Pediatric Hodgkin Lymphoma

Children's Oncology Group Educational Presentation

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Presentation Outline

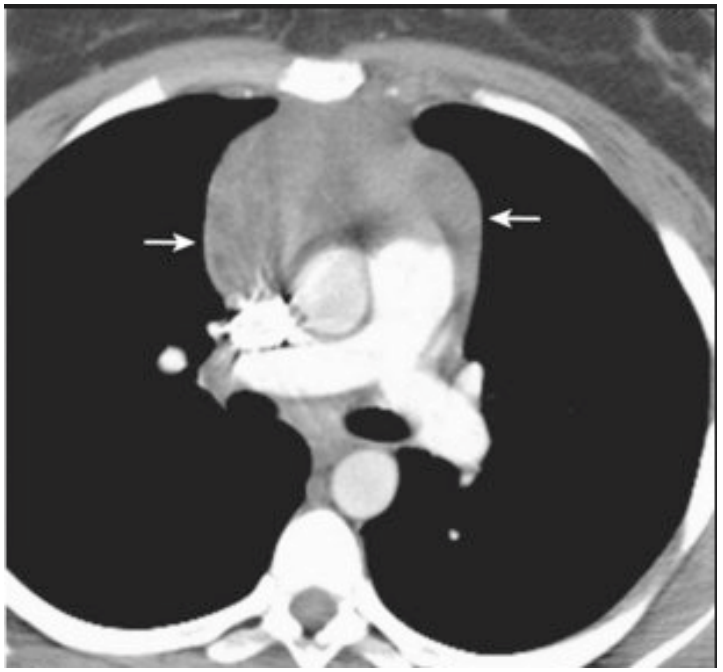
1. Overview of pediatric Hodgkin lymphoma (HL)
2. Favorable-risk disease
3. Intermediate-risk disease
4. High-risk disease
5. Radiation therapy
6. Nodular lymphocyte predominant HL
7. Refractory and relapsed disease

Epidemiology

- Two distinct forms of HL among childhood and adolescents/young adults
- Childhood
  - 10-14 years of age
  - Male predominance
  - Associated with increasing family size, lower socioeconomic status (SES), and recent primary EBV infection
- Adolescent/young adult
  - 15-35 years old
  - Approximately equal incidence between males and female
  - Associated with higher SES, early birth order, fewer siblings, and delayed EBV exposure

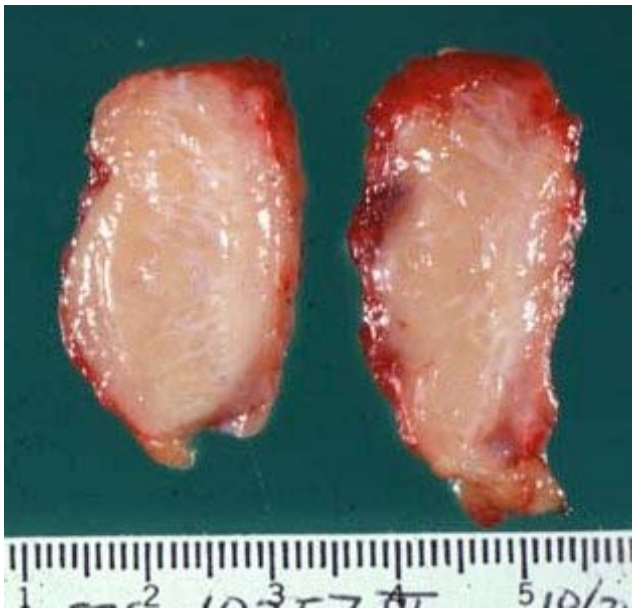
Clinical Presentation

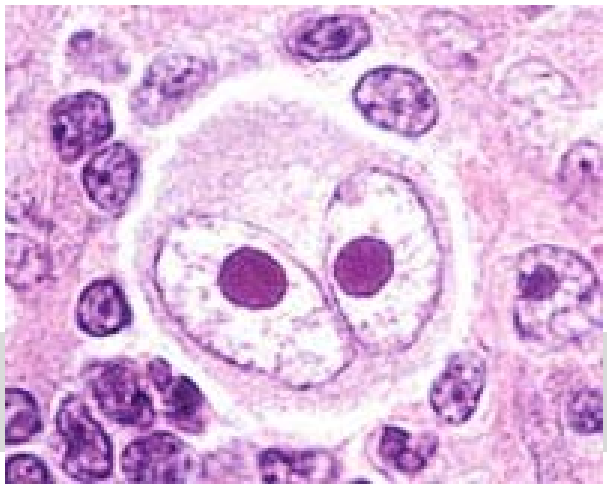
- Most common presenting sign is painless lymphadenopathy
- Mediastinal disease at presentation
  - More common in AYA than in young children
- B symptoms
  - fever >38°C, drenching night sweats, and/or unexplained weight loss of >10% of body weight within 6 months
  - Present in approximately 1/3 of patients
  - More common in AYA than in young pediatric patients



Pathologic Classification

- Diagnosis ideally made by pathologic exam of entire lymph node obtained by excisional biopsy
- Effacement of involved LN with destruction of its normal architecture, an inflammatory cellular infiltrate, and presence of the malignant Reed-Sternberg (RS) cells





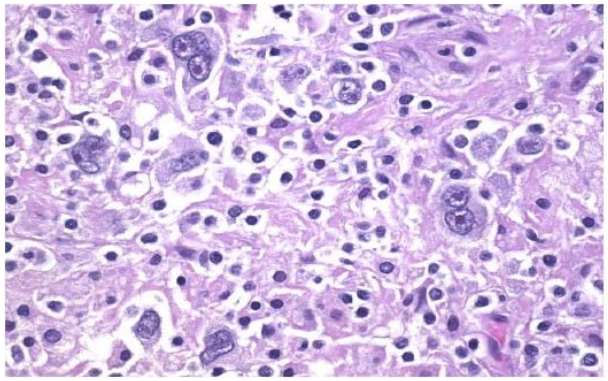
Histologic Subtypes

- Classical Hodgkin Lymphoma (cHL): 85-90%

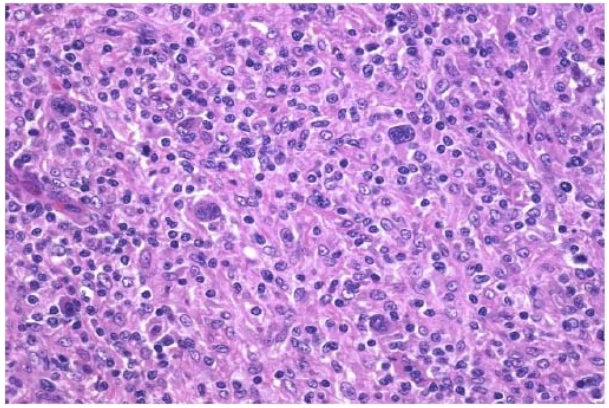
  (CD15+, CD20-, CD30+, CD45-)

  – Lymphocyte-rich
  – Mixed-cellularity
  – Nodular sclerosis
  – Lymphocyte-depleted
- Nodular lymphocyte-predominant HL (nLPHL): 10-15%

  (CD15-, CD20+, CD30-, CD45+)



Nodular sclerosing HL



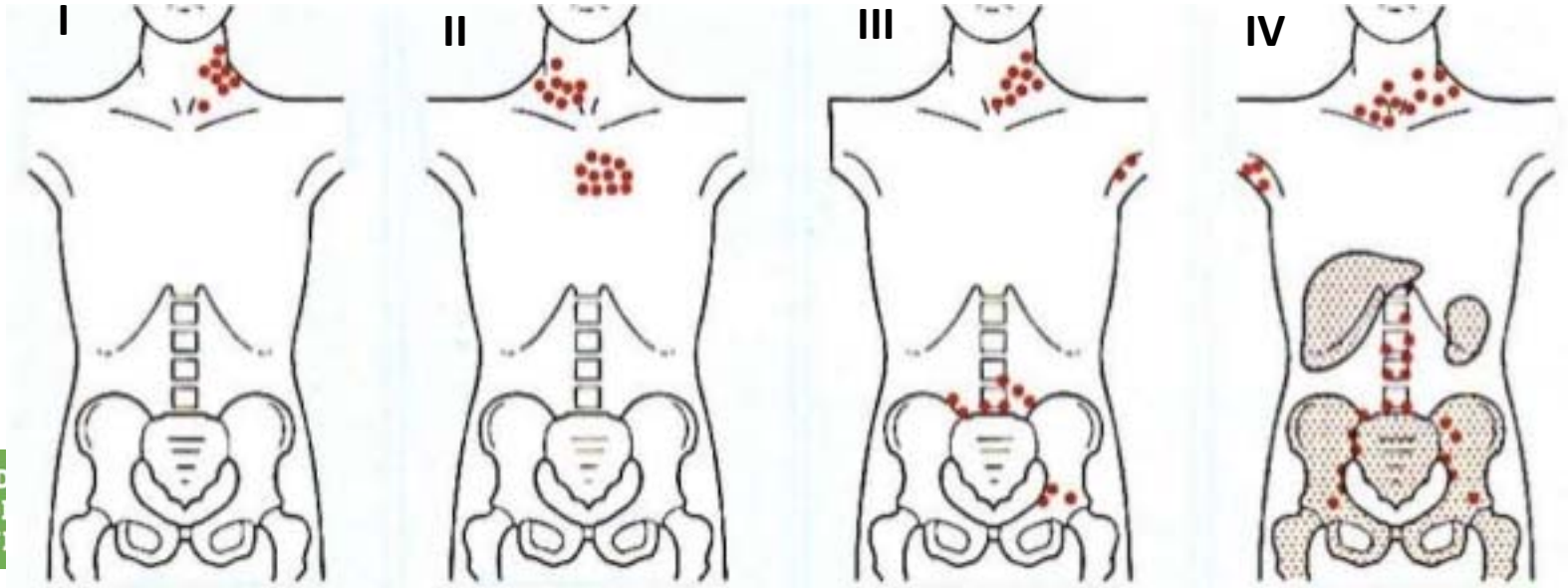
Mixed-cellularity HL

Diagnostic Workup

- History and physical examination
- Labs
  - CBC, LFTs, ESR, CRP
- Imaging
  - CT neck, thorax, abdomen, pelvis with IV and oral contrast is standard
  - FDG-PET
    - To assist in clinical staging
    - To evaluate response during and after treatment
- Bone marrow biopsy if B symptoms or stage III/IV

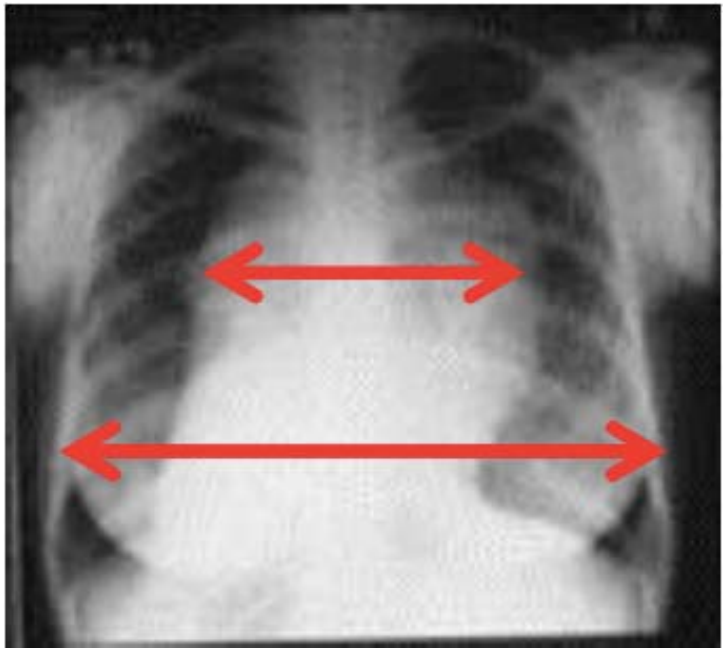
Ann Arbor Staging

- I: 1 lymph node region or single extra-lymphatic organ or site
- II: Multiple regions or sites on 1 side of diaphragm
- III: Multiple regions or sites on 2 sides of diaphragm
- IV: Marrow, liver, lung, bone – not by direct extension
- "E": direct extension from node to adjacent extranodal tissue
- Bulk: Mass/thoracic diameter>0.33
  - Nodal area >6cm
- "B": Drenching night sweats, fever. 10% weight loss.



Bulky disease

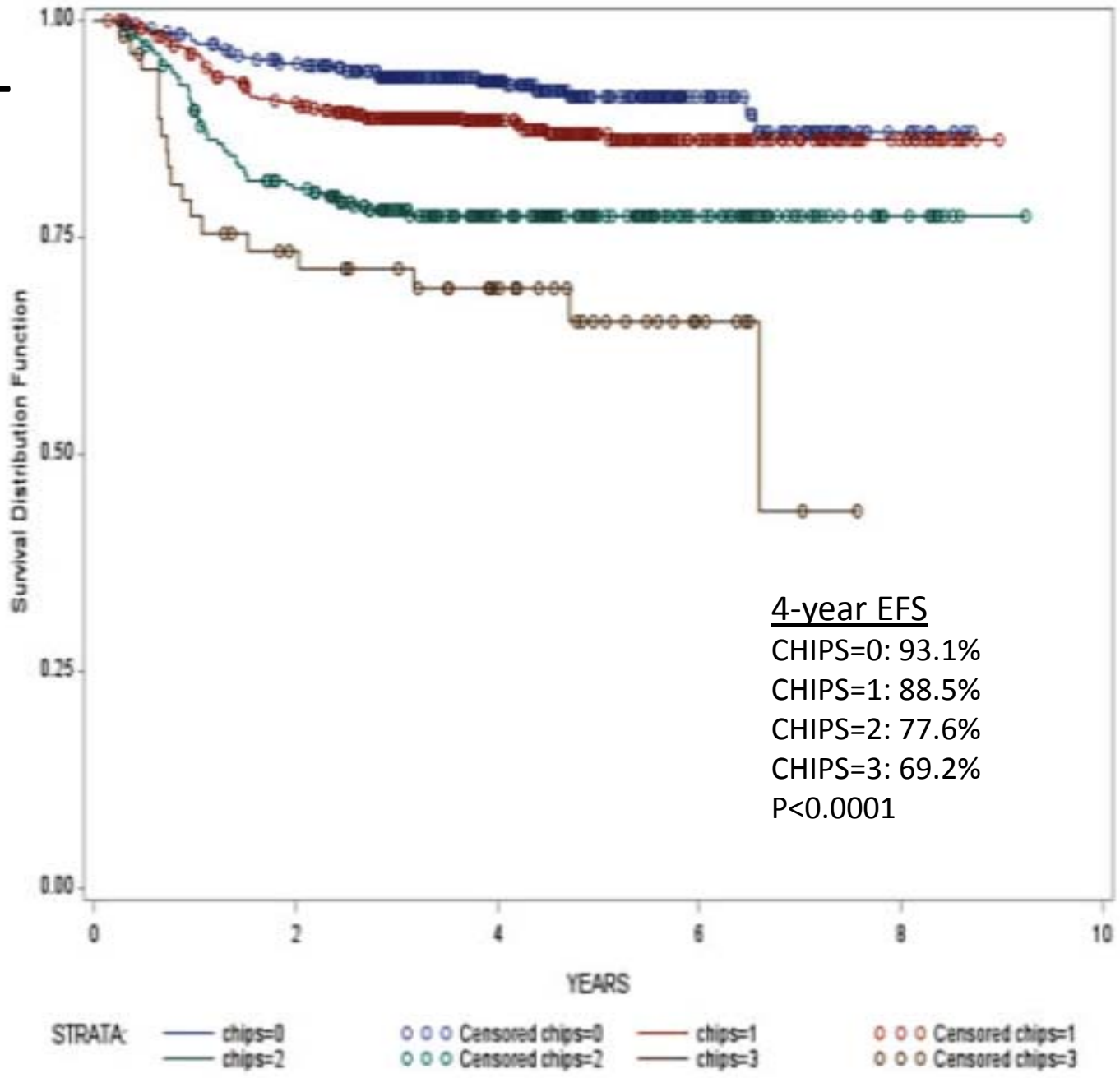
- Definitions of bulky disease are variable
- Historical definition
  - transverse mediastinal diameter >1/3 of maximum intrathoracic diameter on upright PA chest radiograph
- Cotswolds modification of Ann Arbor Classification
  - lymph nodes ≥ 10cm in greatest dimension on CT
- COG intermediate-risk HL trial
  - continguous nodal aggregate that measures >6cm in longest transverse diameter
  - mediastinal mass in which tumour diameter> 1/3 thoracic diameter on upright PA chest x-ray



Childhood Hodgkin International Prognostic Score (CHIPS)

- Predictive model for EFS developed using data from COG AHOD 0031 (ABVE-PC and RT)
- Independent predictors
  - Stage 4 disease
  - Large mediastinal mass
  - Albumin (<3.5)
  - Fever

AHOD 0031 by CHIPS



4-year EFS
CHIPS=0: 93.1%
CHIPS=1: 88.5%
CHIPS=2: 77.6%
CHIPS=3: 69.2%
P<0.0001

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Schwartz et al. Pediatr Blood Cancer. 2017 Apr;64(4). Epub 2016 Oct 27.

Risk Categories

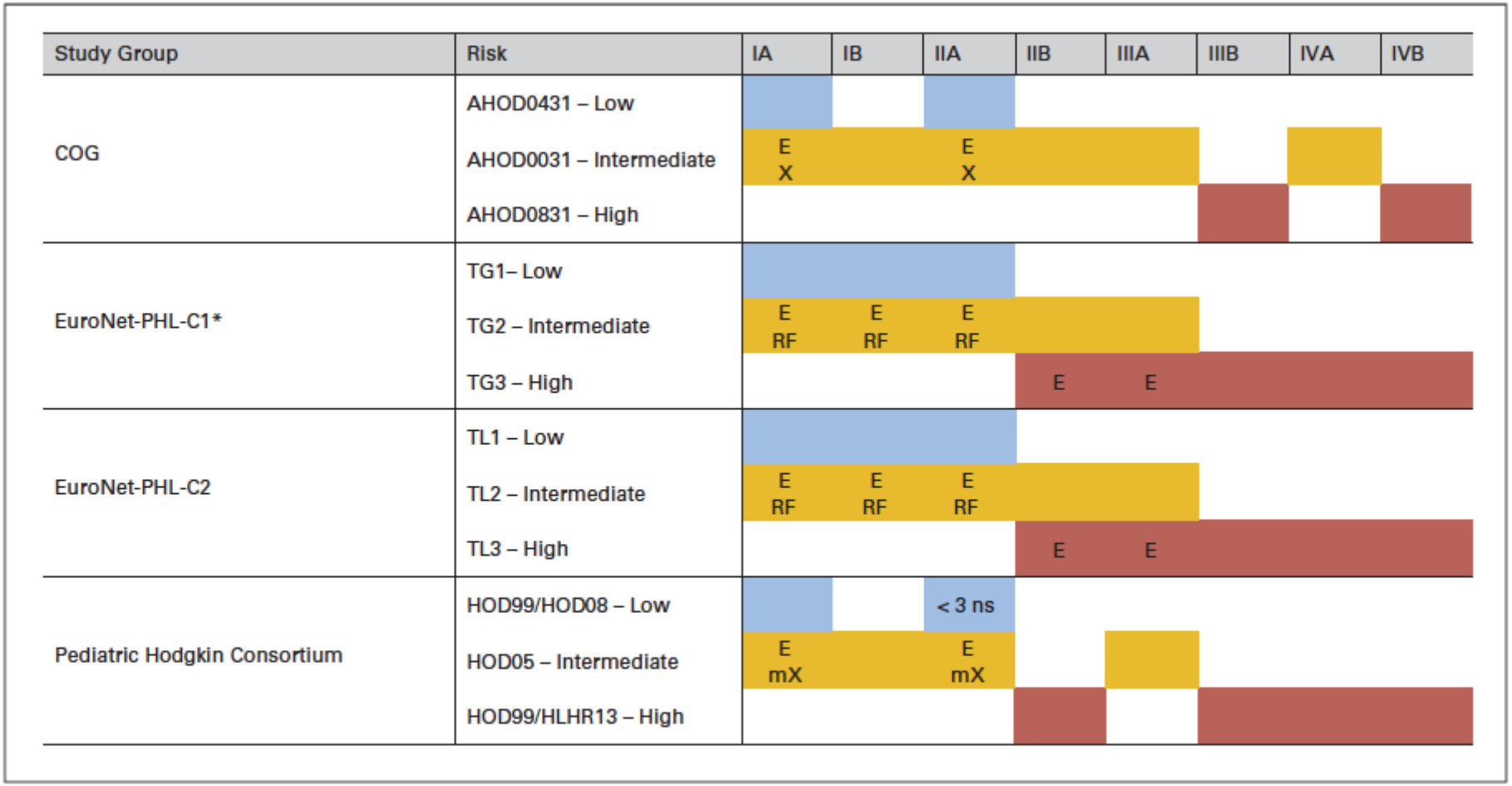

Fig 2. Variation in risk stratification across pediartic Hodgkin study groups and protocols. E, extranodal extension; X, bulky disease (peripheral > 6 cm and mediastinal bulk); mX, mediastinal bulk (≥ 0.33 mediastinal to thoracic ratio); ns, nodal site; TG, treatment group; TL, treatment level; RF, risk factors: erythrocyte sedimentation rate ≥ 30 mm/hour and/or bulk ≥ 200 mL. (*) EuroNet-PHL-C1 was amended in 2012: Low-risk (TG1) patients with ESR ≥ 30 mm/hour and/or bulk ≥ 200 mL were treated in TG2 (intermediate risk).

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The world's childhood cancer experts

Mauz-Korholz. J Clin Oncol. 2015 Sep 20;33(27):2975-85.

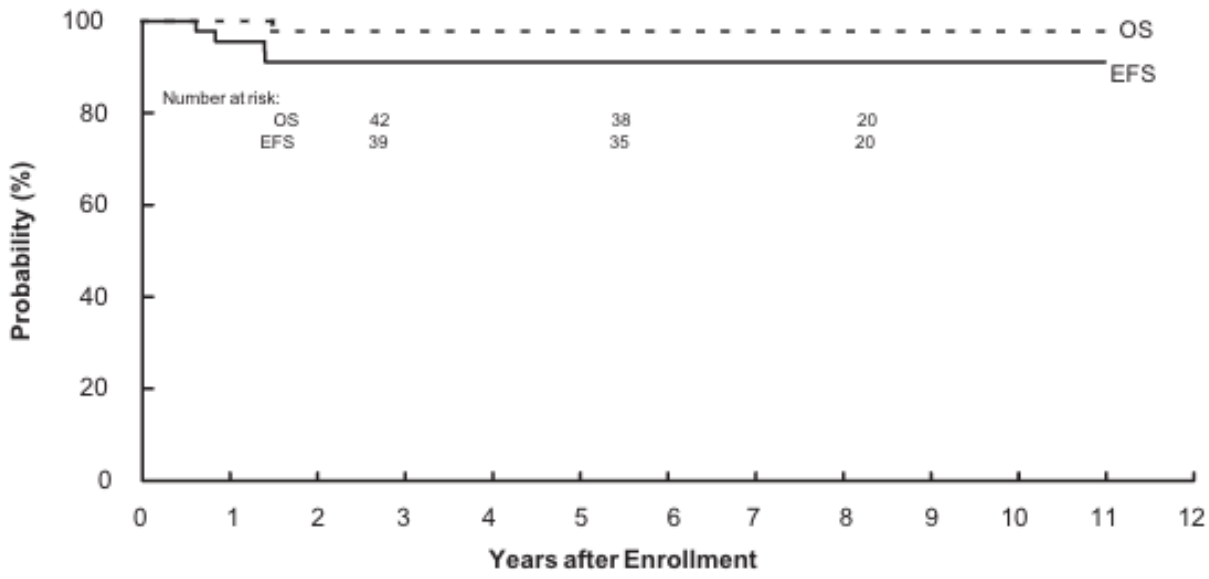
Favorable-risk disease

Definition of favorable-risk HL

- Definition of favorable risk varies from group to group
- Generally, defined as localized stage I and II disease without adverse prognostic features (i.e., without B symptoms, extranodal extension, peripheral or mediastinal bulky disease, hilar adenopathy, or ≥3 nodal regions)

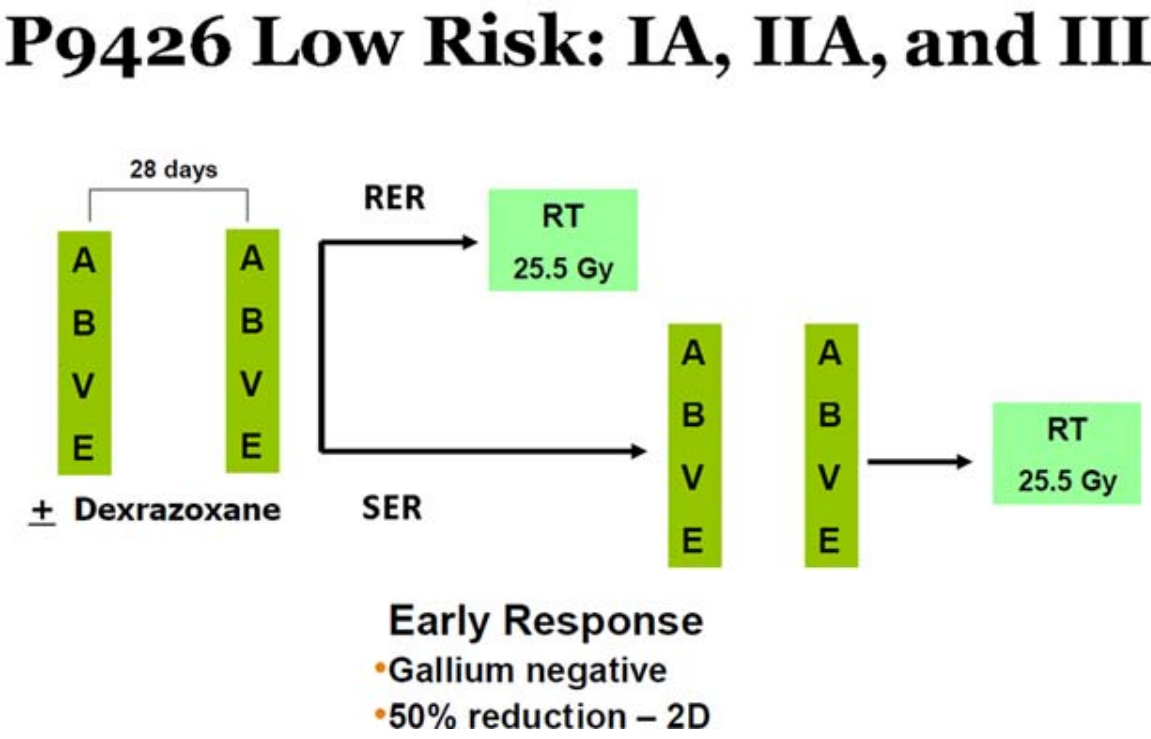
Combined-modality therapy

- Pediatric Oncology Group (single-arm study)
  - Stage IA, IIA, and IIIA HL
  - DBVE x 4 cycles, followed by IFRT to 25.5Gy
  - Median FU 8.4 yrs
  - 6-year OS: 98%
  - 6-year EFS: 91%
  - Remission after completion of therapy: 98%



Tebbi CK et al. Pediatr Blood Cancer. 2006;46(2):198-202.

Response-based reduction of chemotherapy



- RER = CR after 2 cycles of DBVE
- SER = less than CR after 2 cycles of DBVE
- 5-year OS: 98%
- 5-year EFS: 88%
- Supports reduction of chemotherapy in early responders

Tebbi CK et al. Pediatr Blood Cancer. 2012;59(7):1259-1265.

Response-based reduction of RT

- CCG trial C5924
  - COPP/ABV alone vs. risk-adapted combined-modality therapy with low-dose IFRT
  - If CR to chemotherapy (≥70% decrease in tumour volume by CT and resolution of gallium avidity) → randomized to low-dose IFRT vs. no further therapy
  - Trial terminated early due to significantly greater relapse rate in chemotherapy alone group
    - 3-year EFS: 92% after combined-modality therapy vs. 87% after chemotherapy alone (P=0.057)
      - Remained significant in the "as treated" analysis
    - Estimates of OS not different between groups
  - However, chemotherapy was less intensive than most contemporary trials

Nachman et al. J Clin Oncol 2002 Sep 15; 20:3765-3771.

POG 8625 study

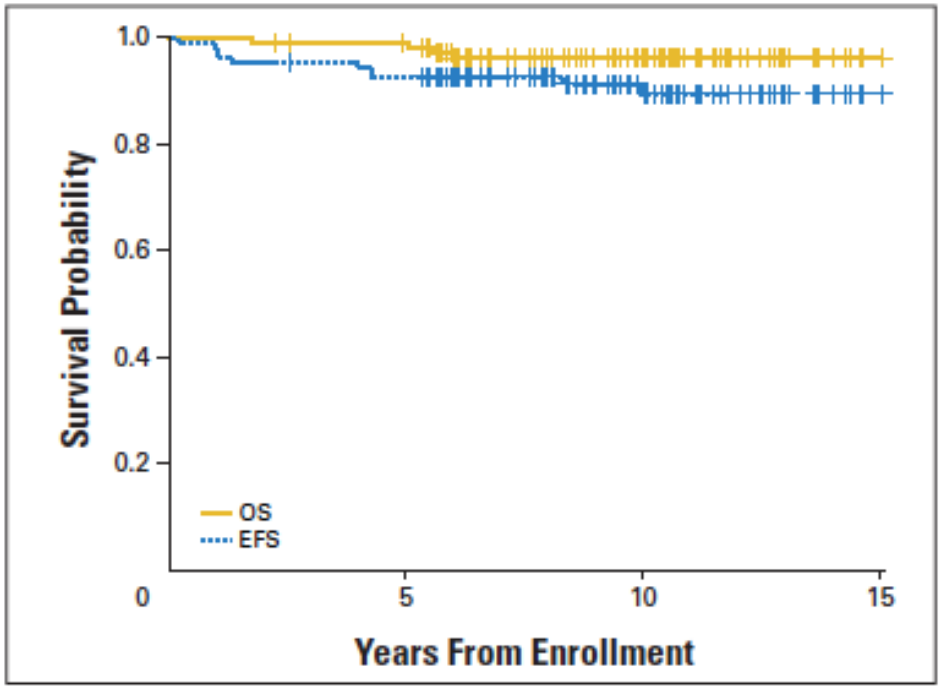
- Stage I, IIA, or IIIA HL → MOPP/ABVD x 4 → if CR or PR, randomized to MOPP x 2 vs. IFRT to 25.5Gy
- At median FU of 8.25 years
  - 8-year EFS: 83% after chemo alone vs. 91% chemo + RT
  - 8-year OS: 94% after chemo alone vs. 97% after chemo + RT
  - Differences not statistically different (but powered to detect a 15% difference in 3-year EFS rates with 80% power)

Kung et al. J Pediatr Hematol Oncol. 2006 Jun;28(6):362-8

Stanford, Dana-Farber and St. Jude consortium study

- Clinical I/II, nonbulky HL (N=110), treated with VAMP (vinblastine, doxorubicin, methotrexate, and prednisone) x 4 cycles
- Response-based IFRT after 2 cycles with 15 Gy after anatomic CR and 25.5 Gy after anatomic PR

- 5-year EFS = 93%
- 10-year EFS = 89%
  - 95% for patients achieving CR after VAMP x 2 vs. 84.5% for those achieving PR after VAMP x 2 (P=0.02)
- Suggests that risk-adapted dose reduction of RT is effective



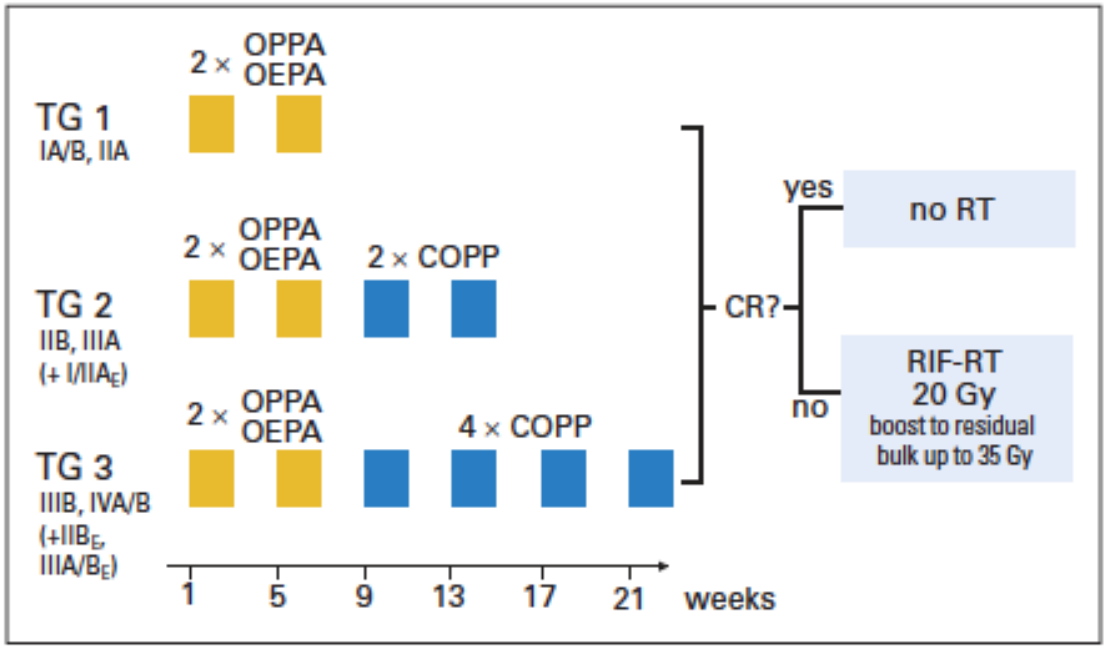
Donaldsen et al. J Clin Oncol 2007 Jan 20;25(3):332-7

Subsequent Stanford, Dana-Farber and St. Jude consortium study

- More stringent definition of low-risk disease
  - Stage I-IIA, non-bulky, no ENE, <3 nodal regions
- VAMP x 4, then IFRT to 25.5Gy if no CR after 2 cycles
  - CR = negative gallium scan or PET scan **and** either ≥75% reduction of the sum of the products of the perpindicular diameters of the lesions of all measurable or evaluable disease or return of nodes to normal size
- 2-year EFS was 89.4% after CR and no RT vs. 92.5% after no CR plus RT (P=0.61)
- Suggests that RT can be omitted after CR with high rate of 2-year EFS
- Of note, patients with nLP HL were included and represented 36% of patients overall and 55% of patients with a CR

GPOH HD-95

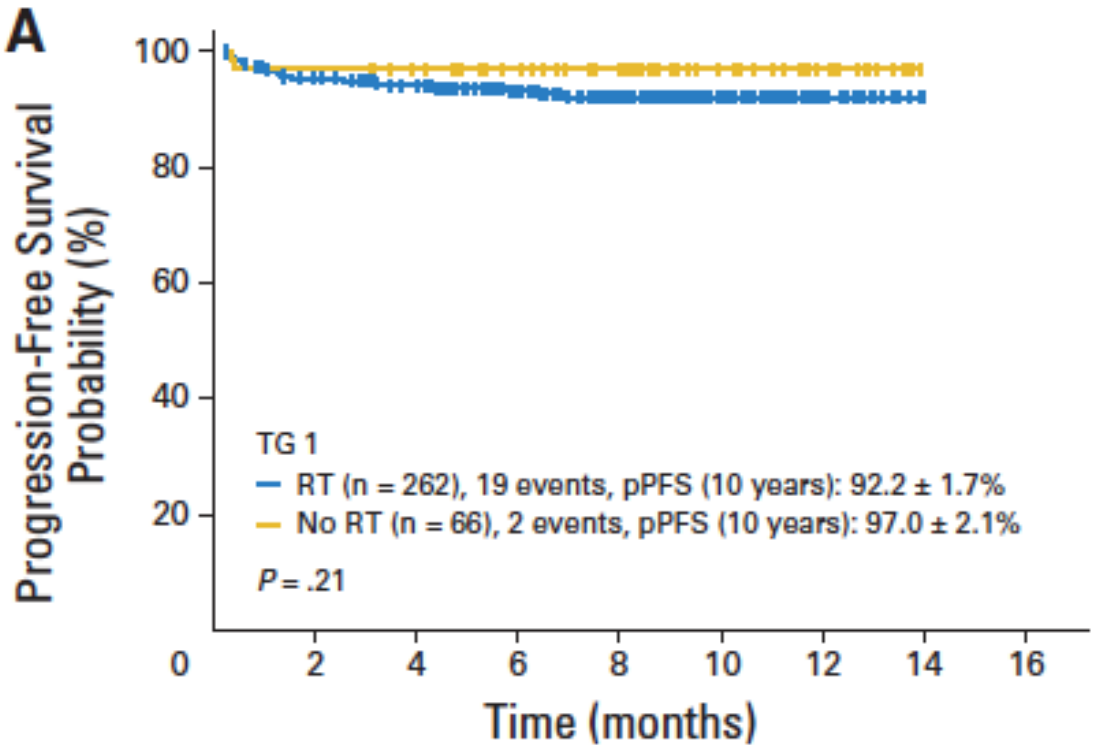
- Investigated whether RT could be omitted in patients achieving an anatomic complete response (CR) to chemotherapy
- CR
  - Volume reduction of ≥95% and ≤2 mL of the initial volume
- Unconfirmed CR
  - volume reduction ≥75% or <2 mL
  - <30% of favorable-risk patients fell into this category



Dorfell et al. J Clin Oncol. 2013 Apr 20;31(12):1562-8

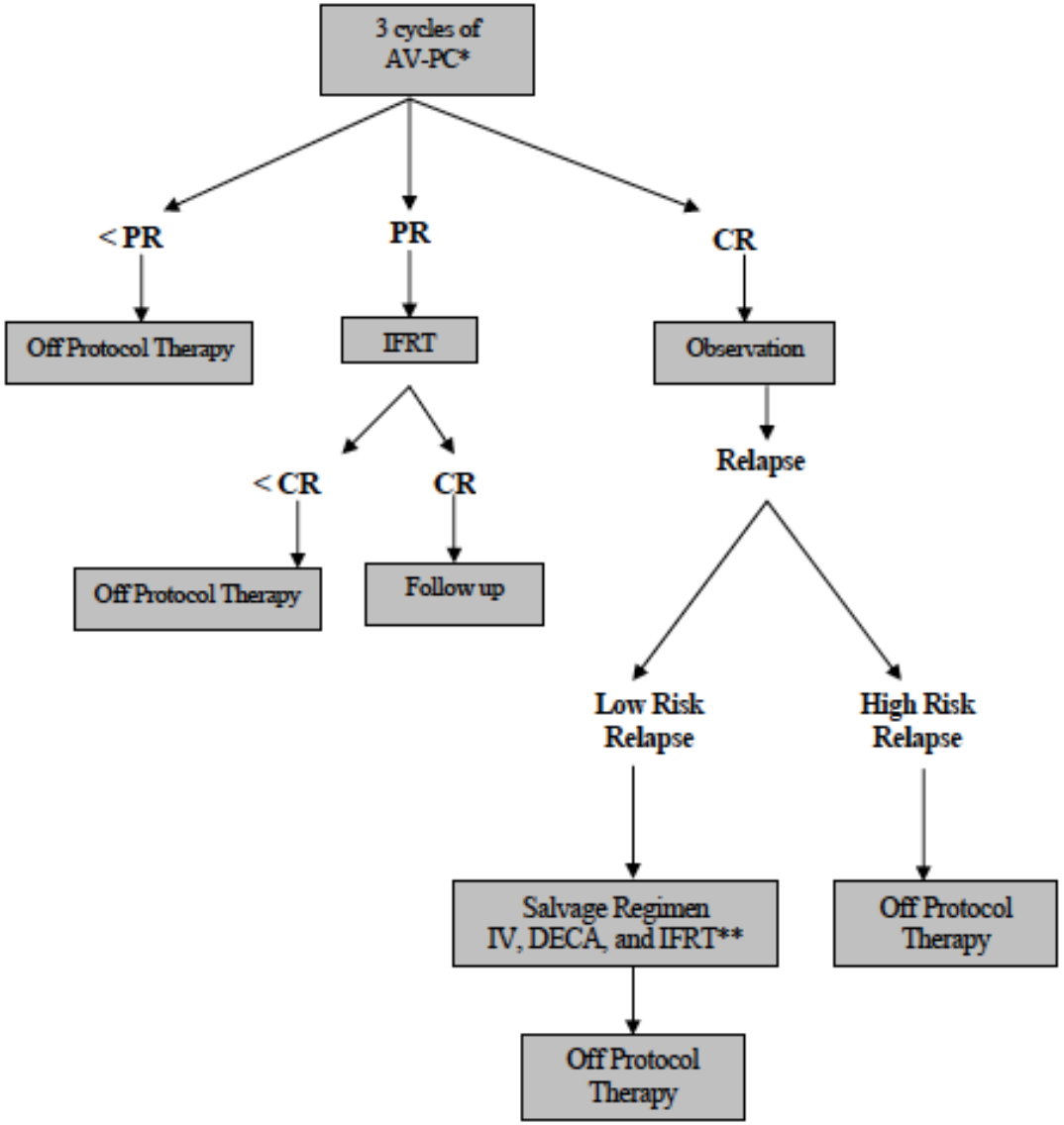
GPOH HD-95

No difference in outcome between early-stage patients treated with chemotherapy alone vs. chemotherapy plus RT



Dorfell et al. J Clin Oncol. 2013 Apr 20;31(12):1562-8

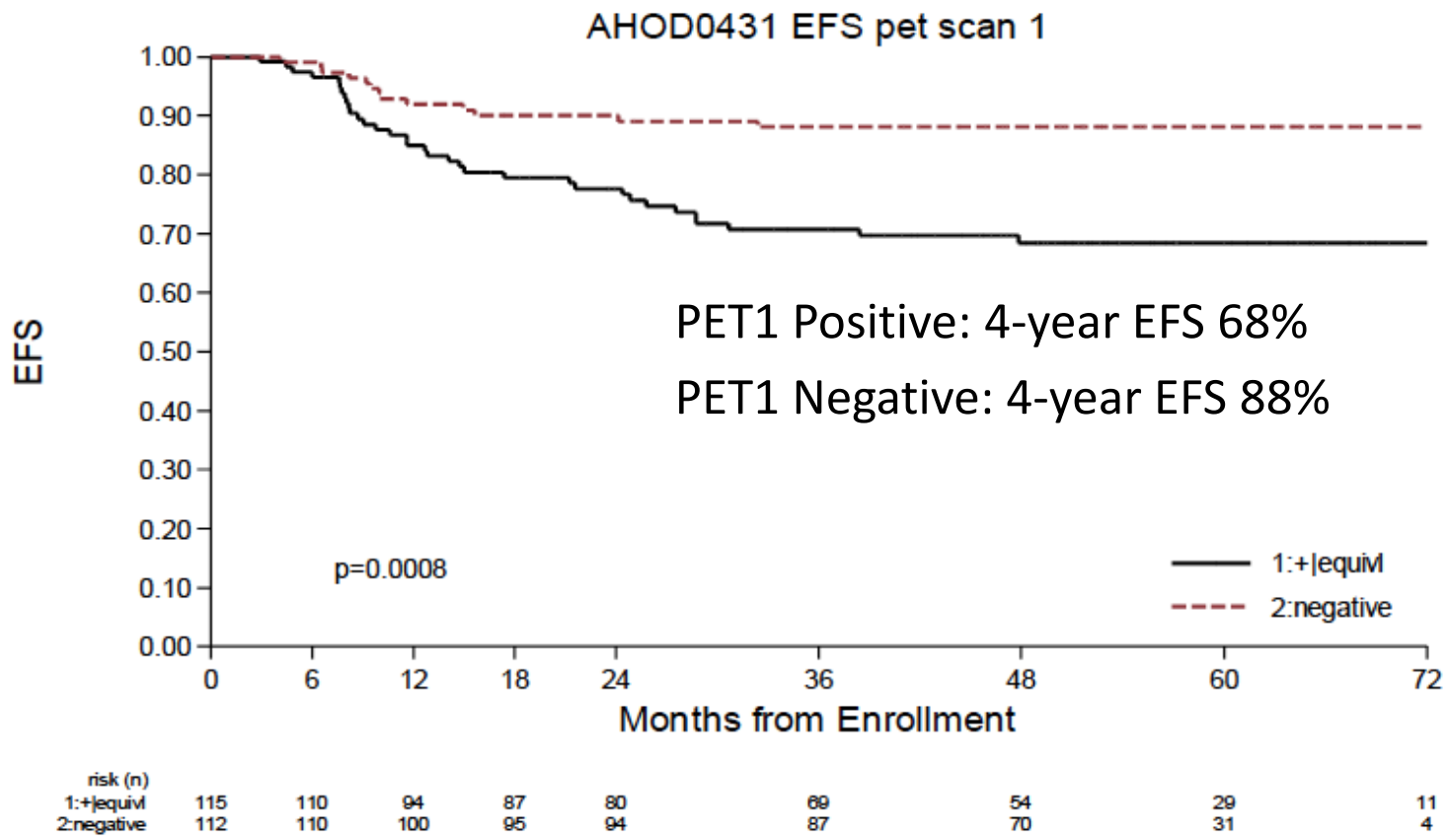
COG AHOD 0431



- Stage IA/IIA, no bulk
- CR = 80% decrease in axial plane & PET or Gallium negative
- If PR, IFRT to 21Gy
- CR after 3 cycles: 63%
- 4-year EFS: 79.8%
  - 2-year EFS: 80% after CR vs. 88% after PR + IFRT (P=0.11)
- 4-year OS: 99.6%

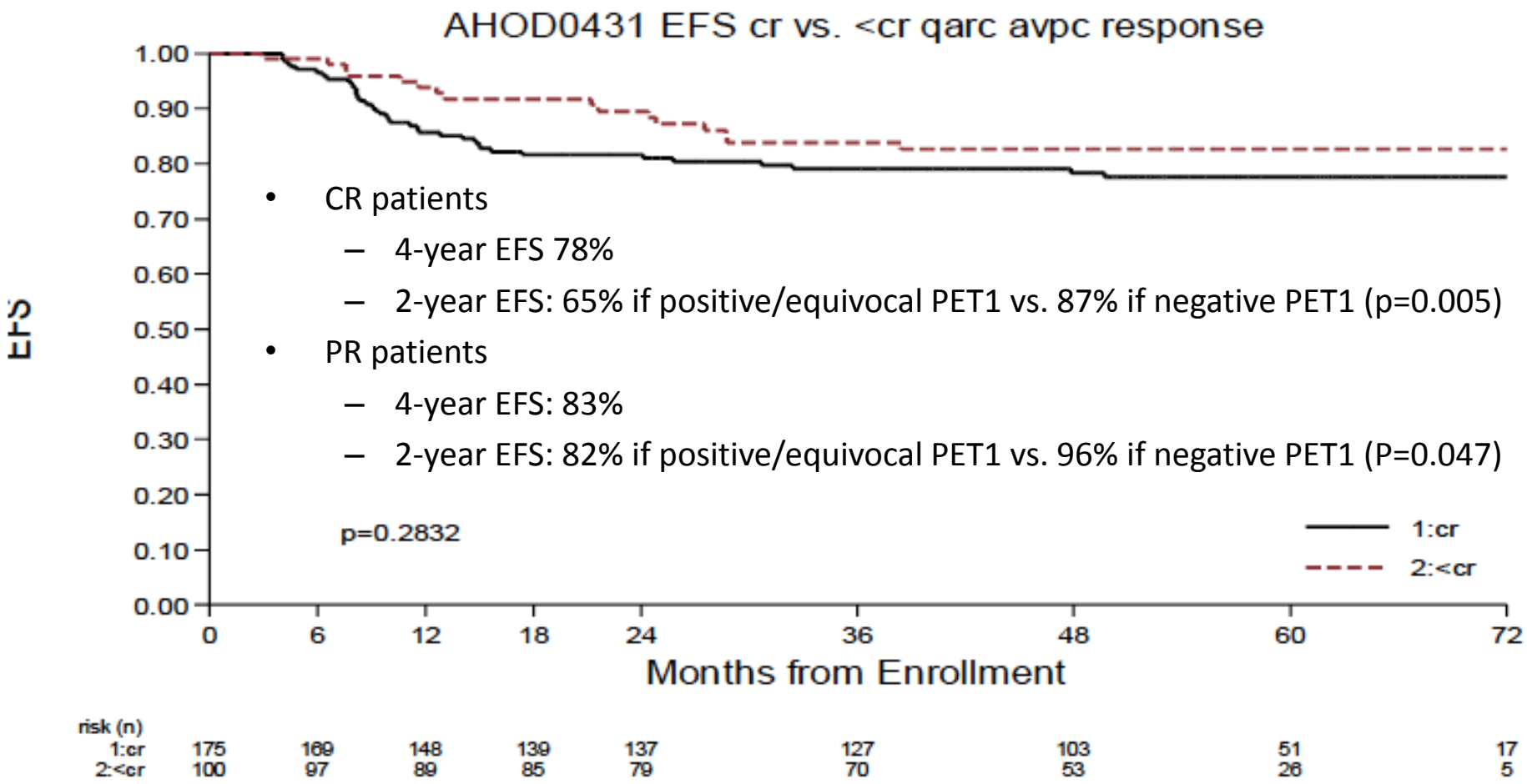
Castellino et al. 2011. Pediatric Blood & Cancer 56;883.
Keller et al.. 2014. Klin Padiatr 226;105.
Keller et al.2010. Blood 116:767.

Of the evaluable patients with FDG-PET after 1 cycle of chemotherapy



Keller et al.. 2014. Klin Padiatr 226;105.

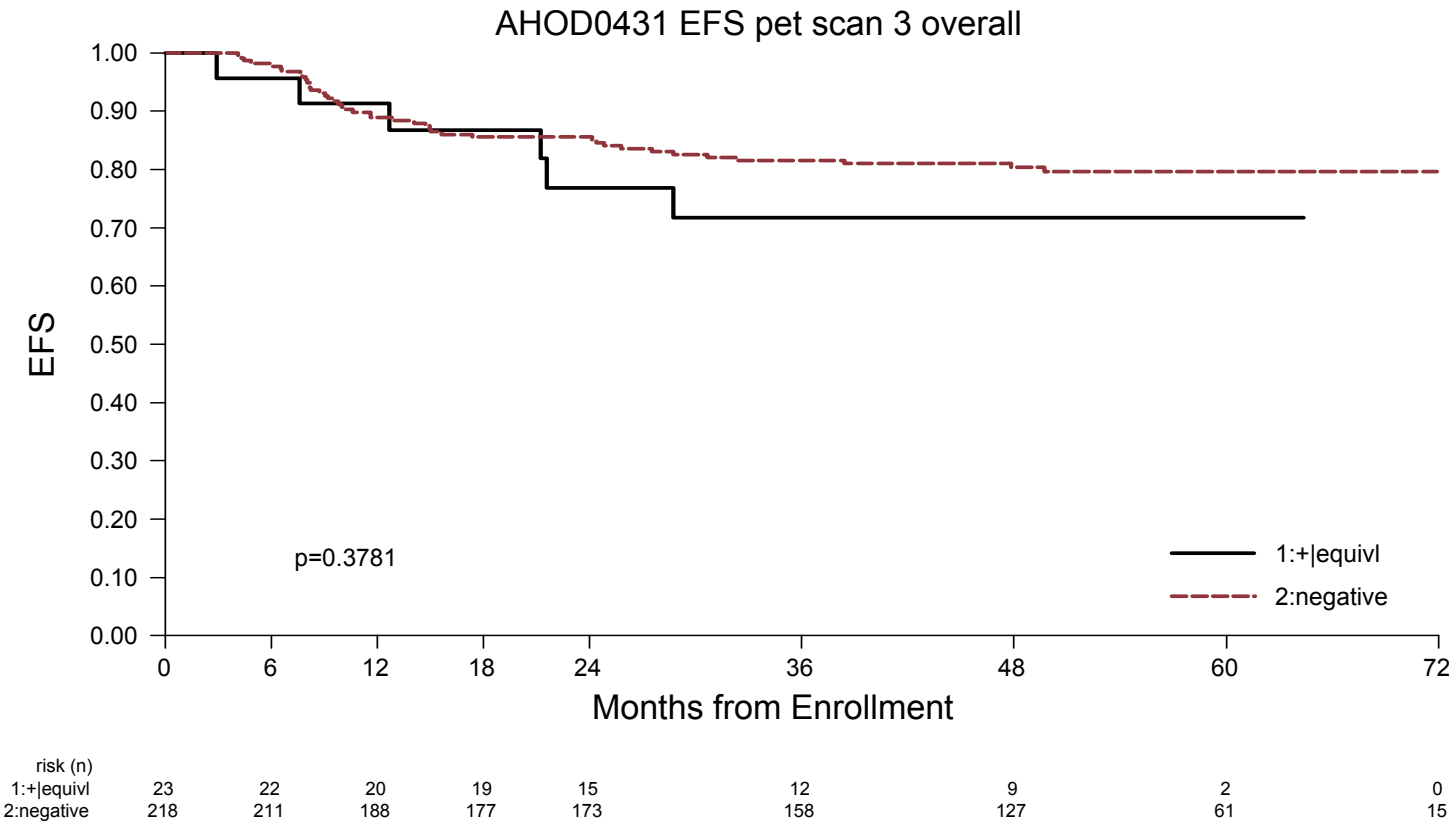
EFS: CR vs. PR patients



- CR patients
  - 4-year EFS 78%
  - 2-year EFS: 65% if positive/equivocal PET1 vs. 87% if negative PET1 (p=0.005)
- PR patients
  - 4-year EFS: 83%
  - 2-year EFS: 82% if positive/equivocal PET1 vs. 96% if negative PET1 (P=0.047)

Keller et al. 2014. Klin Padiatr 226;105

EFS by PET3+ vs. PET3-



- PET3 Positive: 4-year EFS 72%
- PET3 Negative: 4-year EFS 80%

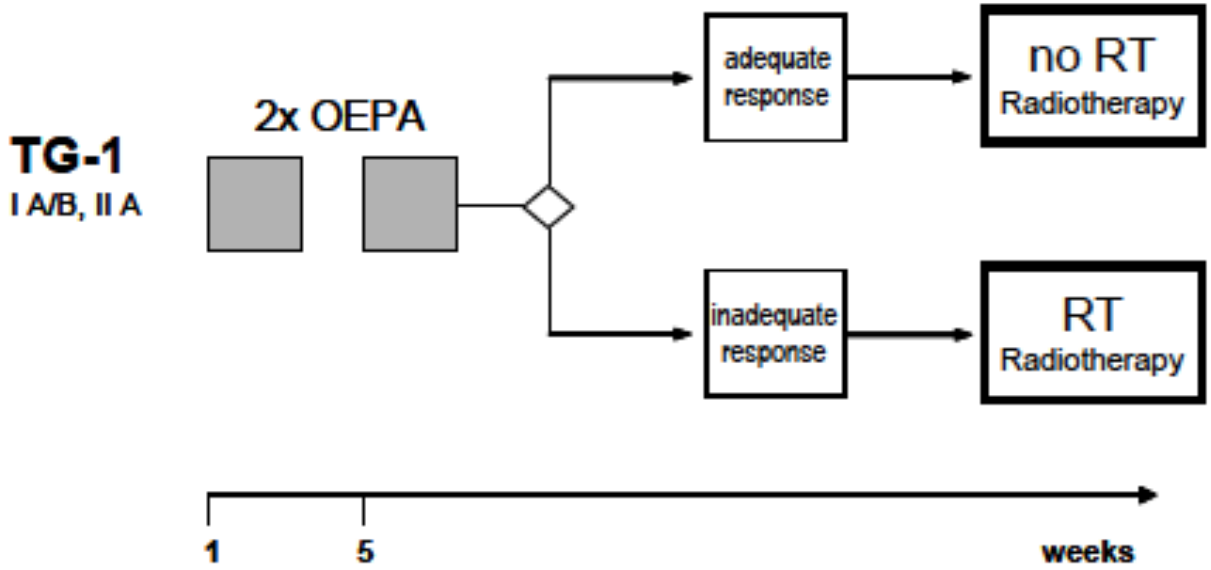
Amendment for PET1 Positive/CR Subjects

- December 2008 Recommendation:
  - All PET1 positive/CR subjects within one year of completing therapy receive 21 Gy IFRT
  - 13 subjects received IFRT based on this recommendation, with 1 relapse within this group

COG AHOD 0431 Conclusions

- EFS was not as good as expected for this patient cohort when treated with 3 cycles of AVPC alone, and was not accepted as the "standard of care".
- PET1 is more effective than PET3 in identifying subjects with more favorable prognosis.

Euronet-PHL-C1



RT dose: 19.8Gy + additional 10Gy boost if poor response

- poor response = residual volume >25% of initial volume and residual volume >5cm^3 OR residual volume>100cm^3

Fig. 5. Response group definition

overall response	worst local PET response: PET negative	PET unclear, but local CR / undetectable	PET unclear, detectable and not local CR	PET positive
CR	☐ AR1	☐ AR1		☐ AR1
CRu	☐ AR2	☐ AR2	☐ IRu	☐ IR
PR	☐ AR2	☐ AR2	☐ IRu	☐ IR
NC	☐ IRu	☐ IRu	☐ IRu	☐ IR

CR = cocmplete response; CRu = CR unconfirmed; PR = partial response; NC = no change

AR1 = adequate response group 1 ⇨ no radiotherapy

AR2 = adequate response group 2 ⇨ no radiotherapy

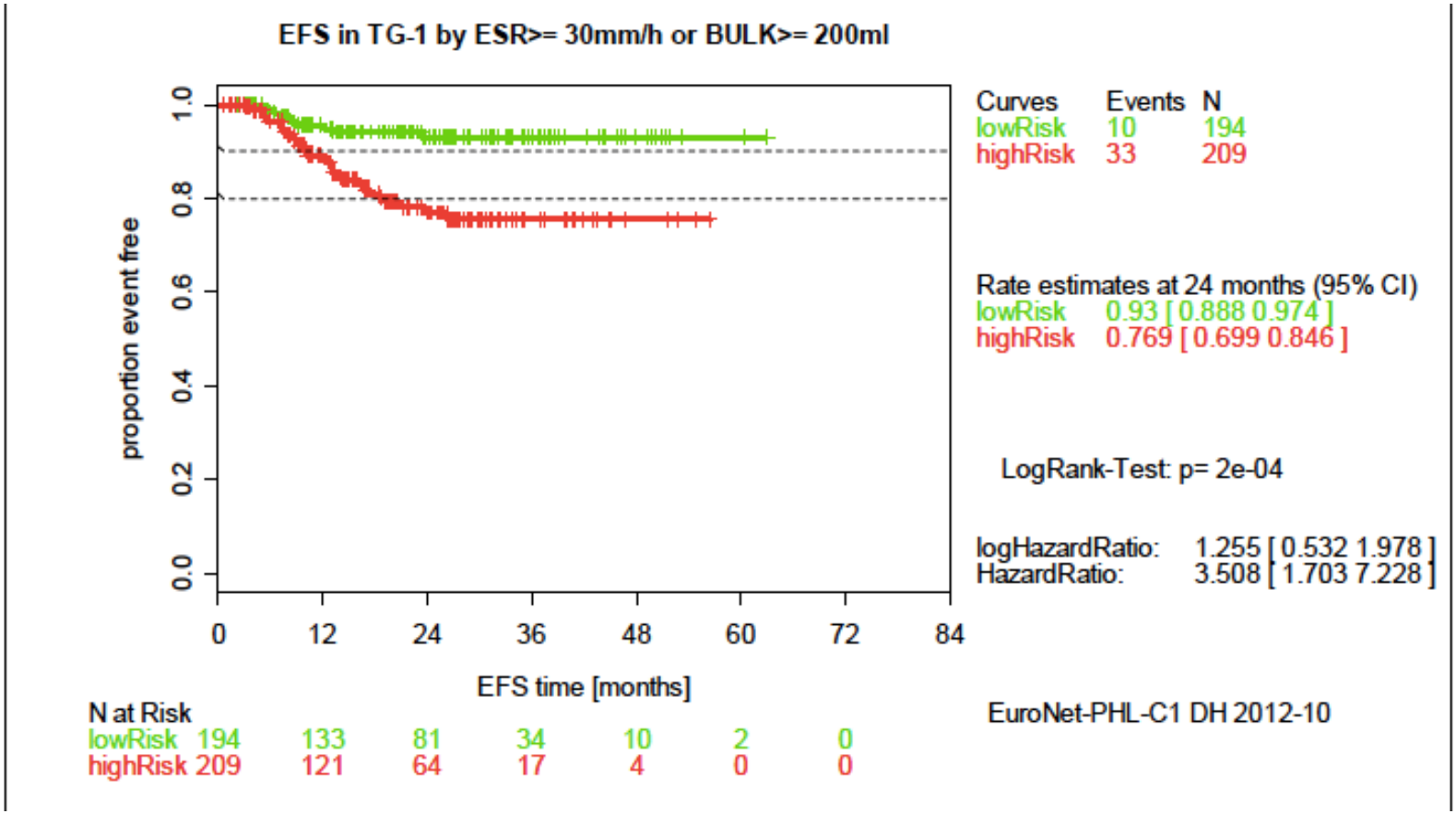
IRu = inadequate response qroup unconfirmed ⇨ radiotherapy

IR = inadequate response group ⇨ radiotherapy

Preliminary results suggest that this strategy is feasible to identify patients who can have a good long-term survival without RT.

www.anzchog.org/docs/public-resources/euronet-recommendation.pdf?sfvrsn=0 Mauz-Korholz. J Clin Oncol. 2015 Sep 20;33(27):2975-85.

Third interim analysis



Patients with a high ESR ≥ 30 mm/h and/or a bulk volume ≥ 200 mls had a worse prognosis (EFS below 80%) when compared to TG-1 patients without these risk factors (EFS 97%).

www.anzchog.org/docs/public-resources/euronet-recommendation.pdf?sfvrsn=0

Treatment of favorable-risk HL

- No single standard treatment for favorable risk HL
- Chemotherapy (OEPA, VAMP, COPP-ABV, AV-PC) x 2-4 cycles
- Response-based low-dose, Involved-Site RT to 15-25.5Gy
  - Questions to be answered
    - Optimal definition and timing of response
    - Best imaging modalities to evaluate response
    - How to integrate imaging and clinical factors

Castellino et al. 2011. Pediatric Blood & Cancer 56;883.
Keller et al.. 2014. Klin Padiatr 226;105.
Keller et al.2010. Blood 116:767.

Intermediate-risk disease

Definition of intermediate-risk HL

- In risk-adapted treatment regimens, intermediate-risk disease is defined as:
  - Stage IA, IIA with unfavorable features
  - Stage IIIA

Procarbazine-free chemotherapy regimen in boys to decrease gonadotoxicity

- In GPOH-HD-95, 5-year DFS was significantly worse in boys vs. girls (86% vs. 93%; P=0.005), partially attributed to procarbazine replacement by etoposide in OEPA for boys
- Thus, in GPOH-HD-2002, procarbazine-free regimen was also used, but with escalated etoposide dose and IV dacarbazine

Mauz-Korholz et al. J Clin Oncol. 2010 Aug 10;28(23):3680-6

GPOH-HD-2002

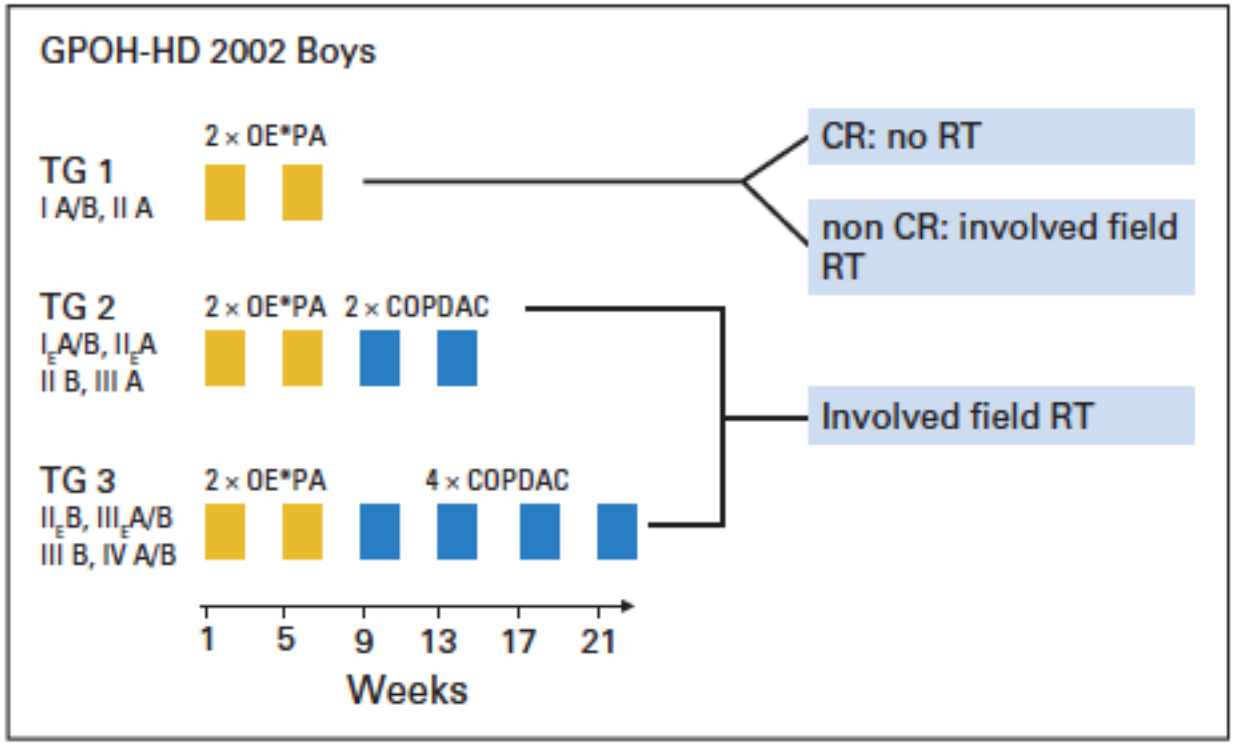
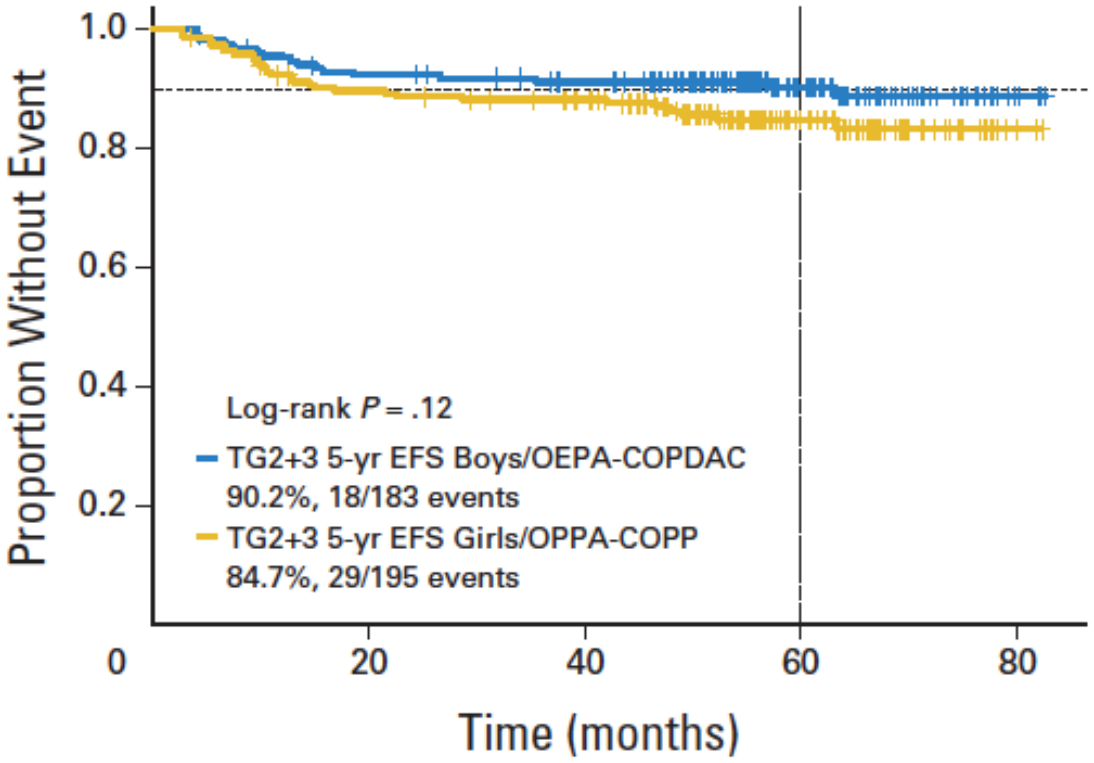


Fig 1. Study design of the German Society of Pediatric Oncology and Hematology–Hodgkin's Disease (GPOH-HD) 2002 study for male patients. Girls were similarly treated with standard two cycles of vincristine, procarbazine, prednisone, and doxorubicin instead of vincristine, etoposide, prednisone, and doxorubicin (OE*PA) and cyclophosphamide, vincristine, procarbazine, and prednisone instead of cyclophosphamide, vincristine, prednisone, and dacarbazine (COPDAC) in treatment group (TG) 2+3. CR, complete remission; RT, radiotherapy.

Mauz-Korholz et al. J Clin Oncol. 2010 Aug 10;28(23):3680-6

GPOH-HD-2002

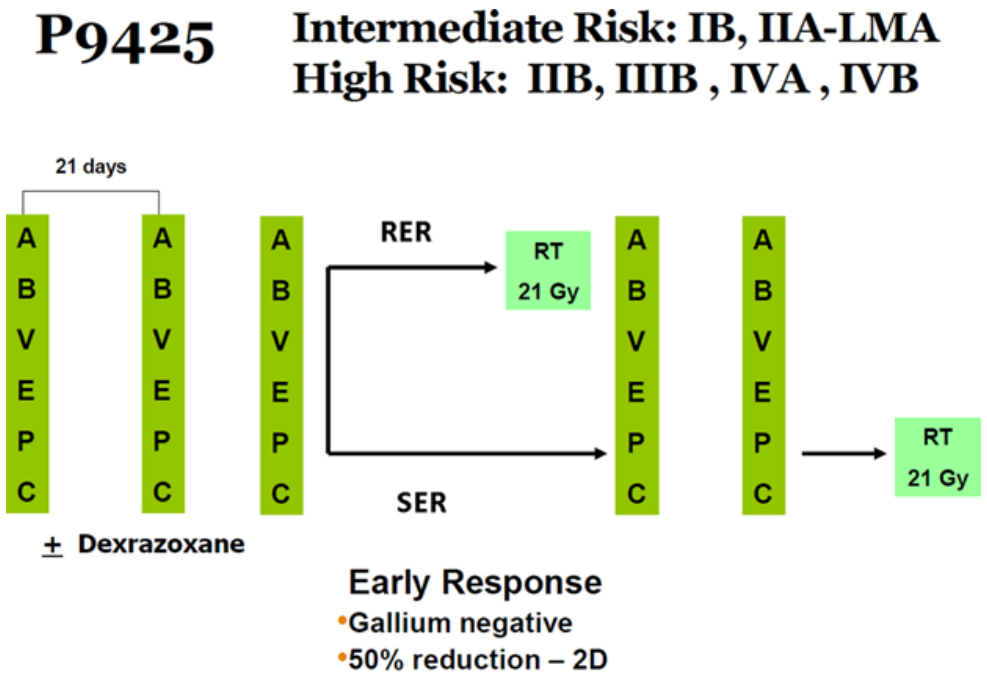
- In TG-2+3, EFS did not significantly different between boys and girls (90.2% vs. 84.7%, P=0.12)



- (In TG-1, 5-year EFS was similar without RT (93.2%) vs. with RT (91.7%), confirming results of GPOH-HD-95)

Mauz-Korholz et al. J Clin Oncol. 2010 Aug 10;28(23):3680-6

Response-based therapy

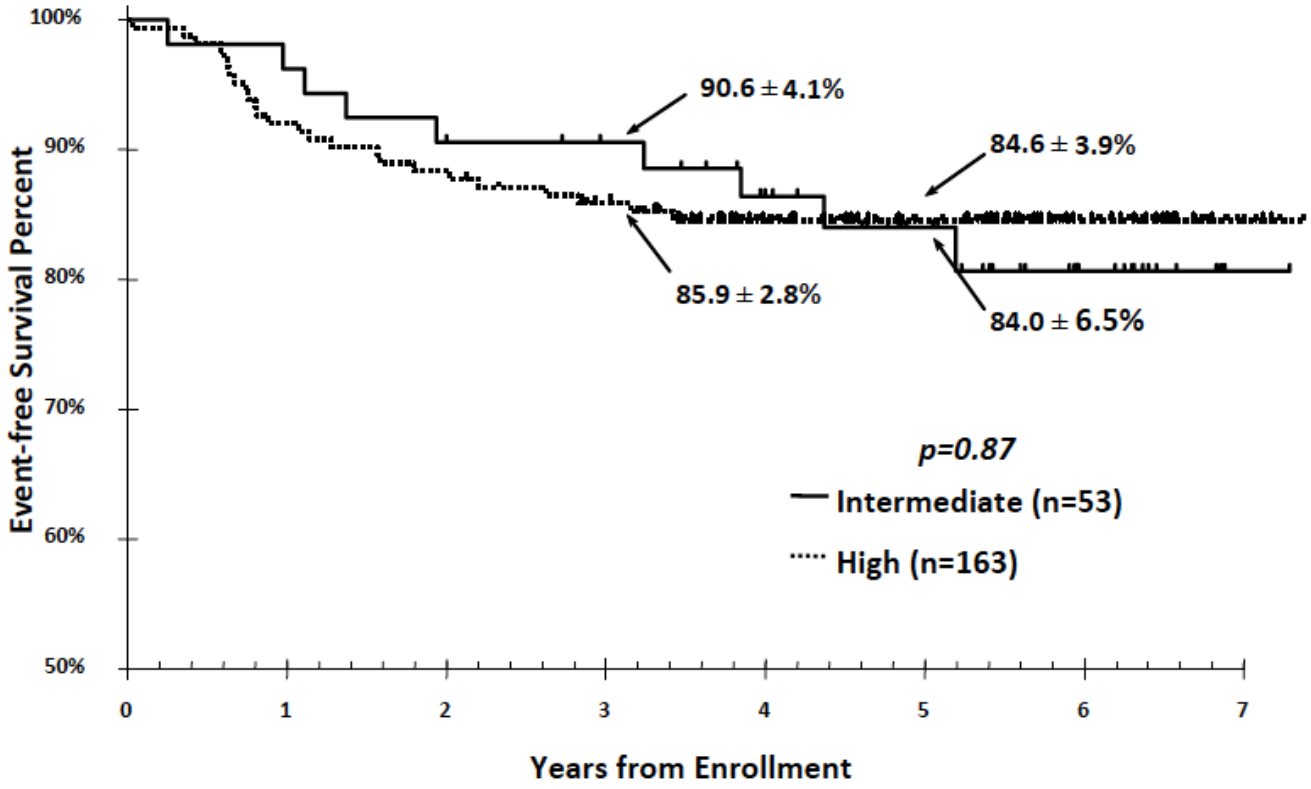


Large mediastinal adenopathy (LMA) = ratio of the mediastinal mass diameter divided by the trans-thoracic diameter at the dome of the diaphragm was >0.33 on posterior-anterior chest radiograph

- For whole cohort (both intermediate- and high-risk patients)
  - 5-year EFS: 86% for RER patients vs. 83% for SER patients (P=0.85)
  - 5-year OS: 95%
  - For those with LMA vs. without LMA, 5-year EFS was 80% vs. 91% (P=0.015)

Schwartz CL et al. Blood 2009;114:2051–2059.

P9425 study



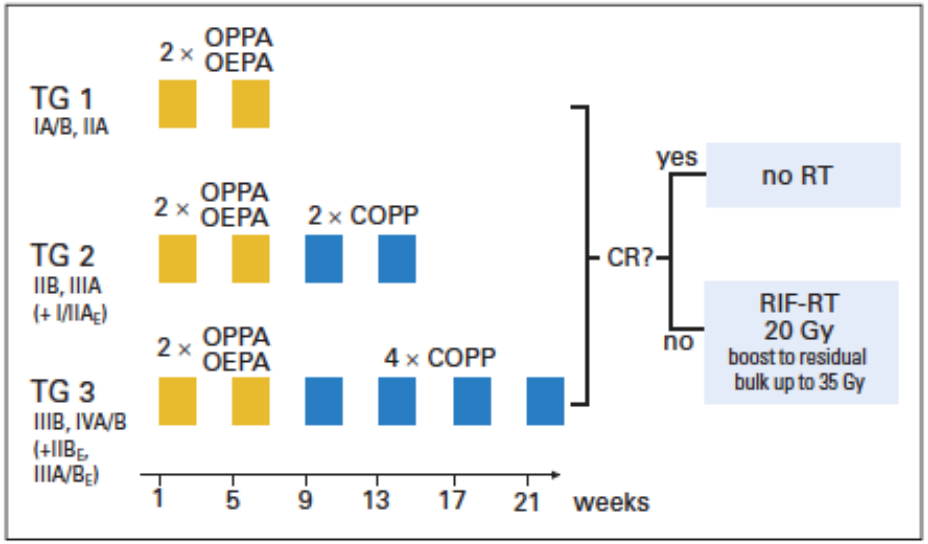
For intermediate-risk patients, 5-year EFS was 85%

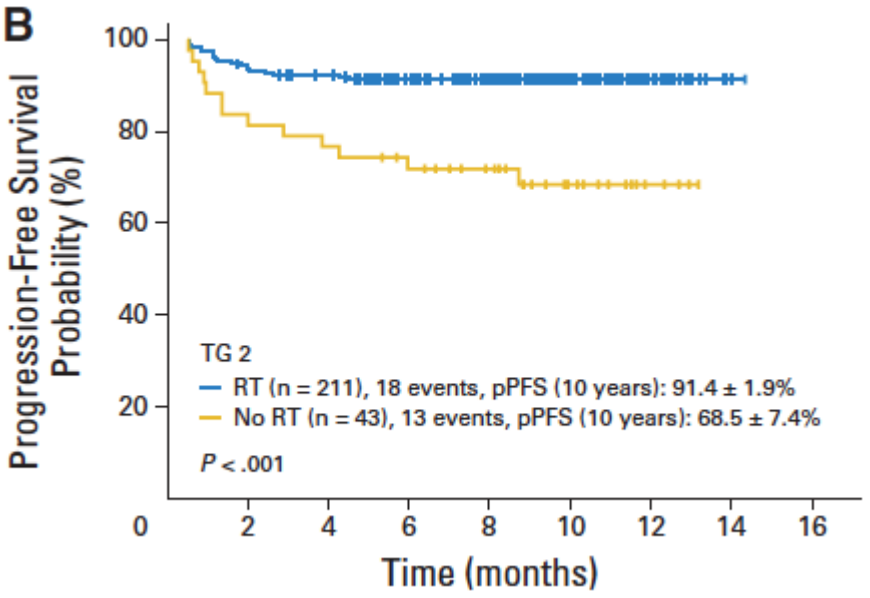
Schwartz CL et al. Blood 2009;114:2051–2059.

Response-based reduction of RT

GPOH HD-95

- Significant difference in outcome between intermediate-risk patients treated with chemotherapy alone vs. chemotherapy plus RT: 10-year PFS 69% vs. 91% (P<0.0001)





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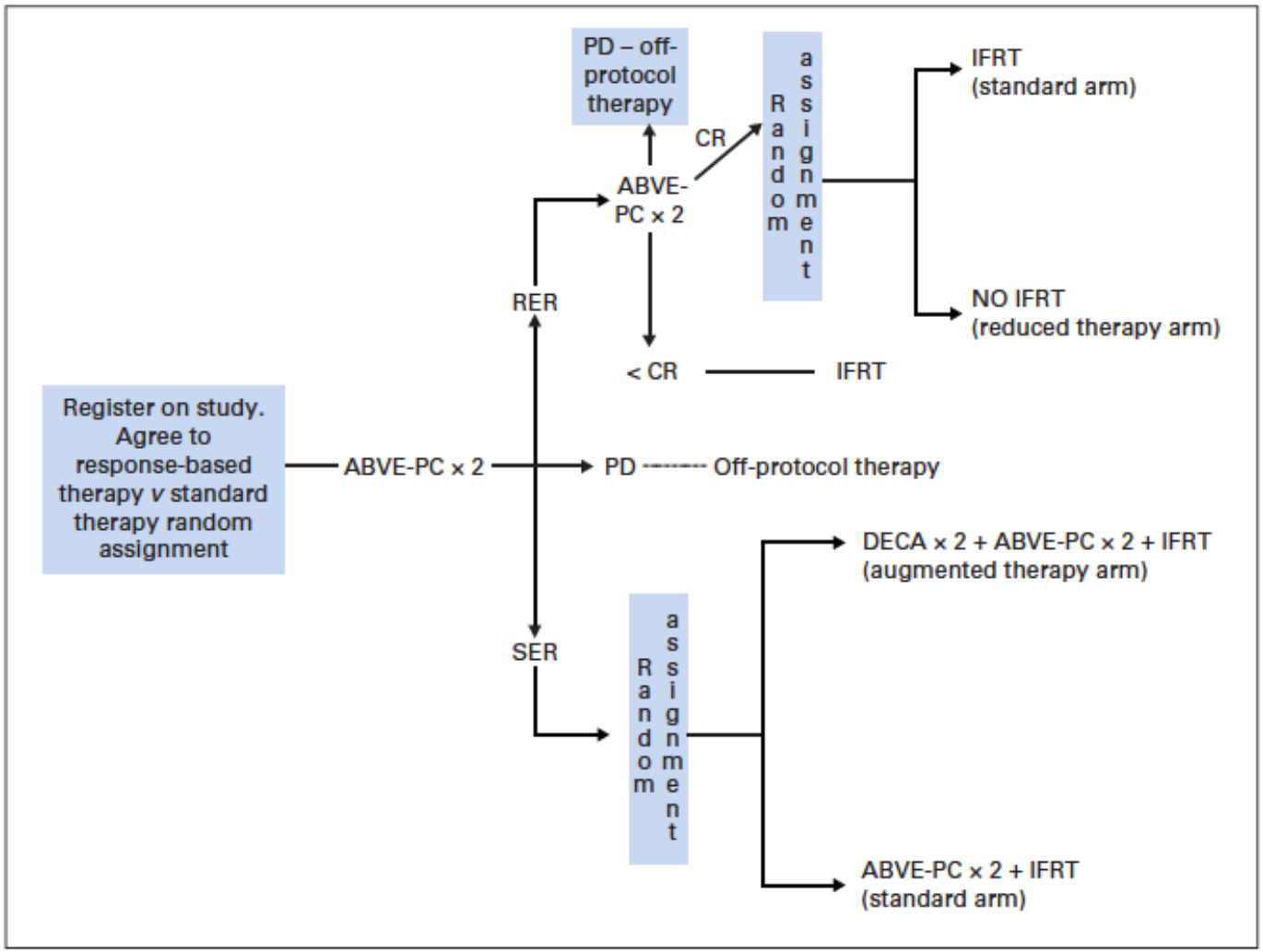
Dorfell et al. J Clin Oncol. 2013 Apr 20;31(12):1562-8

COG AHOD 0031



Stages IB, IAE, IIB, IIAE, IIIA, IVA, and IA or IIA with bulk

RER = ≥60% reduction in the product of perpendicular diameters (PPD) for all target lesions or return to normal size (regardless of PET response)

SER = rapid early response not achieved

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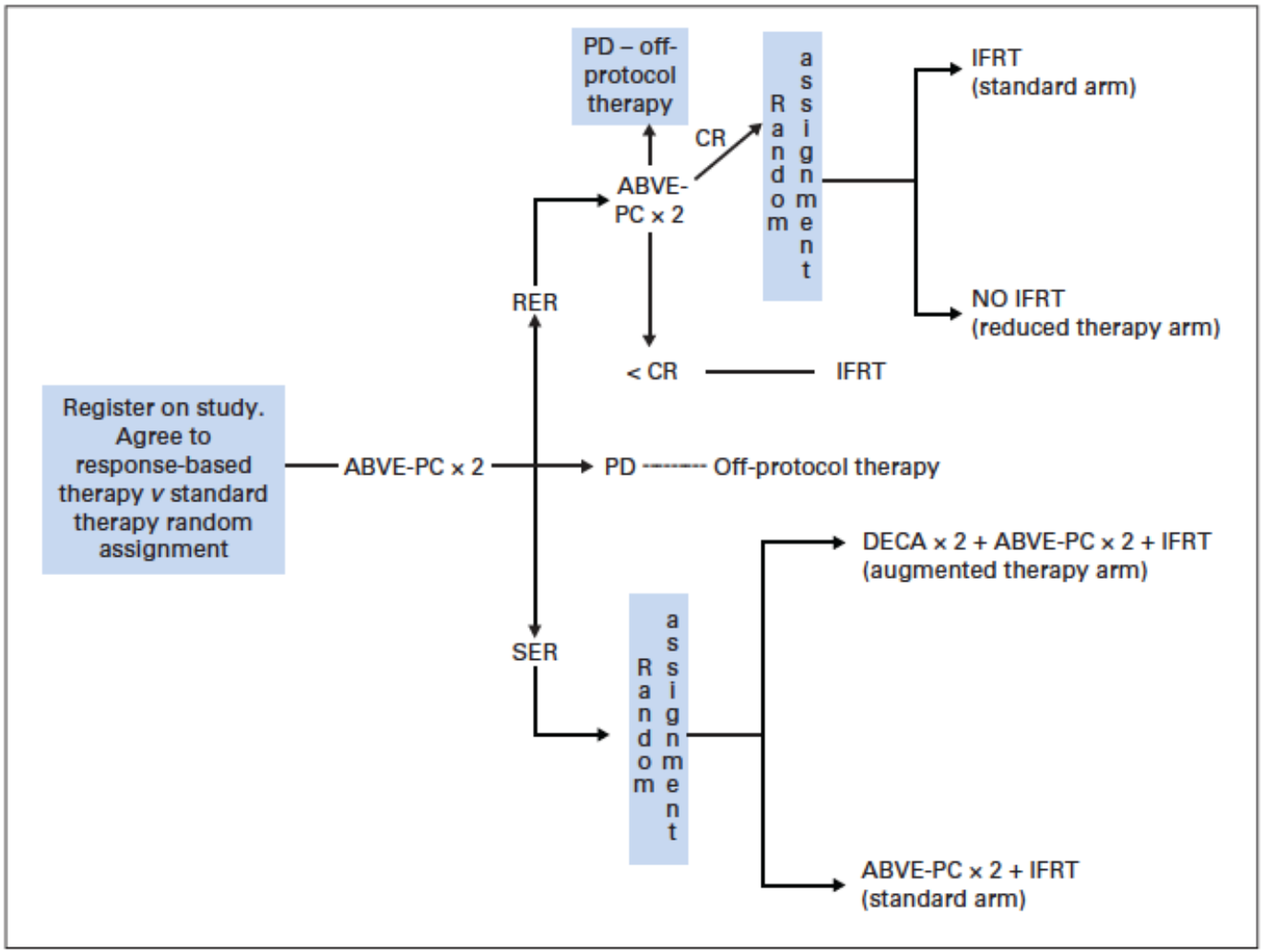
Friedman et al. J Clin Oncol. 2014 Nov 10;32(32):3651-8

COG AHOD 0031



CR = ≥80% reduction in PPD or a return to normal size for all target lesions; no residual extramediastinal nodal mass >2cm; no residual in non-measurable sites, and a negative galium or FDG-PET scan

IFRT to 21Gy

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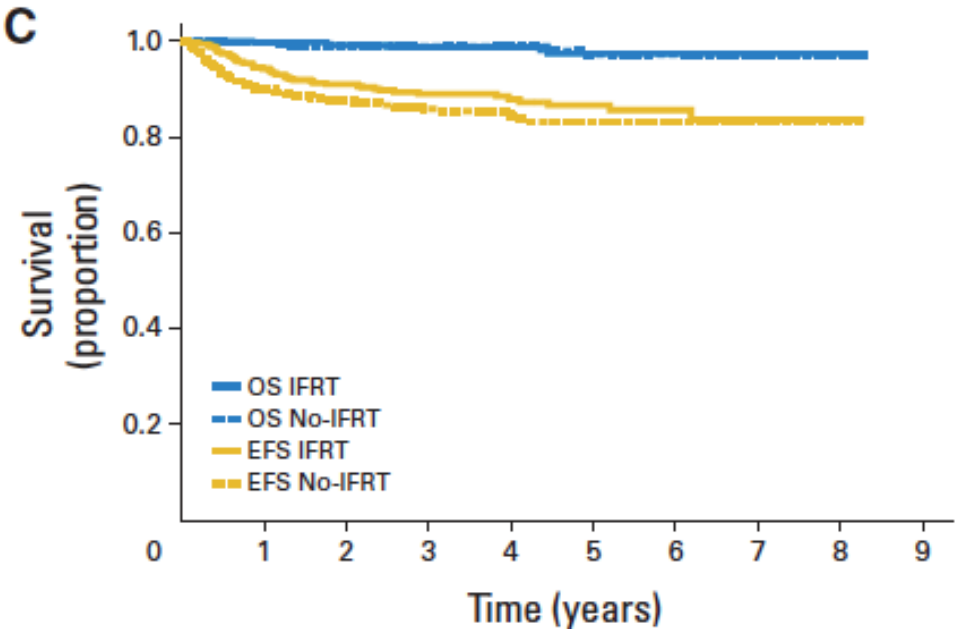
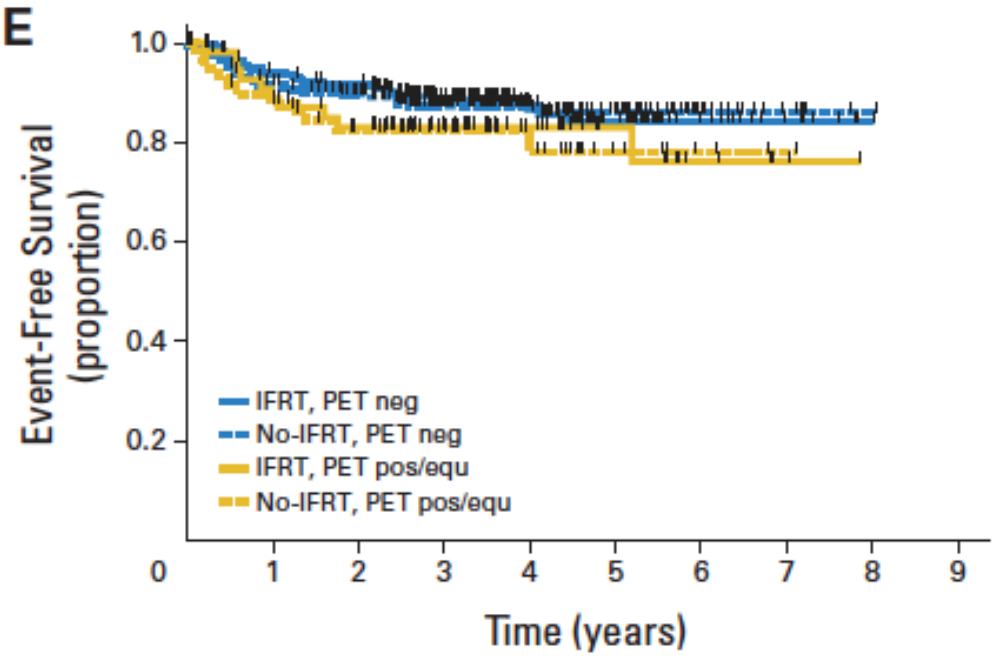
- 4-year EFS: 86.9% for RERs and 77.4% for SERs (P<0.001)
- 4-year OS: 98.5% for RERs and 95.3% for SERs (P<0.001)
- For IFRT random assignment, 4 year EFS:
  - 87.9% after IFRT vs. 84.3% after no IFRT (P=0.11)
  - 86.7% after IFRT vs. 87.3% after no IFRT (P=0.87)





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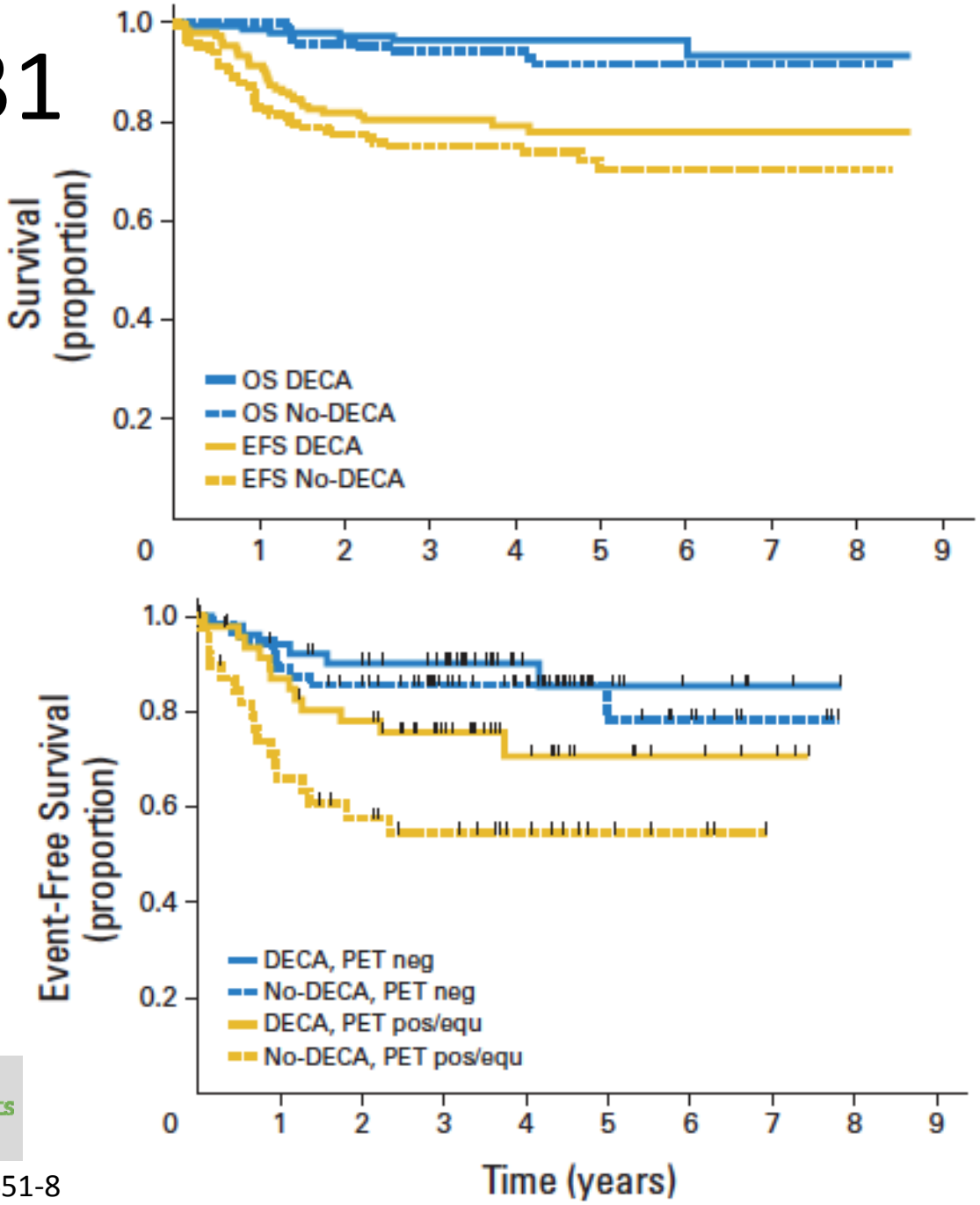
- For SER patients,
  - 4-year EFS: 79.3% after DECA vs. 75.2% after no DECA (P=0.11)
- For SERs with PET-positive results at response assessment
  - 4-year EFS: 70.7% after DECA vs. 54.6% after no DECA (P=0.05)



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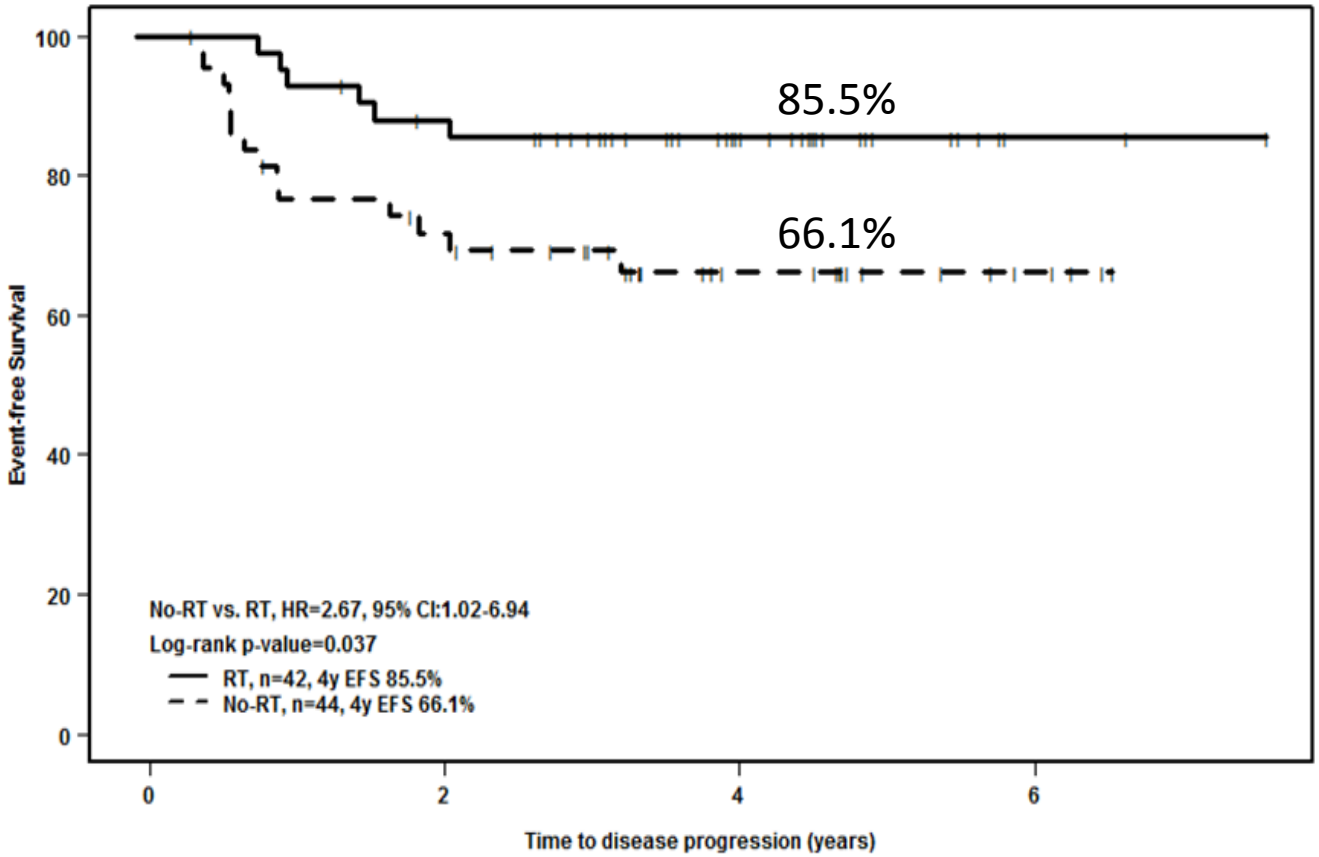
Friedman et al. J Clin Oncol. 2014 Nov 10;32(32):3651-8

Patients with Anemia and Large Mediastinal Mass (LMA)



RT significantly improved EFS in patients with anemia and LMA, even if achieving RER/CR (26% of RER/CR patients)

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Charpentier et al. Int J Radiat Oncol Biol Phys. 2016; 96(5):943-950.

COG AHOD 0031

- Confirms prognostic significance of early response to chemotherapy
- Chemotherapy augmentation improves EFS for SERs with PET-2-positive results (borderline significance)
- Suggests that RT can be omitted in patients with **both** rapid early response **and** complete response
  - PET used to confirm/supplement anatomic RER and CR status, not replace
- However, patients with LMA + anemia did significantly better with RT regardless of RER/CR status.

Friedman et al. J Clin Oncol. 2014 Nov 10;32(32):3651-8

Treatment of Intermediate-risk HL

- Dose-intensive chemotherapy (OEPA/COPP, ABVE-PC) x 3-6 cycles plus ISRT to 15-25.5Gy
- Consider omitting RT after ABVE-PC x 4 cycles in patients who achieve rapid early response and complete response

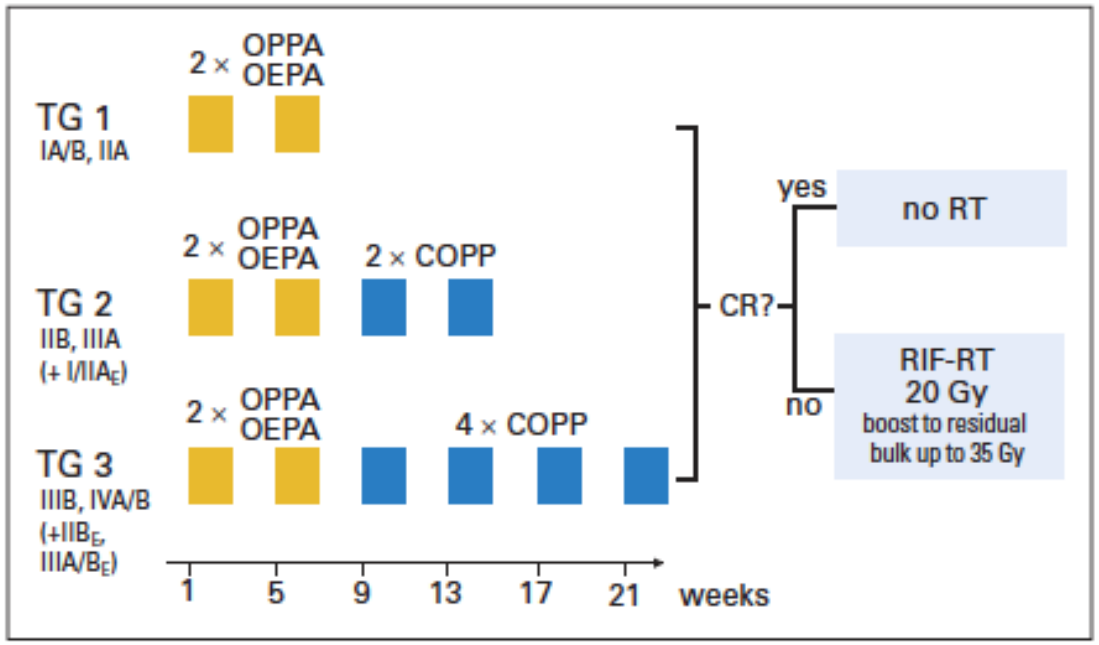
Unfavorable-Risk Disease

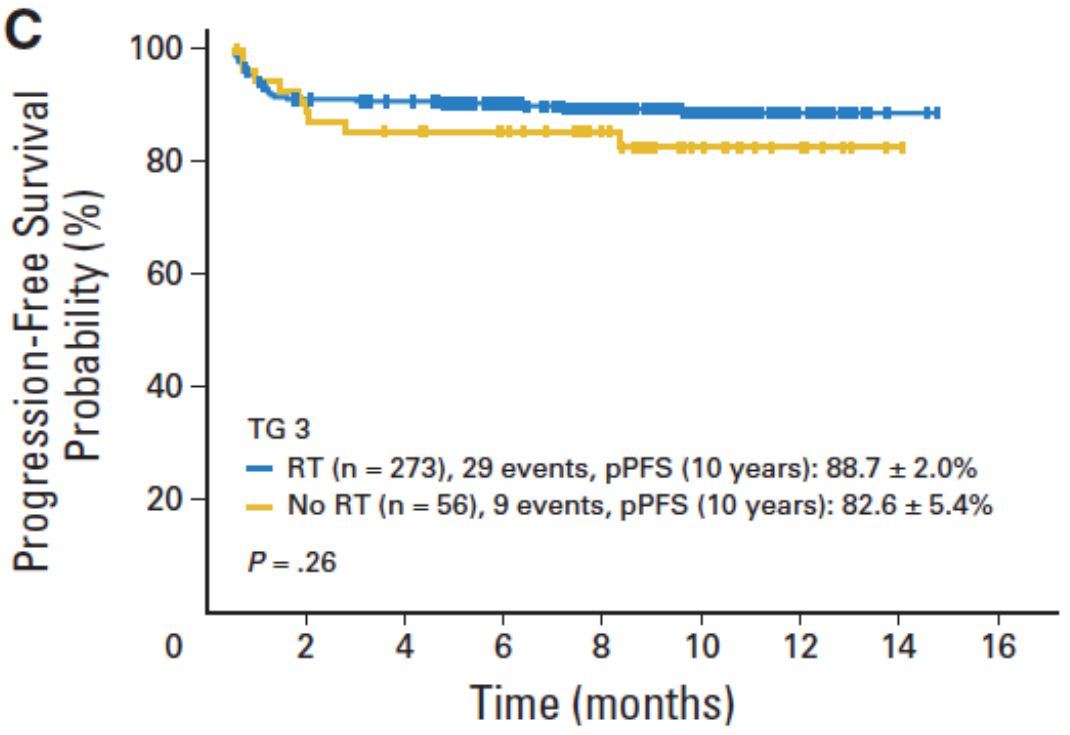
Definition of unfavorable-risk disease

- Typically includes presence of B symptoms, bulky lymphadenopathy, hilar lymphadenopathy, ≥3 nodal regions, extranodal extension to contiguous structures

GPOH HD-95

- TG3 = IIB_E, $IIIA_E$, IIIB, $IIIB_E$, IV,
- Unfavorable-risk patients treated with chemotherapy alone vs. chemotherapy plus RT: 10-year PFS 83% vs. 89% (P=0.26)





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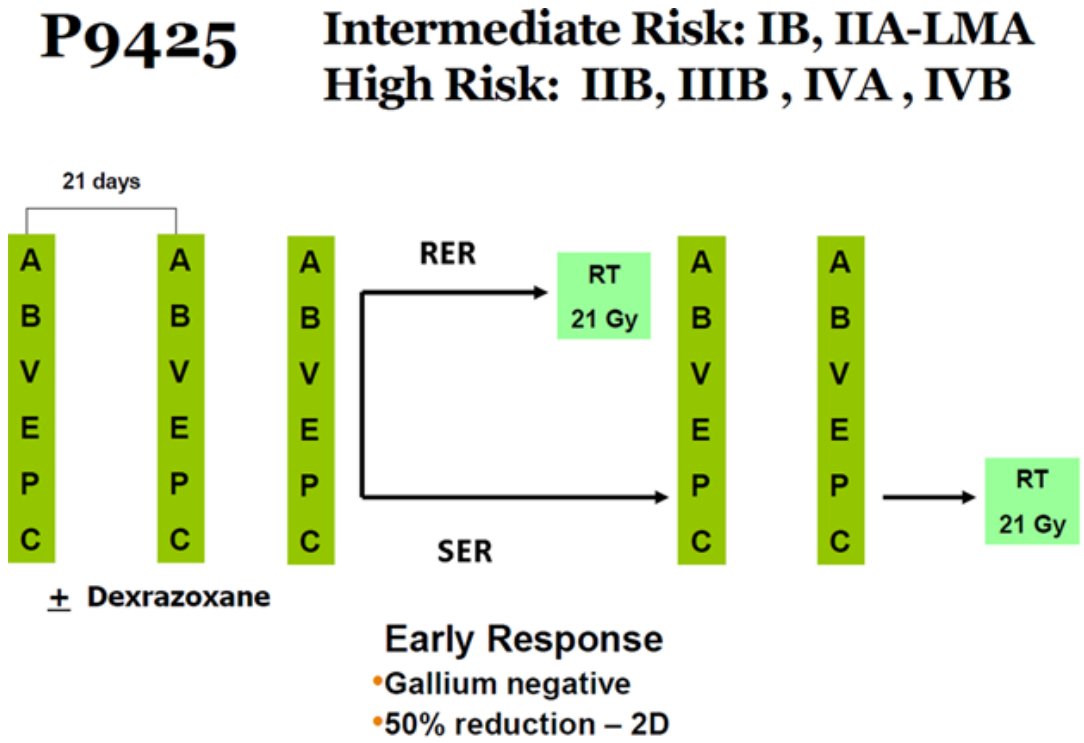
Dorfell et al. J Clin Oncol. 2013 Apr 20;31(12):1562-

POG9425

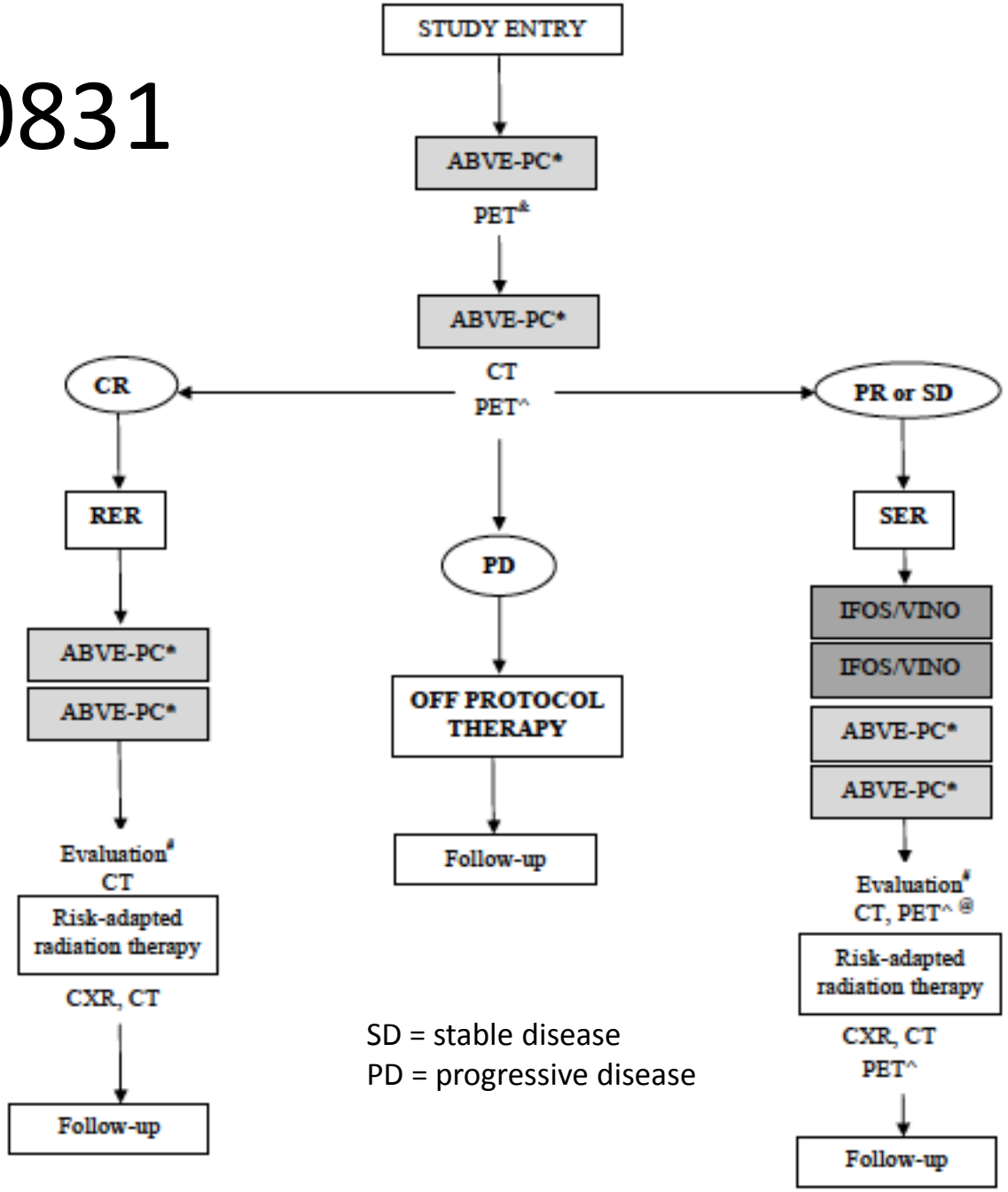


- High risk = IIB, IIIB, IV
  - 5-year EFS for high-risk HL = 85%
- 37 Stage IIIB patients and 51 Stage IVB patients
  - Estimated 5-year EFS: 92% for Stage IIIB and 74% for Stage IVB

Schwartz CL et al. Blood 2009;114:2051–2059.

COG AHOD 0831

- Stage IIIB/IVB
- Slightly more intensified version of the DBVE-PE chemotherapy of POG9425
- RT to 21 Gy in 14 fractions



SD = stable disease
PD = progressive disease

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Sites of RT for RER patients:

- **Initial bulky disease** (large mediastinal mass (LMM), nodal aggregate (NA)>6cm and macroscopic splenic nodules)

Sites of RT for SER patients:

- **Initial bulky disease** (LMM, NA>6cm and macroscopic splenic nodules)
- **Slow responding non-bulky disease** (FDG-PET residual activity after first 2 cycles of chemotherapy)
- **Residual disease > 2.5 cm** at end of chemotherapy

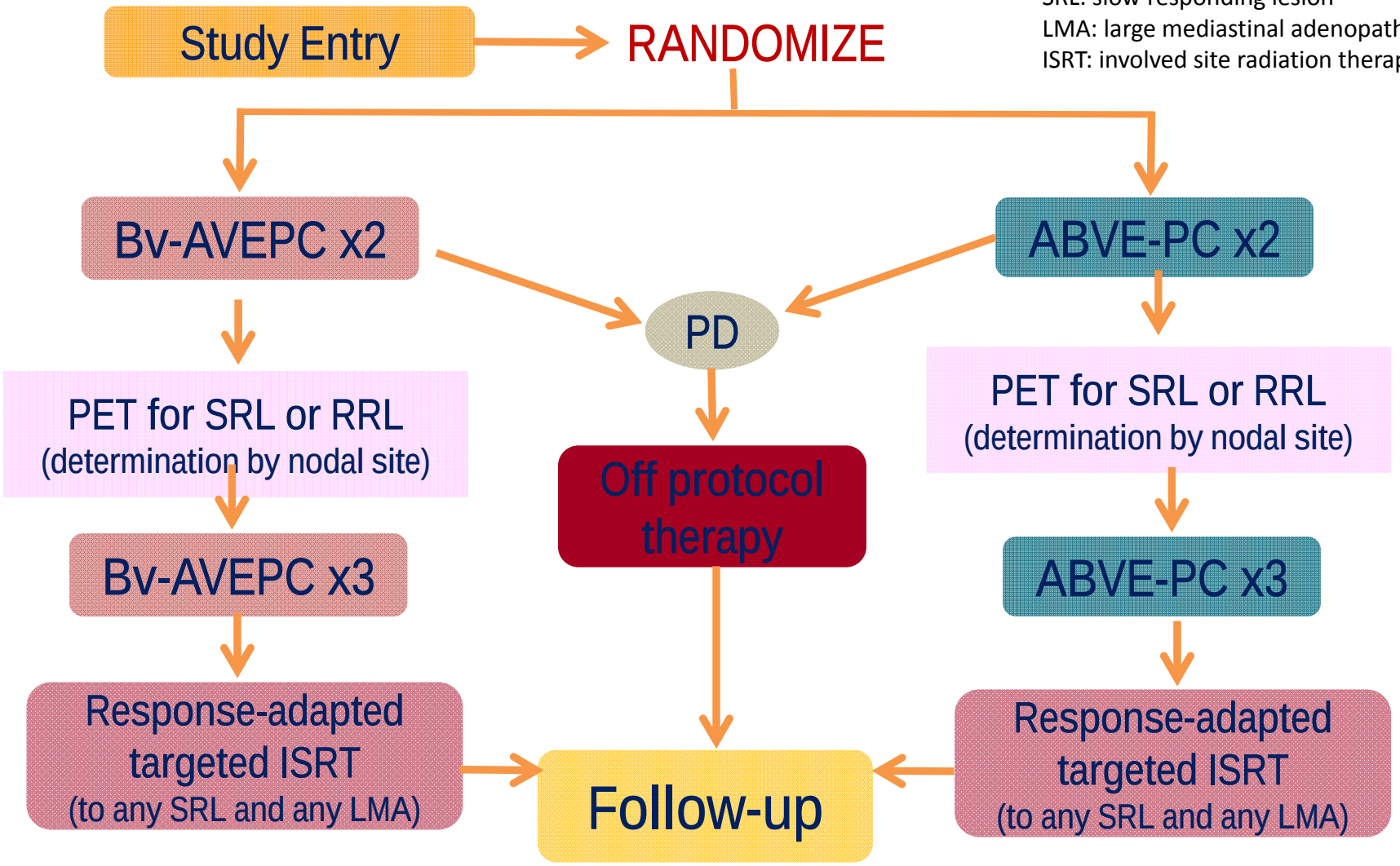
COG AHOD 0831

- Median FU 42 months
- Primary endpoint = “Second-Event” (e.g. second relapse or malignant neoplasm) free survival
  - Reasonable estimate of long term OS
- 4-year 2nd EFS: 89.9%
  - RER patients: 91.9%
  - SER patients: 87.8%
  - Stave IVB: 89.6%
- 4-year OS: 95.9%
- 12 SER patients had persistent PET+ lesions at end of chemotherapy
  - 8/12 had clinical evidence of active disease
- Similar outcomes to POG 9425 despite reduction in RT volumes
- Persistent PET+ at end of chemo → especially high risk for relapse/early progression

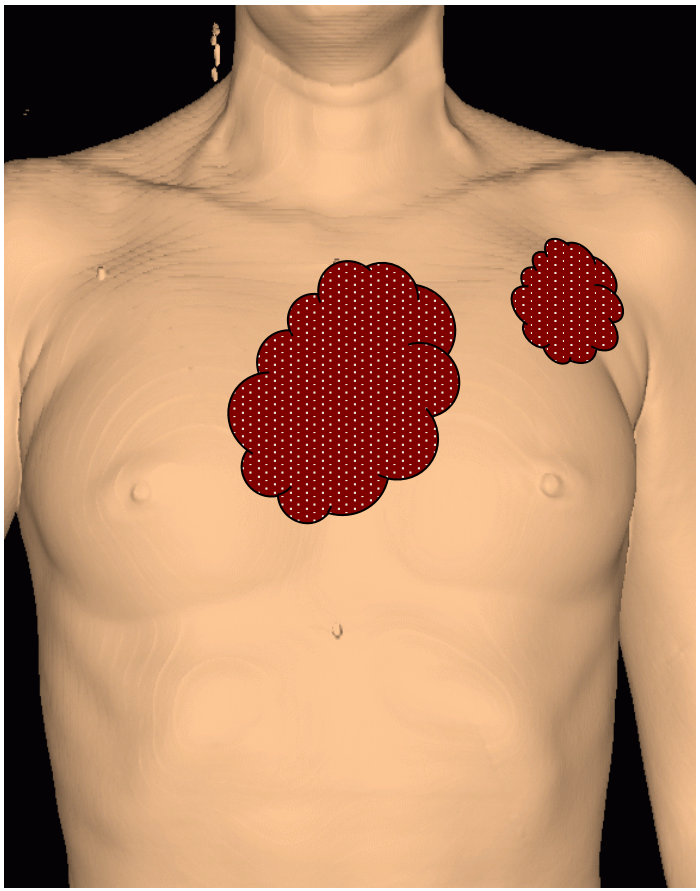
Kelly et al. ASH 2015.

High Risk: AHOD1331: Experimental Design

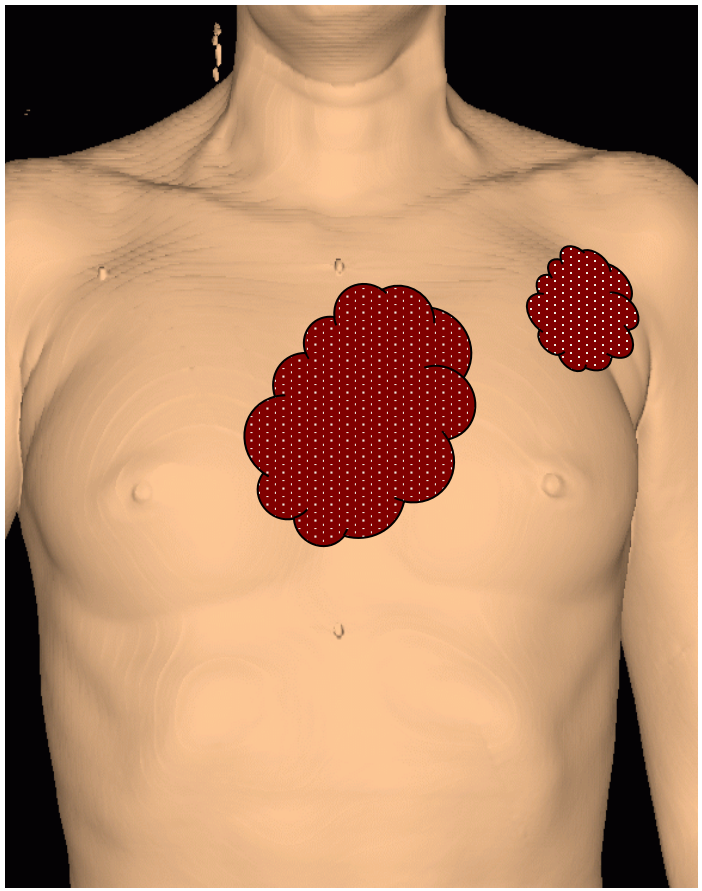
RRL: rapid responding lesion
SRL: slow responding lesion
LMA: large mediastinal adenopathy
ISRT: involved site radiation therapy



COG AHOD 1331: Modification of RT Volume for Patients with LMA

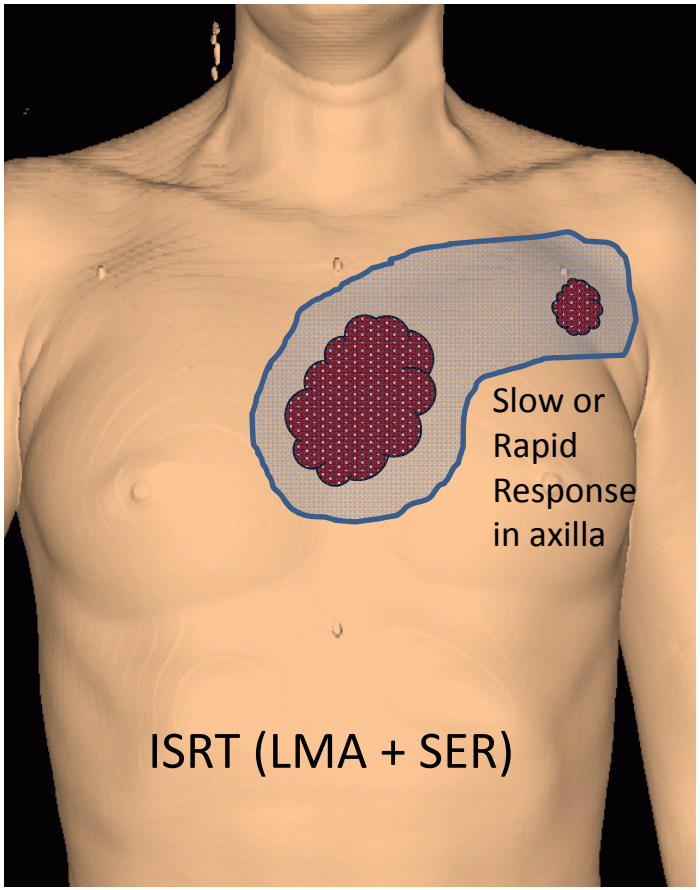


Prior Trials

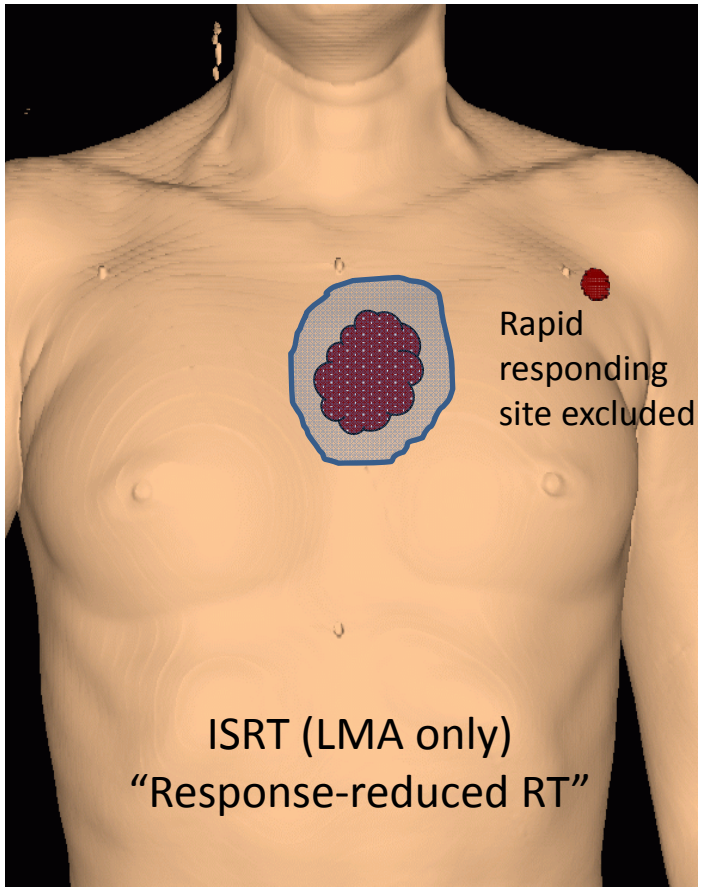


AHOD 1331

COG AHOD 1331: Modification of RT Volume for Patients with LMA



Prior Trials



AHOD 1331

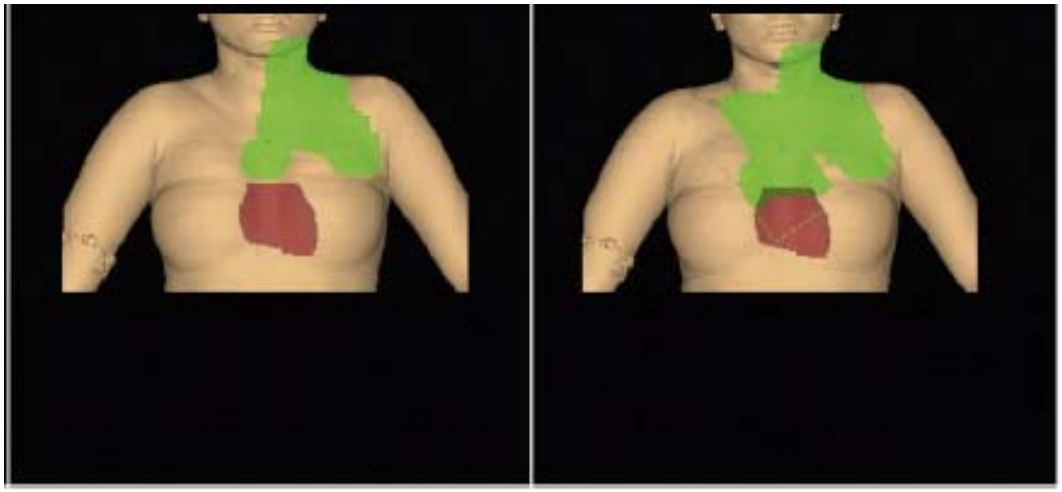
Treatment of unfavorable-risk disease

- Compacted, dose-intensive chemotherapy (COPP/OEPA, ABVE-PC) x 4-6 cycles plus ISRT to 15-25.5 Gy
- RT to areas of initial bulky disease, slowly-responding non-bulky disease, and post-chemotherapy residual disease

Radiation therapy

Radiation therapy volumes

- Radiation volumes must be cautiously designed to maximize disease control while minimizing toxicities
- Increased efficacy of combination chemotherapy, as well as advances in imaging, treatment planning, and RT delivery have allowed further decrease of RT fields



Adolescent female with stage IIA nonbulky Hodgkin lymphoma. Left: Involved-site RT. Right: Involved-field RT. (Green=PTV)

Hodgson et al. Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92

Radiation therapy volumes

- **Involved nodal RT (INRT)**: CTV includes individual lymph nodes (LNs) that have macroscopic evidence of lymphomatous involvement at diagnosis based on anatomic and functional imaging, and excludes adjacent uninvolved LNs and enlarged tissues
- **Involved site RT (ISRT):** similar to INRT, but used when imaging leaves some uncertainty regarding the exact location of involved LNs to be targeted as CTV (e.g. pretreatment imaging not done in the RT treatment position, no fusion of CT and PET images, etc.). May include nodal tissue immediately adjacent to involved nodes (e.g. adjacent nodes on the same axial planning CT slice) recognizing that available imaging may not identify small spatial differences in the location of HL involvement.

Specht et al. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62
Hodgson et al. Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92

Radiation therapy volumes

- **Modified involved field RT** is used in the EuroNet PHL-C1 trial. Treatment volumes contain the involved lymph node(s) prior to chemotherapy plus ITV-PTV margins of 1-2 cm depending on area of involvement. Comparable with ISRT, but developed before widespread availability of CT-based planning.
- Larger field RT is now limited to salvage treatment in patients in whom chemotherapy is unsuccessful and who are unable to embark on more intensive salvage treatment schedules

Hodgson et al. Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92

Involved site RT

- ISRT is the favored approach in the current era
- <u>Pre-chemotherapy GTV</u>
  - Imaging abnormalities indicating lymphomatous involvement before any intervention that might have affected lymphoma volume

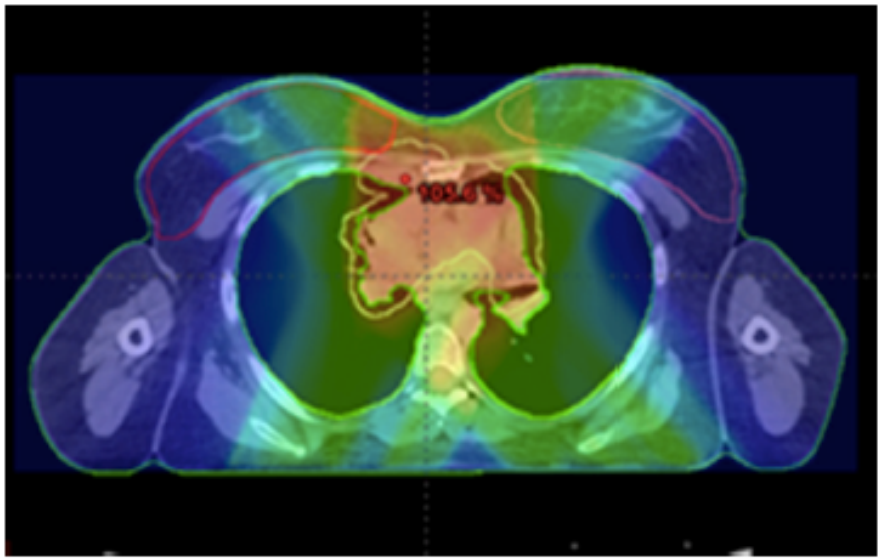


Fig. 3. Involved site radiation therapy with intensity modulated technique, dose distribution.

- <u>No chemotherapy or postchemotherapy GTV</u>
  - Imaging abnormalities of lymphomatous involvement, untreated or after chemotherapy

Specht et al. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62

Involved site RT

- CTV
  - Encompasses pre-chemotherapy GTV, modified for normal tissue boundaries and expanded to accommodate uncertainties in determining the prechemotherapy volume
  - The following points need to be considered:
    - Quality and accuracy of imaging
    - Concerns of changes in volume since imaging
    - Spread patterns of the disease
    - Potential subclinical involvement
    - Adjacent organ constraints

Specht et al. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62

Involved site RT

- ITV
  - CTV plus a margin taking into account uncertainties in size, shape, and position of CTV within the patient
  - Most relevant when the target is moving (e.g. chest and upper abdomen with respiratory movements), while not needed if CTV unlikely to change shape or position during or between treatments (e.g. neck)
  - In the chest or upper abdomen, margins of 1.5-2cm in the sup-inf direction may be necessary
    - 4D imaging or deep-inspiration breath-hold technique is encouraged

Specht et al. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62

Involved site RT

- PTV
  - Includes CTV (or ITV, when relevant) and accounts for setup uncertainties in patient positioning and alignment of beams during treatment planning and throughout treatment

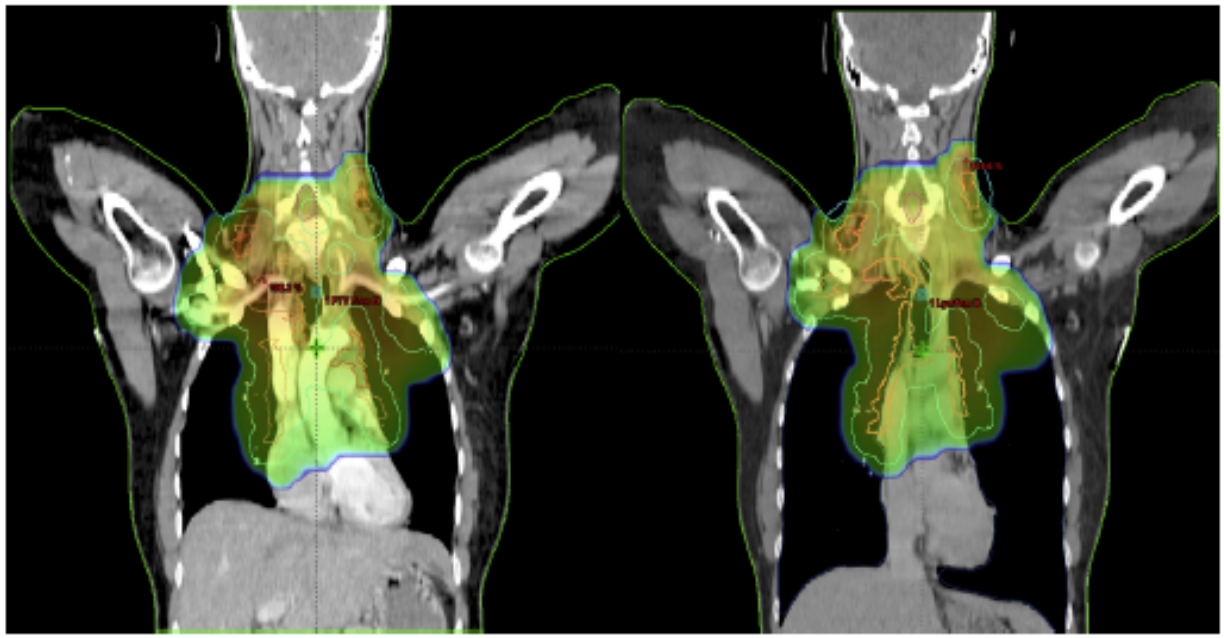


Fig. 5. Treatment plans for a patient with extensive mediastinal disease in free breathing (left) and inspiration breath-hold (right). Mean lung dose in free breathing was 15.7 Gy; in inspiration breath-hold it was 11.2 Gy.

Specht et al. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62

Radiation techniques

- Intensity-modulated radiation therapy (IMRT) provides improved PTV coverage ($D_{mean,}$ V_{95}, conformity index) compared with 3D-CRT
- In selected patients with mediastinal involvement (particularly, large and involving the anterior mediastinum), IMRT reduces pulmonary and cardiac toxicity
- However, greater attention needed regarding target definition and treatment delivery verification given tightly conformal doses and steep gradient.

Specht et al. Int J Radiat Oncol Biol Phys. 2014 Jul 15;89(4):854-62

Radiation dosimetry

- Heart
  - Mean cardiac dose associated with 25-year incidence of clinically significant coronary artery disease, congestive heart failure, valvular disease, or pericarditis
    - Mean <15Gy: <3% of each complication above
    - Mean >25Gy: 6-10%
    - Typically mean heart dose can be kept <10Gy
- Lung
  - 5% pneumonitis with V24 = 30%
  - Increased risk if received bleomycin

Hodgson et al. Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92

Radiation dosimetry

- Thyroid
  - >15Gy to thyroid: ~30% risk of abnormal thyroid function
  - >26Gy: 65-75% risk of abnormal thyroid function
  - 20-29Gy: thyroid cancer risk peaks, but appears to declines with higher doses
- Breast
  - 5-10Gy may lead to breast hypoplasia
  - Risk of breast cancer thought to increase linearly with dose
  - Typical mean breast dose is <3Gy.

Hodgson et al. Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92

Radiation dosimetry

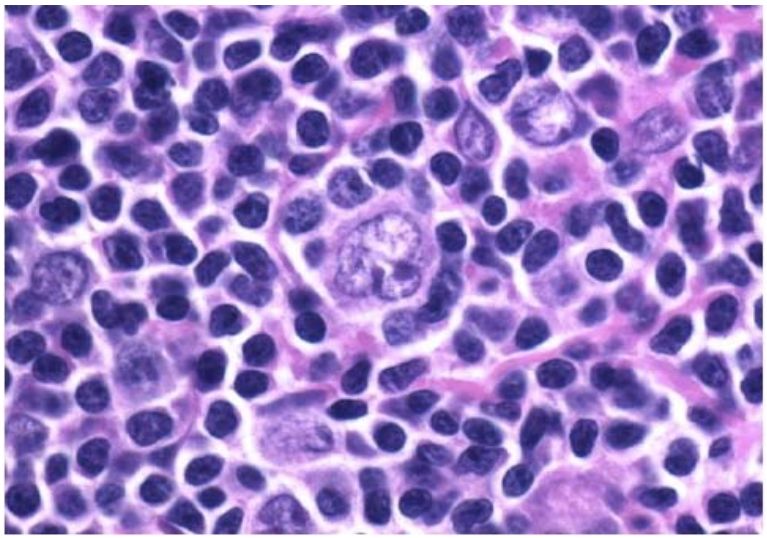
- Skeletal system
  - Growth impacted from >8Gy, potentially in dose-dependent fashion
- Soft tissues
  - >25-30Gy (<25Gy if age <10): impairment of growth of muscles and subcutaneous fat
  - <20Gy if age >10: only slight soft tissue growth effects expected
- Ovaries
  - If prepubertal, <4-6Gy tolerable, but tolerance may be lower in those receiving alkylating agent

Hodgson et al. Pract Radiat Oncol. 2015 Mar-Apr;5(2):85-92

Nodular Lymphocyte Predominant Hodgkin Lymphoma

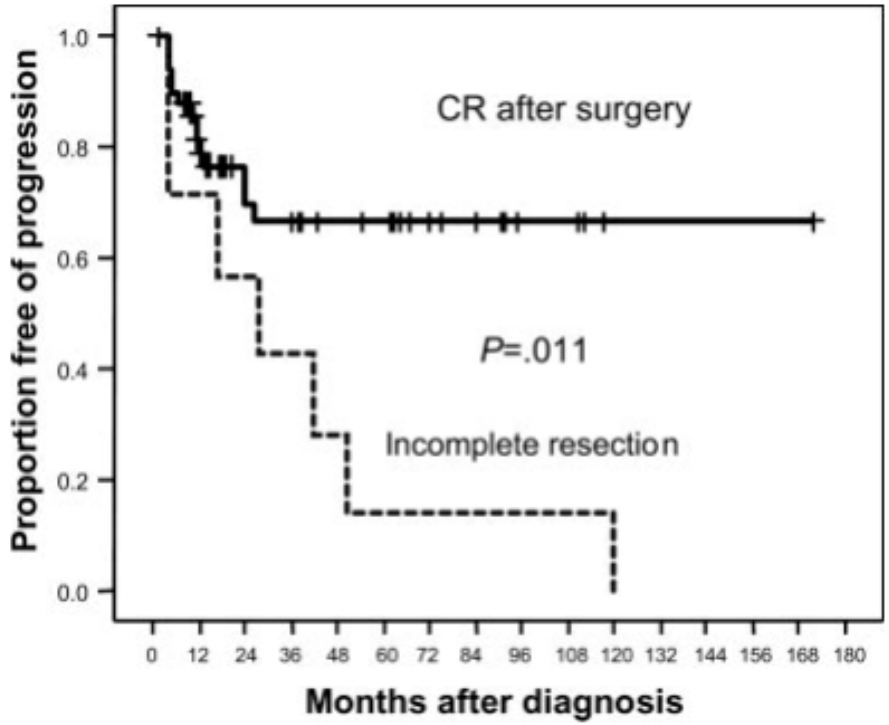
Nodular lymphocyte-predominant HL

- Nodular lymphocyte-predominant HL (nLPHL) is rare, CD-20+ subtype
- Indolent disease with a good prognosis
- Usually stage IA disease with peripheral LN involvement
- Male predominance



European retrospective study

- Stage IA/IIA/IIIA
  - 50/58 patients had Stage IA disease
- Median FU of 43 months
- OS 100%, PFS 57%
- 51/58 patients achieved complete remission (CR) after surgery
  - In CR group, overall PFS was 67%



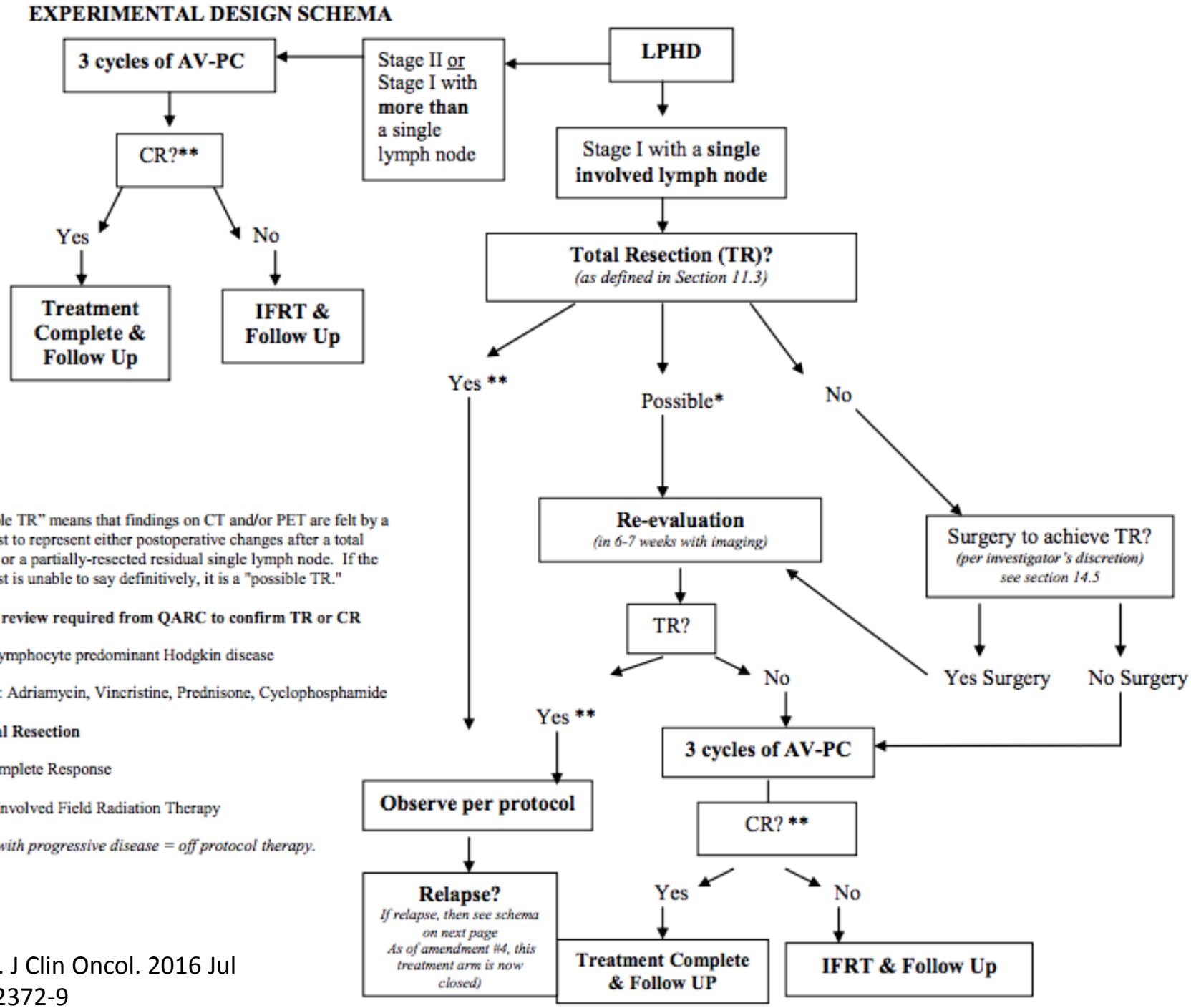
- 7/58 patients who had residual disease after initial surgery all developed recurrences

Mauz-Korholz et al. Cancer. 2007 Jul 1;110(1):170-85

COG AHOD03P1

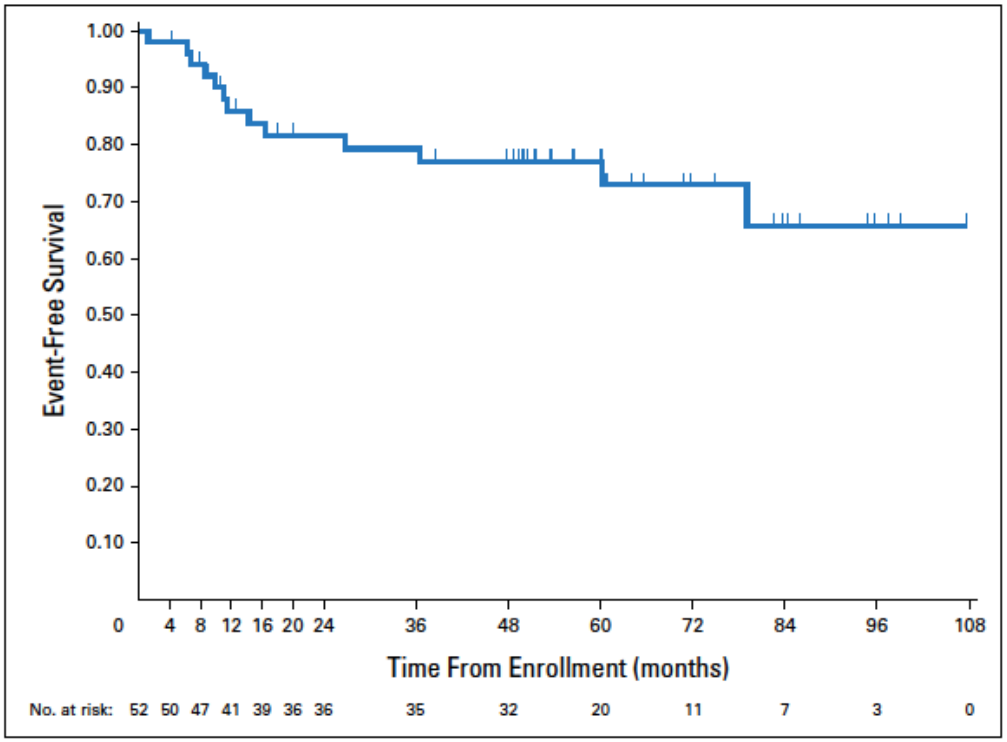
- 183 patients enrolled; 178 evaluable
- 52 patients had complete resection of a single node
- 126 patients were treated with AV-PC at diagnosis; 9 patients treated with AV-PC at relapse after surgery alone
- 11 patients had less than CR and received IFRT
- For entire cohort, 5-year EFS was 85.5% and OS was 100%

Appel et al. J Clin Oncol. 2016 Jul 10;34(20):2372-9

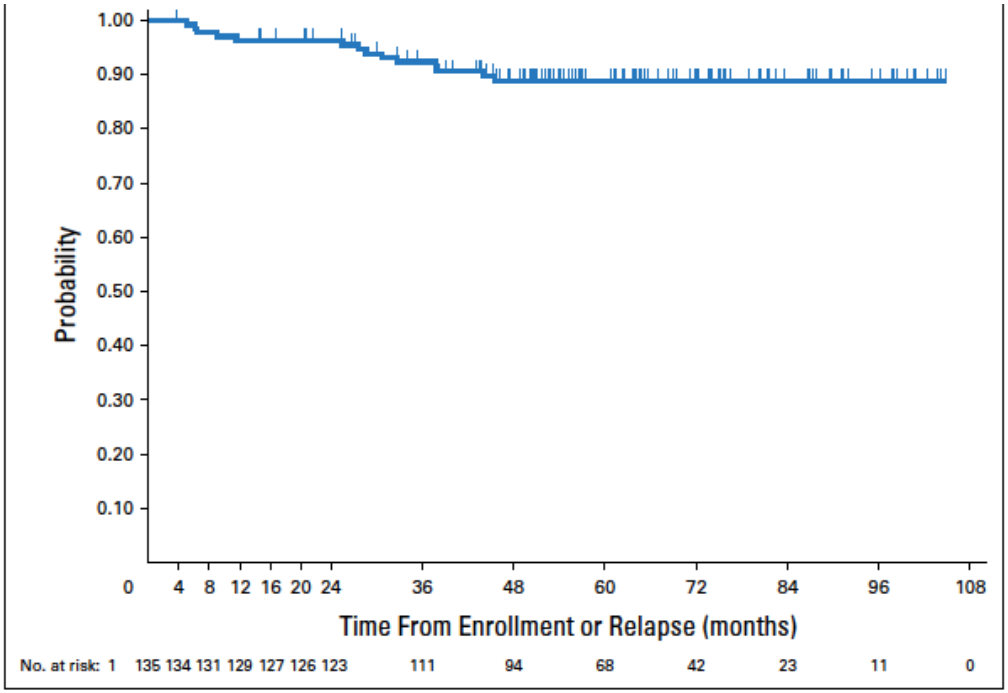


Appel et al. J Clin Oncol. 2016 Jul 10;34(20):2372-9

EFS, after observation, in patients who underwent total resection: 77.1% at 5 years



EFS after AV-PC with or without RT: 88.8% at 5 years



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Appel et al. J Clin Oncol. 2016 Jul 10;34(20):2372-9

Treatment of nLPHL

- Stage I single node completely resected: observation
- Stage I LPHL with more than one lymph node or stage II:
  - 3 cycles of AV-PC chemotherapy
  - Response assessed by CT and PET:
    - CR on both: no RT
    - Less than CR: 21Gy IFRT
- Relapse after complete resection: AV-PC +/-RT as per stage II
- More advanced disease is usually treated according to an appropriate Hodgkin protocol

Appel et al. J Clin Oncol 34:2372-2379, 2016

Refractory and Relapsed Disease

Refractory and relapsed disease

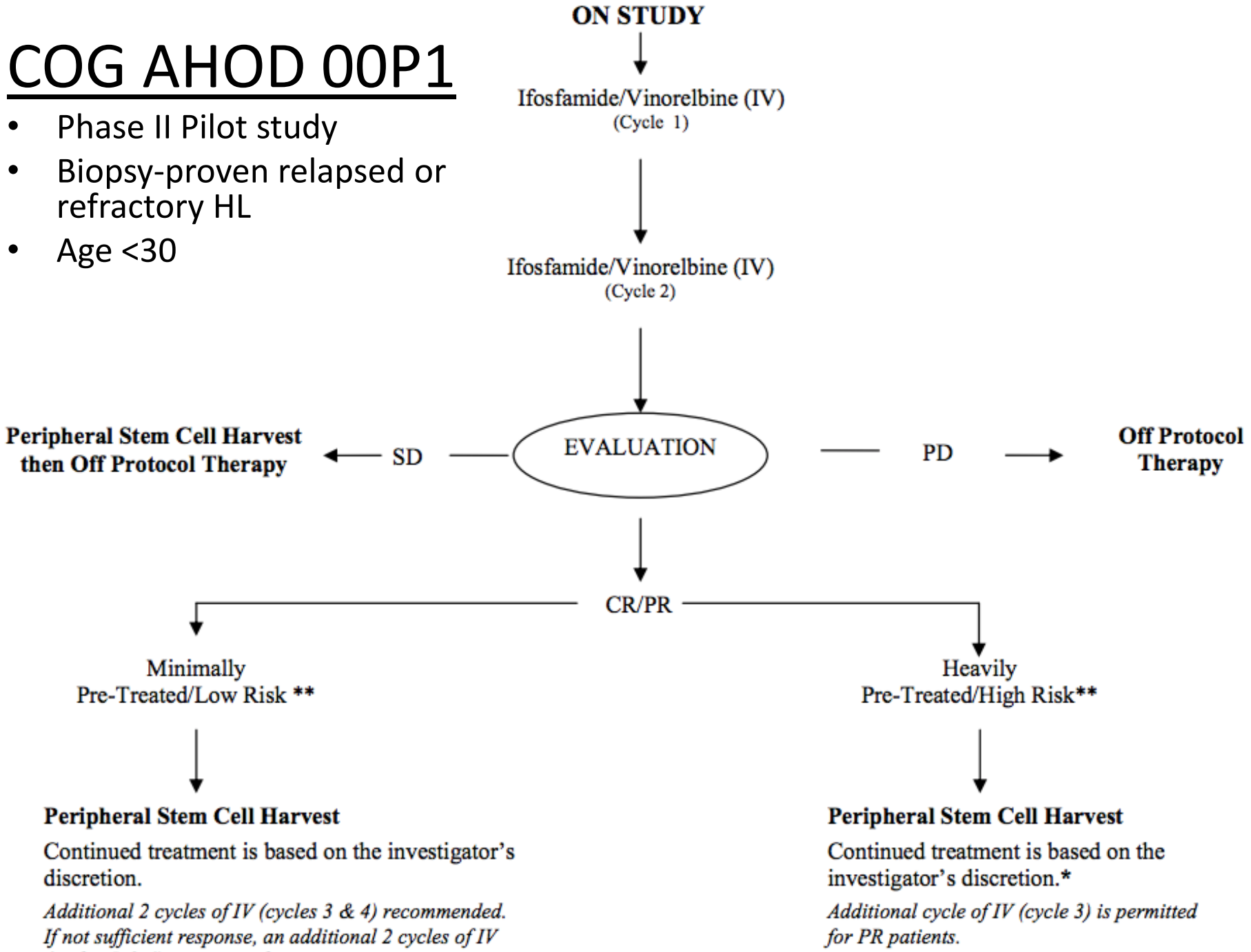
- Prognostic factors for relapsed disease
  - Site of relapse (nodal better than extranodal)
  - Stage at relapse
  - Histology
  - Response to first-line salvage chemotherapy
- Factors to consider in deciding on salvage regimen
  - Whether a complete resection was achieved
  - Durability of remission
  - Extent of disease at relapse
  - Intensity of initial treatment

Refractory and relapsed disease

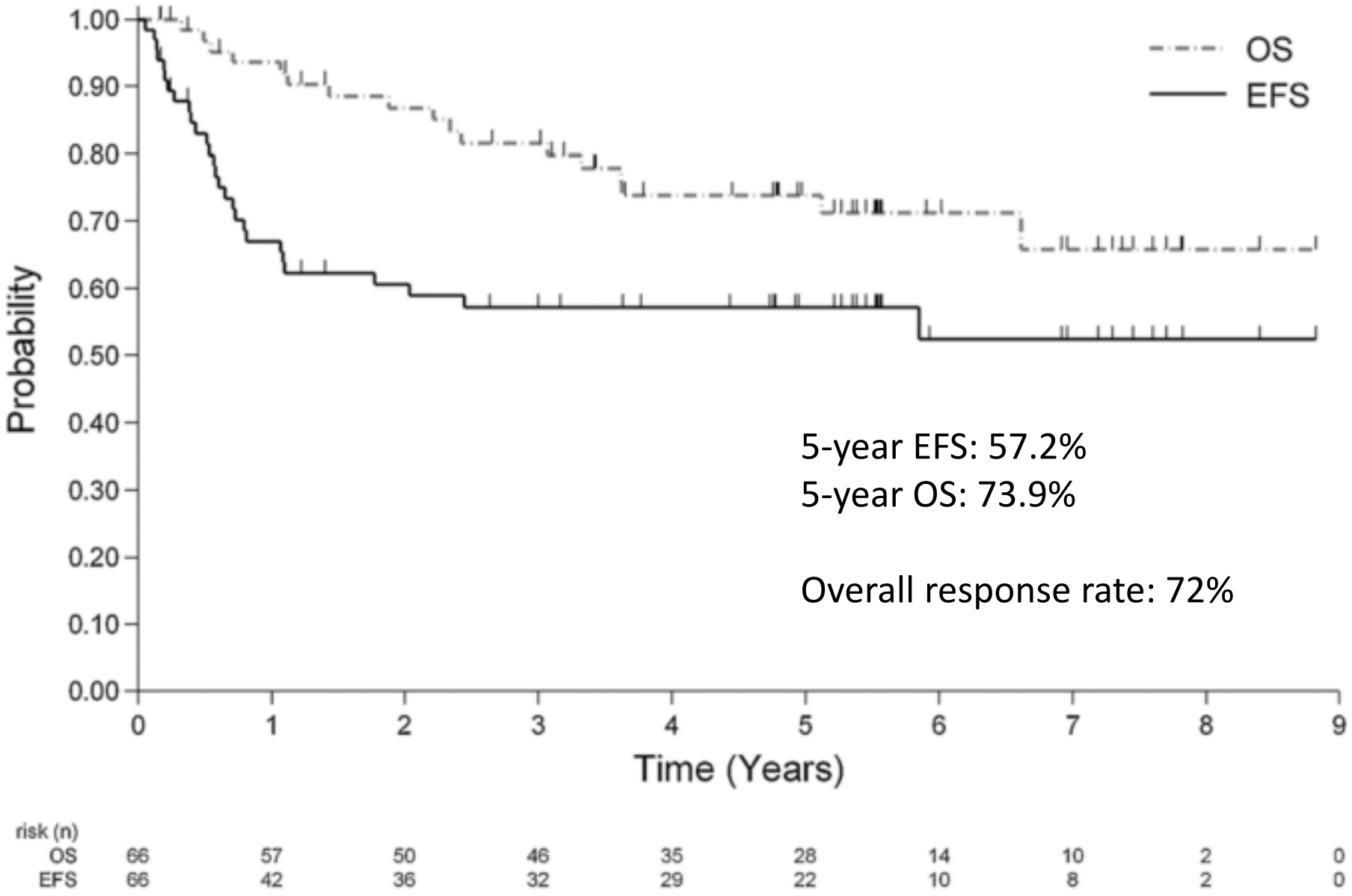
- Treatment options include:
  - Standard-dose chemotherapy +/- RT
  - RT alone
  - High-dose chemotherapy +/- RT, then stem cell transplant +/- immunomodulation
  - Palliative treatment
  - Targeted therapy under investigation
    - Brentuximab vedotin
    - HDAC inhibitors
    - MTOR inhibitors

COG AHOD 00P1

- Phase II Pilot study
- Biopsy-proven relapsed or refractory HL
- Age <30



Trippett et al. Pediatr Blood Cancer. 2015 Jan;62(1):60-4



5-year EFS: 57.2%
5-year OS: 73.9%

Overall response rate: 72%

Trippett et al. Pediatr Blood Cancer. 2015 Jan;62(1):60-4

COG AHOD 0121

- Phase II/III study to assess the efficacy of immunotherapy after high dose myeloablative therapy with autologous stem cell rescue (ASCR) for refractory/relapsed HL
- BEAM = BCNU, etoposide, cytarabine, melphalan
- Immunotherapy = cyclosporine, interferon-γ, interleukin-2
- Hyperfractionated IFRT, 21Gy in 1.5Gy bid to all involved sites that have not been previously treated to maximum tissue tolerance

EXPERIMENTAL DESIGN SCHEMA: PART II