

سنة ١٤٤٤





Role of radiotherapy in the management of Classic Hodgkin lymphoma: When can it be omitted?



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Definition of HL Risk groups

According to the EORTC/LYSA and the GHSG

*Large mediastinal mass: Mediastinum-to-thorax ratio ≥ 0.35 (EORTC/LYSA); mediastinal mass larger than one-third of the maximum thoracic width (GHSG)

†Elevated ESR: > 50 mm/h without B symptoms; > 30 mm/h with B symptoms (B symptoms: Fever, night sweat, unexplained weight loss $> 10\%$ over 6 months)

‡Nodal areas: Involvement of ≥ 4 out of 5 supradiaphragmatic nodal areas (EORTC/LYSA); involvement of ≥ 3 out of 11 nodal areas on both sides of the diaphragm (GHSG)

	EORTC/LYSA	GHSG
Treatment group		
Limited stages	CS I–II without risk factors (supradiaphragmatic)	CS I–II without risk factors
Intermediate stages	CS I–II with ≥ 1 risk factors (supradiaphragmatic)	CS I, CS IIA with ≥ 1 risk factors CS IIB with risk factors C and/or D, but not A/B
Advanced stages	CS III–IV	CS IIB with risk factors A and/or B CS III/IV
Risk factors		
	A: Large mediastinal mass* B: Age ≥ 50 years C: Elevated ESR† D: ≥ 4 nodal areas‡	A: Large mediastinal mass* B: Extranodal disease C: Elevated ESR† D: ≥ 3 nodal areas‡

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NCCN Guidelines Version 2.2023 Hodgkin Lymphoma (Age ≥18 years)

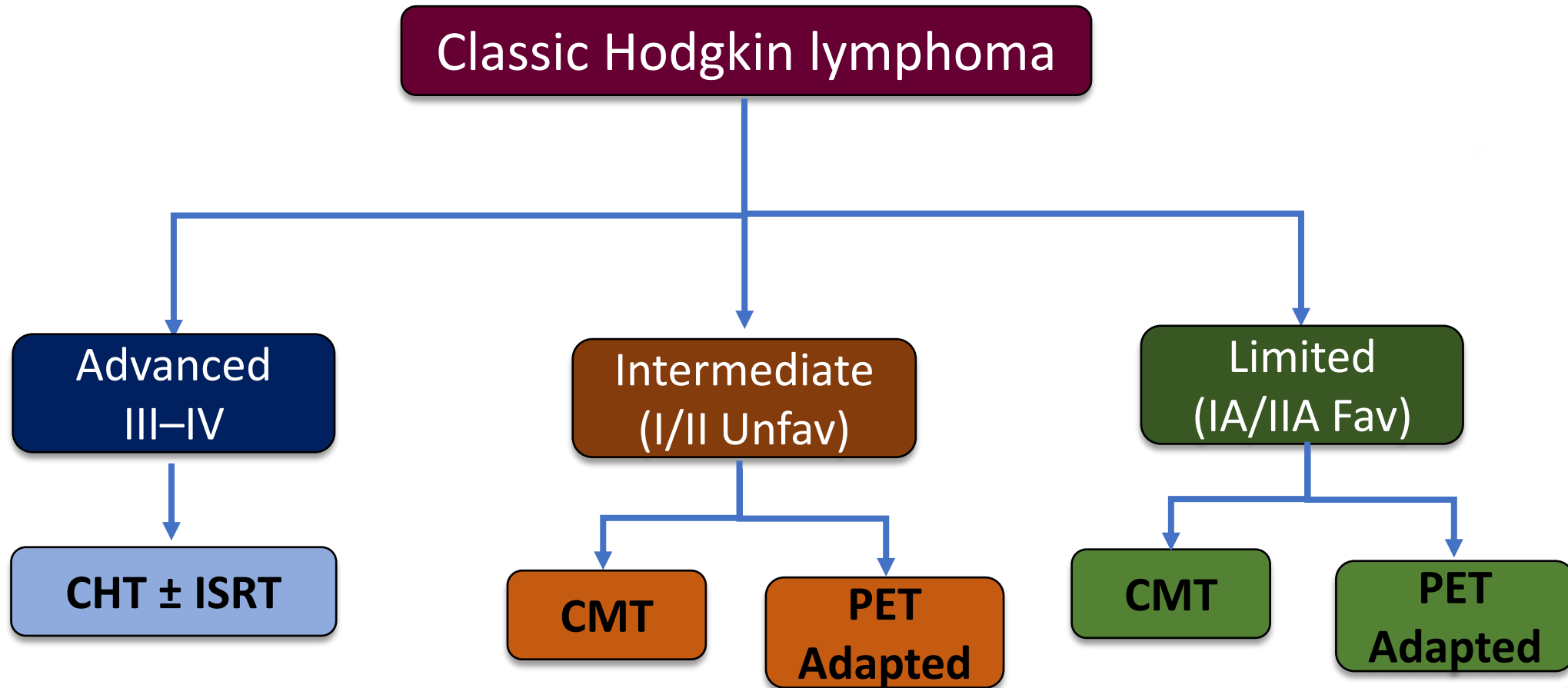


STAGING/RISK CLASSIFICATION OF CHL^j

Stage	Bulky Mediastinal Disease ^j or >10 cm Adenopathy	ESR >50 or # Sites >3	Type	Guidelines Page
IA/IIA	No	No	Favorable Disease	HODG-3
	No	Yes	Favorable/Unfavorable Disease	HODG-3 or HODG-4
	Yes	Yes/No	Unfavorable Disease	HODG-4
IB/IIB	Yes/No	Yes/No	Unfavorable Disease	HODG-4
III–IV	Yes/No	N/A	Advanced Disease	HODG-5

- Selection of treatment (combined modality therapy or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- Most patients will benefit from multidisciplinary input prior to final treatment decisions
- See [HODG-E](#) for the Management of CHL in Adults Age >60 Years

Classic Hodgkin lymphoma treatment





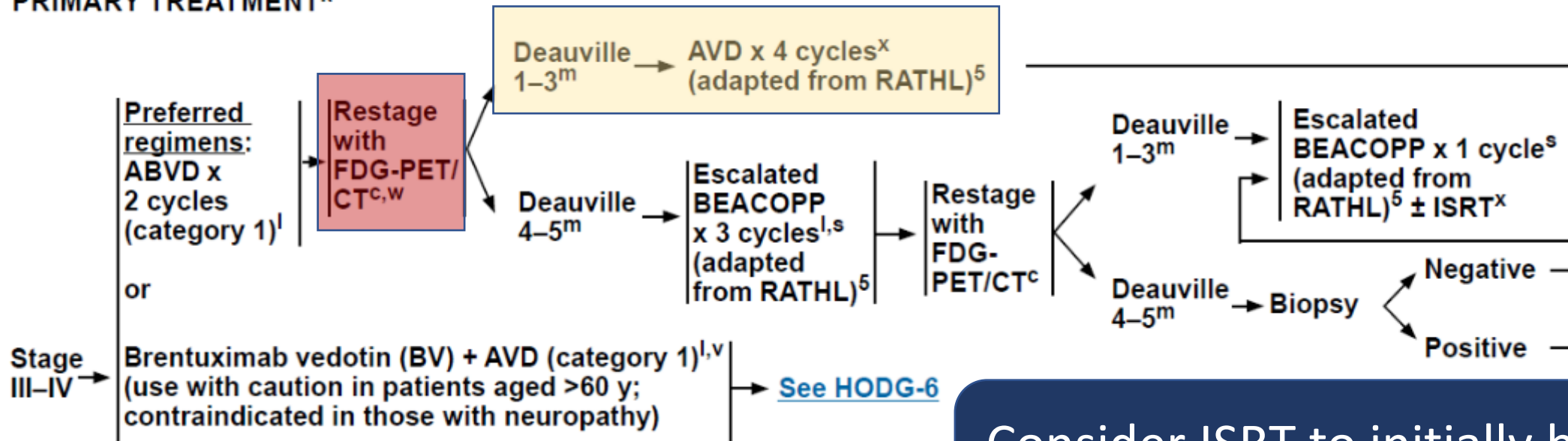
NCCN Guidelines Version 2.2023 Hodgkin Lymphoma (Age ≥18 years)

Advanced
III–IV



CLINICAL PRESENTATION:
Stage III–IV CHL^k

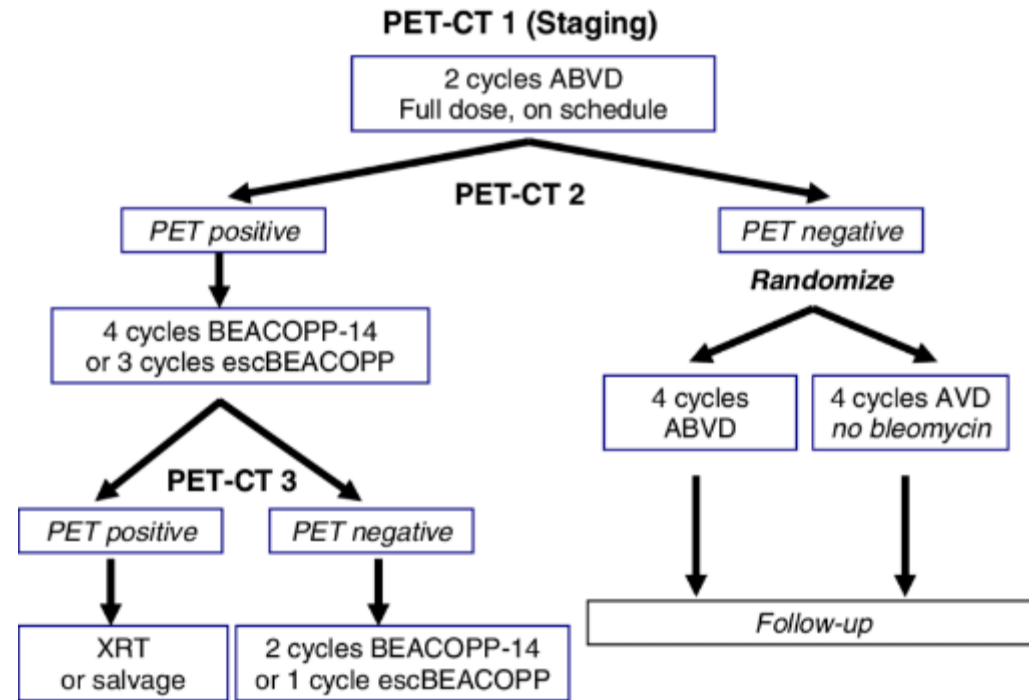
PRIMARY TREATMENT^k



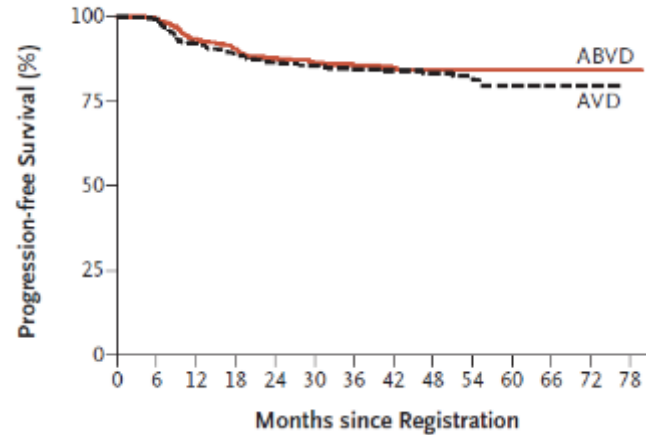
Consider ISRT to initially bulky or FDG-PET–positive sites



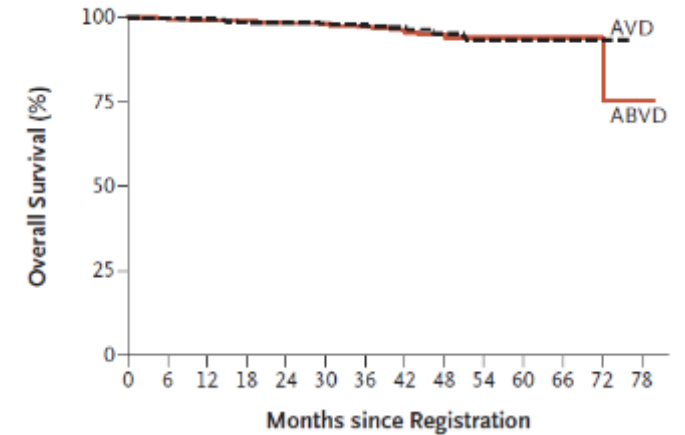
Adapted Treatment Guided by Interim PET-CT Scan in Advanced Hodgkin's Lymphoma



Progression-free Survival among Patients with Negative PET Findings



Overall Survival among Patients with Negative PET Findings



Patients with Negative PET Findings

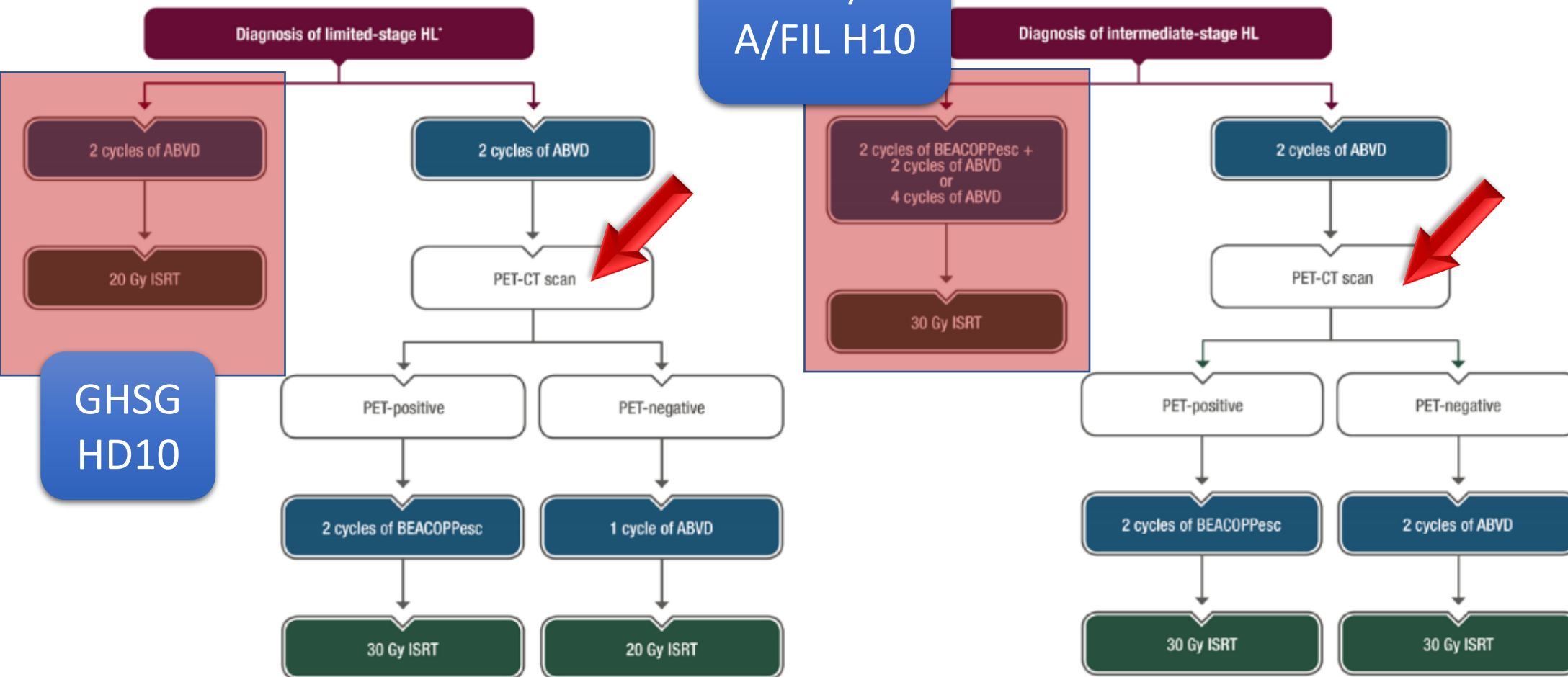
41.6% had stage II disease



Early stage Hodgkin lymphoma



EORTC/LYS A/FIL H10



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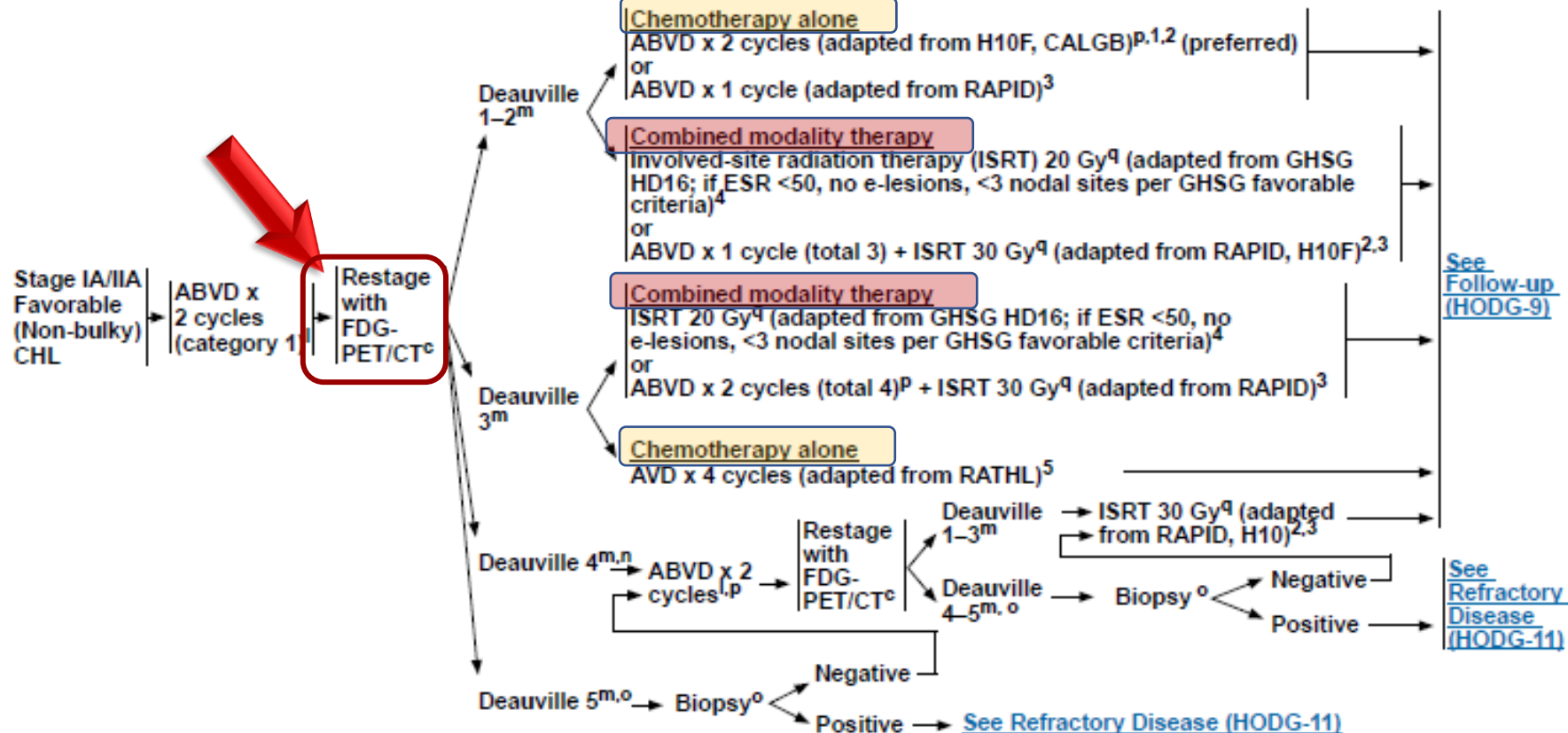
CLINICAL PRESENTATION:
Stage IA/IIA Favorable (Non-Bulky)
CHL^k

Important Considerations:

- Selection of treatment (combined modality therapy or chemotherapy alone) should be based on patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement (especially within mediastinum or axilla).
- In general, treatment with combined modality therapy provides for a better progression free survival (PFS)/freedom from progression (FFP), but no difference in overall survival.
- Most patients will benefit from multidisciplinary team input prior to final treatment decisions.

PRIMARY TREATMENT

ADDITIONAL THERAPY



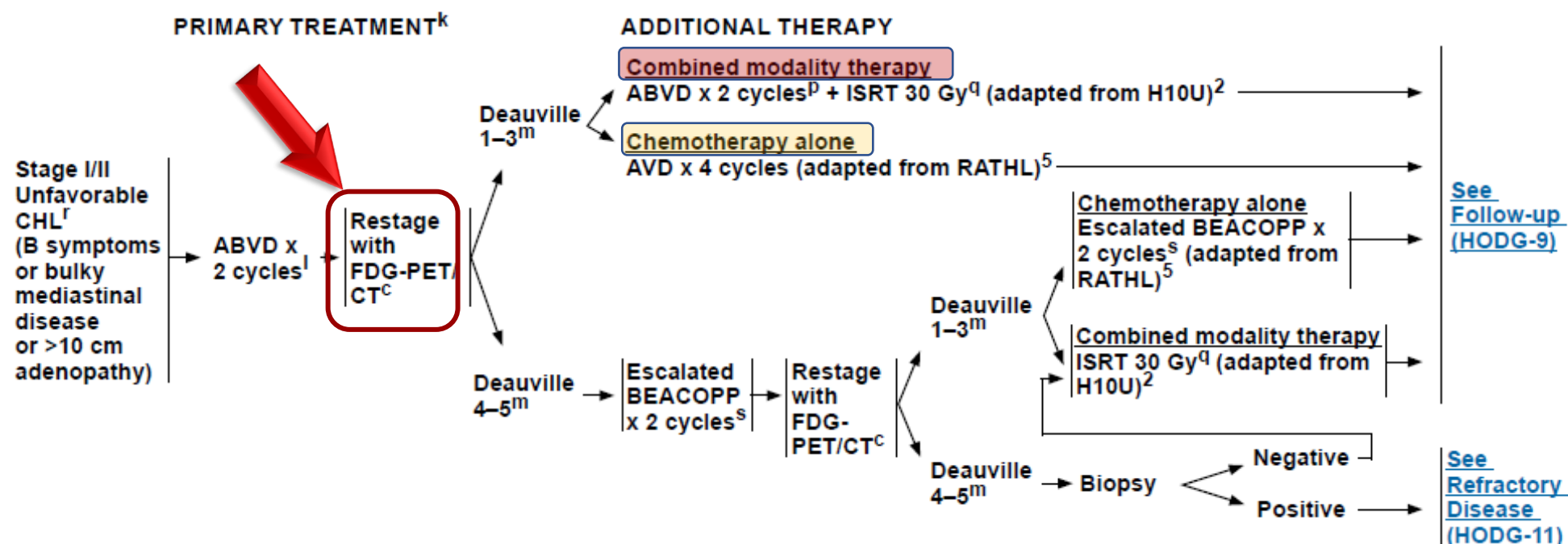
NCCN Guidelines Version 2.2023 Hodgkin Lymphoma (Age ≥18 years)



CLINICAL PRESENTATION:
Stage I/II Unfavorable
CHL^k
(B symptoms or bulky mediastinal
disease or >10 cm adenopathy)

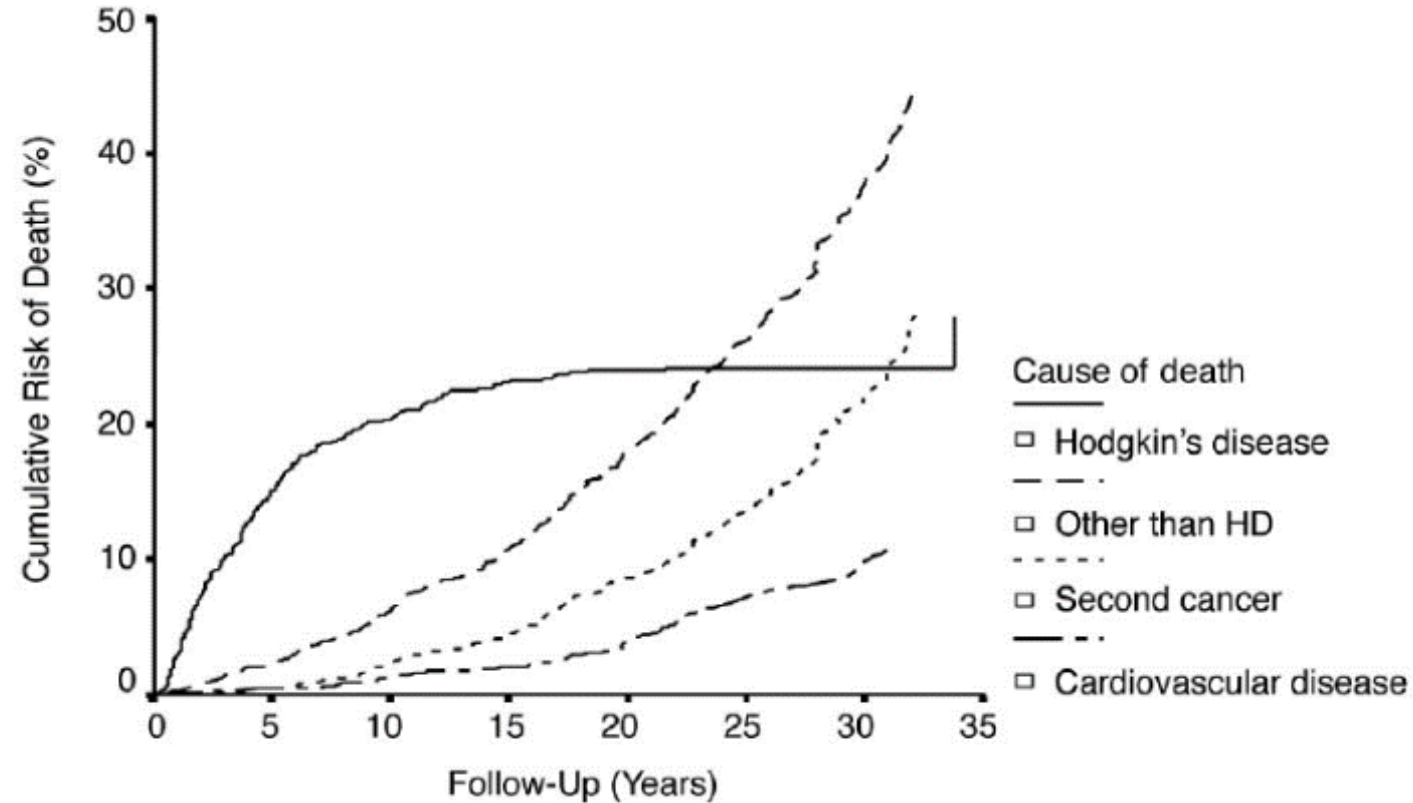
Important Considerations:

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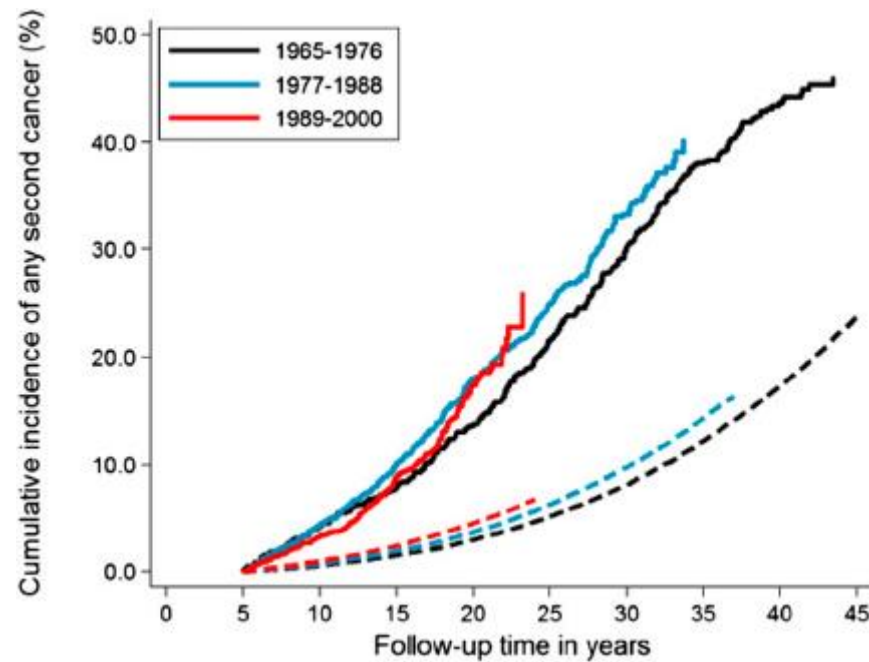
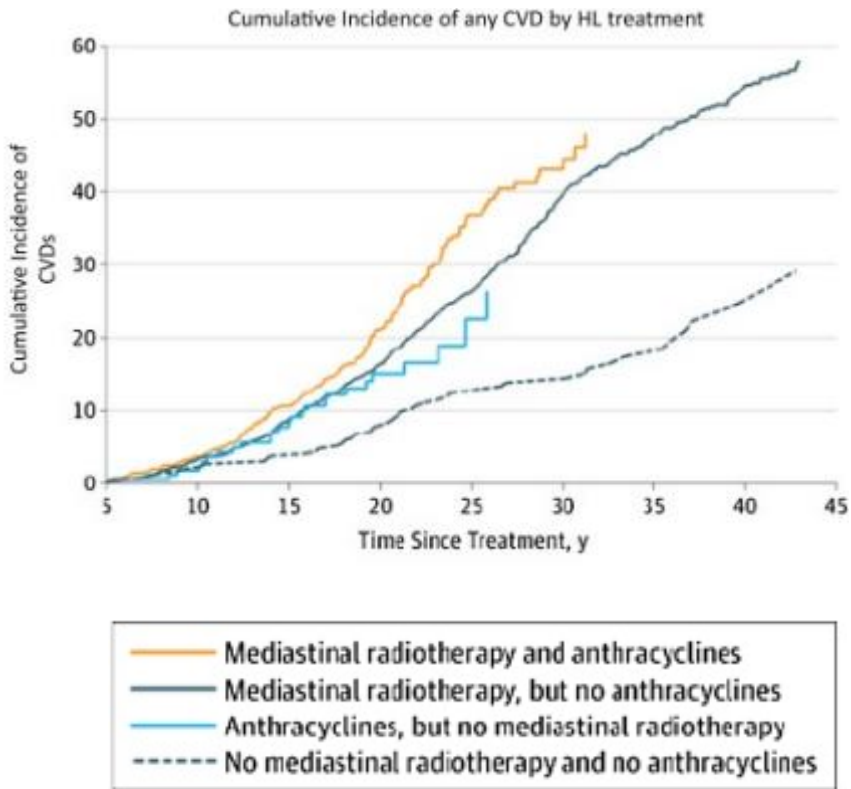




- 1,261 patients with HD as the first malignancy,
- were no older than 40 years when diagnosed and treated for HD.
- were treated between 1965 and 1987 in the Netherlands



Aleman et al. J Clin Oncol. 2003 Sep 15;21(18):3431-9.



Cumulative
incidence 40
years after
HL:
43.6%



Patients treated with mediastinal radiotherapy had a 40-year cumulative incidence of any CVD of 54.6% compared with 24.7% in patients not treated with mediastinal radiotherapy or anthracyclines

2013

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org



Clinical Investigation

Modern Radiation Therapy for Hodgkin Lymphoma: Field and Dose Guidelines From the International Lymphoma Radiation Oncology Group (ILROG)



use of RT in HL in the modern era of combined modality treatment

Lena Specht, MD, PhD,* Joachim Yahalom, MD,[†] Tim Illidge, MD, PhD,[‡] Anne Kiil Berthelsen, MD,[§] Louis S. Constine, MD,^{||} Hans Theodor Eich, MD, PhD,[¶] Theodore Girinsky, MD,[#] Richard T. Hoppe, MD,** Peter Mauch, MD,^{††} N. George Mikhaeel, MD,^{‡‡} and Andrea Ng, MD, MPH^{††}, on behalf of ILROG

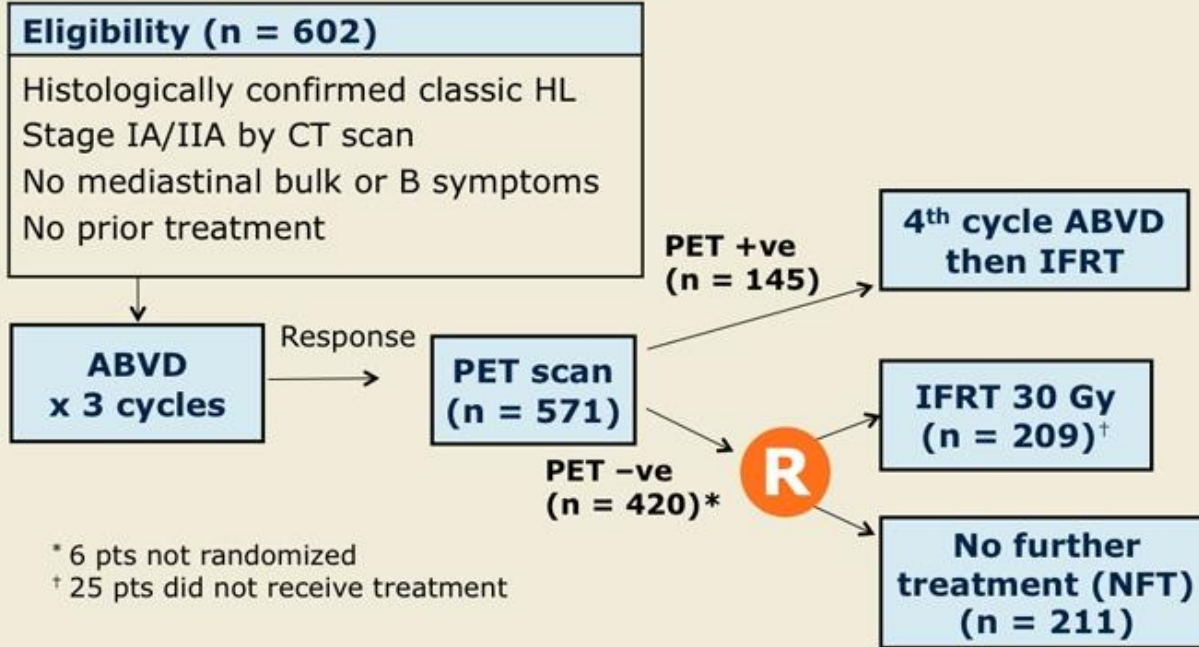
- A new concept, involved site radiation therapy (ISRT), is introduced as the standard conformal therapy for the scenario



PET-Directed Therapy

UK RAPID(2015), EORTC H10(2017), CALGB 50604(2018), GHSG HD16(2019)

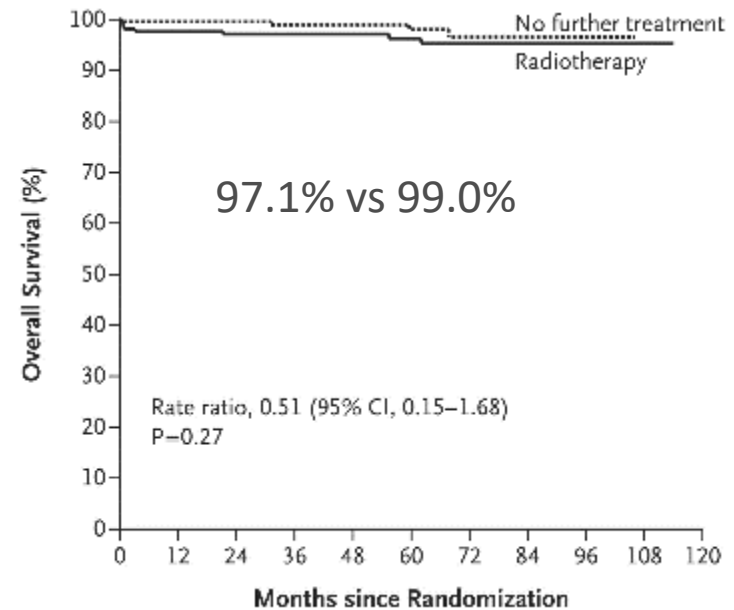
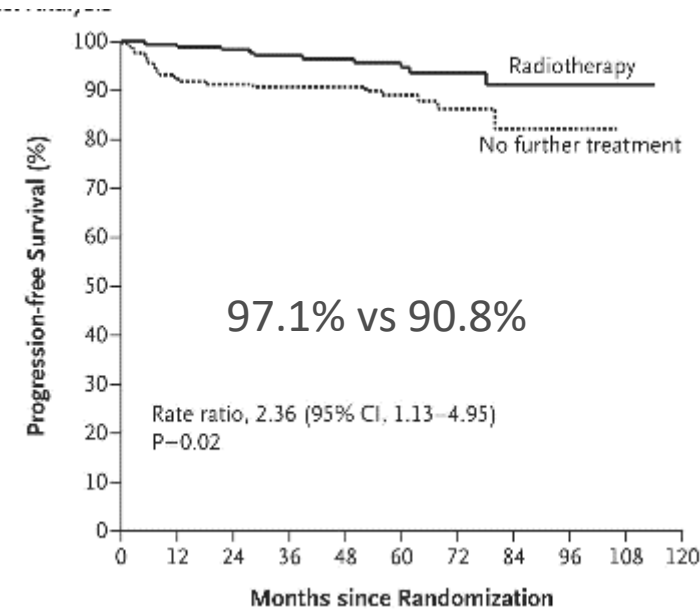
Phase III RAPID Study Design

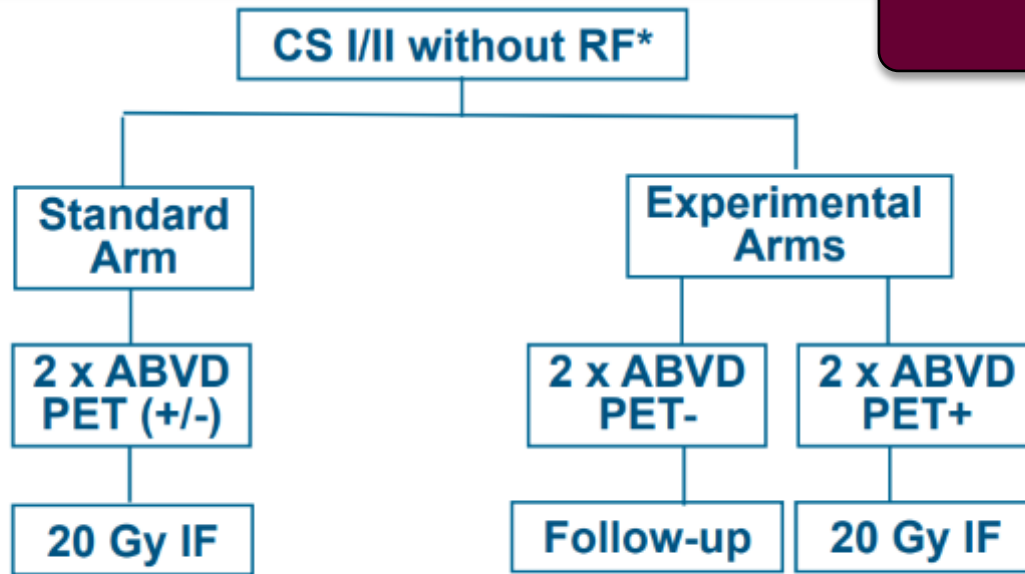


this study did not show the noninferiority of the strategy of no further treatment after chemotherapy with regard to PFS

a very good prognosis either with or without consolidation radiotherapy

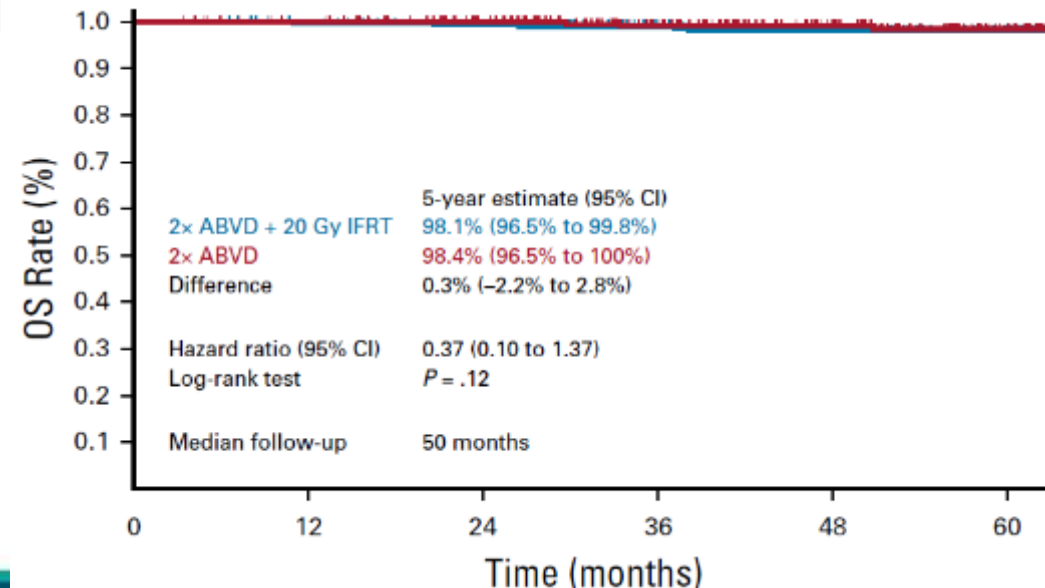
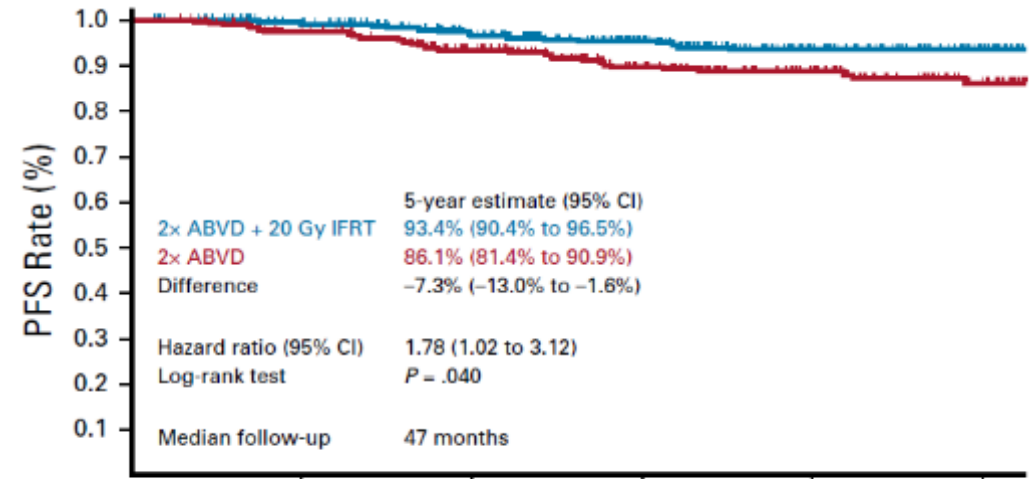
3-yr
PFS





*a) large mediastinal mass; b) extranodal disease; c) high ERS; d) 3 or more areas

In PET-2–negative patients, radiotherapy cannot be omitted from CMT without clinically relevant loss of tumor control





**Cochrane
Library**

Cochrane Database of Systematic Reviews

2017

**Chemotherapy alone versus chemotherapy plus radiotherapy
for adults with early stage Hodgkin lymphoma (Review)**

Blank O, von Tresckow B, Monsef I, Specht L, Engert A, Skoetz N

seven RCTs

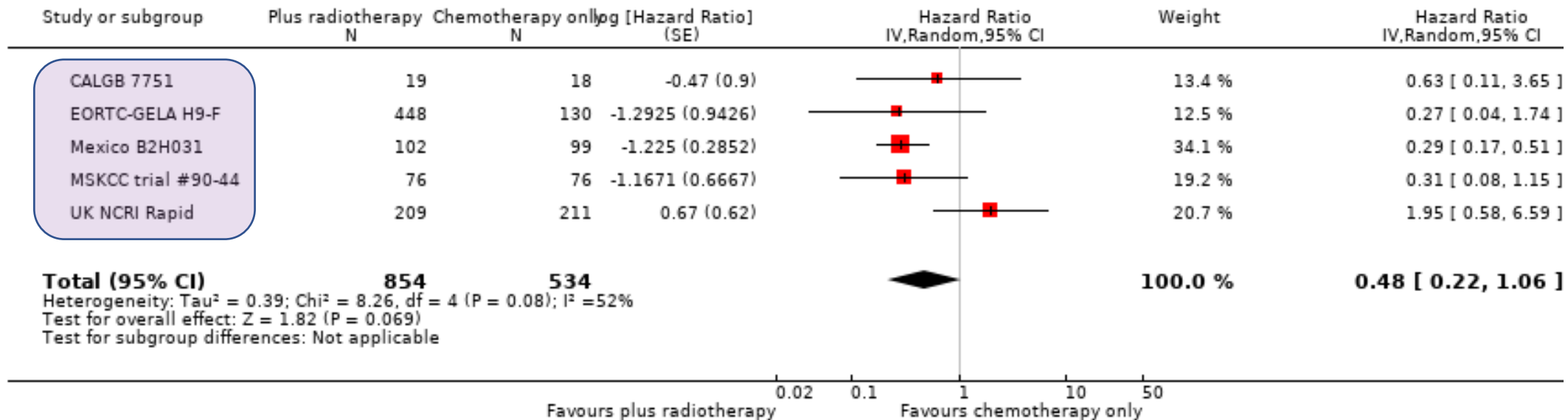
2564 patients



Same numbers of chemotherapy cycles



Review: Chemotherapy alone versus chemotherapy plus radiotherapy for adults with early stage Hodgkin lymphoma
Comparison: 1 Overall survival – same number of chemotherapy cycles
Outcome: 1 All trials



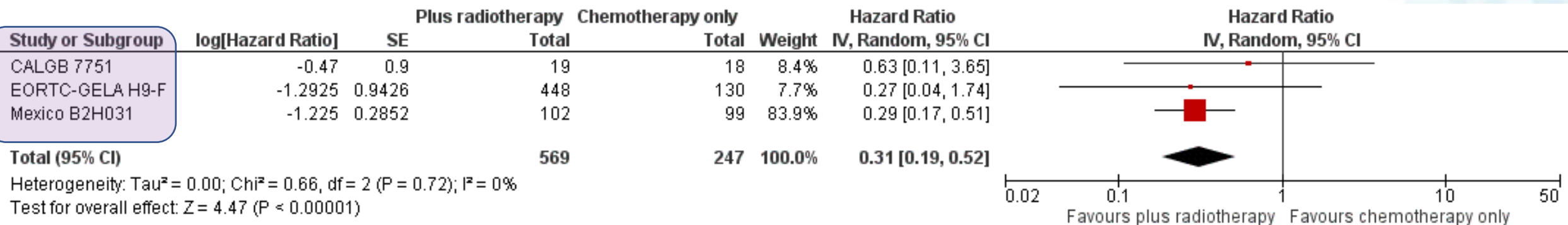
**moderate-
quality
evidence**

The addition of radiotherapy to chemotherapy has probably **little or no** difference on **OS**

- a sensitivity analysis
- high risk of bias
 - high number of patients not receiving planned radiotherapy
- UK NCRI Rapid and MSKCC trial #90-44

moderate-quality evidence

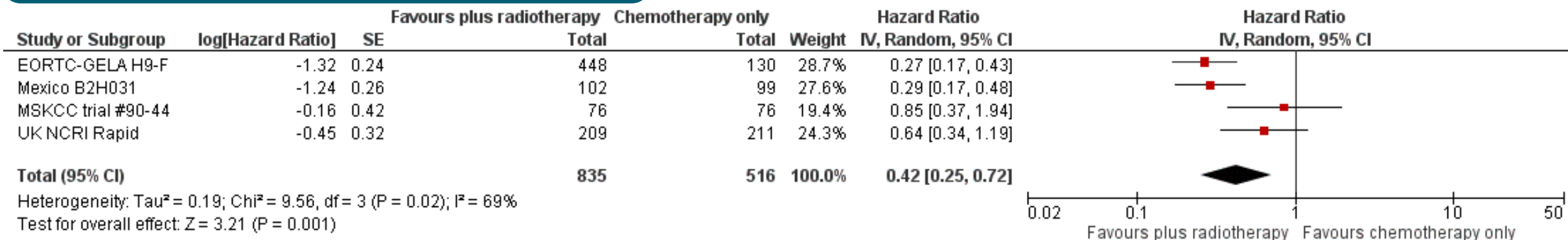
the combination of chemotherapy and radiotherapy **improved OS** compared to chemotherapy alone



Same numbers of chemotherapy cycles



Progression-free survival



**moderate-
quality
evidence**

PFS is superior in patients receiving CMT than in those receiving chemotherapy alone.

**Chemotherapy alone versus chemotherapy plus radiotherapy
for adults with early stage Hodgkin lymphoma (Review)**

Blank O, von Tresckow B, Monsef I, Specht L, Engert A, Skoetz N



different numbers of chemotherapy cycles

no implications for OS and PFS possible,
because of the **low quality of evidence** of the results

PFS

Combined
Modality
Therapy



Chemotherapy
alone



NCCN

National
Comprehensive
Cancer
Network®

Selection of treatment (combined modality therapy or chemotherapy alone) should be based on

- **patient age, sex, family history of cancer or cardiac disease, comorbid conditions, and sites of involvement** (especially within mediastinum or axilla).

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- a patient group that can be safely treated with ChT alone could not yet be defined
- as patients treated with ChT alone still have **a good overall prognosis**, this approach may be offered to **individual patients** when **the late risk** of delivering RT is thought to outweigh the short-term benefit of improved disease control

individualization of treatment



slightly increased risk of relapse

potential radiation-associated complications



young (age <30) females
with disease requiring irradiation of
the breast tissue.



Original Study

Cost-Effectiveness of PET Directed Versus Combined Modality Therapy for Early-Stage Favorable Hodgkin's Lymphoma

Clayton P. Smith¹  , Bethel Adefres¹, Eric M. Chang², Tina Q. Huang¹, Neil Parikh¹, Ann Raldow¹

Table 2 Results of Cost-Effectiveness Analysis.

Strategy	Cost (\$)	Incremental Cost (\$)	Effectiveness (QALY)
CMT	41,167	—	3.4
PET-Directed	47,362	6195	3.4

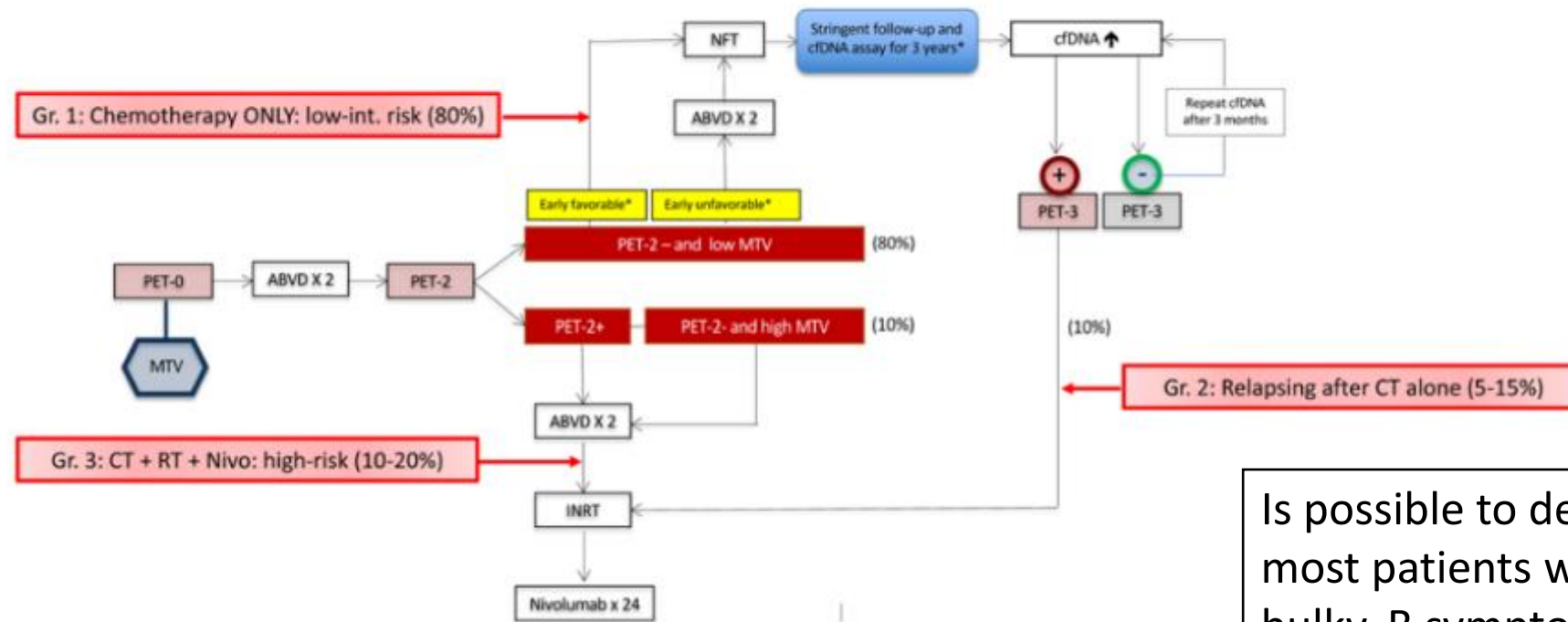
- 5 year outcomes for 1 million patients with early-stage HL treated with either PET-directed therapy consisting of 2 cycles of [ABVD](#) chemotherapy ± ISRT or CMT consisting of 2 cycles of [ABVD](#) + ISRT
- combined modality therapy is the cost-effective strategy in this study, in large part due to **the high cost** and **quality of life impact** of salvage high dose chemotherapy and stem cell transplant associated with the higher rates of disease recurrence when radiotherapy is not utilized in the upfront treatment setting.



Radiation-Free Therapy for the Initial Treatment of Good Prognosis Early Non-bulky HL, Defined by a Low Metabolic Tumor Volume and a Negative Interim PET After 2 Chemotherapy Cycles- RAFTING



RAFTING study workflow



2021-2026
27 centers
Italy- Poland- Spain

HL: Hodgkin Lymphoma
 NFT: No Further therapy
 INRT : Involved Nodal Radiotherapy
 MTV: Metabolic Tumor Volume
 cDNA: Cell-free circulating DNA

Modified EORTC criteria for early-stage HL prognosis

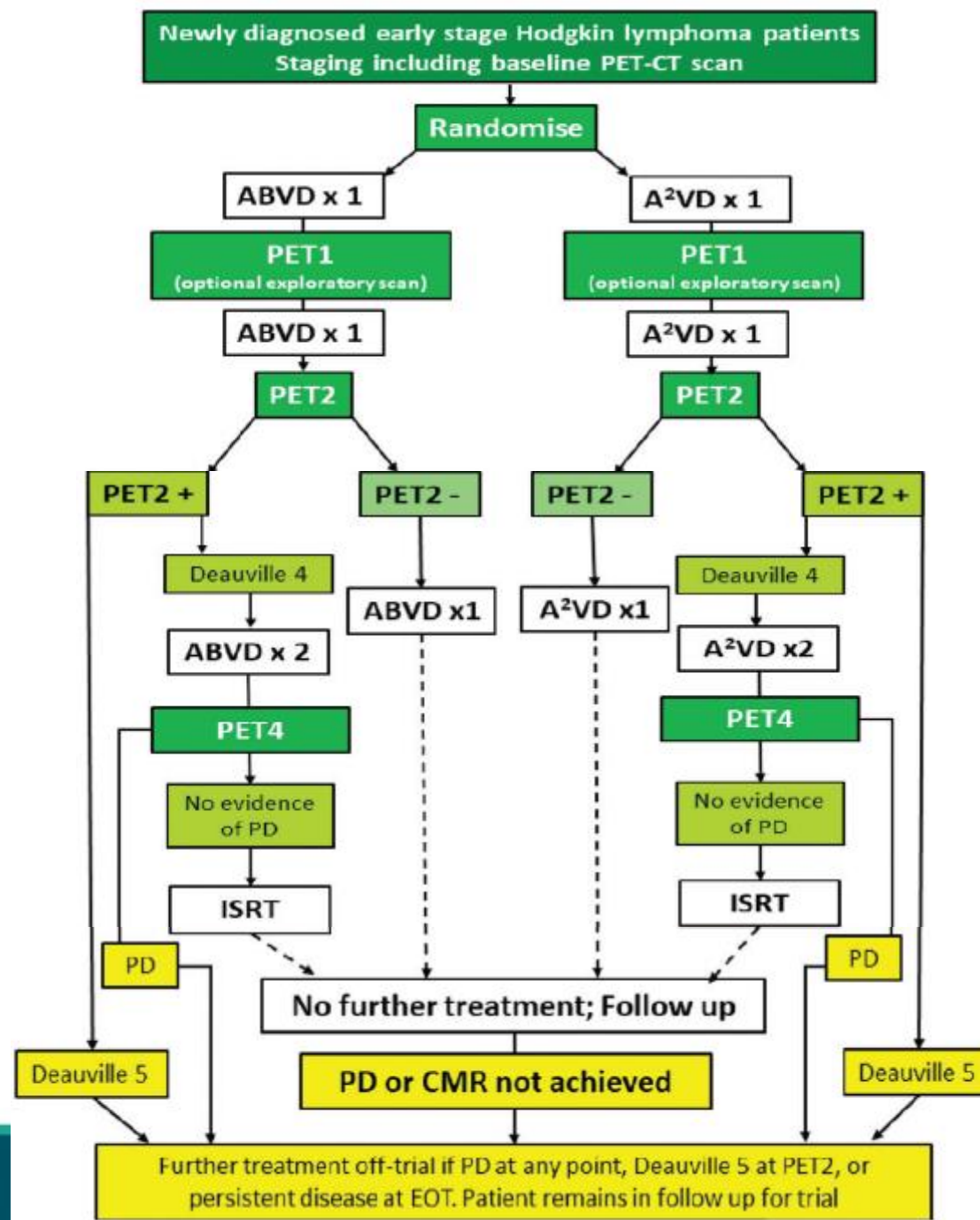
- Large nodal mass (⊙ >5 cm., < 10 cm.)
- Age > 50 Y.
- ESR > 50 mm
- ≥ 4 involved regions

Is possible to deliver a RT-free treatment in most patients with good-prognosis (no bulky, B symptoms or extranodal) Early stage Hodgkin Lymphoma, with a similar efficacy to CMT?

RADAR opened to
recruitment in April 2022

comprises **2 parallel** identical phase III
randomized multicentre trials in the **UK,
Europe, Australia, New Zealand** (trial 1;
642 pts), **Canada and the USA** (trial 2;
400 pts)

**brentuximab
vedotin**



Take Home message



- **Advance stage**: No consolidataion RT for initially non-bulky and PET-2 negative disease
- **Early stage(Fav & Unfav)**:
 - Combined modality treatment: improved PFS
 - Individualization of treatment based on patient **risk for late complications**: chemotherapy alone
 - PET directed therapy



**THANK YOU
FOR YOUR
ATTENTION**