

A Review of Follicular Lymphoma in 4 Cases

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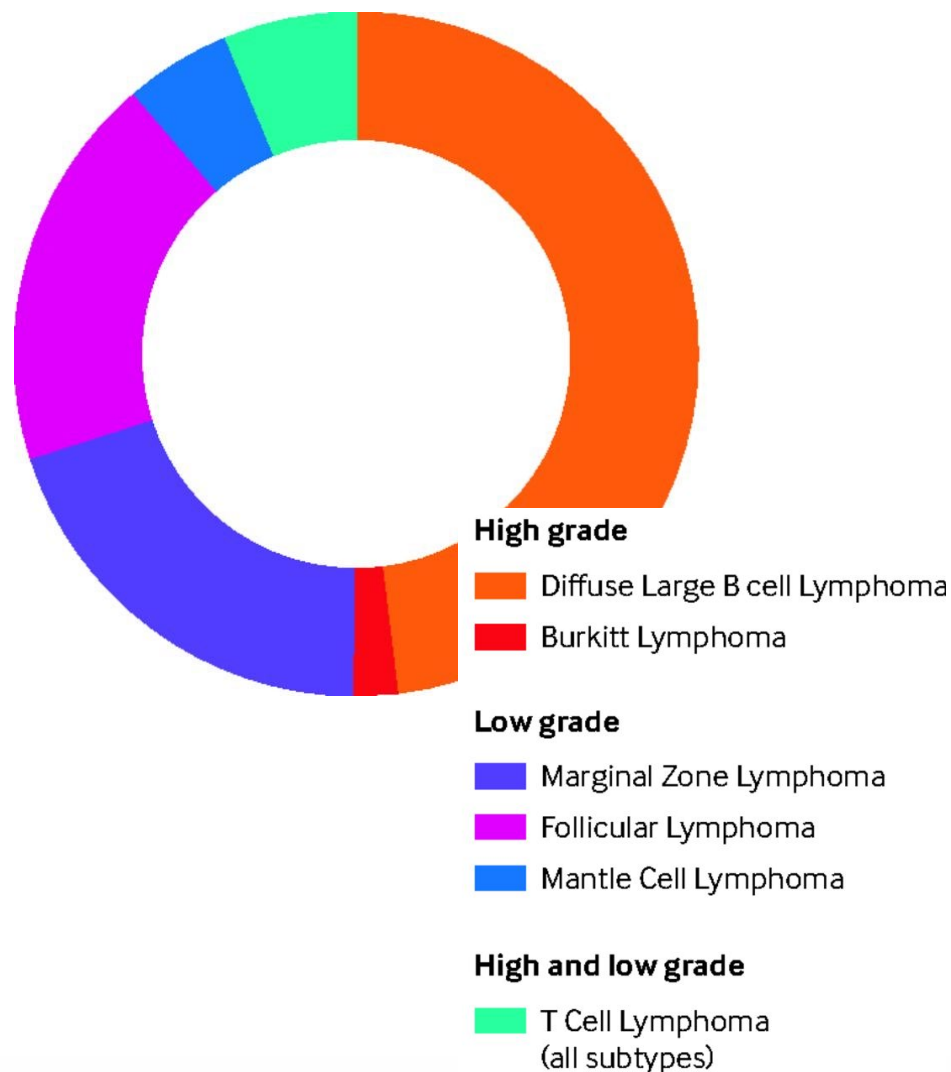
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Non-Hodgkin Lymphoma Overview

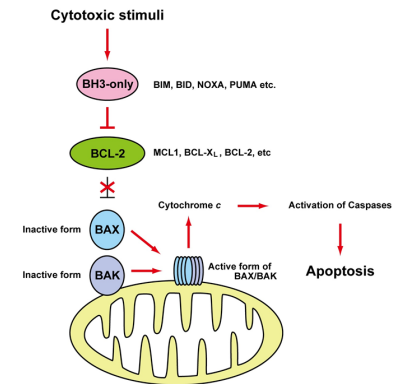
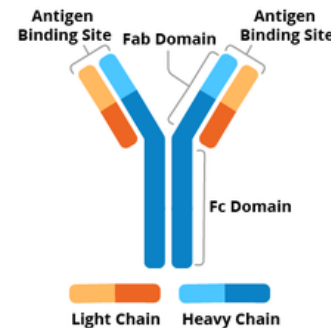
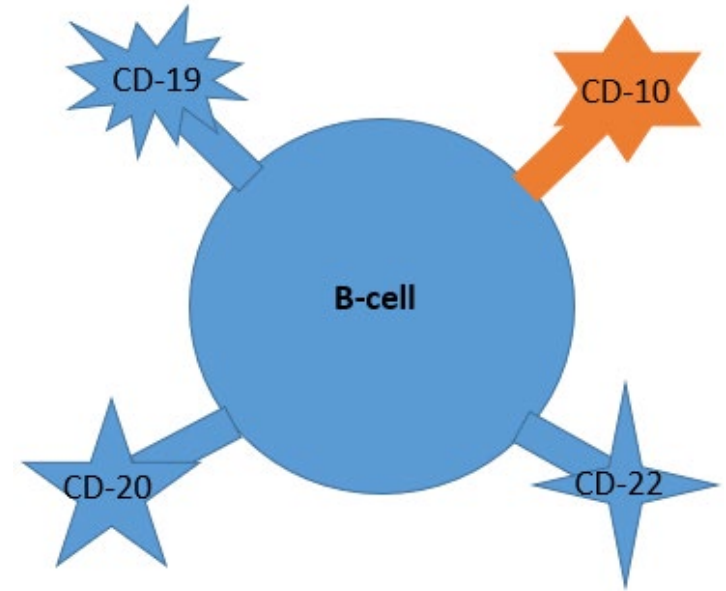
- Over 74,000 new cases in 2018
- Risk factors:
 - Autoimmune diseases
 - Bacterial and viral infections
- **Follicular lymphoma** ~20% of NHL diagnoses
- **Marginal zone lymphoma** ~6% of NHL diagnoses
- **Mantle cell lymphoma** ~3% of NHL diagnoses



Follicular Lymphoma Quick Hits

- Indolent B-cell neoplasm
- t(14; 18)  BCL-2 + IgH
- Positive B-cell markers:
CD19, CD20, CD22, CD10
- CD5, CD23 negative

BCL-2: anti-apoptotic gene
 IgH: make antibody heavy chains
 The t(14; 18) translocation, in which the anti-apoptotic BCL-2 is relocated next to IgH, leads to de-regulated B-cells not subject to apoptosis



Clinical Manifestations of Follicular Lymphoma (and other NHL too)

- May present in any part of the body
 - Lymph nodes
 - Extra-nodal sites
- Symptoms depend on involved site(s)
- B-symptoms:
 - Fevers > 100.4 F
 - Night sweats
 - Unintentional weight loss: $> 10\%$ of body mass within 6 months

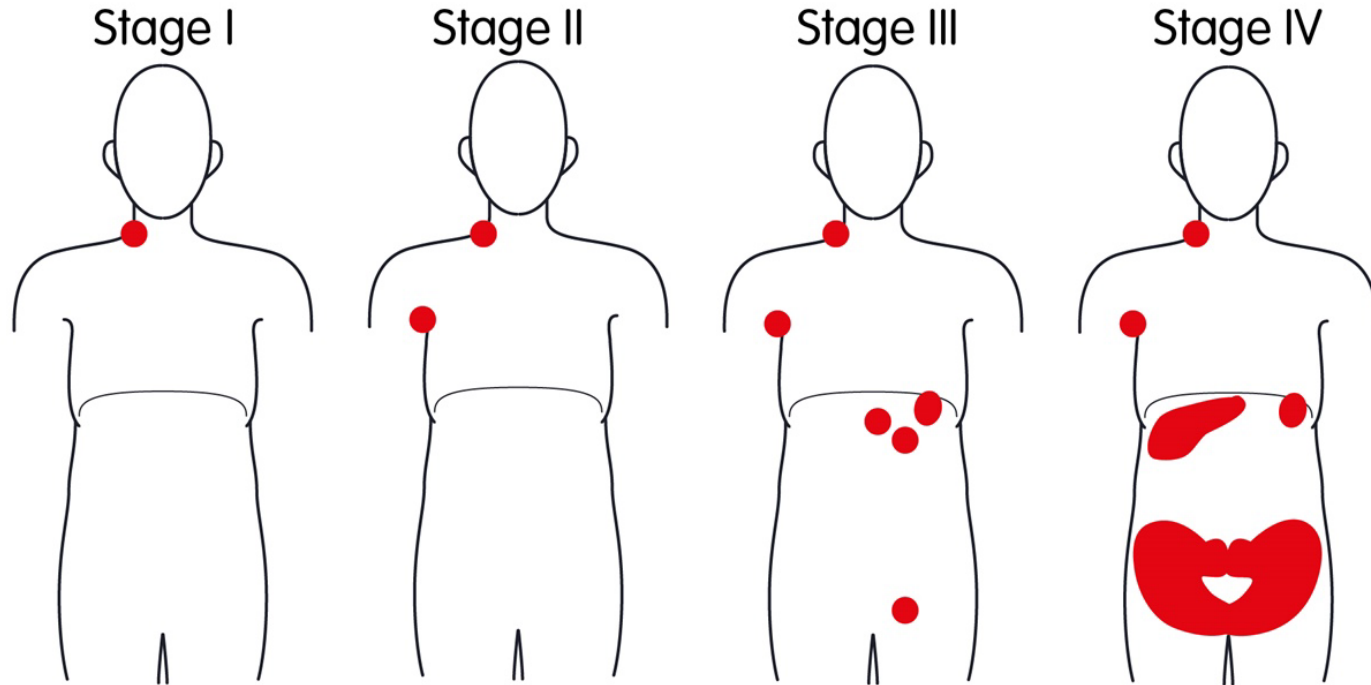
FL Work-up

- History & physical
- Labs: CBC, CMP, LDH
- Pathology – excisional biopsy consider core biopsy if excisional biopsy not possible, but FNA is not sufficient
- Imaging of involved site(s)
- PET / CT SUV max is lower, on average, compared to DLBCL
- + / - bone marrow biopsy Indicated if the results could change management

Staging NHL

Lugano Modification of the Ann Arbor Staging System

Staging of lymphoma

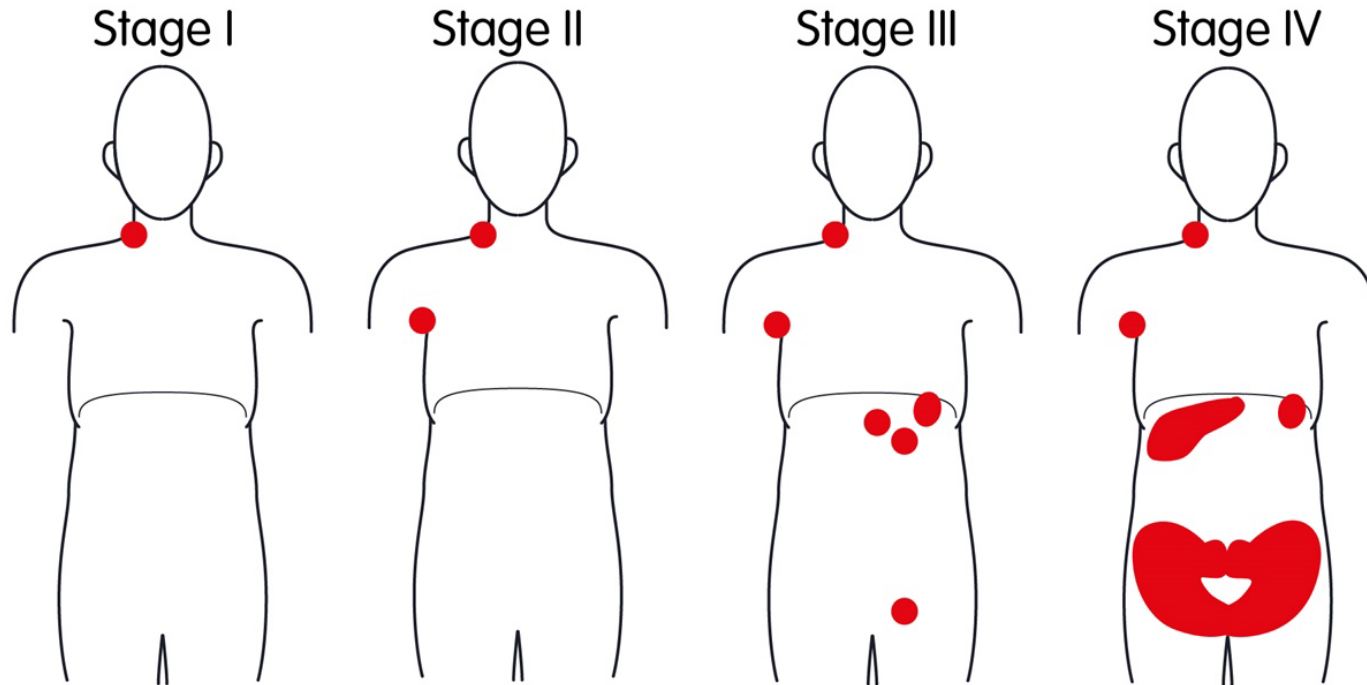


B symptoms no longer included in staging NHL

Definition of “bulky” varies by study, but 7.5 cm is often used

More on Staging

Staging of lymphoma



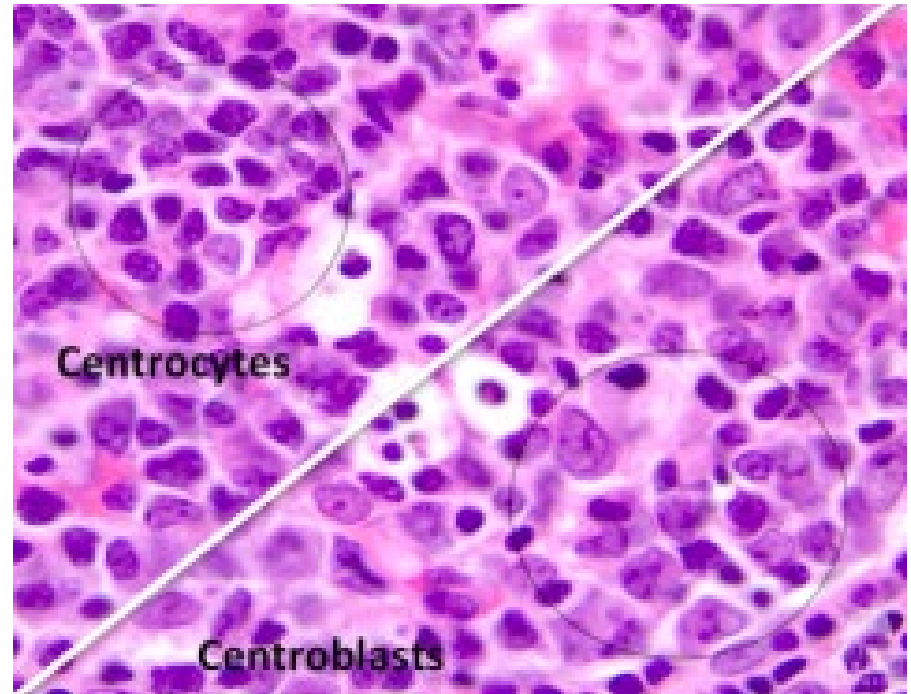
Stages I & II may designate E for “extra-nodal site”

Note: **stage IIE** indicates extranodal disease contiguous with nodal disease;

stage IV indicates extranodal disease and non-contiguous nodal disease

Grading Follicular Lymphoma

- Based on number of centroblasts
 - More centroblasts → higher grade → more aggressive clinical course
- Grade 1: 0-5 / hpf
- Grade 2: 6-15 / hpf
- Grade 3:
 - A*: > 15 / hpf*
 - B**: solid sheets of large blastic cells



Centroblast = activated B cell, promotes secretion of immunoglobulins

*Grade 3A typically managed like to grade 1-2, but this is an area of uncertainty

**Grade 3B is treated like DLBCL

Note – a simplified grading system is on the horizon

The International Consensus Classification (ICC) of Mature Lymphoid Neoplasms (2022)	WHO Classification of Hematolymphoid Tumors: Lymphoid Neoplasms (2022; 5th edition)
Mature B-cell lymphomas	Mature B-cell lymphomas
<i>Follicular lymphoma</i>	
<ul style="list-style-type: none"> • Follicular Lymphoma (FL) grades 1, 2, 3A • FL grade 3B • Not Included • In situ follicular neoplasia • Duodenal-type follicular lymphoma 	<ul style="list-style-type: none"> • Classic FL (cFL) • Follicular large B-cell lymphoma (FLBCL) • Follicular lymphoma with unusual cytological features (ucFL) • In situ follicular B-cell neoplasm • Duodenal-type follicular lymphoma
Pediatric-type follicular lymphoma	Pediatric-type follicular lymphoma
<i>BCL2-R</i> negative, CD23-positive follicle center lymphoma	FL with predominantly diffuse growth pattern (dFL)
Testicular follicular lymphoma	Not included
<i>Mantle cell lymphoma</i>	
Mantle cell lymphoma	Mantle cell lymphoma
<ul style="list-style-type: none"> • In situ mantle cell neoplasia • Leukemic non-nodal mantle cell lymphoma 	In situ mantle cell neoplasm
	Leukaemic non-nodal mantle cell lymphoma
<i>Transformations of indolent B-cell lymphomas</i>	
Not included	Transformations of indolent B-cell lymphomas

WHO grading is combining grades 1 – 2 and 3A into “classic FL,” while it classifies grade 3B as “follicular large B-cell lymphoma”

This assumes all grades other than 3B will be treated similarly – but stay tuned for any future changes!

Case 1: 61 M with lump in right cheek

- Initially palpated the mass while shaving
- CT face obtained nearly 1 year later showed a solid, 2.5 cm mass abutting right parotid gland
 - Took a while to order imaging due to waxing / waning nature of the lump
- FNA showed a low-grade B-cell lymphoma suggestive of follicular lymphoma
 - FNA was ordered by an ENT who must not have had FL on the differential!
- PET / CT showed intense uptake in the soft-tissue mass in the right parotid gland but not other sites of pathologic avidity
- Core-needle biopsy confirmed grade 1-2 FL
- Bone marrow biopsy was without evidence of involvement

What is this patient's stage?

Case 1: 61 M with lump in right cheek

Stage IE (extranodal) Follicular Lymphoma

What's next?

What's the evidence for treating early stage, low-grade FL?

- Analysis of SEER data compared upfront RT vs upfront observation among patients with stage I/IE or II/IIIE, grade 1-2, FL
 - Upfront RT included those treated within 1 year of dx

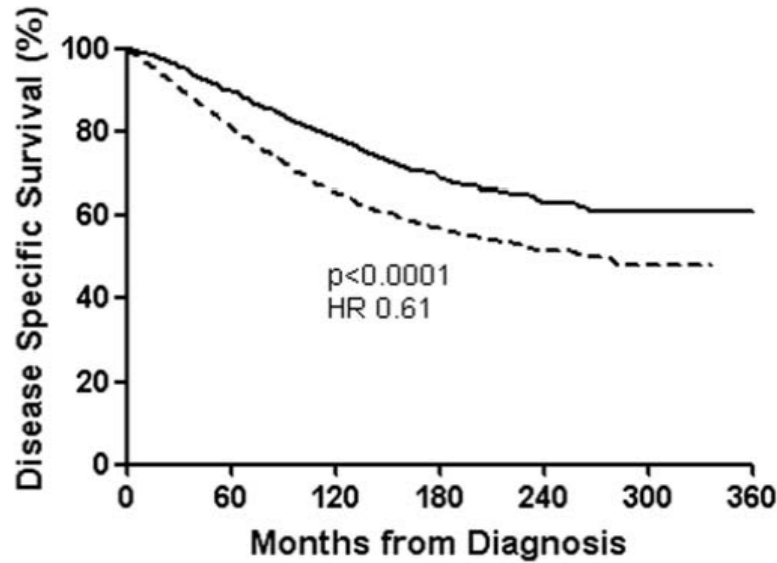
Pugh et al., 2010. *Cancer*.

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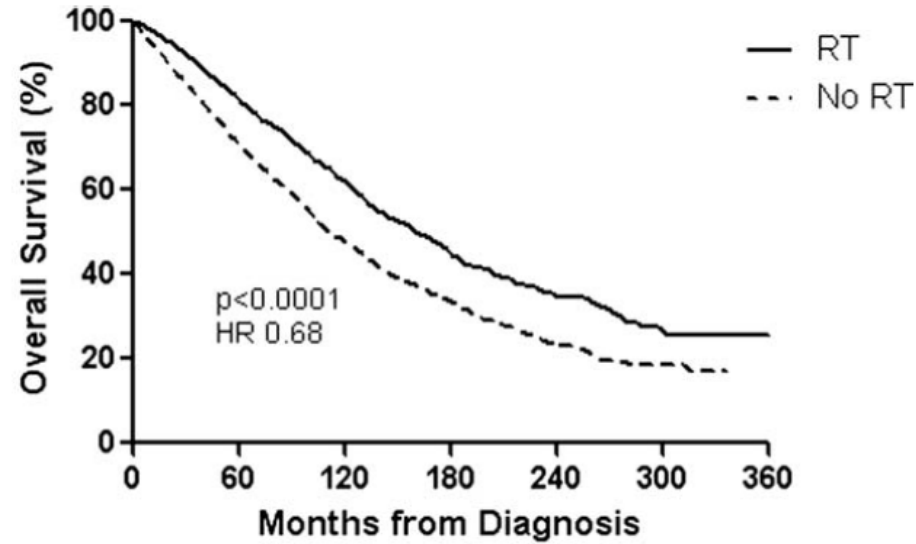
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Improved DSS & OS with early RT



RT	2206	1349	680	282	98	26	1
No RT	4280	2159	947	378	128	29	0



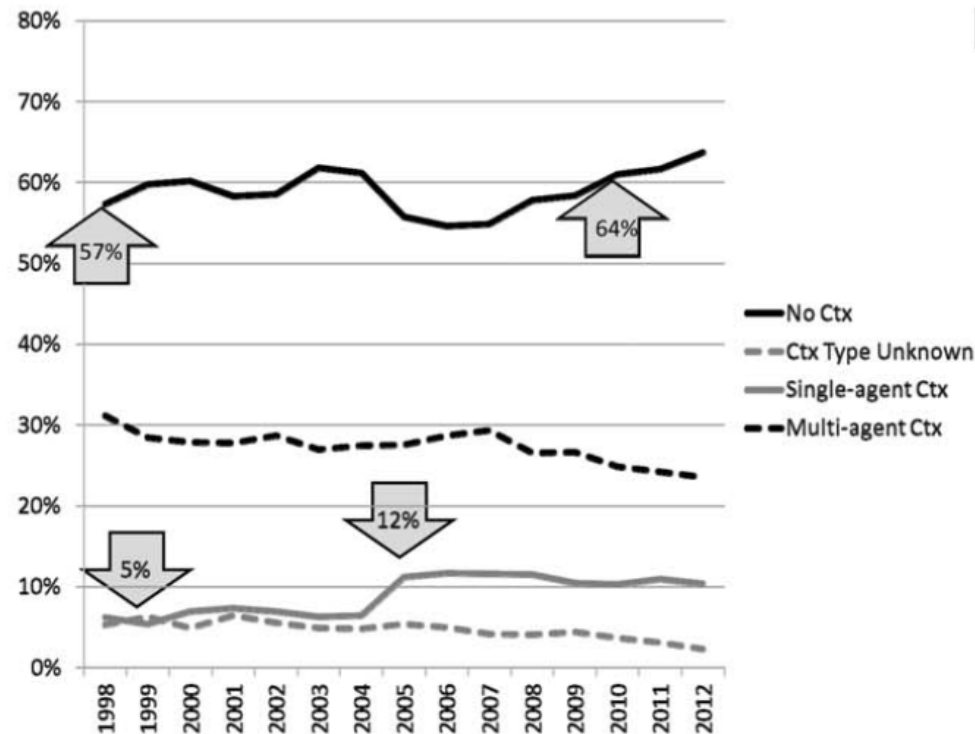
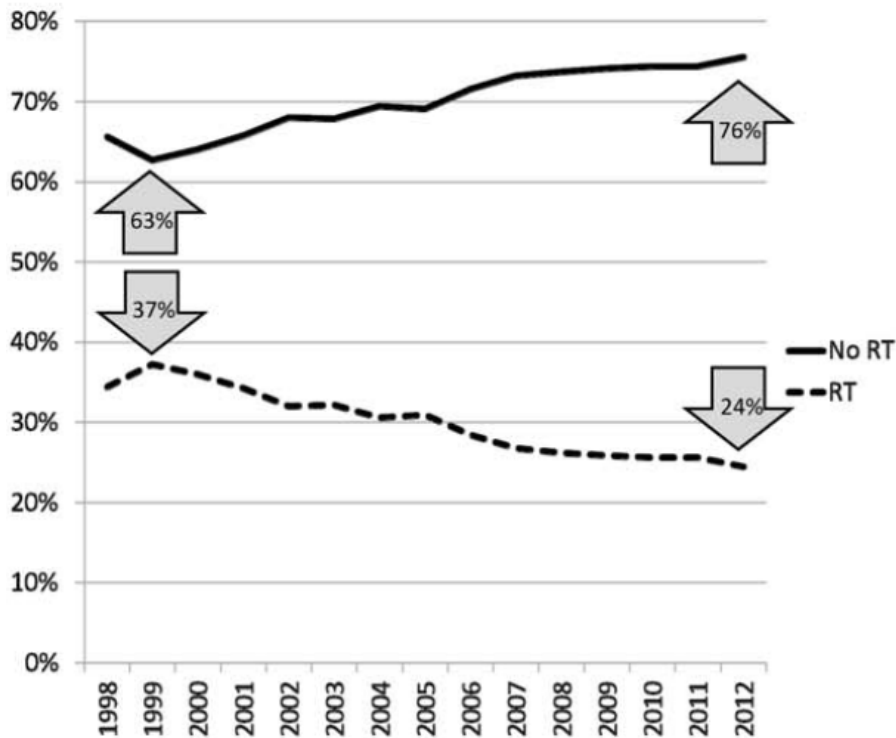
RT	2222	1358	685	285	99	26	1
No RT	4346	2207	968	387	129	29	0

Pugh et al., 2010. *Cancer*.

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What are the trends in treatment of early-stage FL?

- Analysis of NCBD data
- Population of patients with stage I – II, grade 1 – 2 FL



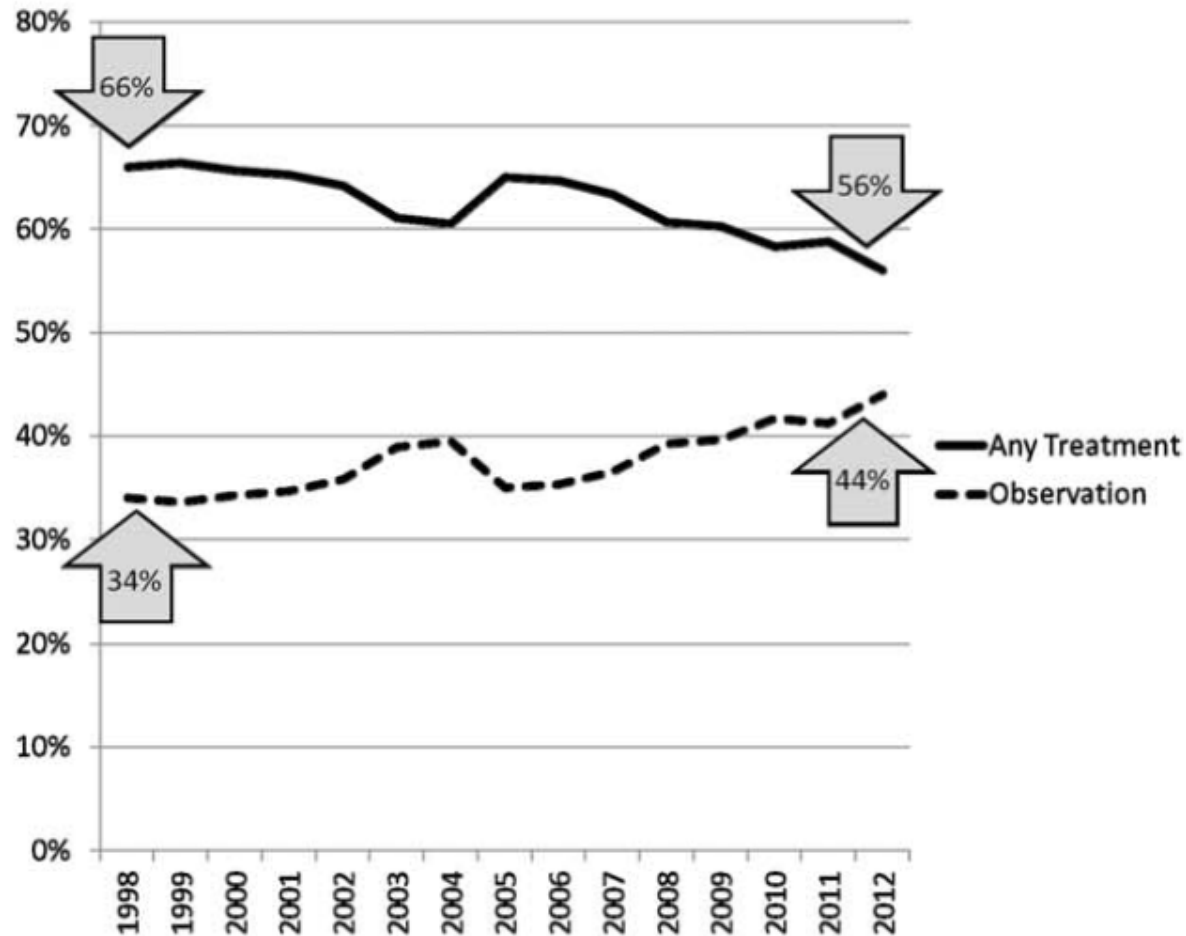
Vargo et al., 2015. *Cancer*.

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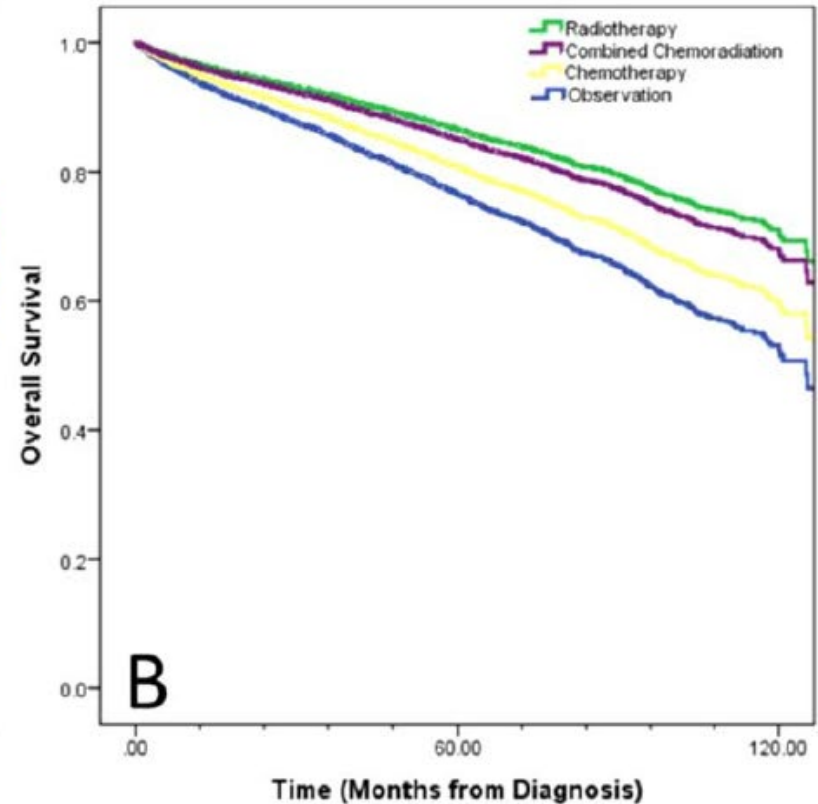
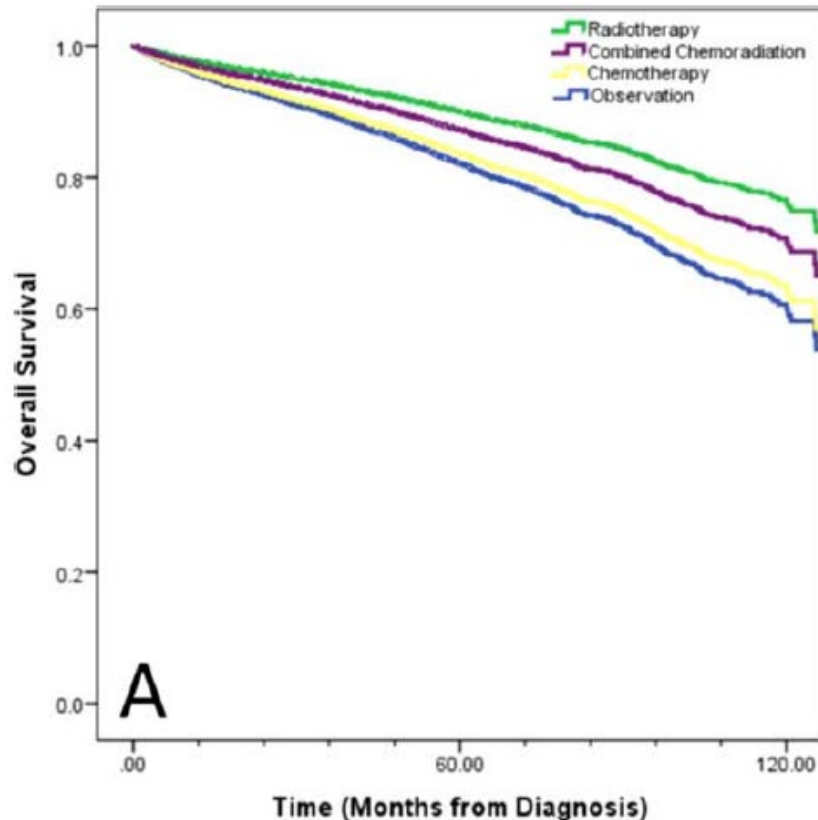
Increased rates of observation as an initial strategy



Vargo et al., 2015. *Cancer*.

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Yet, radiotherapy is associated with improved OS



Vargo et al., 2015. *Cancer*.

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So the data support early RT for early-stage FL, but *what* exactly should we treat?

For indolent NHL like FL, guidelines (NCCN & ILROG) recommend:

- Consider volumes that treat potential microscopic disease in adjacent nodes or the immediate vicinity
- For extra-nodal FL, treat the entire affected organ

Remember, these patients are likely not receiving systemic therapy (in contrast to DLBCL), and our goal is to cure them with RT!

What will be the prescription dose?

- RCT including patients with any stage and any NHL sub-type
- Stratified by histological grade
 - Indolent (primarily FL (64%), marginal zone)
 - Aggressive (primarily DLBCL)
- Randomized to high dose vs low dose tx
- Primary outcome: overall response rate (ORR) within the RT field at 1 month post-tx
 - ORR included complete responses + partial responses

Randomization for indolent lymphomas

24 Gy / 12 fx	40 – 45 Gy / 20 – 23 fx
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	Indolent	
	24 Gy N = 180	40–45 Gy N = 181
Age median (range)	62 (29–85)	64 (30–89)
Male gender N (%)	84 (47)	97 (54)
First-line treatment: stage N (%)		
I	69 (40)	72 (41)
IE	38 (22)	47 (27)
II/III	11 (6)	13 (7)
III/IV	6 (3)	12 (7)
Relapsed/refractory; any stage N (%)	50 (29)	30 (17)
Not known N	6	7
B symptoms N (%)	13 (8)	4 (2)
Time from diagnosis to randomisation; median months (range)	3.1 (0.2–220)	2.8 (0–179)
Indication for RT radical	119 (66)	130 (72)
Palliation	56 (31)	46 (25)
Consolidation	5 (3)	5 (3)
Previous/contemporaneous chemotherapy N (%)	46 (26)	36 (20)
Previous radiotherapy N (%)	15 (8)	24 (13)
Previous rituximab exposure N (%)	2 (1)	2 (1)
Karnofsky scale N (%)		
60–80	16 (12)	16 (11)
90	44 (34)	34 (24)
100	70 (53)	90 (64)
Not known	50	41

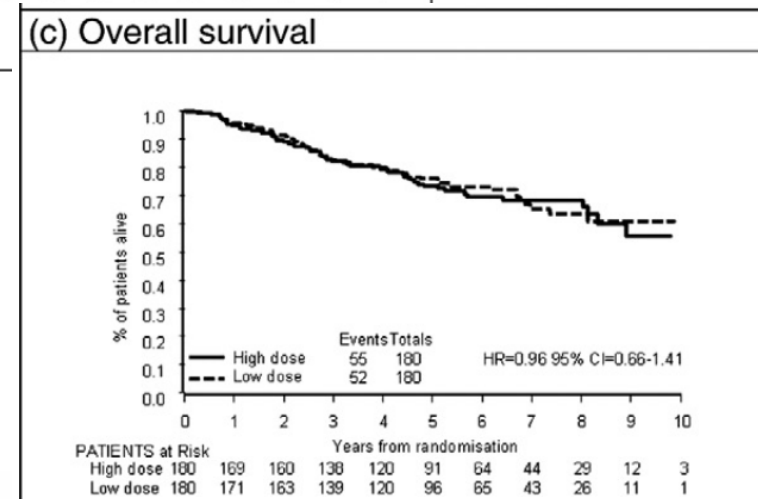
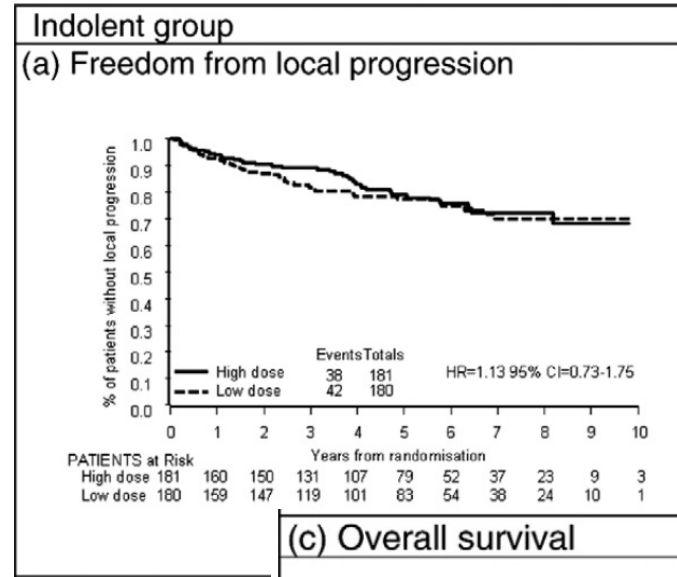
Note: Aggressive group randomized to high dose (same high dose as indolent group) vs low dose (30 Gy / 15 fx)

Lowry et al., *Radiotherapy & Oncol.* 2011.

No difference in ORR, FFLP, or OS for low and high dose groups

Response	Indolent	
	24 Gy	40–45 Gy
CR	145 (82%)	138 (79%)
PR	18 (10%)	24 (14%)
SD/ progression	14 (8%)	12 (7%)
Death	0 (0%)	0 (0%)
Not assessable	2	2
No RT received	1	1
Missing	0	4
Total	180	181

ORR 93% (high dose) vs 92% (low dose)

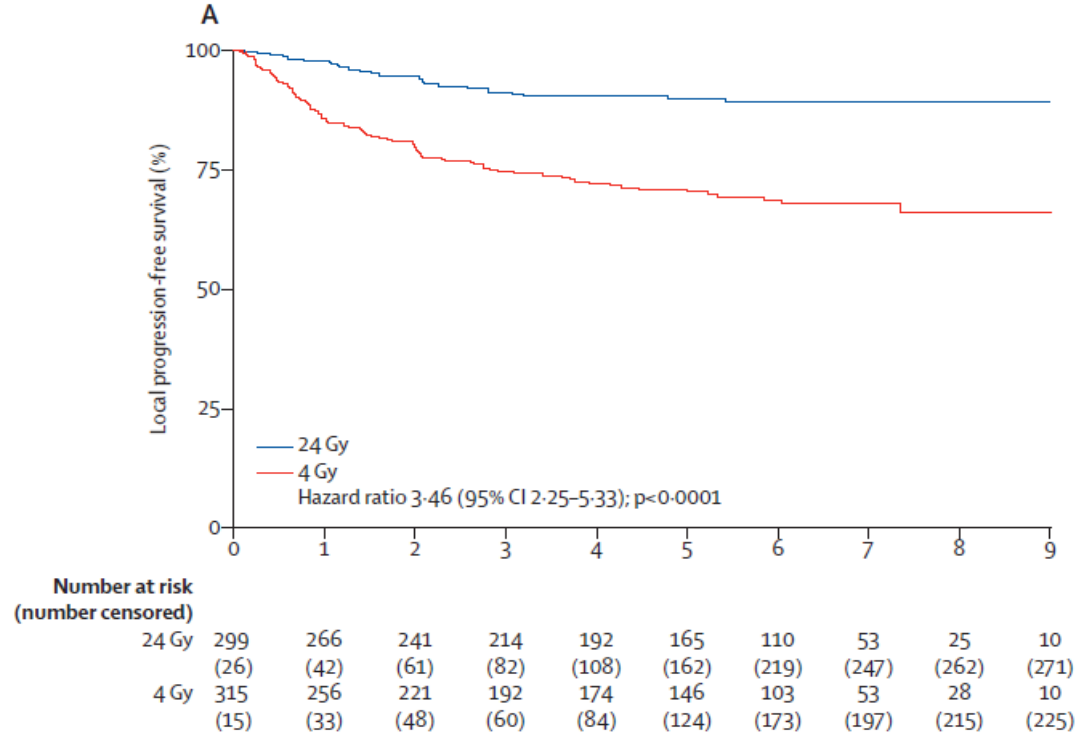


Lowry et al., *Radiotherapy & Oncol.* 2011.

More on dose: Lessons from FoRT

Patients with FL and marginal zone lymphomas randomized to 24 Gy / 12 fx vs 4 Gy / 2 fx

Results: 24 Gy resulted in a progress-free survival benefit, though there was no difference in OS



Hoskin et al., 2021. *Lancet Onc.*

Case 1: 61 M with lump in right cheek

Treatment recommendations & planning considerations:

- Target volumes: right parotid, including the mass
- Rx: 24 Gy / 12 fx
- Simulation: head first, supine with a mask for immobilization
- Technique: VMAT
- Special considerations: aim to spare contralateral parotid by keeping mean dose ALARA (see slides on dose constraints later in this slide deck)

Case 2: 74 F with sore throat and weight loss

- History of stage IV FL diagnosed 14 years ago
- Complete response to systemic therapy and was without evidence of disease while off therapy for 14 years
- Physical exam revealed an enlarged left tonsil

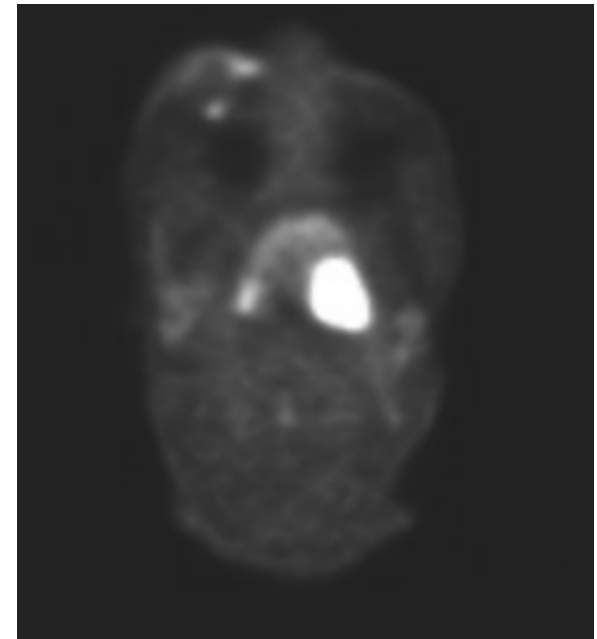


Case 2: 74 F with sore throat and weight loss

- CT head / neck showed enlarged bilateral tonsils and base of tongue lymphoid tissue, and an enlarged left level IIb node
- CT chest / abdomen / pelvis was without evidence of distant disease
- Biopsies of bilateral tonsils and base of tongue were consistent with follicular lymphoma, grade 1-2 and grade 3A (but no evidence of grade 3B disease)

Case 2: 74 F with sore throat and weight loss

- PET / CT revealed bilateral tonsil avidity and avidity of multiple, small, bilateral cervical nodes
- No other sites of pathologic avidity suspicious for lymphoma



What's this patient's stage?

Case 2: 74 F with sore throat and weight loss

Stage IV, recurrent Follicular Lymphoma

What's next?

Case 2: 74 F with sore throat and weight loss

- Started on rituximab by her medical oncologist and referred to radiation oncology
- What's the role of RT in treating recurrent indolent lymphomas?

A phase II study of low-dose RT in recurrent indolent lymphoma

- Patients with symptomatic, recurrent indolent B-cell lymphomas were treated with involved-field RT
 - 90% had FL
 - Most received multiple prior systemic tx regimens
 - Patients received 4 Gy / 2 fx or 4 Gy / 1 fx at the discretion of the treating physician
- End points were time to progression and time to local progression

Haas, et al., 2003. *JCO*.

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92% of patients had a partial or complete response to RT

Table 2. Response Rates Median Time to Progression and Median Time to Local Progression

	No. of Patients (baseline)	%	Duration (months)	Median TP (months)	Median TLP (months)
First low-dose treatment					
All	109	100		14	25
CR	67	61	1-77+	25	42
PR	34	31	1-28+	9	10
Nonresponders	8	8	1-29+	2	2
Retreatment					
All	41	100		14	25
CR	29	71	2-35+	15	25
PR	11	27	2-37+	8	NR (>37)
Nonresponders	1	2	—	—	—

NOTE. NR (> 37) = not reached but exceeds 37 months; however, the numbers are small.

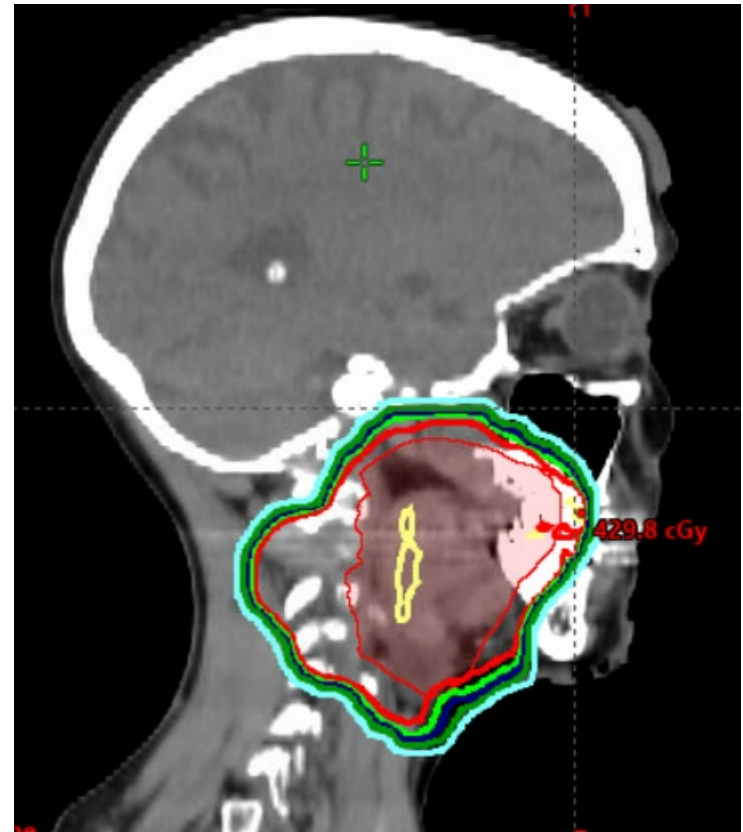
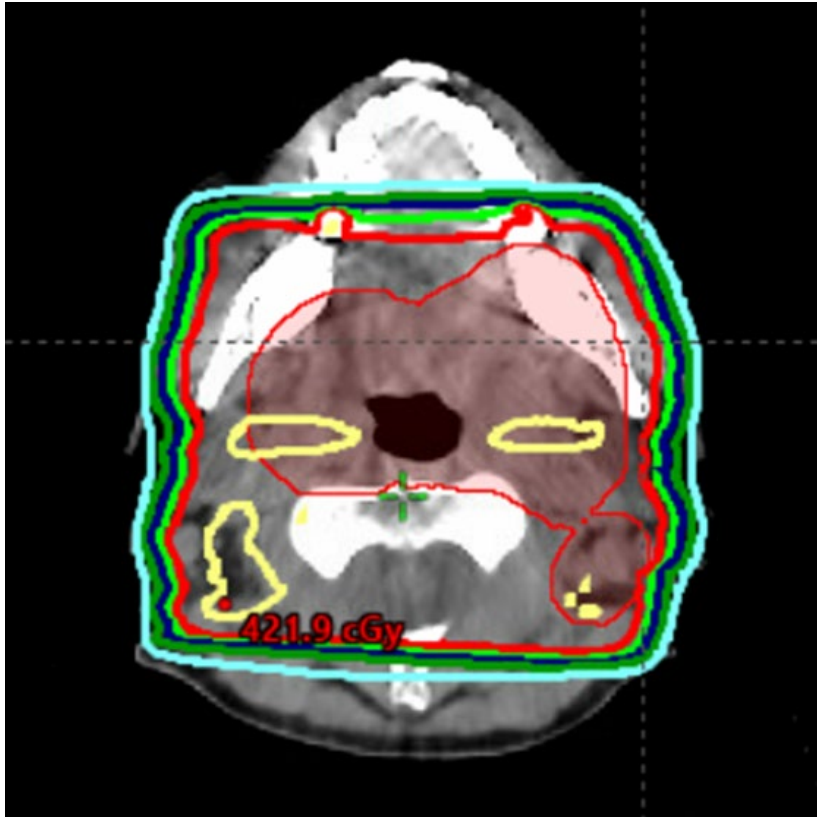
Abbreviations: TP, time to progression; TLP, time to local progression; CR, complete remission; PR, partial remission; NR, not reached.

Case 2: 74 F with sore throat and weight loss

Treatment recommendations & planning considerations:

- Target volumes: bilateral tonsil and cervical nodes
- Rx: 4 Gy / 2 fx
- Simulation: head first, supine, with an open face mask for immobilization
- Technique: 3D with opposed laterals

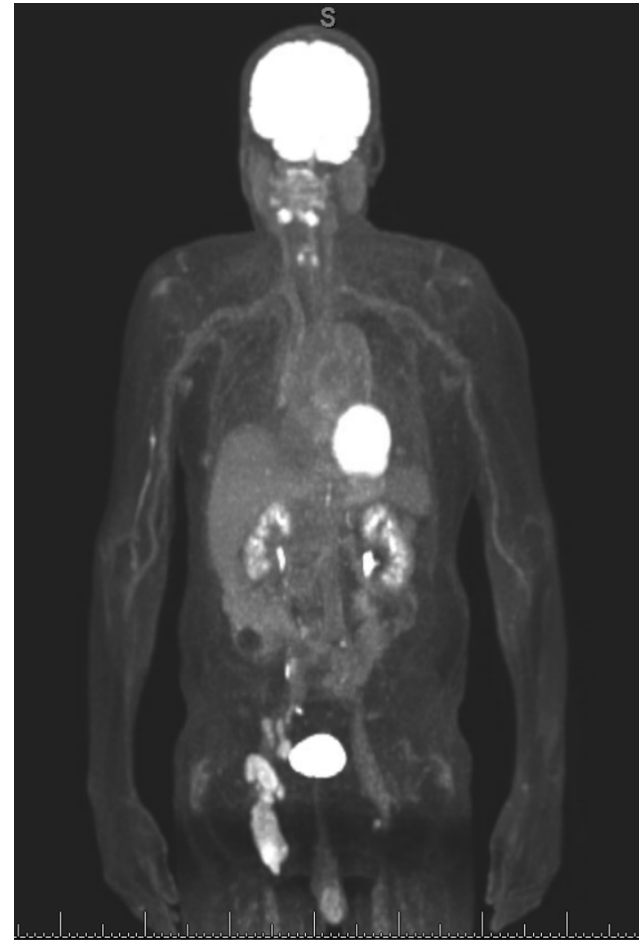
Case 2: 74 F with sore throat and weight loss



Patient evaluated with PET in 3 months after finishing tx and was without evidence of active disease. Additional treatment could be considered in the future, pending her response.

Case 3: 82 M with enlarging groin mass

- Excisional biopsy was consistent with grade 1 follicular lymphoma
- PET / CT revealed extensive right inguinal adenopathy and FDG-avid nodes in right iliac and aortocaval regions
- No evidence of bone marrow involvement



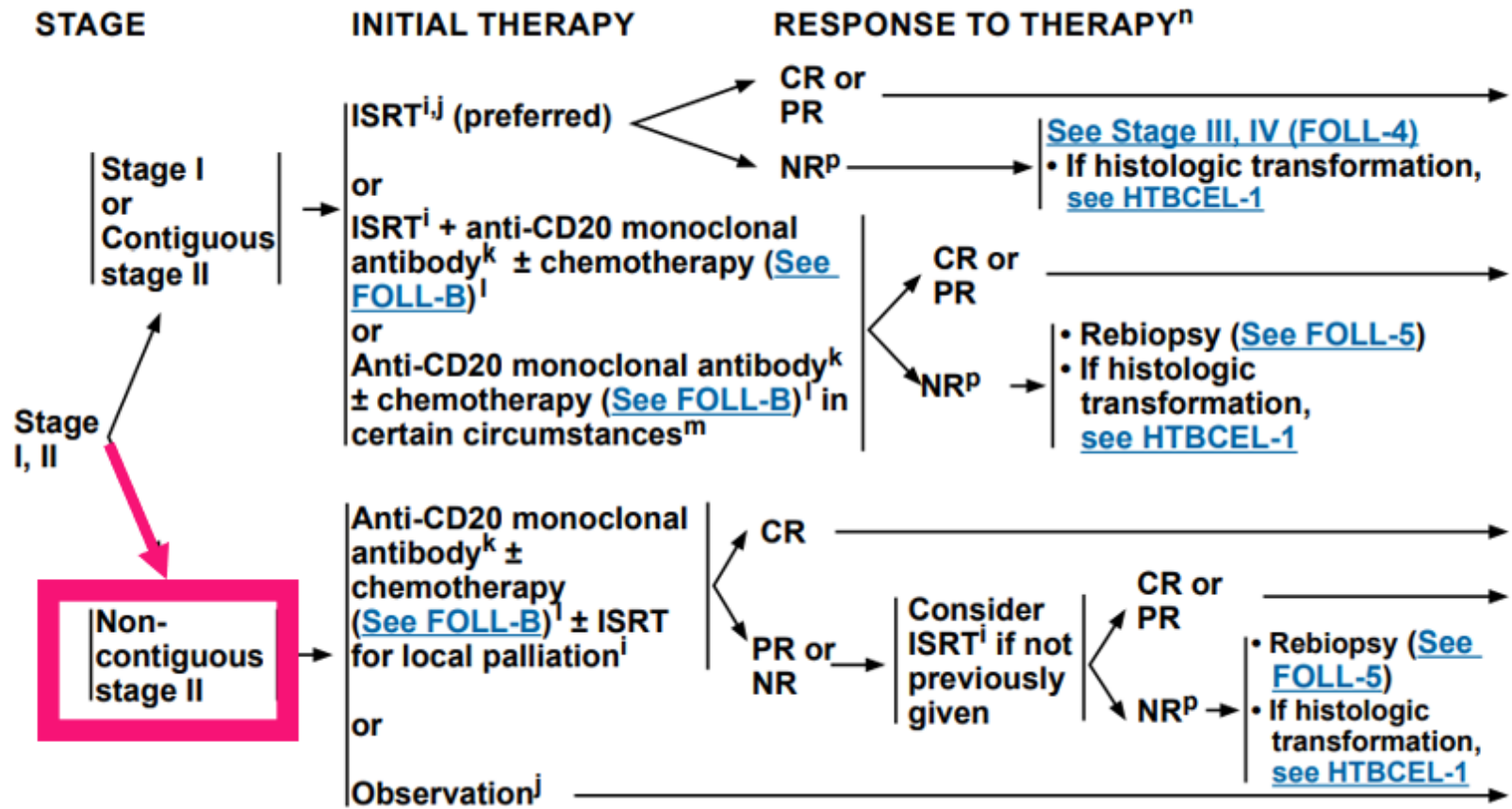
What is his stage?

Case 3: 82 M with enlarging groin mass

Stage II, non-contiguous Follicular Lymphoma

What's next?

Case 3: 82 M with enlarging groin mass

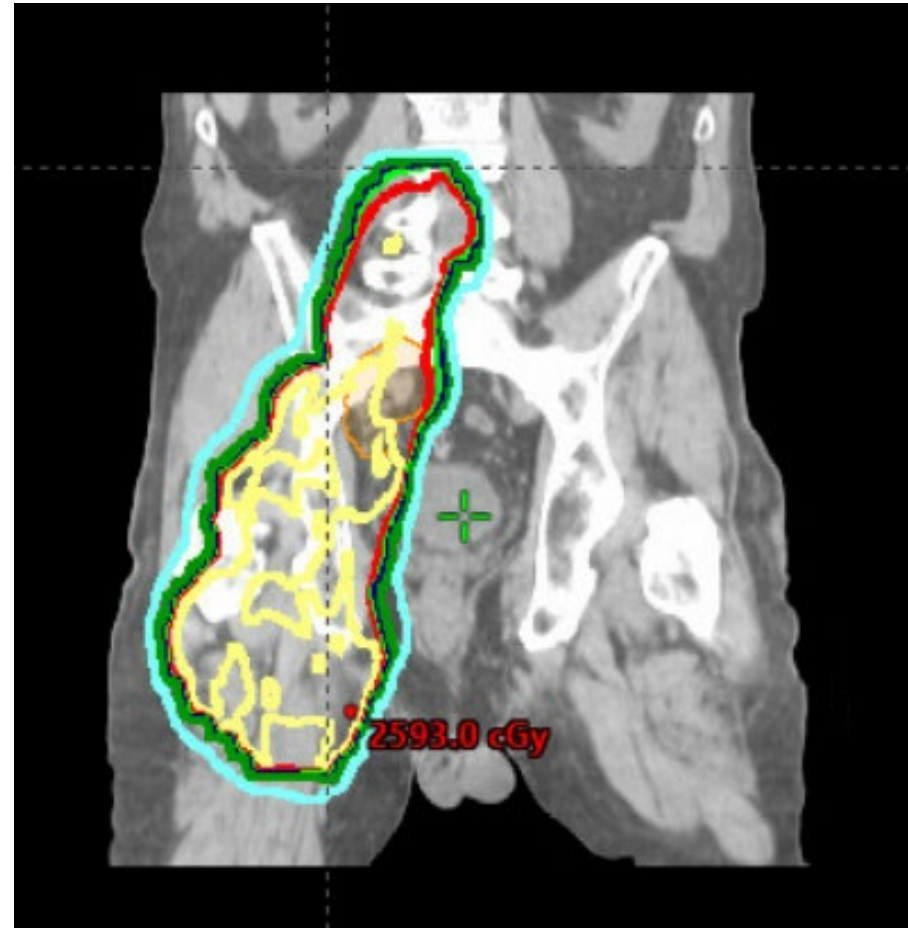


Case 3: 82 M with enlarging groin mass

- Received 4 Gy / 2 fx radiotherapy to groin and had a partial response
- Noted enlargement of the groin mass 6 months later
- PET revealed increased size of the mass
- Biopsy was consistent with grade 2 follicular lymphoma

Case 3: 82 M with enlarging groin mass

- Received additional RT, as disease was fairly localized, in order to delay initiation of systemic therapy
- Received an additional 24 Gy / 12 fx with good and durable response
- Follow-up imaging revealed new avidity in left groin



Case 3: 82 M with enlarging groin mass

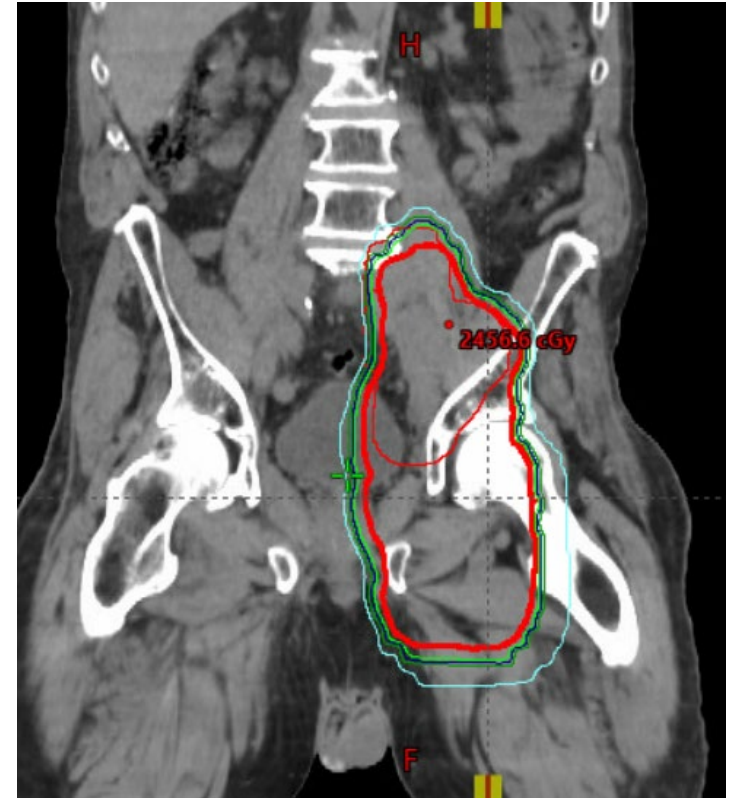
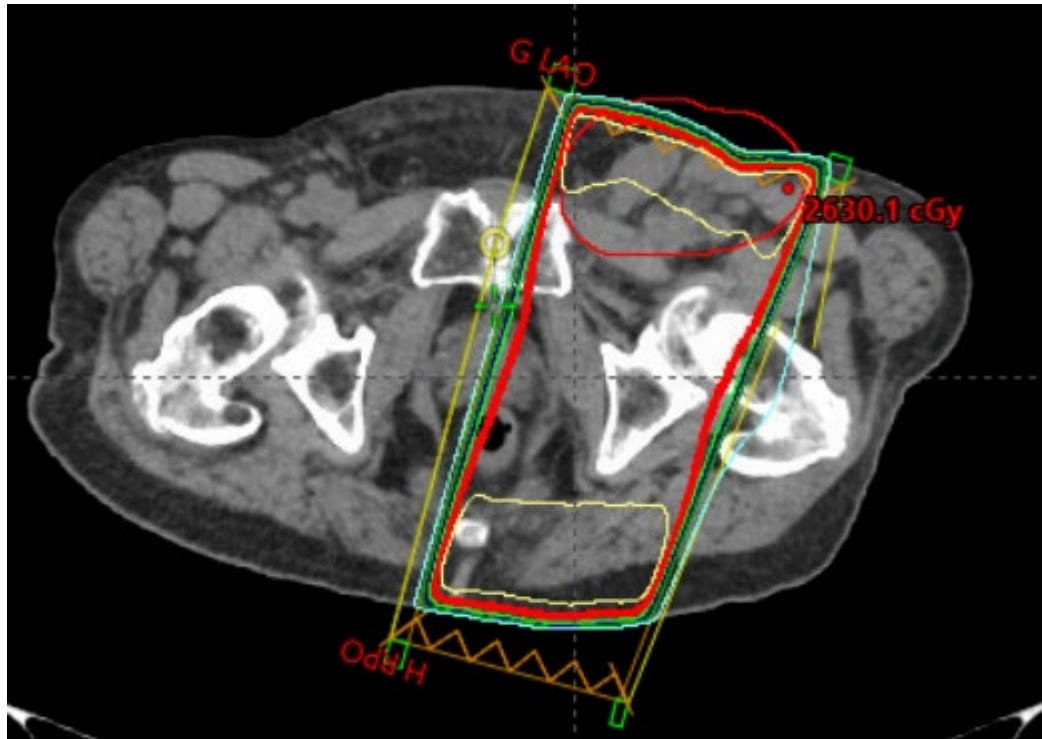
- Began to experience swelling in LLE
- Plan was made to initiate rituximab and administer RT

Case 3: 82 M with enlarging groin mass

Treatment recommendations & planning considerations:

- Target volumes: FDG avid disease in left groin and para-aortic nodes
- Rx: 24 Gy / 12 fx (given prior response to RT)
- Simulation: head first, supine, frog-legged
- Technique: 3D with opposed obliques

Case 3: 82 M with enlarging groin mass



Case 4: 81 M with incidental adenopathy

- CT obtained to evaluate sciatic-like back pain revealed incidental peri-aortic adenopathy suspicious for lymphoma
- Biopsy was consistent with grade 1-2 follicular lymphoma
- PET / CT without distant involvement



- Bone marrow without evidence of involvement

What is the patient's stage?

Case 4: 81 M with incidental adenopathy

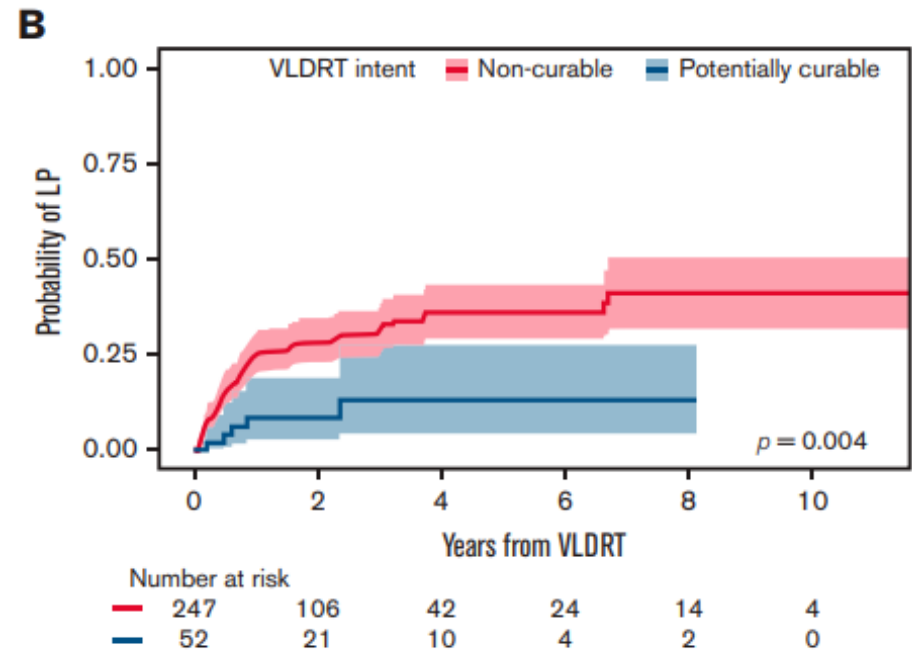
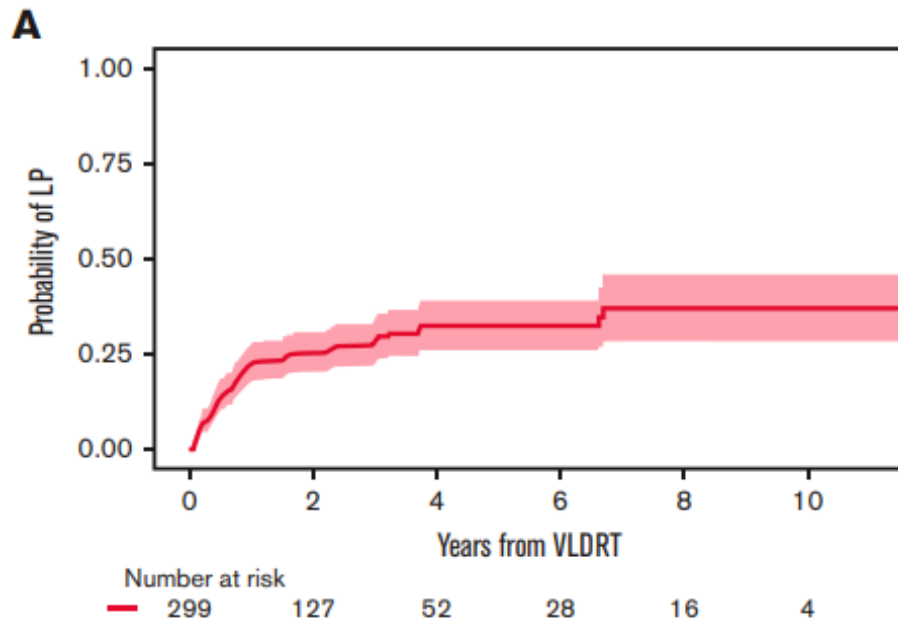
Stage I Follicular Lymphoma

What's next?

Is 4 Gy suitable for curable patients?

- A retrospective review examined the role of very-low dose RT (VLDRT), defined as 4 Gy / 2 fx, in indolent B-cell lymphomas
- Patients received 4 Gy of ISRT (involved-site RT)
- 17% of lesions were potentially-curable (defined as stage I-II disease without prior lymphoma-directed tx)
- Primary outcome was local progression within the treatment field

Incidence of local progression at 2 years was 9% for potentially-curable lesions

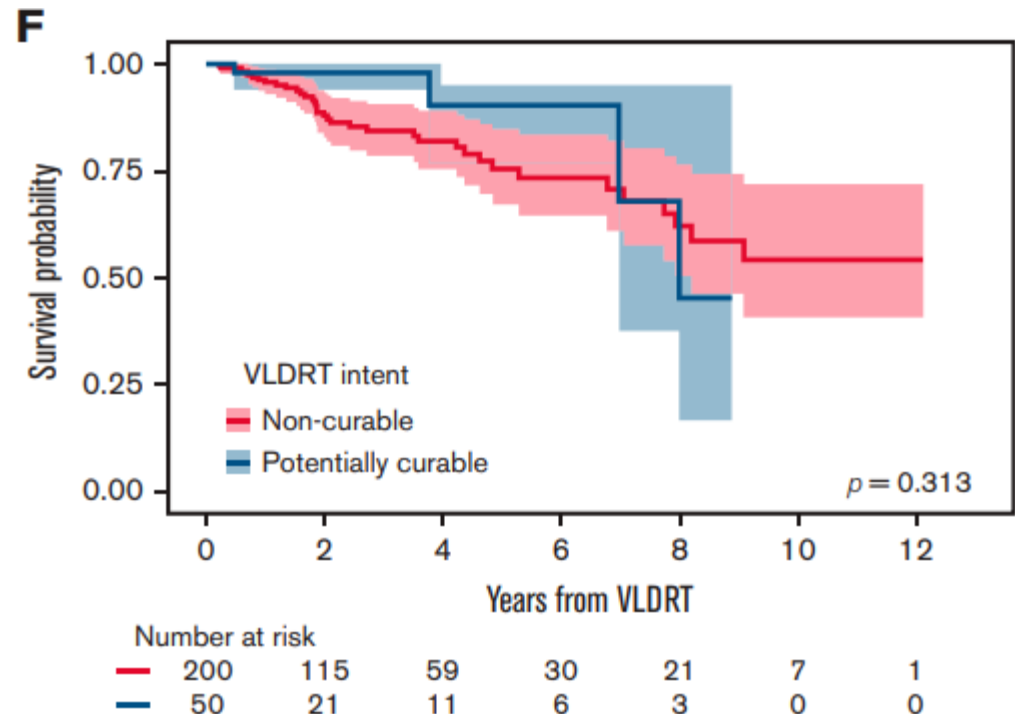


Imber et al., 2021. *Blood*.

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Other important points


- 2 year incidence of distant progression was 46% vs 25% for local progression
- Median time to local progression not reached
- No difference in OS between arms



Case 4: 81 M with incidental adenopathy

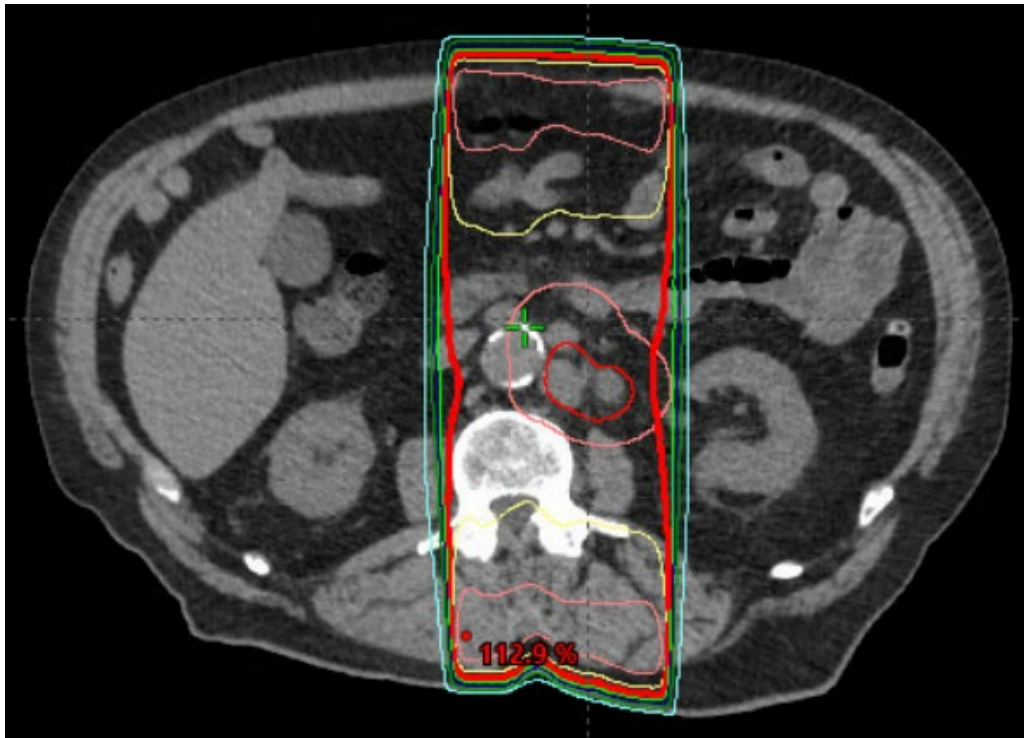
Treatment recommendations & planning considerations:

- Target volumes: involved site radiotherapy (ISRT) to include FDG avid nodes plus margin to include additional para-aortic fossa
- Rx: 4 Gy / 2 fx
- Simulation: head first, supine
- Technique: 3D AP / PA



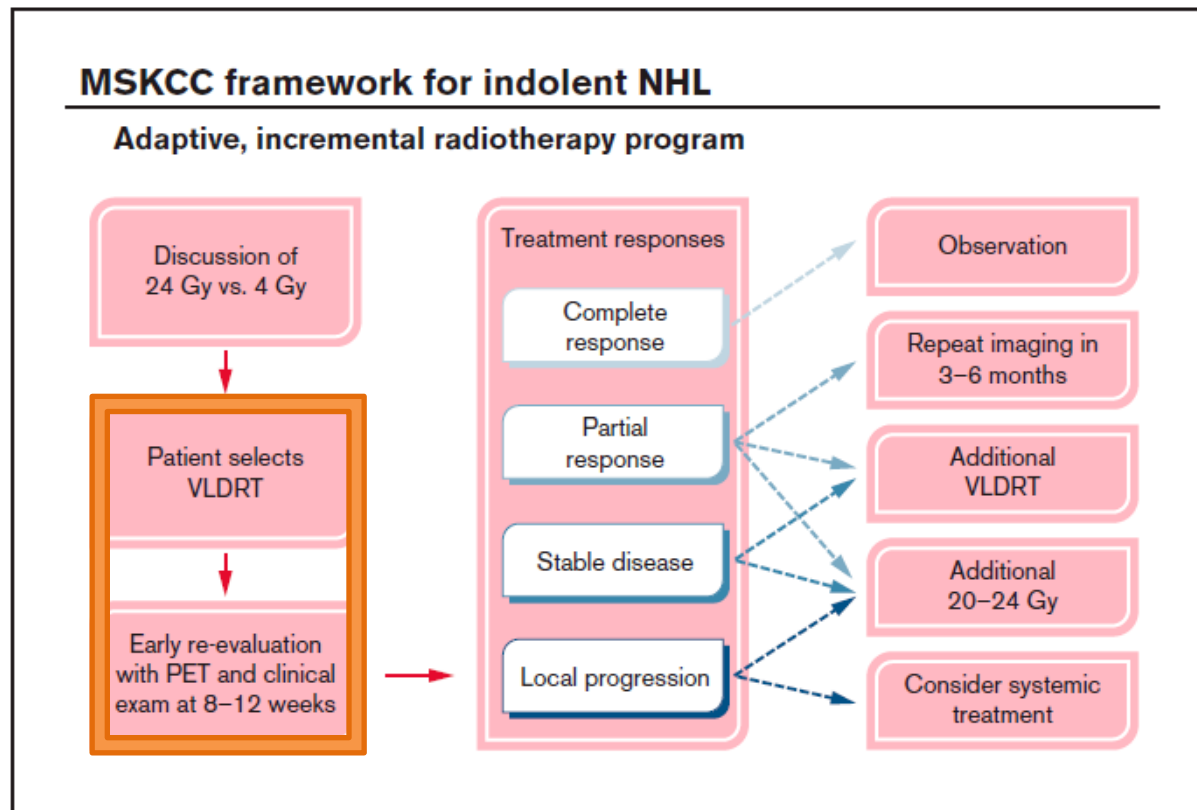
Remember, this is stage I disease, so err on the side of larger volumes (involved site), rather than involved node

Case 4: 81 M with incidental adenopathy



Case 4: 81 M with incidental adenopathy

Close follow-up is important. A proposed schedule includes:



Imber et al., 2021. *Blood*.

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These 4 cases illustrate some guiding principles regarding management of FL:

- Stage I / II FL: localized disease is curable with RT alone
 - Keep this in mind when drawing volumes. Be more generous than in DLBCL cases, where patients are also receiving systemic tx.
 - 24 Gy / 12 fx is the standard of care
 - There is emerging evidence for 4 Gy / 2 fx even in the curative setting, but chose patients carefully (and go with 24 Gy on the oral boards, for now)

Reference cases 1 & 4 for details

These 4 cases illustrate some guiding principles regarding management of FL:

- Stage III / IV: watchful waiting may be the best initial strategy, with intervention – RT and / or systemic therapy - reserved until patients become symptomatic. Indications for RT include pain, threatened end-organ function, or otherwise symptomatic disease.
 - If offering RT, consider 4 Gy / 2 fx, with the option to increase dose pending clinical response

Reference cases 2 & 3 for details

A word on follow-up

- For definitive treatments using standard dose (24 Gy), NCCN recommends a comprehensive H&P every 3 – 6 months for the first 5 years and annually or as clinically indicated thereafter. Imaging with CT can be considered as a frequency of no more than every 6 months for the first 2 years.
 - However, there is institutional variation, and some centers may image with PET every 3 months for the first few years.
- For palliative cases, patients are often seeing medical oncology regularly, so follow-up should be tailored as appropriate.

A word on Dose Constraints

- In general, doses used to treat FL are low and often below what we think of as typical dose constraints for many OARs
- However, the NCCN does recommend lymphoma-specific dose constraints, which can be found on the following slides
- ALARA is best, which is obviously true no matter the disease site, but because many FL patients present with curable disease and may be quite young, every effort is made to keep toxicities as low as possible

Head & Neck

OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Head and Neck	Parotid glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: as low as reasonably achievable (ALARA)	Xerostomia ^{15,16}
	Submandibular glands	Ipsilateral: Mean <11 Gy (recommended); <24 Gy (acceptable) Contralateral: ALARA	Xerostomia ¹⁷
	Oral cavity (surrogate for minor salivary glands)	Mean <11 Gy	Xerostomia, dysgeusia, oral mucositis ¹⁷
	Thyroid	V25 Gy <63.5% Minimize V30 Gy	Hypothyroidism ¹⁸
	Lacrimal glands	V20 Gy <80%	Dry eye syndrome ¹⁹
	Larynx/Pharyngeal constrictors	Mean <25 Gy	Laryngeal edema, dysphagia ²⁰
	Carotids	Ipsilateral: Avoid hotspots Contralateral: ALARA	Carotid artery atherosclerosis

Thorax

OAR		Dose Recommendation (1.5–2 Gy/fraction)	Toxicity
Thorax	Heart ^c	Mean <8 Gy (recommended) Mean <15 Gy (acceptable); ALARA given increased risk with even lower doses	Major adverse cardiac events ²¹⁻²⁴
	Aortic and mitral valves	Dmax <25 Gy	Valvular heart disease ^{22,25,26}
	Tricuspid and pulmonic valves	Dmax <30 Gy	
	Left ventricle	Mean <8 Gy (recommended) Mean <15 Gy (acceptable)	Heart failure ^{22,27}
	Coronary vessels including the left main, left anterior descending (LAD), left circumflex (LCx), and right coronary artery (RCA) ^c	LAD V15 Gy <10% ^c LCx V15 Gy <14% Coronary vessels (total)- Mean <7 Gy Minimize the maximum dose to individual coronary arteries	Major adverse cardiac events ²⁸
	Lungs	Mean dose <13.5 Gy V20 <20% (recommended); <30 Gy (acceptable) V5 <55%	Pneumonitis ²⁹⁻³¹

Breast	Minimize volume >4 Gy (ideally <10%)	Breast cancer (adenocarcinoma) ⁵¹
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Abdomen & Bone

OAR		Dose Recommendation (1.5–2 Gy/fraction)		Toxicity
Abdomen	Liver	Mean <15 Gy V20 <30% V30 <20%		Hepatic toxicity ^{35,36}
	Stomach	Dmax <45 Gy		Ulceration ³⁷
	Spleen	Mean <10 Gy V5 ≤30% V15 ≤20%		Late infections ³⁸ Lymphopenia ³⁹
	Pancreas	Minimize volume >36 Gy (especially to pancreatic tail)		Diabetes ⁴⁰
	Small bowel	V15 <120 cc Dmax <45 Gy		Diarrhea ³⁷ Obstruction, ulceration, fistula ³⁷
	Kidney	Single organ Mean <8 Gy V10 <30% V20 <15% (recommended); <25% (acceptable)	Bilateral V5 <58%	Renal insufficiency ⁴¹⁻⁴³
Other	Bone marrow ^d	V5: ALARA V10 <50% V25 <25%		Acute cytopenias ^{44,45} Chronic cytopenias ⁴⁶
	Long bone	V40 <64%		Fracture ⁴⁷

Other tidbits to about follicular lymphoma

FLIPI: Follicular Lymphoma International Prognostic Index

FLIPI

1 point for each:

Hemoglobin < 12

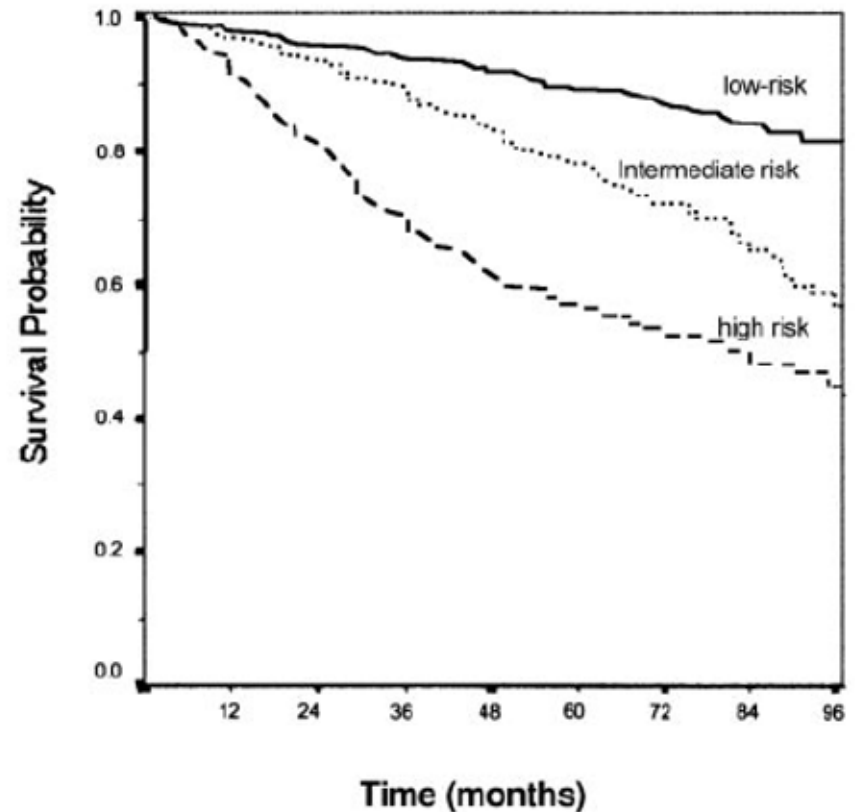
Age 60 or older

Stage III - IV

> 4 nodal sites involved

LDH elevated

	# of positive risk factors
Low	0 - 1
Intermediate	2
High	3 or more



FLIPI - 2

1 point for each:

Elevated beta-microglobulin

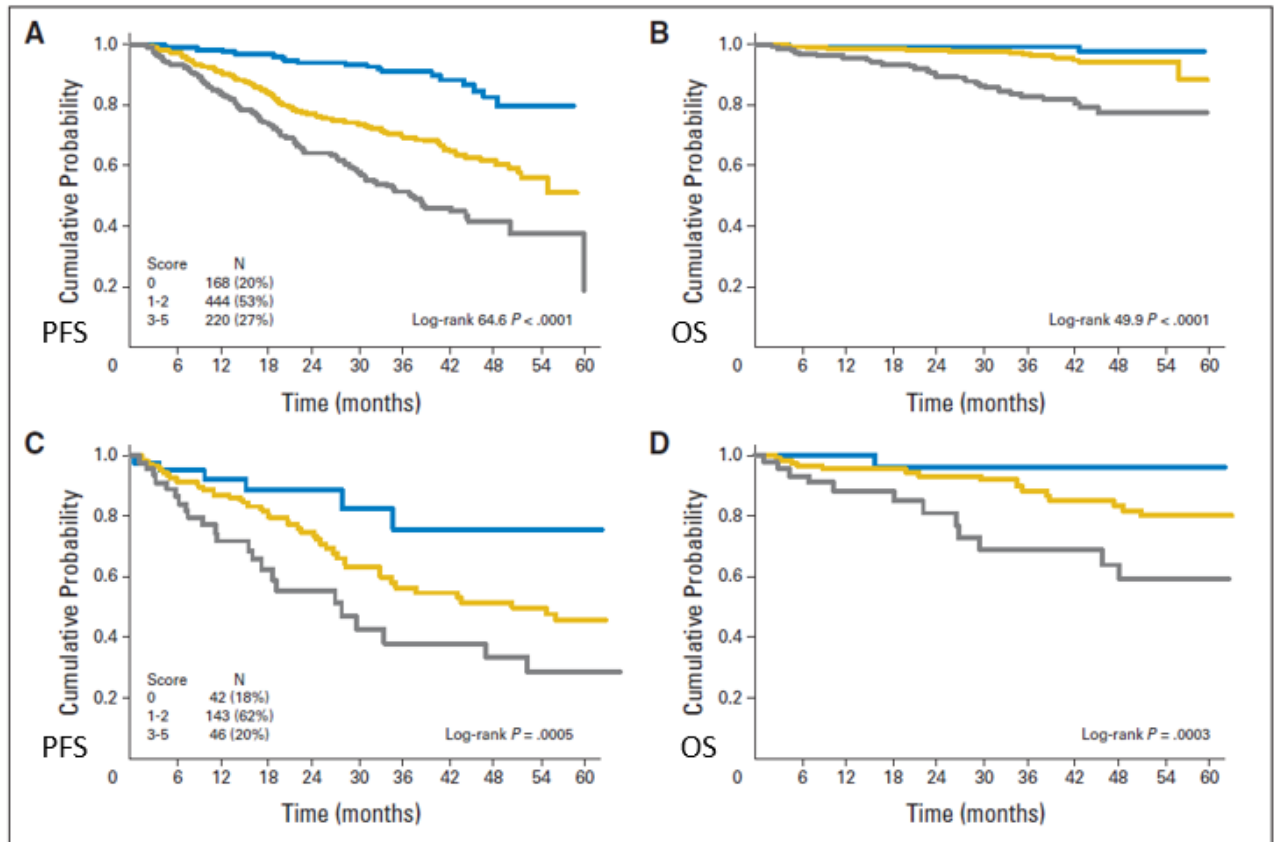
Bone marrow involvement

Age > 60

Lymph node > 6 cm in largest dimension

Hemoglobin < 12

	Risk factors
Low	0
Intermediate	1-2
High	3 or more



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