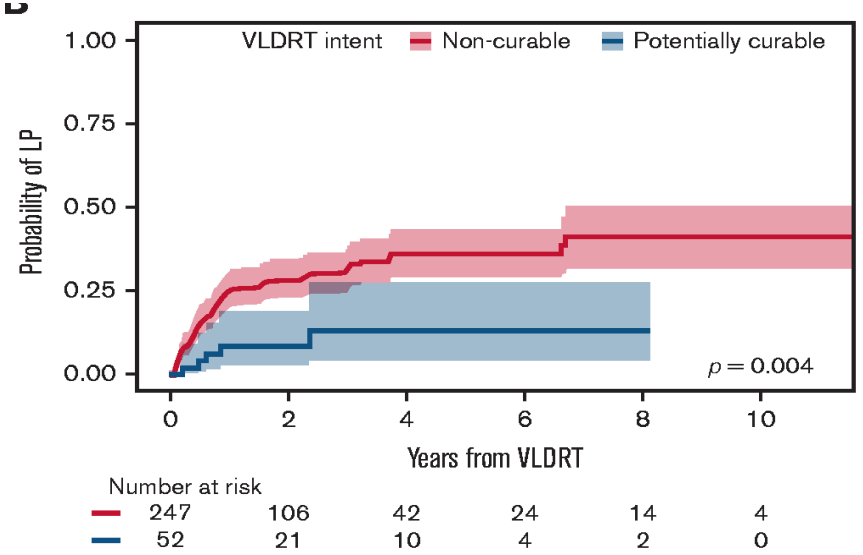
Best overall response by 6 months	Overall N = 227	Intent of VLDRT	
		Non curable, N = 181	**Potentially curable, N = 46**
CR	154 (68%)	117 (65%)	37 (80%)
PR	49 (22%)	42 (23%)	7 (15%)
SD	13 (5.7%)	11 (6.1%)	2 (4.3%)
PD	11 (4.8%)	11 (6.1%)	0 (0%)

- Distribution of response was similar using re-assessment intervals of 1.5-3 or 1.5-12 months
- No significant differences in ORR were observed when stratifying the cohort by histology ($p>0.9$) or **VLDRT treatment intent ($p=0.2$)**

Imber et al. Blood Advances, 2021

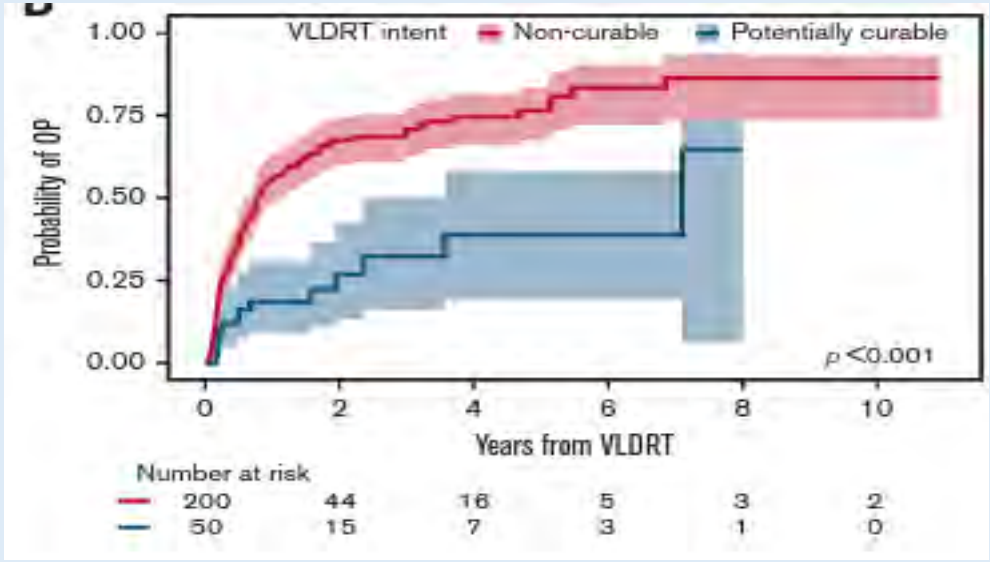
Early signals do not suggest poorer local control or PFS for definitive treatment

Cumulative incidence of LP assuming death as competing risk after VLDRT



	Median follow-up (reverse KM)	2-year Cum. Incidence of LP
Overall	2.4 (95% CI: 2.2-3.1)	25% (95% CI: 20-31%)
Non-curable	2.5 (2.3-3.5)	29% (23-34%)
Potentially curable	1.7 (1.2-3.5)	9% (3-19%)

Cumulative incidence of overall progression after VLDRT

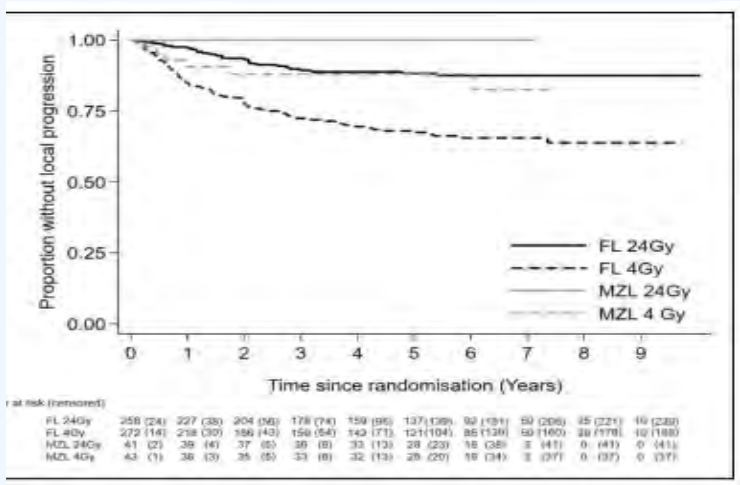


	2-year Cum. Incidence of OP
Overall	60% (95% CI: 53-66%)
Potentially curable	27% (13-42%)

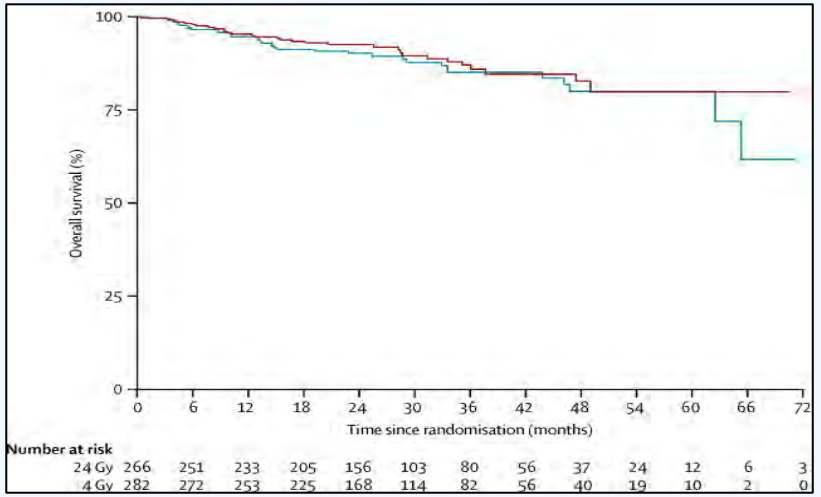
Source: Imber et al. Blood Advances, 2021

Little debate that 24 Gy has more durable local control but there is more to the story

1 **Some subgroups do remarkably well with just 4 Gy**



2 **No OS differences suggests good salvage options**



3 **With similar subsequent systemic therapy requirements irrespective of RT dose**

Supplementary table 1: Additional systemic or to-target local treatments given before local progression

Censored at further treatment	24Gy N=299	4Gy N=315
Total	74 (24.7%)	81 (25.7%)
Systemic	73 (24.4%)	68 (21.6%)
To-target	1 (0.3%)	13 (4.1%)
RT	*1*	*12*
Surgery	*0*	*1*

4 **Dose escalation to 24 Gy *may* be similar in terms of overall progression risks**

ILROG FL series (≥24 Gy)

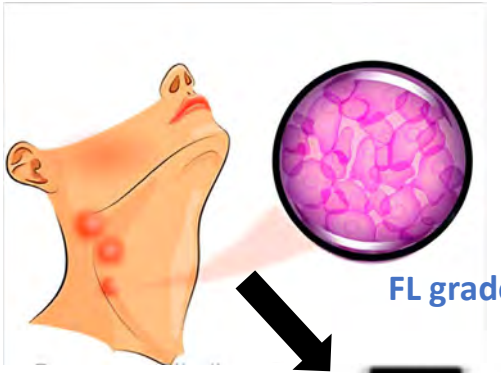
Stage I: 5-year FFP was 74%

Stage II: 5-year FFP was 49%

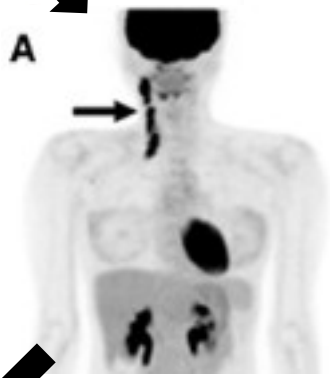
Source: Hoskin et al Lancet Oncology 2021; Brady et al. Blood 2019

FL biology should play a more important role in RT decision making

Past: "One Size" model for definitive ISRT



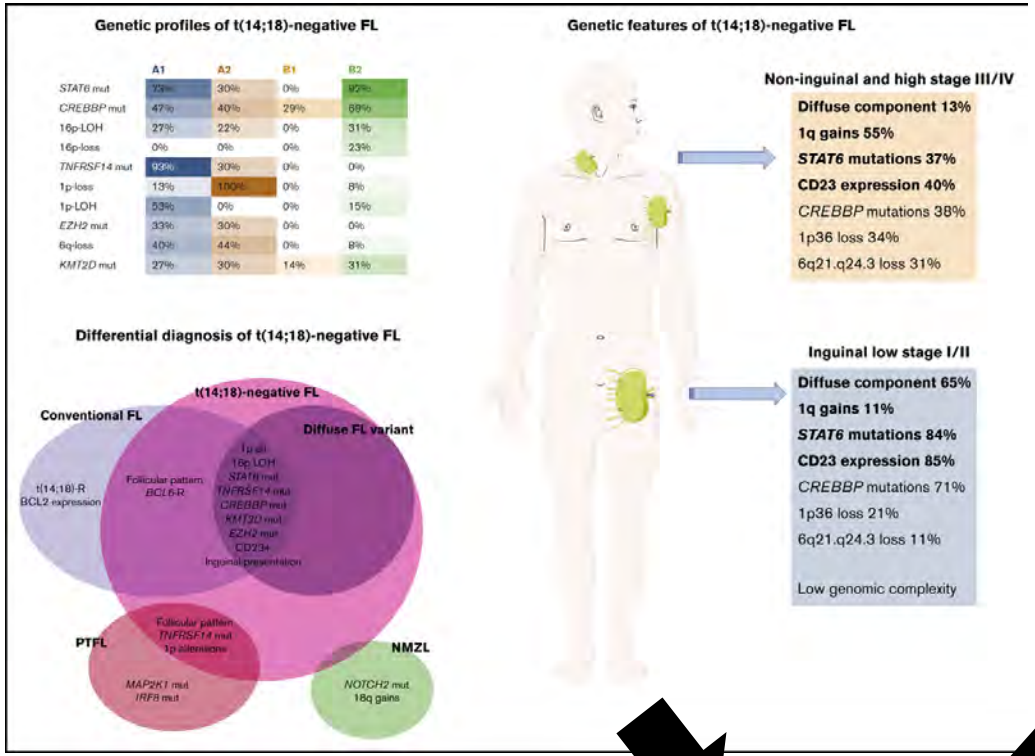
FL grade 1-2



Recommendation for 24-30 Gy

Source: Nann et al. Blood Advances, 2020

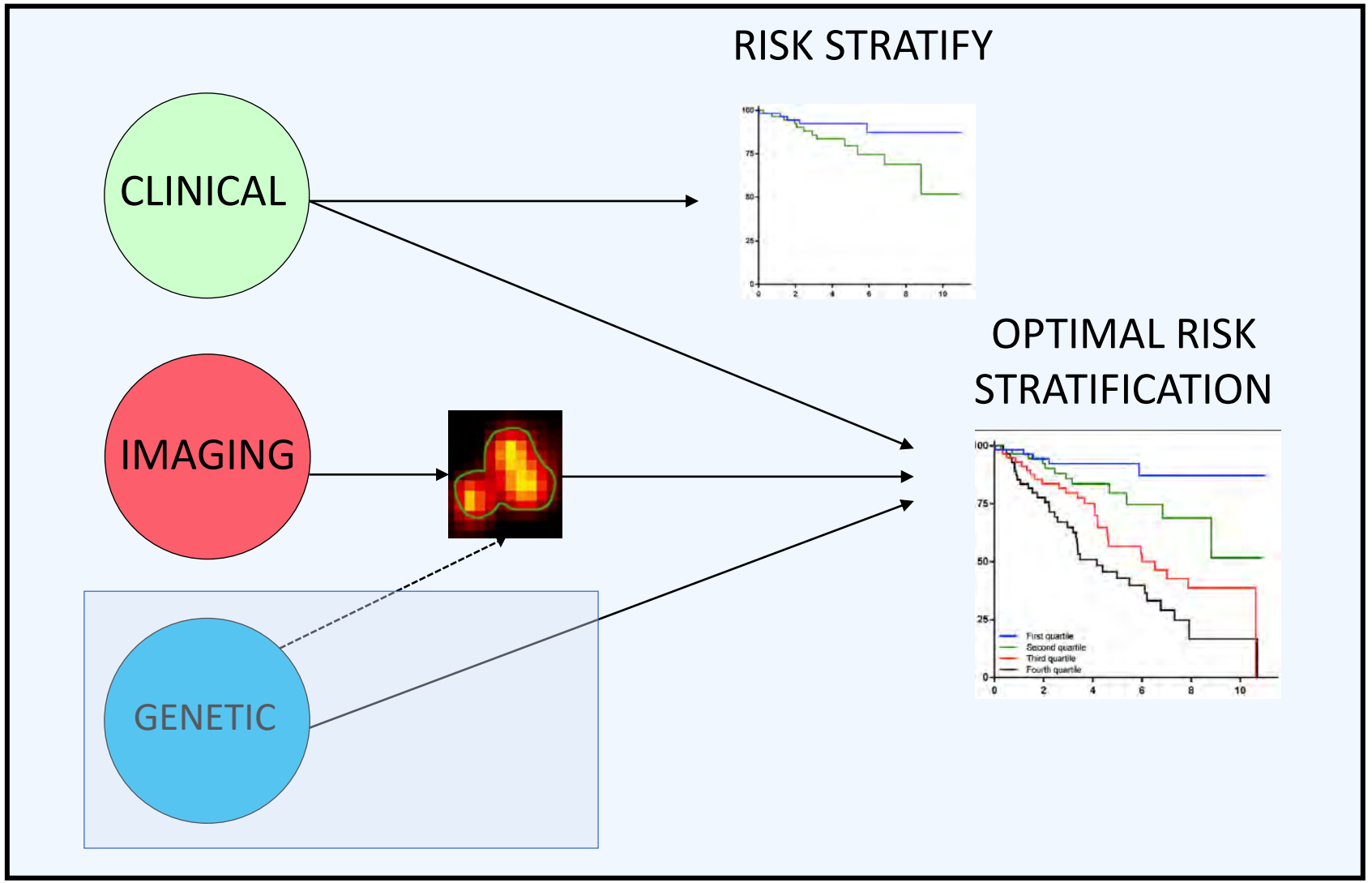
Future: Personalized medicine model for definitive ISRT



Clinical factors (e.g., size, anatomy, nodal status etc.

- **Observation**
- **Systemic therapy**
- **Combined modality therapy**
- **Recommendation for >30 Gy?**
- **Recommendation for 24-30 Gy**
- **Recommendation for adaptive VLDRT**

We hope to further refine progression risk using multi-omic analysis



Molecular profiling of the RT-treated lesions may help to better define markers of radiosensitivity

Methods

- **Cohort**: Single institution database of FL patients (all stages) treated with any dose of radiotherapy for curative or palliative intent between 2005-21
- **Sequencing approach**: MSK-IMPACT targeted exon sequencing panel
- **Outcomes**
  - Response 2-6 months post RT using Lugano criteria
  - Local PFS
- **Statistical approach**
  - Hierarchical clustering to form gene signatures
  - Logistic regression and Kaplan Meier to associate gene alterations with outcomes

Variable	Category	n (%) or median (range)
Irradiated site	Lymph nodes (non-pelvic)	34 (30%)
	Pelvis	43 (38%)
	Other soft tissue	22 (19%)
	Parotid	5 (4%)
	Orbit	5 (4%)
	Bone	4 (4%)
RT dose (Gy)	4	67 (59%)
	12-20	4 (4%)
	24	19 (17%)
	>24	23 (20%)
FL grade*	Grade 1-2	91 (81%)
	Grade 3A	21 (19%)
Diameter	Maximum diameter	3.2 (0-11.9)
SUV	Maximum SUV	9.2 (0 – 19.7)
PET staged pre-RT	PET Staged	106 (94%)
	Staged with other imaging modalities	7 (6%)
Stage at RT	Early stage (Stage 1 or 2)	79 (70%)
	Advanced stage (Stage 3 or 4)	34 (30%)
Treatment Intent	Curative	70 (62%)
	Subset of disease treated	43 (38%)
Prior large cell lymphoma	Yes	8 (7%)
	No	105 (93%)
Prior Chemoimmunotherapy	Yes	47 (42%)
	No	66 (58%)

Wijetunga, Imber, Yahalom et al. *Manuscript in Prep*

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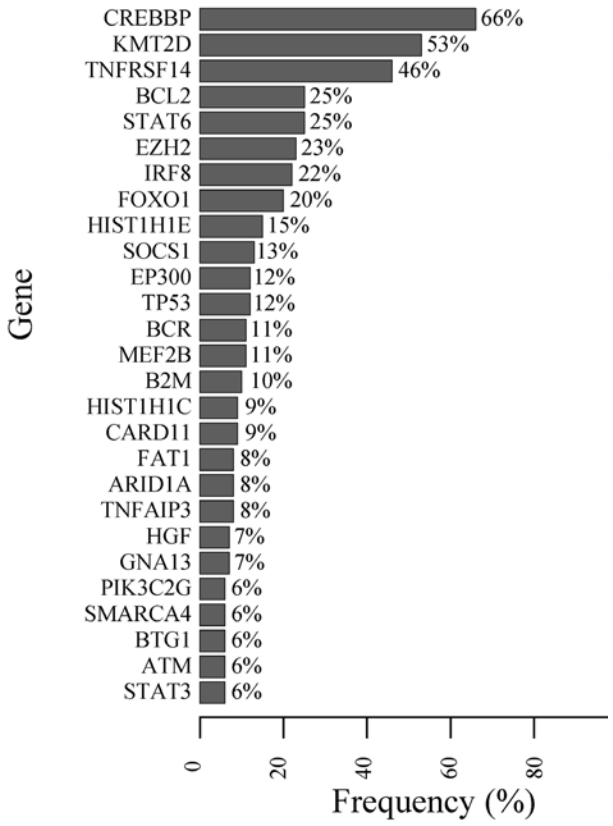
CREBBP was the most frequently observed mutation and alteration was associated with better response to RT

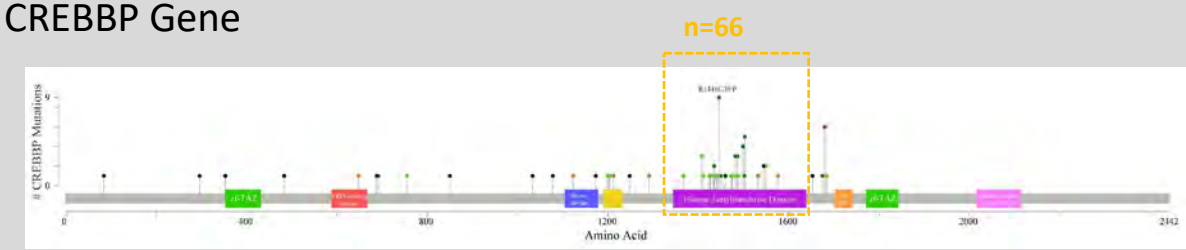
Mutational frequency (n=113)



Logistic Regression of CR

- CREBBP was the only mutated gene associated with increased odds of CR (OR: 2.4, 95% CI: 1.06-5.37, p = 0.04)
- This effect was still significant after adjusting for pelvic disease site (p=0.04)

CREBBP Gene



- Notably, of 75 samples with altered CREBBP, the histone acetyltransferase (HAT) domain was altered in 66 samples with most of these alterations thought to result in a loss of function

Wijetunga, Imber, Yahalom et al. *Manuscript in Prep*

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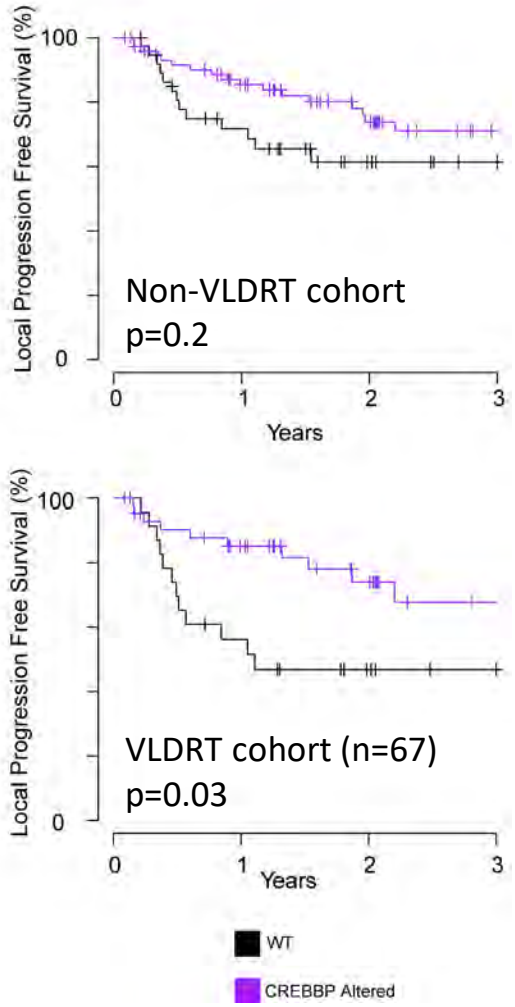
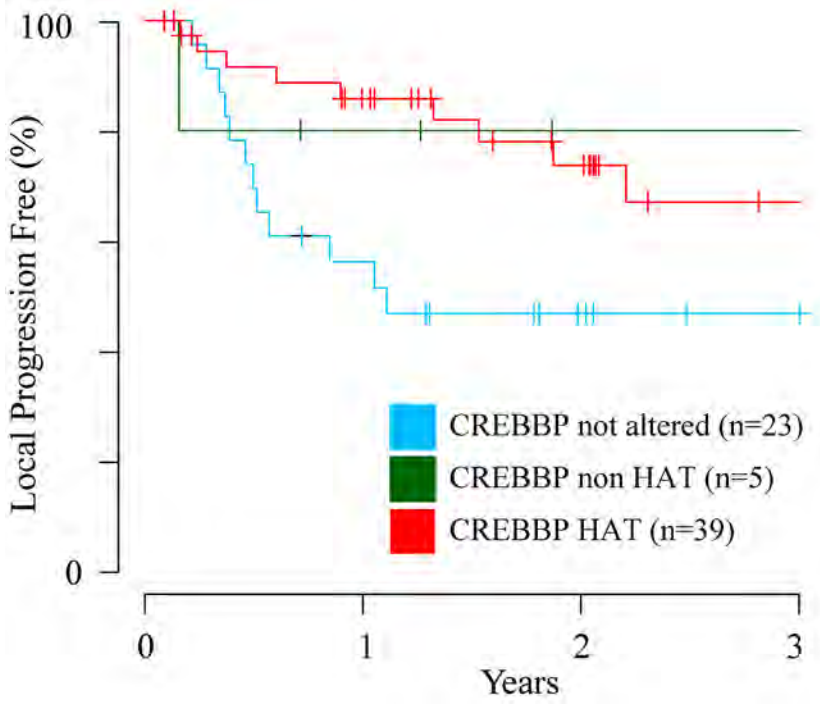
CREBBP HAT alterations are associated with radiosensitivity particularly for VLDRT-treated patients



Local PFS for VLDRT-treated lesions



- CREBBP HAT mutations were associated with improved LPFS (n=39, 2y LPFS 52% vs 74%, HR:0.41 (95% CI: 0.18-0.93, p=0.03))
- This was not observed for lesions receiving >4Gy (n=44, HR: 1.27 (95% CI: 0.32-5.08), p=0.74)).

Next steps
- Expand sequenced cohort
- Translational partnership to validate findings

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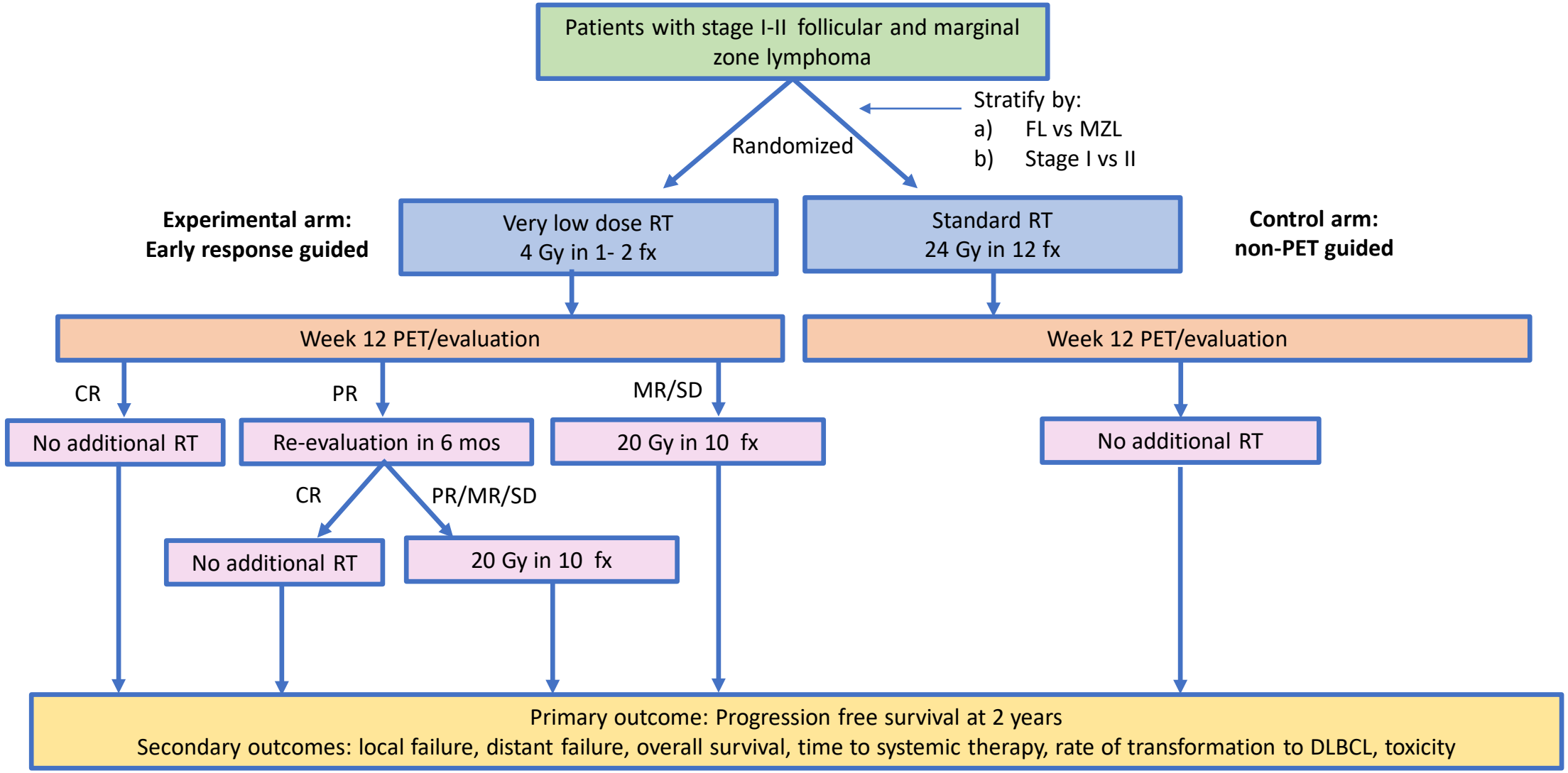
Summary and conclusions

- ISRT remains the guideline preferred strategy for localized FL
- Modern ISRT utilizing PET staging has outstanding local control and may be curative in a moderate share of patients (particularly stage I)
- Dominant pattern of failure following ISRT is outside RT field; predictors of progression are crude
- Given it is unclear that higher RT doses improve overall progression risk, it may be reasonable to consider broader utilization of adaptive very low dose regimens, even for curable patients
- There is preclinical rationale to consider synergies of 4 Gy with novel FL agents (e.g., bispecific engagers)
- Future ISRT studies must incorporate more nuanced consideration of FL biology to guide personalized decision making
- Early data associate CREBBP mutations of the HAT domain with greater radiosensitivity hinting at epigenetic mediation of ISRT response

Trial Schema – Inaugural ILROG Sponsored Trial



Sample size estimate: **N= 355 patients**

Endpoints & Biostatistics

- **Primary endpoint**
  - Progression free survival at 2 years
- **Secondary endpoints**
  - Radiographic response as per RECIL 2017
  - Local progression
  - Distant progression outside of the radiation field
  - Time to start of systemic therapy
  - Overall survival
  - Acute and late toxicity (descriptive, comparison of grade 3+)
  - Rate of transformation to DLBCL
- **Exploratory endpoints**
  - Quality of life, financial toxicity
  - ctDNA, immune, and genomic correlatives

- Design: **non-inferiority**
  - To demonstrate staged approach not worse than 24 Gy upfront
- Sample size estimate: **N= 355 patients**
  - Key assumptions
    - **Baseline 2-year PFS of 80% after 24 Gy** (Estimated from ILROG series, Brady et al Blood 2019)
    - **Non-inferiority margin of 10%**
      - 2-year PFS must be $\geq$70% in experimental arm to deem non-inferior
    - 80% power and alpha of 5%
    - 10% dropout included

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American Society of Hematology
2021 L Street NW, Suite 900,
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
editorial@hematology.org

ILROG Emergency Guidelines for Radiation Therapy of Hematological Malignancies During the COVID-19 Pandemic

Tracking no: BLD-2020-006028R1

Joachim Yahalom (Memorial Sloan-Kettering Cancer Center, United States) Bouthaina Dabaja (MD Anderson Cancer Center, United States) Umberto Ricardi (University of Turin, Italy) Andrea Ng (Brigham and Women's Hospital/Dana-Farber Cancer Institute, United States) N. George Mikhaeel (Guy's & St Thomas' NHS Trust, United Kingdom) Ivan Vogelius (Copenhagen University Hospital, Rigshospitalet, Denmark) Tim Illidge (University of Manchester, United Kingdom) Shunan Qi (National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC), China) Andrew Wirth (Peter MacCallum Cancer Centre, Australia) Lena Specht (Rigshospitalet, University of Copenhagen, Denmark)

Abstract:
The ILROG guidelines for using radiation therapy in hematological malignancies are widely used in many countries. The emergency situation created by the COVID-19 pandemic may result in limitations of treatment resources. Furthermore, in recognition of the need to also reduce the exposure of patients and staff to potential infection with COVID-19, the ILROG task force has made recommendations for alternative radiation treatment schemes. The emphasis is on maintaining clinical efficacy and safety by increasing the dose per fraction while reducing the number of daily treatments. The guidance is informed by adhering to acceptable radiobiological parameters and clinical tolerability. The options for delaying or omitting RT in some hematological categories are also discussed.

Purpose/Objectives

- Indolent lymphomas are exquisitely sensitive to Radiation Therapy (RT)
- ‘Boom Boom’ RT (2Gyx2) is highly effective in controlling irradiated sites
- During the COVID-19 pandemic, the International Lymphoma Radiation Oncology Group (ILROG) proposed guidelines that offered substitution of the ‘Boom Boom’ (2Gy x 2) regimen with ‘Big Boom’ of 4Gy x 1
- In this report, we compare our center’s experience with both regimens

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ILROG Emergency Guidelines for Radiation Therapy of Hematological Malignancies During the

	Standard		Emergency COVID-19 Crisis Alternative Dose-Fractionation				BED Calculations	
	Total Dose	No. Fractions	Comments	Total Dose	No. Fractions	Dose/ Fraction*	EQD2 α/β = 3 Gy	EQD2 α/β = 10 Gy
Aggressive NHL, chemorefractory disease Localized aggressive NHL, primary RT alone (not chemo candidate)	40-50 Gy	20-25	No significant cardiac and/or lung exposure and no overlapping critical organs	30 Gy	6	5 Gy	48 Gy	38 Gy
			Some cardiac/ lung exposure or overlapping critical organs	36-39 Gy	12-13	3 Gy	43 -47 Gy	39-42 Gy
Indolent lymphoma, limited stage	24 Gy	12	Start with 4 Gy x1, reevaluate after 2-3 months→ If insufficient response, proceed to definitive RT	4 Gy 20 Gy	1 5	4 Gy 4 Gy	6 Gy 28 Gy	5 Gy 23 Gy
NK/T-cell lymphoma	45 Gy#	25	In patients treated with effective chemotherapy regimen¤	36 Gy	9	4 Gy	50 Gy	42 Gy
Cutaneous T-cell lymphoma, TSEBT	10-12 Gy	6-10	Give 2-3 treatments, 1 per week, evaluate response after each	8-12 Gy	2-3	4 Gy	11-17 Gy	9—14 Gy
Solitary bone plasmacytoma or Solitary extramedullary plasmacytoma	40-45 Gy	20-25	Non-spine, non-H&N sites	30 Gy	6	5 Gy	48 Gy	38 Gy
			Spine or H&N sites	36 Gy	12	3 Gy	43 Gy	39 Gy

Hoskin et al, 2014; Cerrato et al, 2021; Imber et al, 2021; Chelius et al, 2021

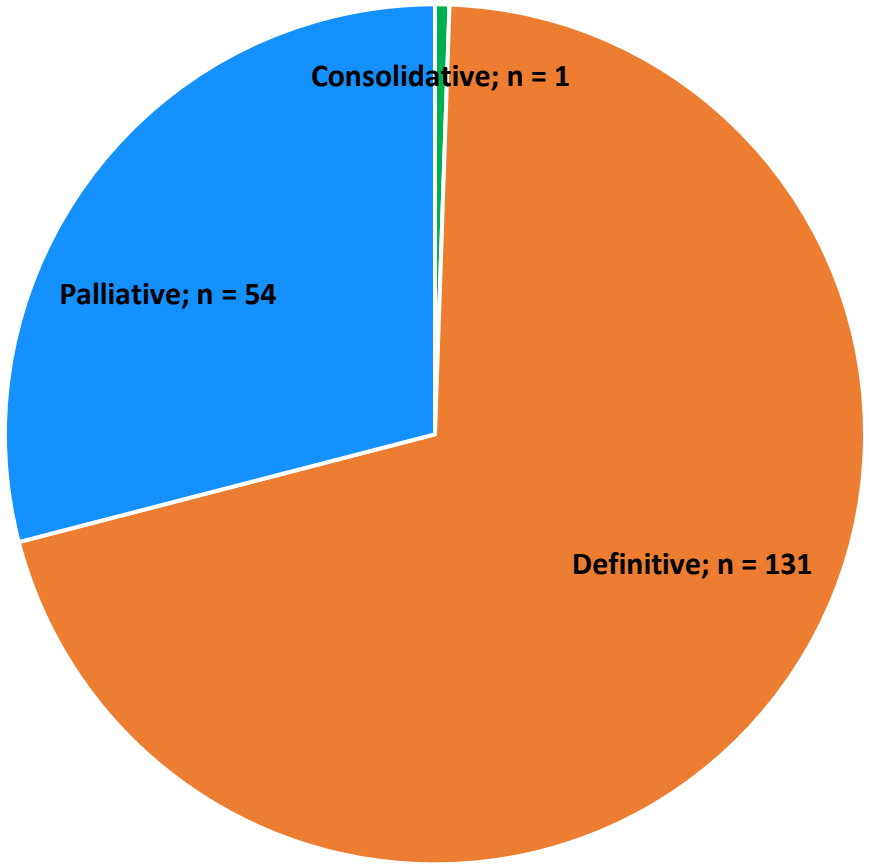
Yahalom et al. 2020

Materials/Methods

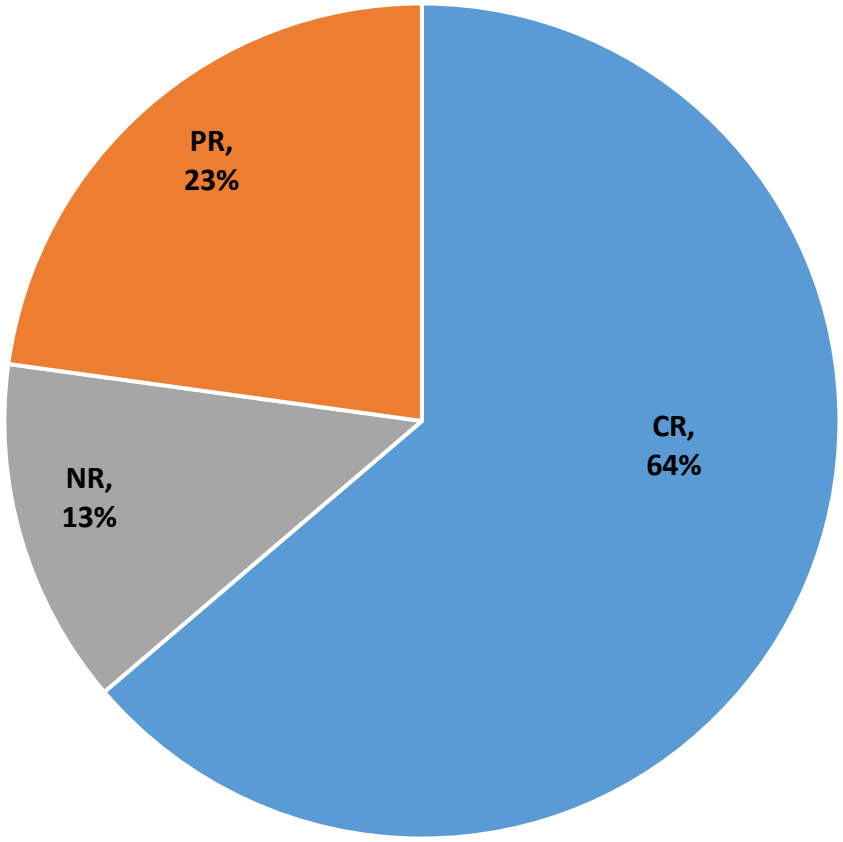
- Single institution study
- Patients treated with 4Gyx1 identified prospectively during the weekly chart rounds
- March 30, 2020- April 4, 2023
  - ✓ After April 2020 both options of very low dose and choice of a standard full dose of 24Gy were discussed with the patient
- Overall response rate (ORR) was assessed clinically and with Lugano PET criteria at the initial post-RT imaging
- The 4Gyx1 cohort was compared to the published cohort treated with 2Gyx2
- Differences between the two groups were examined using the Fisher’s exact test and Mann-Whitney test

Treatment intent

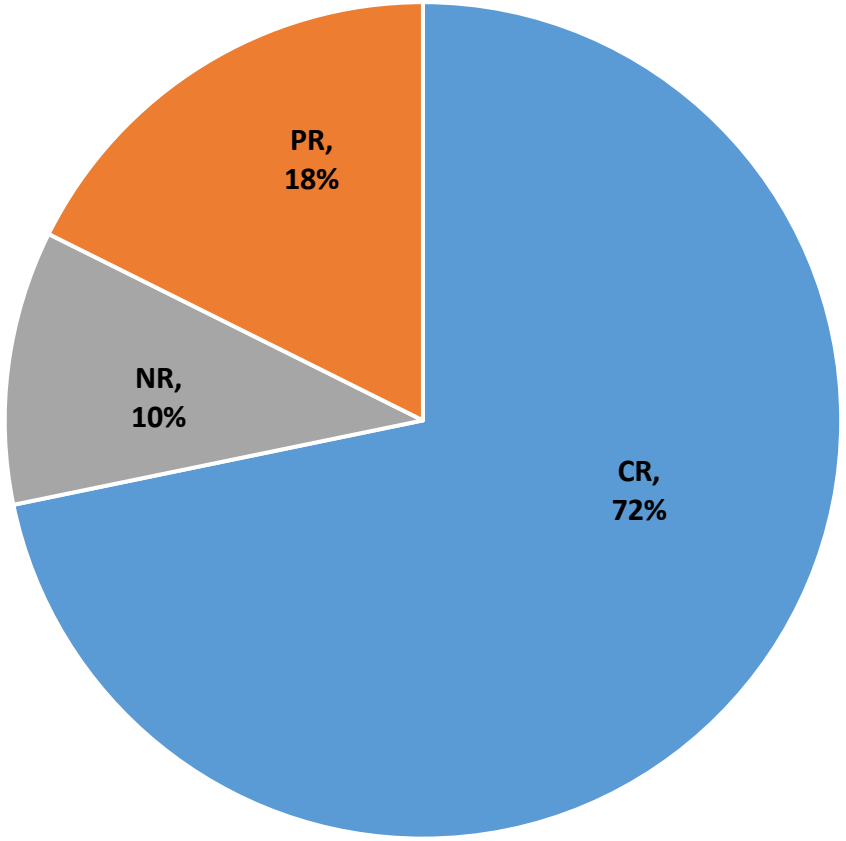
- Patient were treated with definitive or palliative intent depending on disease stage and prior therapy exposure



Overall response rates at first assessment



2Gyx2
N= 298 sites



4Gyx1
N=170 sites

Conclusions

- Both the 4Gyx1 and 2Gyx2 regimens demonstrated excellent ORR at the initial post-RT imaging and clinical assessment among patients with indolent lymphomas
- While longer term follow-up is required to confirm durability of these findings, our initial experience suggests that 4Gyx1 regimen recommended by ILROG during the pandemic is an effective treatment approach
- In progress- A prospective randomized study for early-stage untreated indolent lymphomas comparing standard 24 Gy to an adaptive approach starting with only 4 Gy
-

THANK YOU

Lymphoma Radiation Team

- Emily Silverman
- Kathryn Tringale
- N. Ari Wijetunga
- Reith Sarkar
- Jennifer Ma
- Harper Hubbeling
- Jisun Lee
- Beatrice Fregonese
- Morgan Freret
- Emily Lebow
- Gustav Cederquist
- Alexi Dreyfuss

Faculty

- Joachim Yahalom
- Brandon Imber
- Carla Hajj

Key collaborators

- Lymphoma Service
- Myeloma Service
- BMT Service
- CAR-T Team