Classical Hodgkin Lymphoma –best evidence for treatment

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Objectives

- Case-based discussion of the best treatment for:
  - Limited stage HL
  - Advanced stage HL
  - Relapsed HL
- Answers some big questions in the treatment of HL:
  - what is the role of PET scanning in treatment decisions?
  - when to use BEACOPP over ABVD?

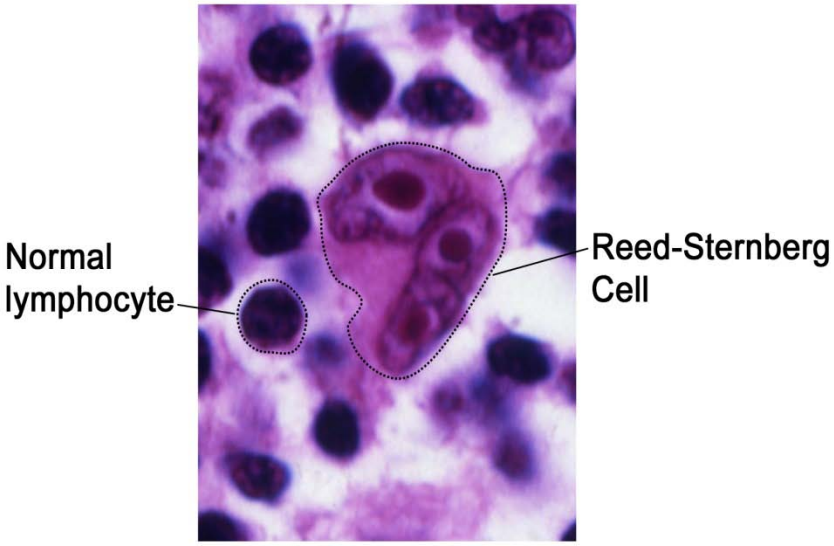
Hodgkin lymphoma (history)

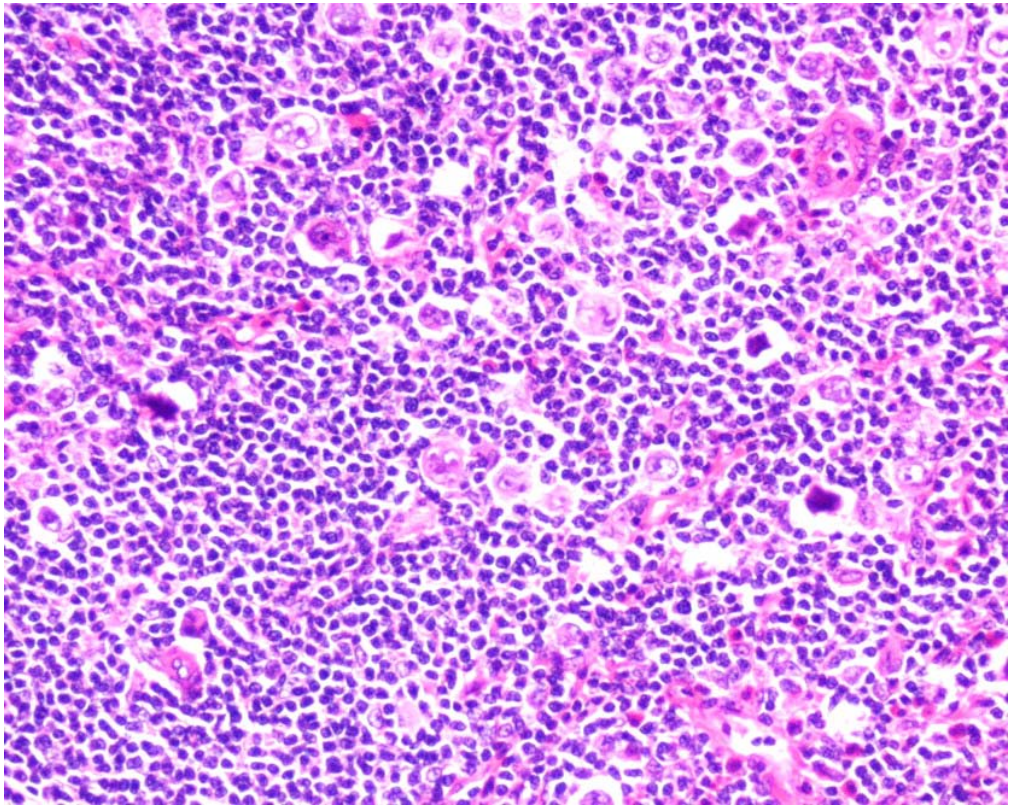
- 1832: Thomas Hodgkin describes 7 patients with massive enlargement of LNs and spleen “On Some Morbid Appearances of the Exorbant Glands and Spleen”
- 1865: Sir S. Wilks describes additional cases and labels then “Hodgkin’s disease”

Hodgkin lymphoma (history)

- 1878: Greenfield publishes sketch of pathognomonic giant cells
- 1898/1902: Sternberg & Reed provide first microscopic descriptions of HL pathology
- 1940s: Radiotherapy used successfully as palliation
- 1960s: RT demonstrated to provide long-term survival for many patients
- 1960s: Trials of limited RT vs entended field
- 1970: MOPP chemo reported to cure 60-70% patients
- 1986: ABVD or MOPP/ABV hybrid > MOPP
- 1992: first German BEACOPP report
- 1996: first documentation of that RS cell is a malignant germinal centre-derived B cell

Reed-Sternberg cell





Treatment of Hodgkin Lymphoma in 2012

Limited Stage

Lymphoma Treatment Approach

- Limited Stage
  - Ann Arbor I/II and
  - Bulk < 10cm and
  - No B symptoms

Advanced Stage

- Ann Arbor III/IV or
- Bulk > 10cm or
- B Symptoms

Lymphoma Treatment Approach

- Limited Stage
  - Ann Arbor I/II and
  - Bulk < 10cm and
  - No B symptoms

Advanced Stage

- Ann Arbor III/IV or
- Bulk > 10cm or
- B Symptoms

Favourable vs unfavourable risk

Prognostication for *limited stage* patients (definitions of high risk)

German (GHSG)	NCIC + ECOG	EORTC	Dana-Farber
Bulky mediastinal mass	Very high: *mass>10cm* Intra-abdo dz	Age (< 40: 0 pts) (40-49: 1 pt) ≥ 50 yrs: 9 pts	*Any mass>10cm*
ESR> 50 >30 with B sx	High: Age ≥ 40	Male sex: 1 pt Systemic sx +ESR	*Bulky mediastinal*
≥ 3 nodal areas	ESR> 50	# sites (2-3: 1pt) 4-5 (9 pts)	
Extranodal dz	≥ 4 nodal areas Mixed cellularity or lymph deplete	*Bulky mediastinal mass (9 pts)* Pathology (1pt)	

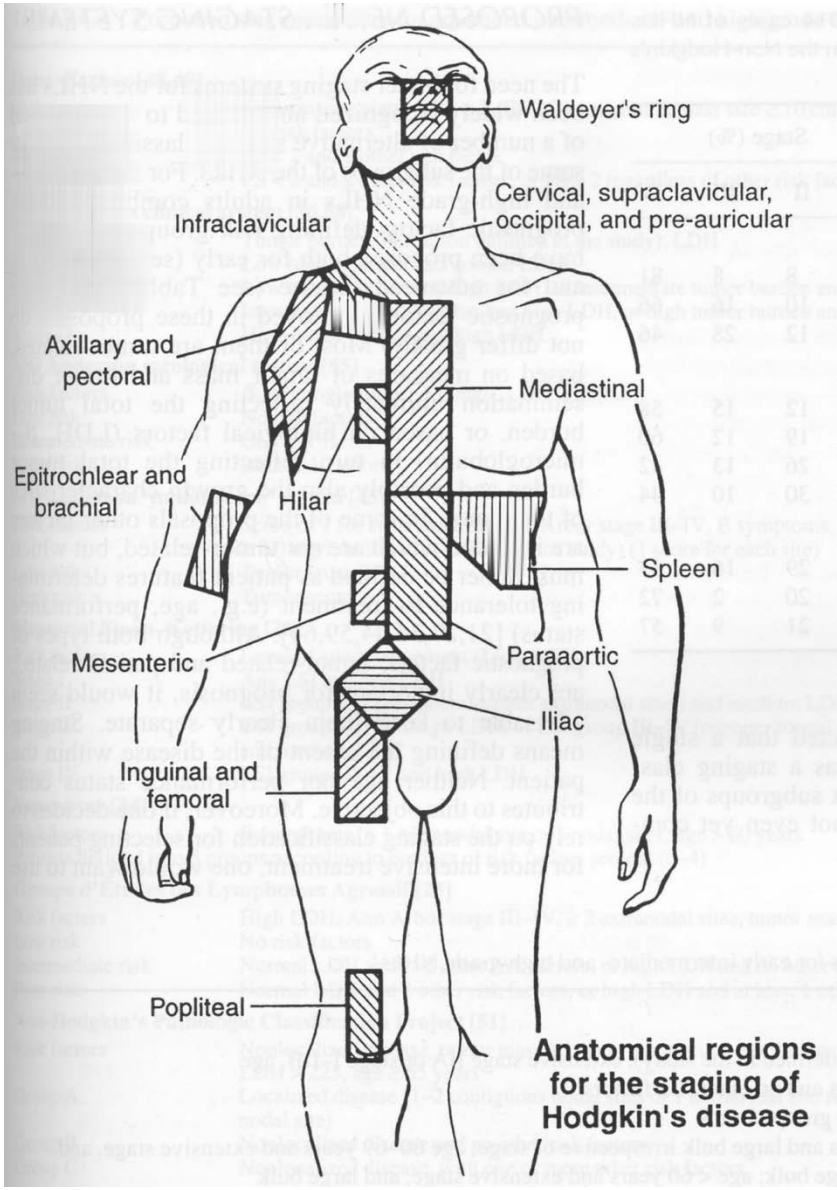
Case 1

- 37yo man, Rt SC mass x 3mo, no B-symptoms, ECOG=0
- CT scan:
  - Rt internal jugular lymph nodes (short axis 1.7 cm)
  - Rt subcarinal, hilar and prevascular nodes, max 2.5 cm
  - no disease noted into the abdomen.
- P/E:
  - <1cm nodes near biopsy site. Otherwise normal
- Lab:
  - WBC 11.0, ANC 6.9, lymphs 2.7, Hb 158, plt 80 (normal morphology)
  - Normal: lytes, Creat 93, Ca, Alb, LFTs, ESR 7,
- Bone Marrow Aspirate And Biopsy:
  - Hypercellular bone marrow (75%) with trilineage hematopoiesis
  - Moderately megakaryocytic hyperplasia with unremarkable morphology
  - No evidence of lymphoma.

STAGE? Favourable or unfavourable risk?

Case 1: Stage IIA (Limited stage) Favourable risk

- Diagnosis:
  - Favourable risk: non-bulky, Stage IIA classical Hodgkin lymphoma, (Rt supraclavicular, subcarinal, Rt hilum and prevascular chest)



Case 1: Stage IIA favourable risk HL

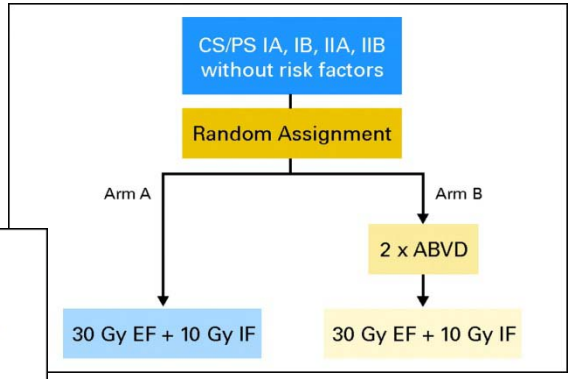
- Chemotherapy vs RT vs combination
- How many cycles of ABVD?

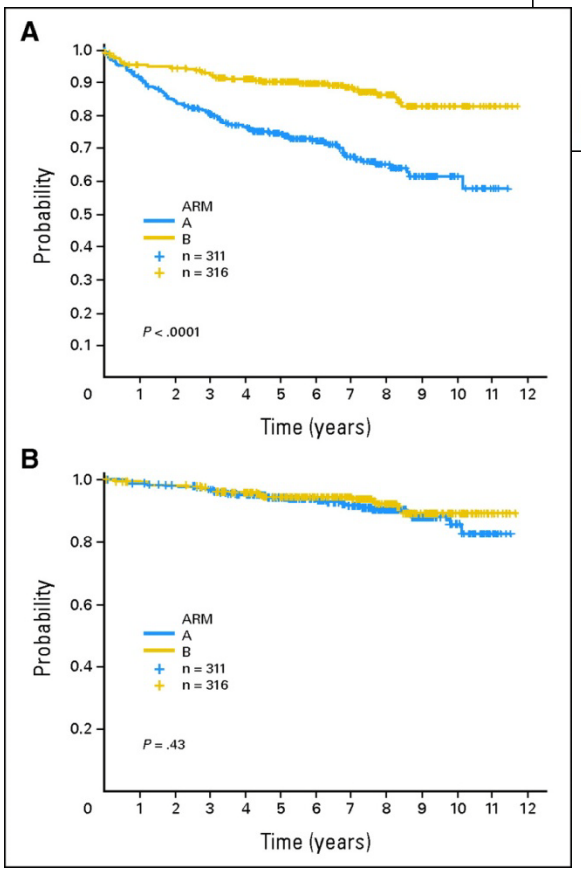
- Radiotherapy?
  - Yes/no
  - Extent of field
  - Amount of RT

- PET scan required?

Treatment of limited stage HL favourable

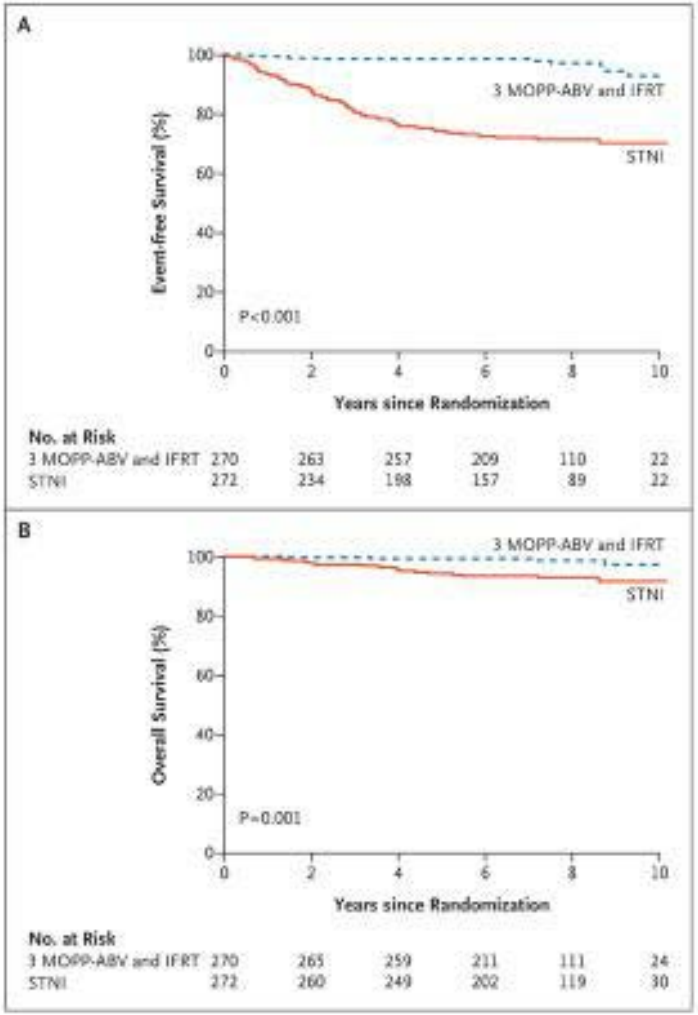
GHSG HD7





Freedom from treatment failure

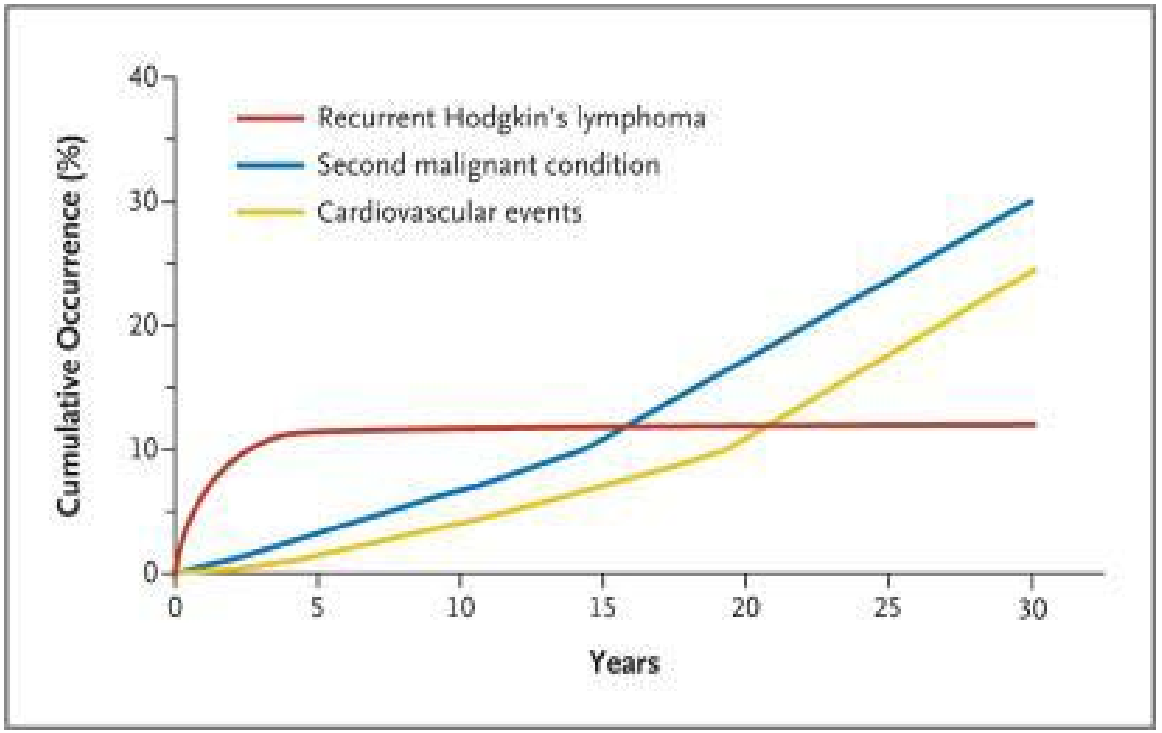
Overall survival



Engert *et al* JCO 2007;25:3495

Ferme *et al* NEJM 2007; 357:1916

Cumulative risk of late events in patients treated with chemo/RT for early stage HL



Armitage NEJM 2010

ABVD x 2 vs 4 cycles & 20Gy vs 30Gy IFRT for Favourable limited stage HL: GHSG HD10

- 1998 to 2003, 1370 pts, 329 centers (mFU 79-91mo)

	ABVDx4	ABVDx2	IFRT 30Gy	IFRT 20Gy
All AE	52%	33%	8.7%	2.9%
CR rate	97%	97%	99%	97%
5yr OS	97.1%	96.6%	97.6%	97.5%
FFTF	93.0%	91.1%	93.4%	92.9%
PFS	93.5%	91.2%	93.7%	93.2%

- no significant differences in OS, FFTF, PFS when all four arms were compared

Engert *et al* NEJM 2010; 363:640

GHSG HD10 for favourable risk limited stage HL

- **2 ABVD + 20Gy standard of care**

- Multivariate analysis risk factors: age > 50years (no infradiaphragmatic disease, low albumin, male sex, systemic symptoms)
  - advantages of 2 over 4 ABVD:
    - 15% alopecia (vs 28%)
    - 15% Grade 3 or 4 heme toxicity (vs 24%)

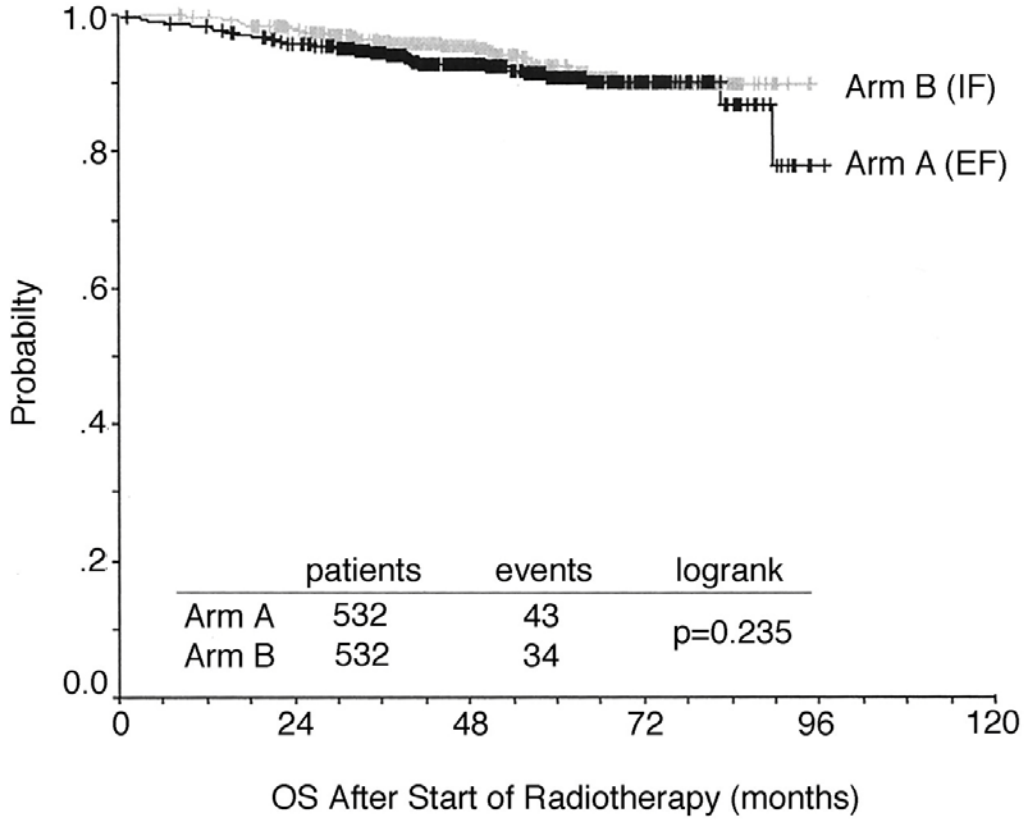
Engert *et al* NEJM 2010; 363:640

Case 2: 22 y.o. woman, NS HL

- Bilateral supraclavicular nodes, anterior mediastinal mass (5.8 x 3.1 cm), additional left mediastinal node (2.5 x 1.9cm) + left perihilar 1.2cm and prominence of Waldeyer's ring of uncertain significance
- normal CBC and chemistry (LDH 181, alb 34), ESR 56

- STAGE? Favourable vs unfavourable risk?

GHSG HD8 (COPP-ABVD x 4 + IFRT vs EFRT



Engert *et al* JCO 2003; 21: 3601

GSHG HD 11: Limited stage unfavourable risk

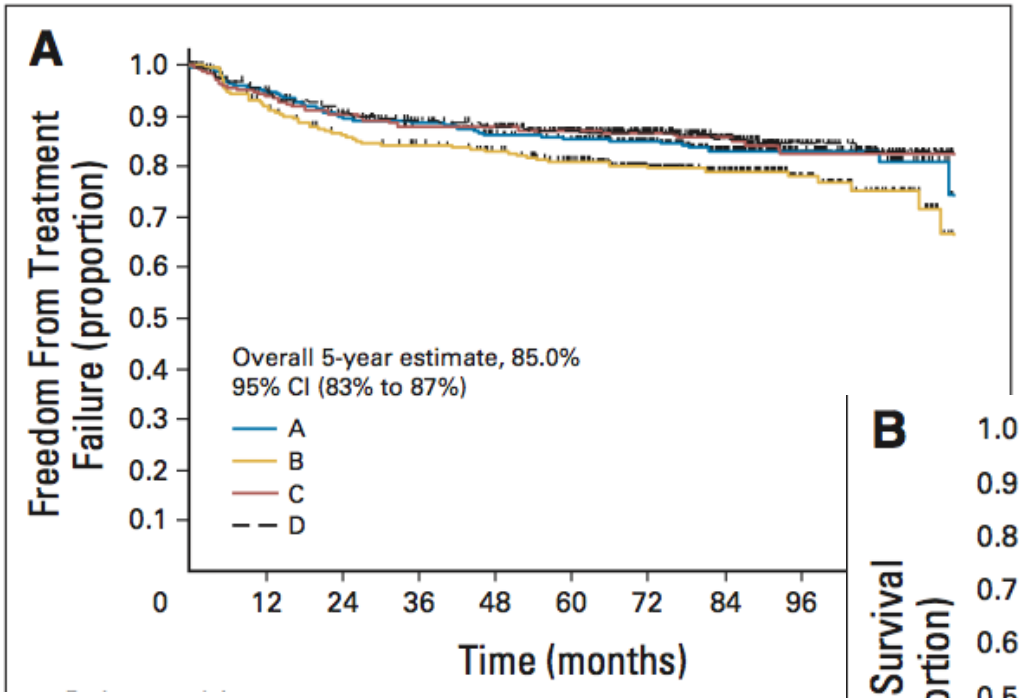
- N=1570
  - ABVD x 4 + 30 cGy IFRT
  - ABVD x 4 + 20 cGy IFRT
  - bBEACOPPx 4 +30cGy
  - bBEACOPPx 4 +20cGy

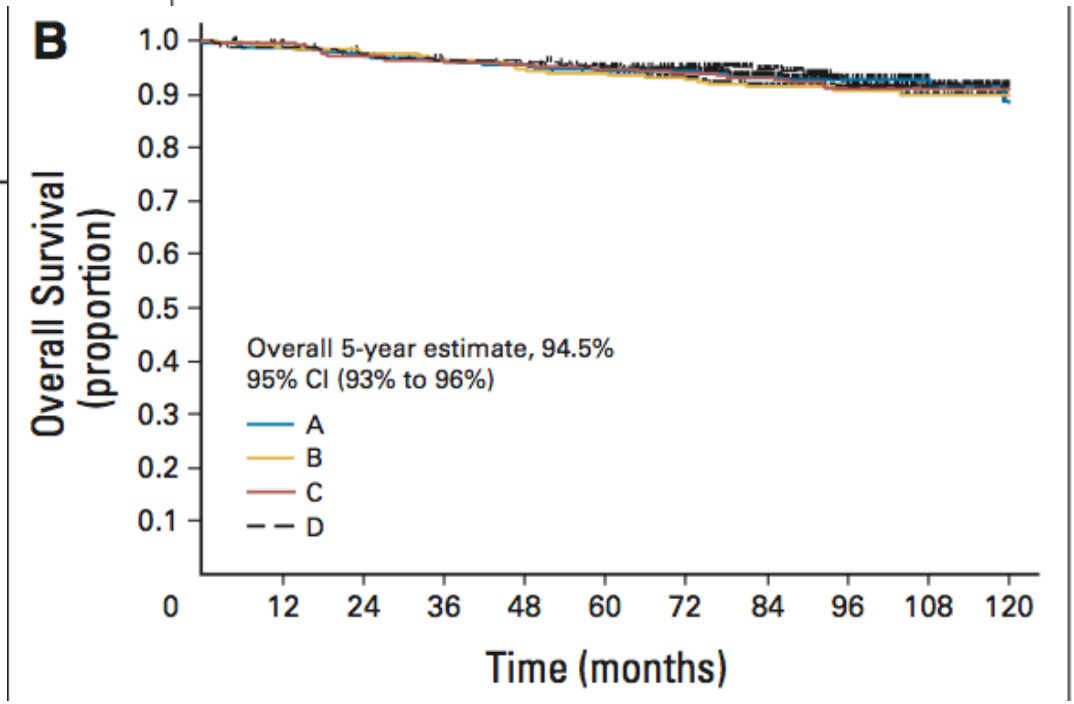
Table 5. Survival and Differences in Survival

Treatment Arm	No. of Patients	5-Year FFTF Rate		5-Year OS Rate		5-Year PFS Rate	
		%	95% CI	%	95% CI	%	95% CI
Survival rate							
4×ABVD + 30 Gy	356	85.3	81 to 89	94.3	91 to 96	87.2	83 to 90
4×ABVD + 20 Gy	347	81.1	76 to 85	93.8	91 to 96	82.1	78 to 86
4×BEACOPP + 30 Gy	341	87.0	83 to 90	94.6	92 to 97	87.9	84 to 91
4×BEACOPP + 20 Gy	351	86.8	83 to 90	95.1	92 to 97	87.0	83 to 90
Difference in survival rates							
4×ABVD + 30 Gy *v* 4×BEACOPP + 30 Gy*	697	1.6	−3.6 to 6.9	0.3	−3.2 to 3.8	0.7	−4.3 to 5.8
4×ABVD + 20 Gy *v* 4×BEACOPP + 20 Gy*	698	5.7	0.1 to 11.3	1.2	−2.3 to 4.8	4.9	−0.6 to 10.4
4×ABVD + 30 Gy *v* 4×ABVD + 20 Gy†	682	−4.7	−10.3 to 0.8	−0.7	−4.1 to 2.8	−4.7	−10.1 to 0.8
4×BEACOPP + 30 Gy *v* 4×BEACOPP + 20 Gy†	669	−0.8	−5.8 to 4.2	1.0	−2.1 to 4.0	−0.6	−5.5 to 4.3

Eich *et al* JCO 2010; 28:4199

GHSG HD11 for limited stage, unfavourable risk HL





Eich *et al* JCO 2010; 28:4199

GHSG HD11: limited stage, unfavourable

- more toxicity with bBEACOPP than ABVD
- chemotherapy intensification to baseline BEACOPP did not result in improved outcomes
- could not exclude inferiority of 20cGy over 30cGy after 4x ABVD

- **best tx = ABVD x 4 + 30cGy IFRT**

Eich *et al* JCO 2010; 28:4199

NCIC HD6 (Canadian limited stage HL study)

Randomize

Standard Arm

- Favourable
  - STNI (35cGy)
- Unfavourable
  - ABVD x 2 + STNI

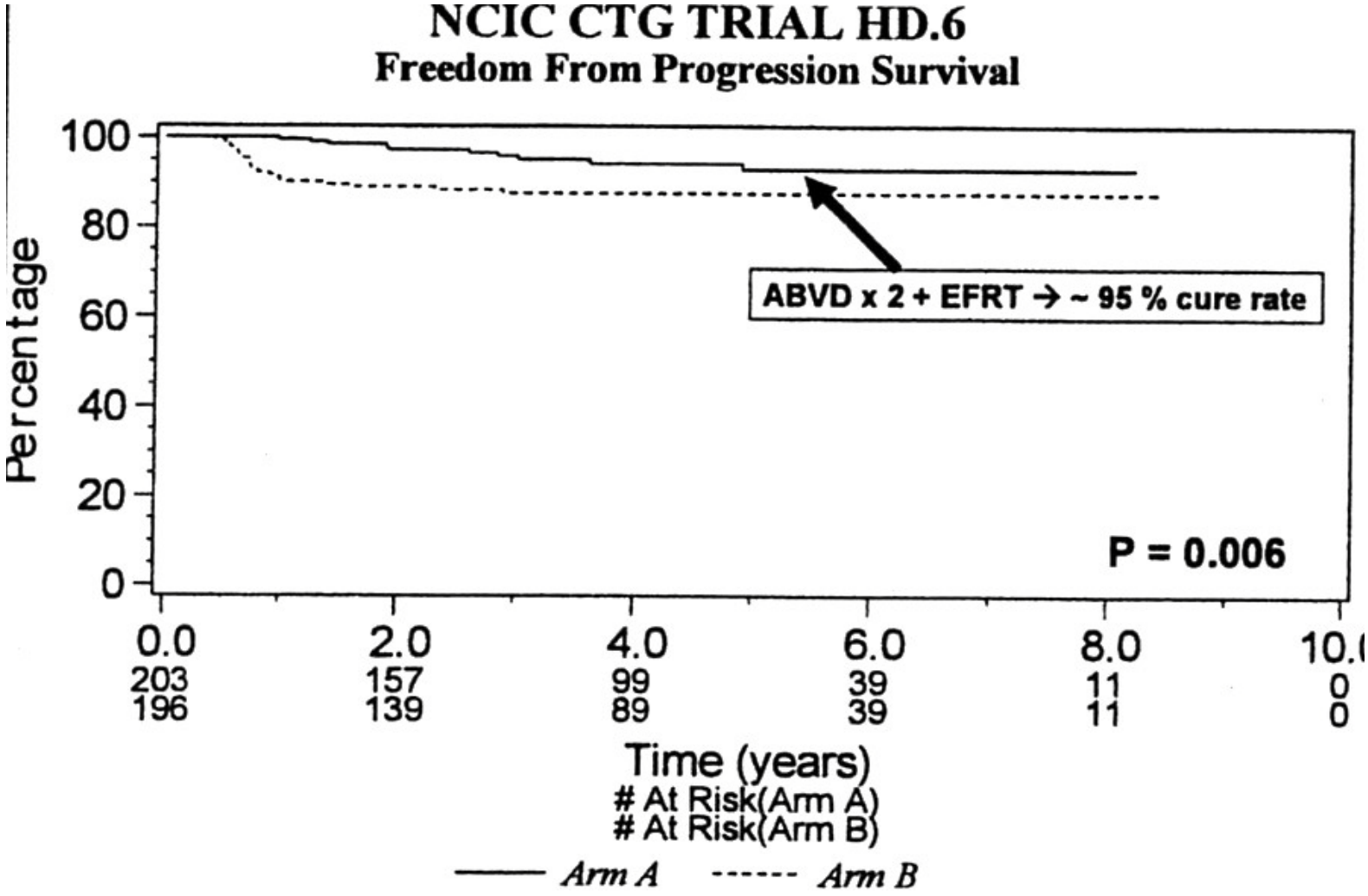
Experimental Arm

- ABVD x 2 then restage:
  - If CR: x2 more = 4 cycles
  - If PR: x4 more = 6 cycles

Primary endpoint: 12yr OS

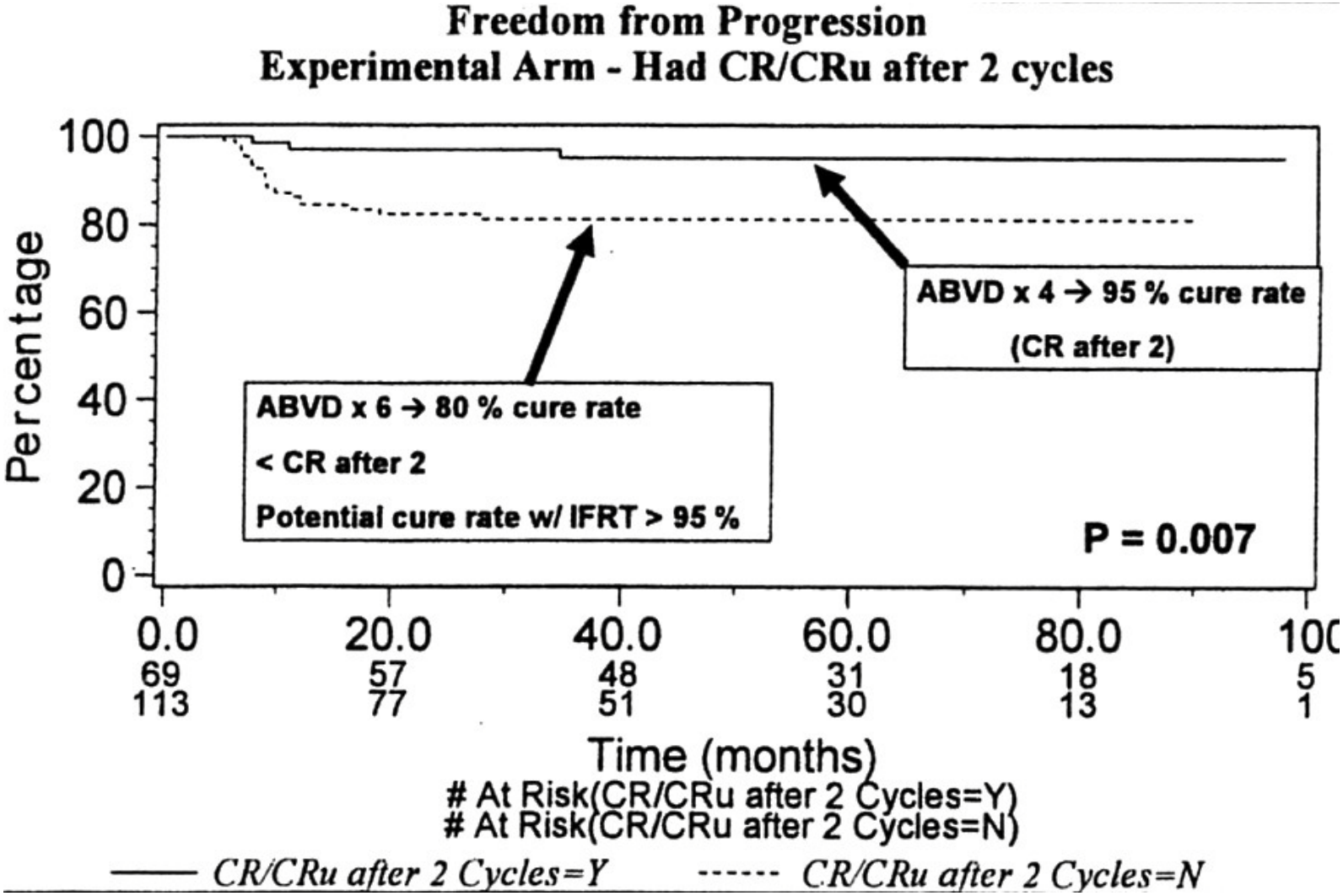
Restaging performed using CT scans

NCIC HD6: PFS at 5 yrs



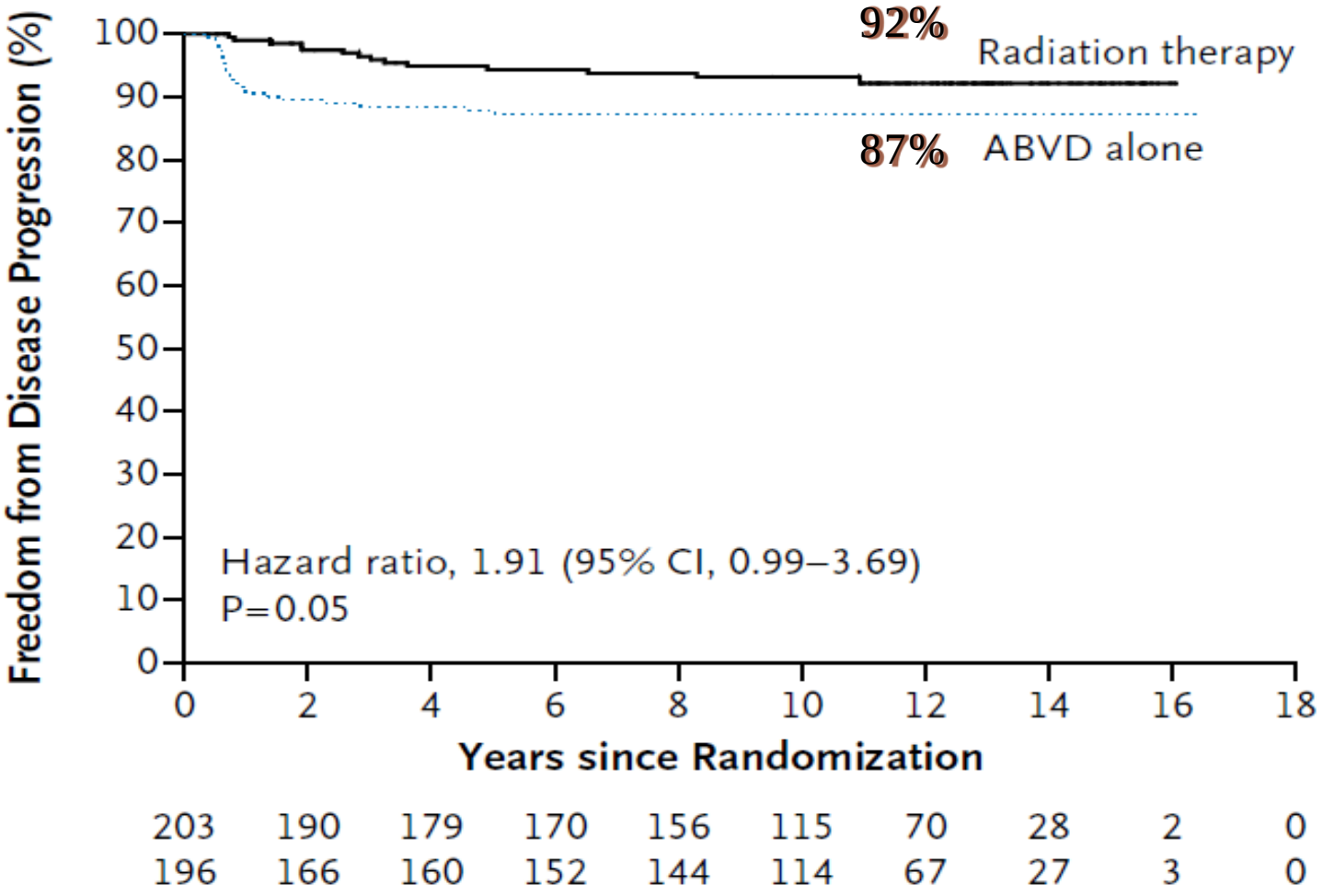
Meyer et al JCO 2005; 23:4634

NCIC HD6: 5 year FFP



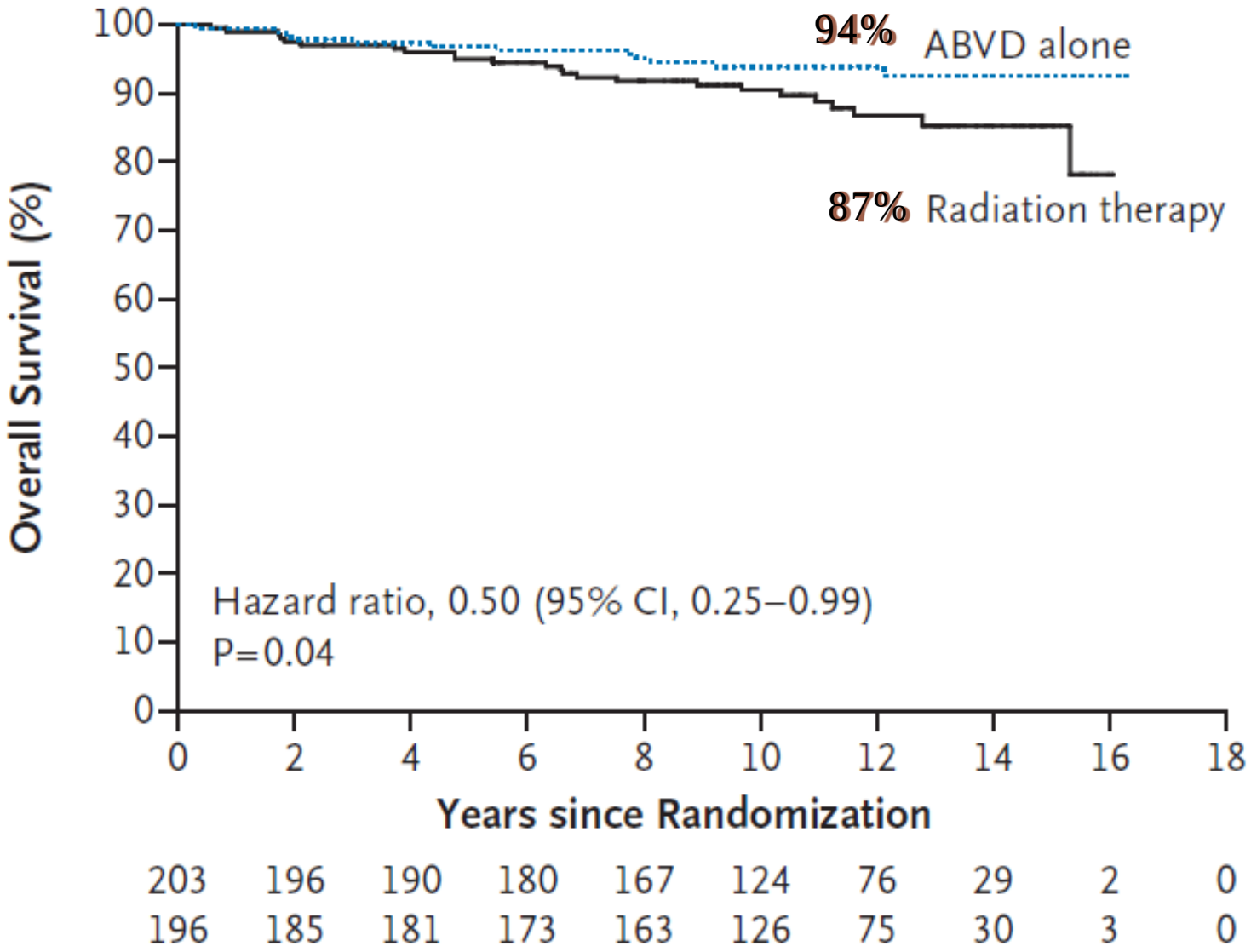
Meyer et al JCO 2005; 23:4634

HD6: Freedom from Disease Progression at 12 yrs



Meyer et al NEJM 2011; Epub Dec 11

NCIC HD6: 12 year Overall survival



Meyer et al NEJM 2011; Epub Dec 11

HD6: Subset Analysis of CR/CRu vs no CR/CRu after 2 Cycles of ABVD*

Outcome	CR/CRu (N = 69)	No CR/CRu (N =108)	HR (95% CI)	P
12-yr FFPD	94%	81%	0.28 (0.10–0.83)	.02
12-yr OS	98%	92%	0.17 (0.02–1.36)	.06

*** 19 of 196 were inevaluable after 2 cycles of ABVD**

Meyer et al NEJM 2011; Epub Dec 11

NCIC HD6: Late Side effects

Event	RT (N = 203)	ABVD (N =196)
Second cancer*	23**	10
Cardiac	26***	16

* Excluding basal cell carcinoma
** Four in favourable cohort
*** One in favourable cohort

Meyer et al NEJM 2011; Epub Dec 11

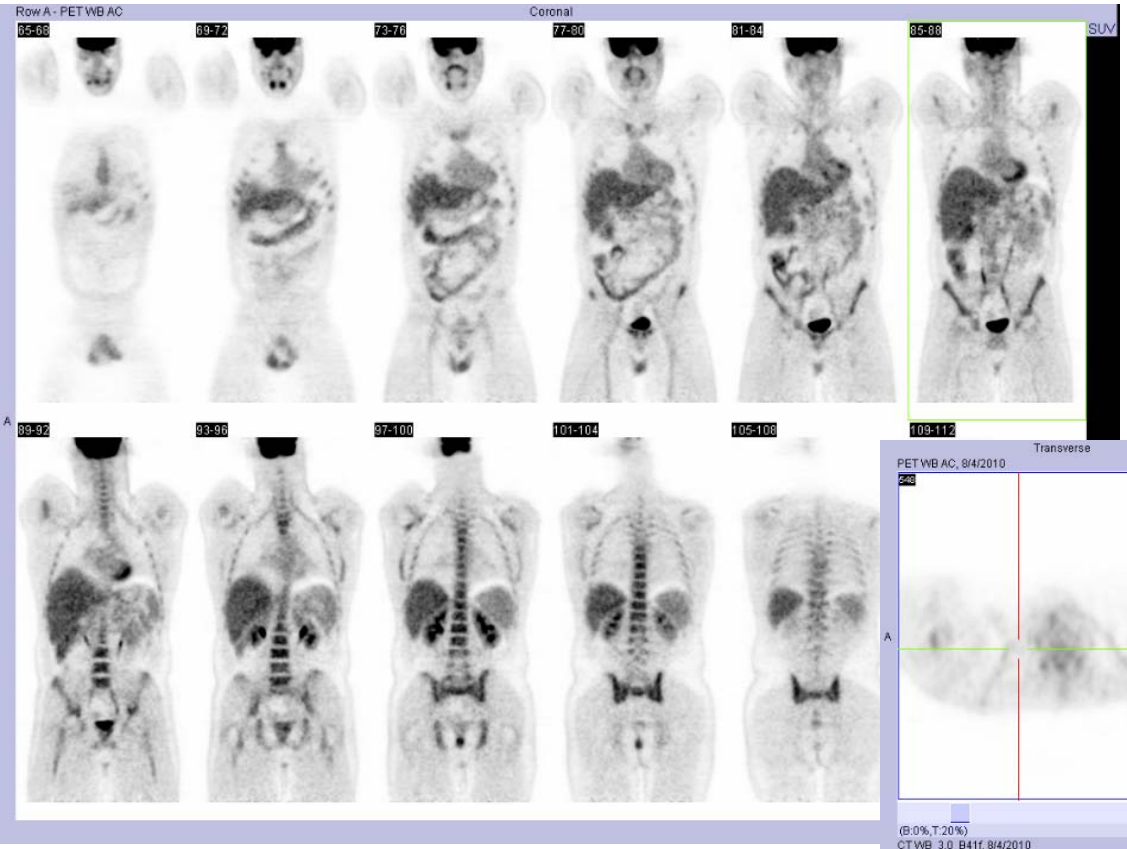
Canadian HD6 conclusions

- STNI associated with worsened long term overall survival in limited stage HL
- outcomes of patients who achieve a CR after 2 cycles of ABVD (including unfavourable risk patients) who are then treated with chemotherapy alone (ABVD x 4) are excellent (this in era of CT guided response assessment)

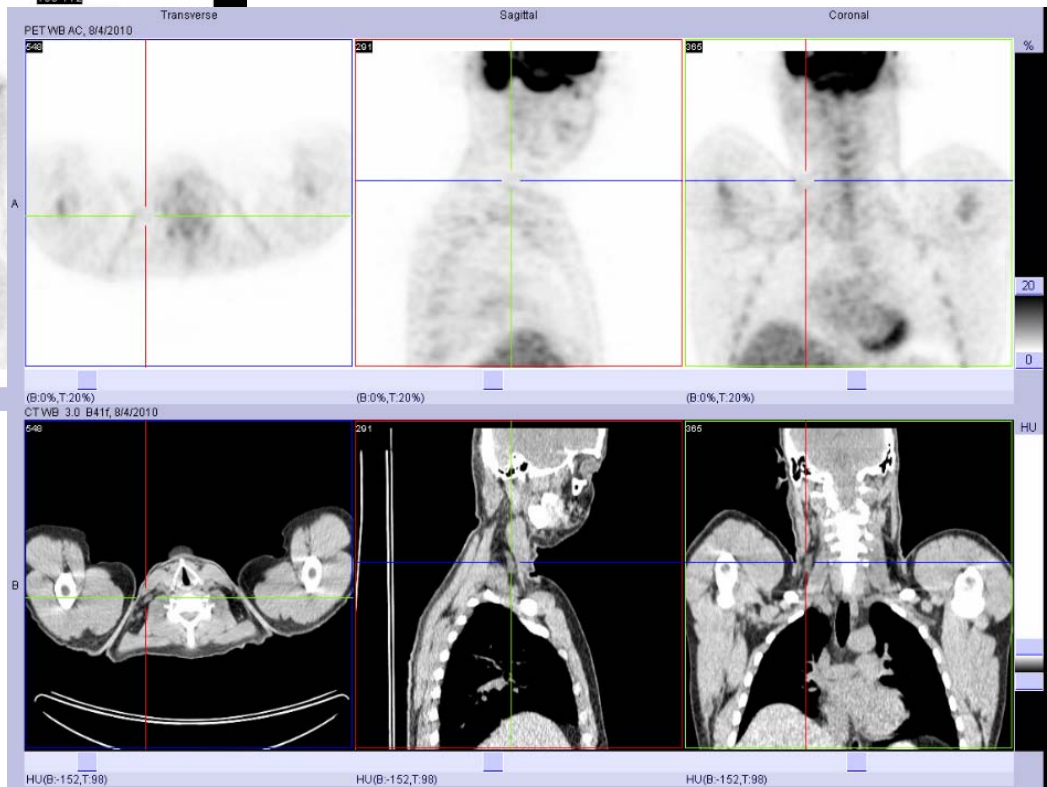
Meyer et al NEJM 2011; Epub Dec 11

WHAT ABOUT PET SCANS IN LIMITED STAGE?

Case 1: Stage IIA Hodgkin Lymphoma



PET/CT
Post-ABVD x2
ie mid-treatment assessment

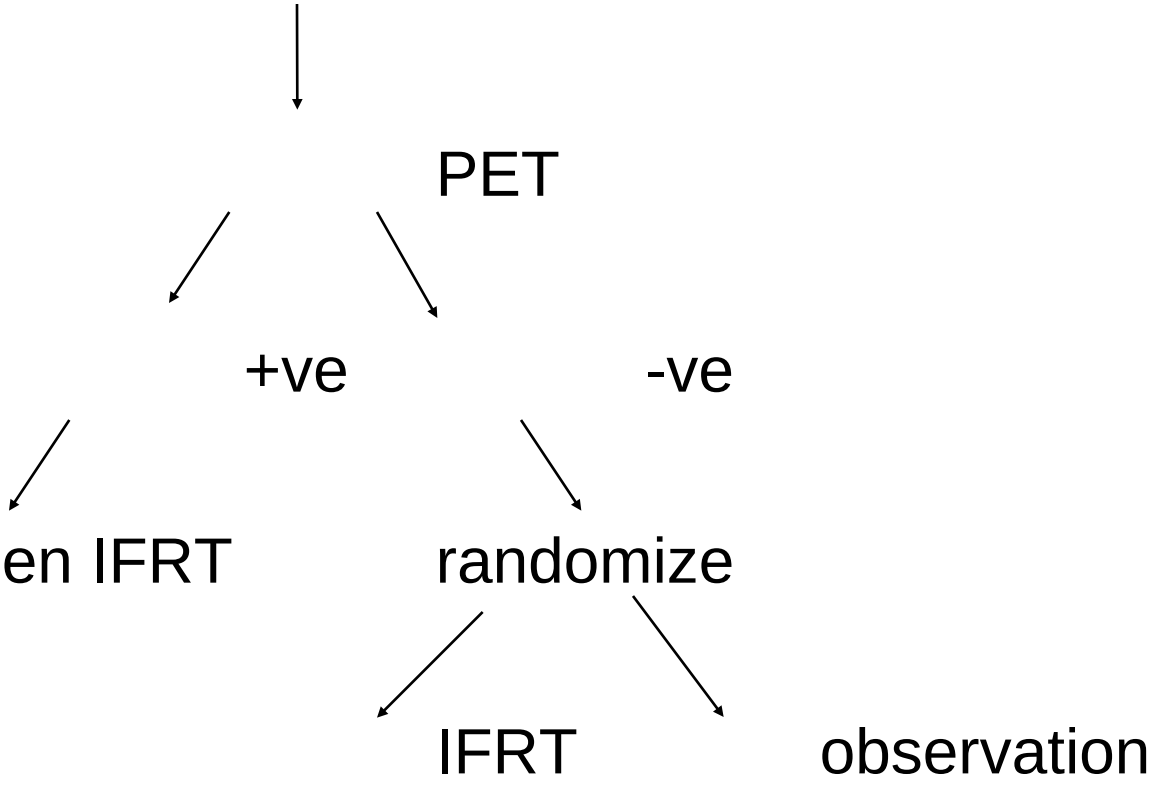


Case 1: Stage IIA Hodgkin Lymphoma

- PET/CT post-ABVD x2
  - CT scan: right supraclavicular area largest node measuring 1.6 x 0.8 cm.
  - PET scan: complete metabolic response with no evidence of FDG uptake in any lymph node areas.
- What now?

UK NCRI RAPID trial of PET Scan-Guided Therapy for Stage I-IIA Hodgkin Lymphoma

- ABVD x3 cycles then PET for PR/CR patients



UK RAPID PET Scan-Guided Therapy for Stage I-IIA Hodgkin's Lymphoma

- 1st interim analysis, 215 pts have had PET scan
- 81% PET-ve
  - IFRT=90 (53%), Observation=81 (47%)
  - mFU=6mo, 2% progressed, 1% died (1 HL, 1 Rx)
- 19% PET+ve

Radford et al

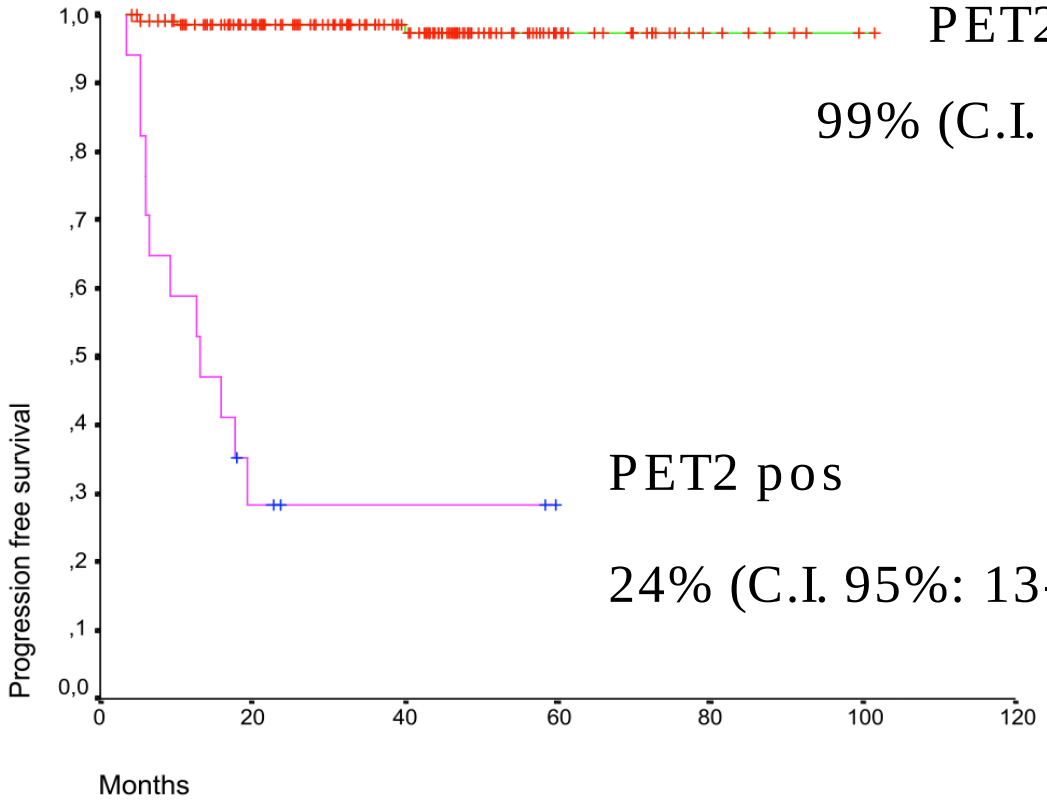
ABVD x2 Followed by FDG-PET Guided Consolidative RT in Patients with Early Stage Hodgkin Lymphoma (BCCA)

- From July 2005 in BC, HL stage I-IIA, no bulk >10cm are treated with ABVD x2 then PET/CT.
  - If PET +ve, IFRT administered if feasible.
  - If PET –ve, then ABVD x2
- 117 patients, median follow-up ~33 mo
- Results:

	PET –ve	PET +ve
Number pts	96 (82%)	21 (18%)
Relapsed	4	2
Death from HL	0	0

Connors unpublished data 2010

PFS based on PET post-2 ABVD (when tx not altered by PET results) (advanced stage or unfavourable risk patients)



PET2 neg

99% (C.I. 95%: 97-100)

PET2 pos

24% (C.I. 95%: 13-35)

By univariate analysis, PET2 result, Stage IV, WBC>15, lymphopenia, IPS, extranodal disease and bulky disease were predictive of outcome
On multivariate analysis, only PET-2 result was predictive

Gallamini et al JCO 2007; 25:3746

GITIL Retrospective study of PET-2 directed therapy

- N= 165
- Patients with advanced stage HL or unfavourable Stage 2
- ABVD x 2 then escBEACOPP x 4 + bBEACOPP x 4 if PET+ and ABVD x 4 if PET – (+ RT to areas of prior bulk)
- Median f/u 34 months
- FFS for PET+= 65% (only 14% of patients required BEACOPP)
- FFS for PET- = 92%

Gallamini *et al* BJHaem 2011; 152:551

Case 1: Stage IIA Hodgkin Lymphoma

- PET/CT Aug 4, 2010 post-ABVD x2
  - CT scan: right supraclavicular area largest node measuring 1.6 x 0.8 cm.
  - PET scan: complete metabolic response with no evidence of FDG uptake in any lymph node areas.
- Treated with 2 further cycles of ABVD (total 4 cycles) – no radiation

Case 2: Limited stage (2A), unfavourable risk

- Best evidence = ABVD x 4 + 30Gy RT
- Treated with 6 cycles of ABVD to avoid RT to chest
- PET negative after 4 cycles

Can we reduce chemo toxicity? GHSG HD13 for Favourable Risk Early Stage HL

- 2 cycles ABVD vs ABV vs AVD vs AV [+30Gy IFRT]
- 1710 pts. Stop AV 2005 (n=156), ABV 2006 (n=191).

	ABVD	AV	p value
4yr FFTF	92.3%	75.3%	0.0007
4yr OS	98.1%	98.7%	0.49

	ABVD	ABV	p value
4yr FFTF	93.5%	84.5%	0.01
4yr OS	98.4%	95.9%	0.38

- Dacarbazine cannot be safely omitted from ABVD .. Final results of HD13 awaited to determine if bleo can be reduced or omitted

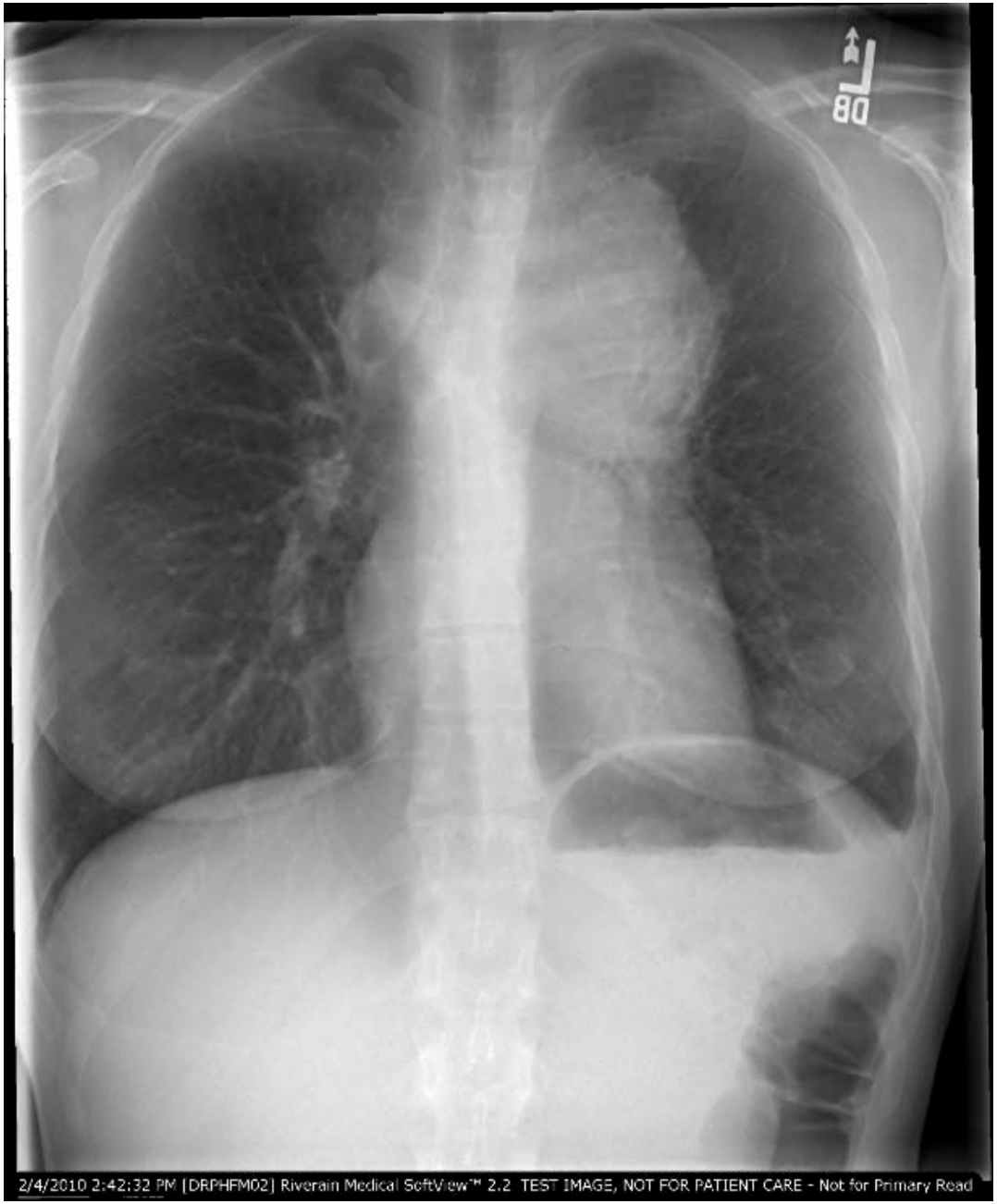
Borchmann *et al* EHA 2010 (abstr 1146)

Treatment of Hodgkin lymphoma

Advanced Stage

Case 3: Advanced stage HL

- 26yo woman, mass left axilla x 2mo.
- Core needle biopsy revealed nodular sclerosing classical Hodgkin lymphoma.
- History/ROS:
  - Chronic cough x 6 mo, pleuritic chest discomfort, daily night sweats, generalized pruritis, weight stable, no fevers. ECOG level 1
  - Delivered 2nd child 8 mo ago, breast feeding
- P/E:
  - lymphadenopathy bilateral neck and supraclavicular areas, bilateral axillae, lungs clear, heart sounds normal. Abdomen: no masses or tenderness.



Bulky mediastinal mass
= > 1/3 diameter of chest

Case 3: Stage IVB HL

- Lab Feb 4, 2010:
  - CBC: Hb 88, WBC 8.8, ANC 7.5, Lymphs 0.4, Plt 420
  - Chem: Creat 59, Ca 2.25, Alb 28, Alt 37, ALP 226, LDH 271, Fe 2, TIBC 32, Ferritin 534
- BMBx: No Lymphoma
- CT Feb 2010:
  - enlarged nodes in neck, axillae, mediastinum, and hila, with bulky mediastinal mass ~12cm
  - left pleural nodularity, small left pleural effusion.
  - 5mm lung nodule.
  - Prognostic risk score? What is the best treatment for this patient?

International Prognostic Score for Advanced Hodgkin's Lymphoma (ABVD-like)

- Adverse Factors:
- Male
- Age ≥ 45yr
- Stage IV
- Hb <105g/L
- WBC ≥15x10^9/L
- L'cyte <0.6x10^9/L
- Albumin < 40g/L

#	Freq	5yr FFS
0-1	29%	79%
2-7	71%	60%
0-2	58%	74%
3-7	42%	55%
0-3	81%	70%
4-7	19%	47%

Hasenclever et al NEJM 1998; 339:1506

ABVD as standard curative therapy for advanced stage HL

	MOPP x 6-8	MOPP/ABVD x 12	ABVD x 6-8
CR	67%	83%	82%
5yr FFS	50%	65%	61%
5yr OS	66%	75%	73%

- ABVD x 6-8 less toxic and more effective than MOPP … combination of MOPP/ABVD not better than ABVD

Canellos *et al* NEJM 1992; 327:1478

Advanced HL treated with MOPP/AVD +/- RT

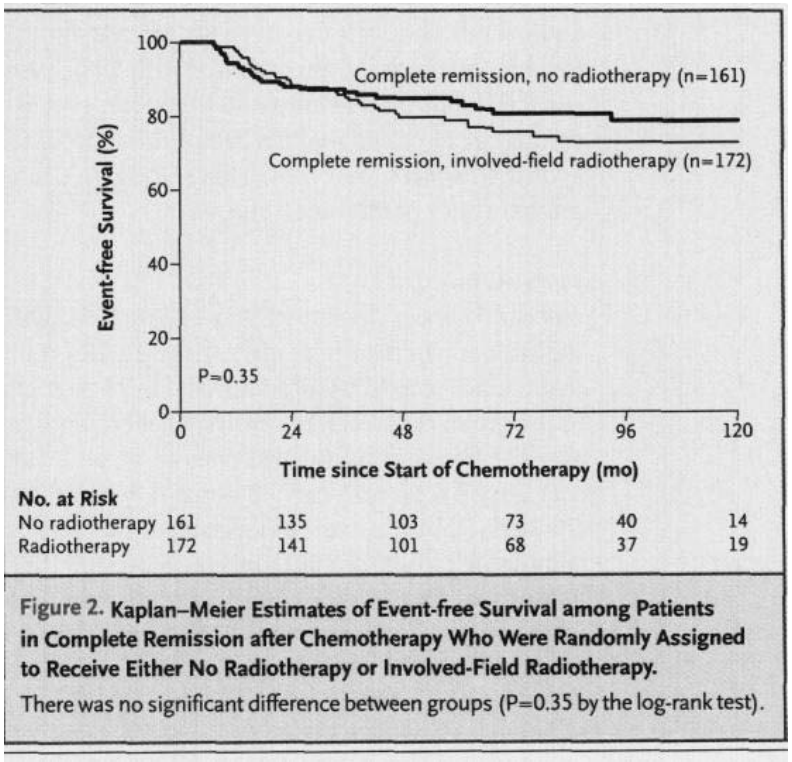


Figure 2. **Kaplan–Meier Estimates of Event-free Survival among Patients in Complete Remission after Chemotherapy Who Were Randomly Assigned to Receive Either No Radiotherapy or Involved-Field Radiotherapy.**
There was no significant difference between groups (P=0.35 by the log-rank test).

Expect cure in 75-80% of patients

- no value to RT if patient achieves CR after 6-8 ABVD
- Value of RT if patient achieves only PR

Aleman *et al* NEJM 2003; 348: 2396

BEACOPP

Escalated			Basic	
Drug	mg/m^2	Day	mg/m^2	Day
Bleomycin	10	8	10	8
Etoposide	100	1-3	200	1-3
Adriamycin	25	1	35	1
Cyclophos	650	1	1250	1
Vincristine	1.4	8	1.4	8
Procarbazine	100 po	1-7	100 po	1-7
Prednisone	40 po	1-14	40 po	1-14
G-CSF				8-14

Repeat cycles q 21 days

BEACOPP for Advanced Stage HL (GHSG: HD9) at 5 years f/u

- 3 Arms: A:COPP/ABVD x8 then IFRT if >5cm or residual
- B:BEACOPP x8 then IFRT if >5cm or residual
- C:escBEACOPPx8 then IFRT if >5cm or residual
- 1212 pts enrolled, analysis 56 mo F/U and 1195pts

	Arm A	Arm B	Arm C	p value
Number	260	469	466 pts	
5yr FFS	69%	76%	87%	AvB 0.035
				A or BvC<0.001
5yr OS	83%	88%	91%	AvC 0.002
				BvC 0.059
TRM	1.9%	1.5%	1.7%	
2^0 ca death	2.3%	1.1%	2.4%	
AML/MDS	1 (0.4%)	4 (0.6%)	9 (2.5%)	

Diehl *et al* NEJM 2003; 348:2386

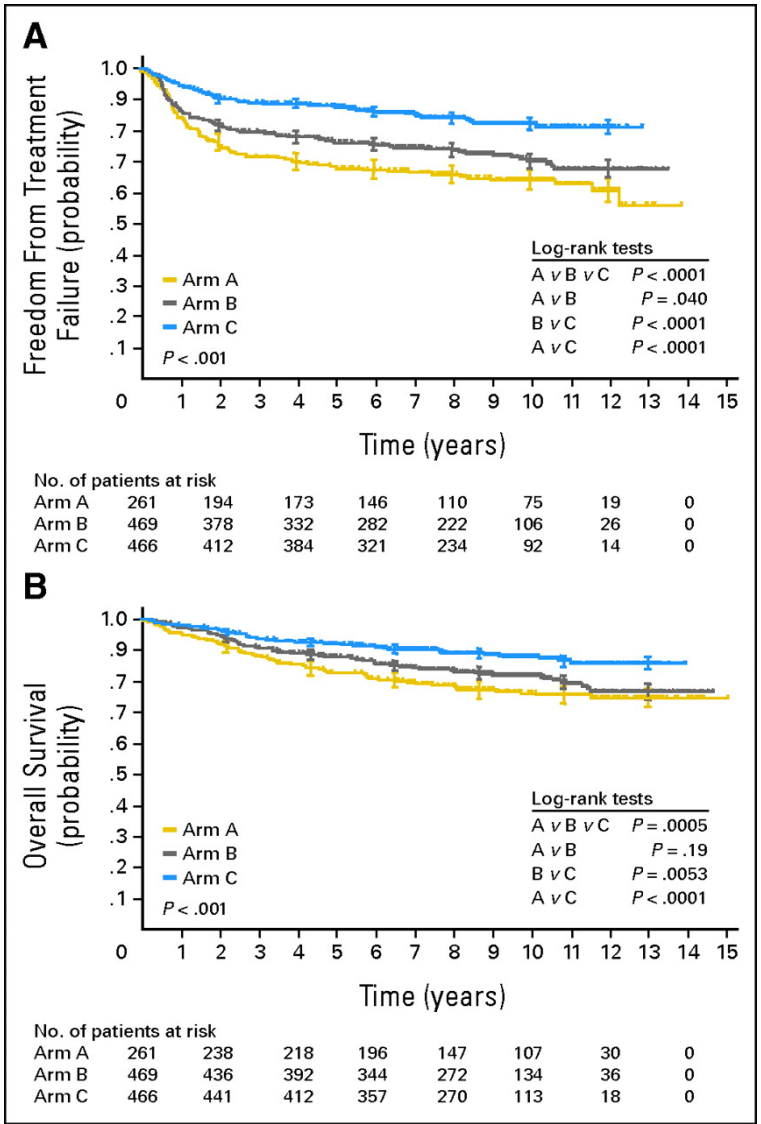
Escalated BEACOPP for Advanced-Stage HL: HD9 10 Years of F/U

- mFU=111 months.

	COPP/ABVD	bBEACOPP	escBEACOPP
10yr FFTF	64%	70%	82%
10yr OS	75%	80%	86%
All 2^0 Ca	5.7%	6.6%	6.0%
AML	0.4%	1.5%	3.0%
NHL	2.7%	1.7%	1.0%
Solid tumors	2.7%	3.4%	1.9%

Engert *et al* JCO 2009; 27: 4548

10 year survival data for BEACOPP in Advanced stage HL

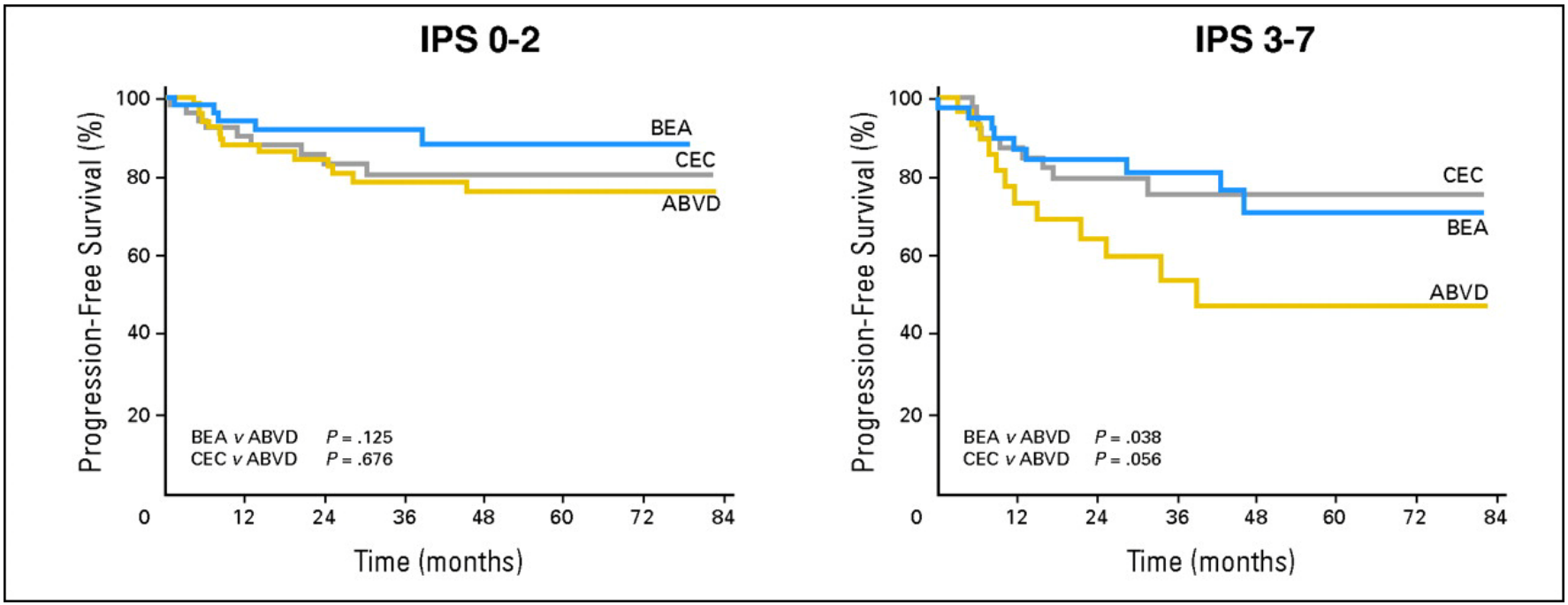


(A) freedom from treatment failure

(B) overall survival

Engert *et al* JCO 2009; 27: 4548

Progression-free survival based on IPS with BEACOPP (Italian HD2000)



Federico *et al* JCO 2009; 27: 805

German HD12: 8 escBEACOPP vs 4xescBEACOPP + 4bBEACOPP +/- RT

- n = 1670
- 2 questions:
  - is less escBEACOPP ok?
  - what is the role of RT post-escBEACOPP?

- RT for residual disease (≥ 1.5cm) or for bulk (more than 5cm)

Borchmann *et al* JCO 2011; 29:4234

German HD12 results

	8 eBEACOPP + RT	8 eBEACOPP - RT	4e + 4b +RT	4e + 4b -RT
deaths	9.2%	9.4%	10.7%	10.4%
deaths from 2 cancer	3.6%	2.3%	2.5%	0.8%
# second cancers	24 (6.1%)	19(4.8%)	20(5.1%)	13(3.3%)
5 yr OS	92.1%	91.9%	90.7%	89.9%
5 yr PFS	88.5%	86.5%	86.6%	83.5%
5y FFTF	87.2%	85.6%	86.6%	83.1%

Borchmann *et al* JCO 2011; 29:4234

German HD12 conclusions

- for chemotherapy comparison, FFTF 86.4% for 8escBEACOPP vs 84.8% for 4esc + 4 baseline - ie. no real difference but no reduction in toxicities & OS 92% for 8esc vs 90% for 4+4
- conclusion: 8esc BEACOPP remains standard

- for RT, FFTF 90.4% for +RT vs 87% for -RT, no difference when treating original bulk if CR achieved
- conclusion: include RT only for residual disease

Borchmann *et al* JCO 2011; 29:4234

GHSG HD15: 8e vs 6e v 8b(at 14d) + PET-Guided RT in Advanced HL

- 2003-2008, 2182 pts, median 33 yrs, stage IIBX, or III-IV:, mFU 48mo, Stage II=16%. Bulk=30%, IPS 0-1=32%, 2-3=52%, 4-7=16%
- After chemotherapy, pts in PR with PET+ mass≥2.5cm got RT 30Gy(11%)

	$8B_{esc}$	$6B_{esc}$	$8B_{14}$
# pts	705	711	710
Heme AE	92.4%	91.7%	79.7%
Deaths	53 (7.5%)	33 (4.6%)	37 (5.2%)
TRM	15	6	6
Death 2nd ca	13	5	8
AML/MDS	19 (2.7%)	2 (0.3%)	8 (1.1%)
5yr FFTF	84.4%	89.3%	85.4%
5yr OS	91.9%	95.3%	94.5%,

Andreas Engert, Blood 2011: a589

German HD15: Advanced HL conclusions

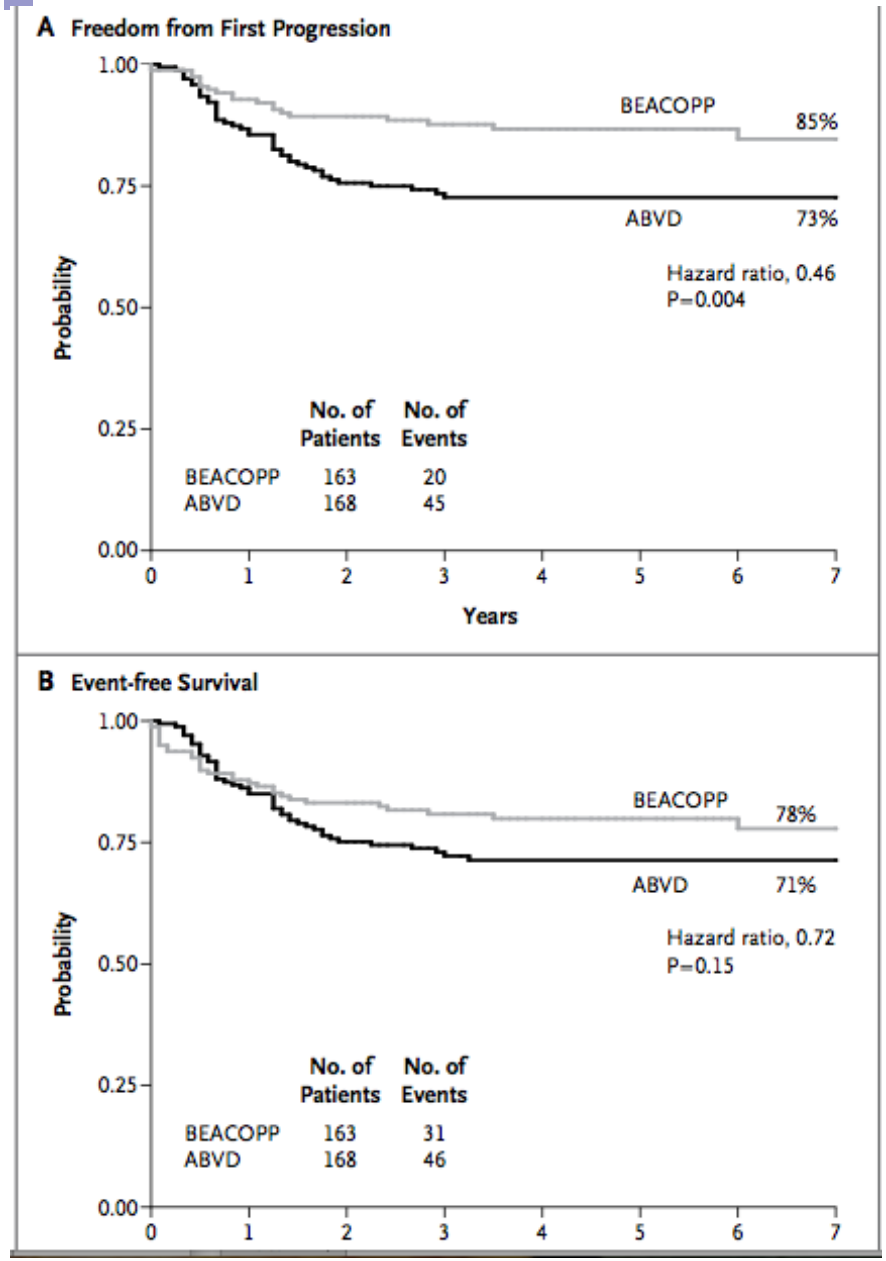
- PET scans 739 pts in PR & mass ≥ 2.5 cm, 548 PET- (74.2%) 191 PET+ (25.8%)
- PFS comparable CR vs PET-negative PR with 4-year PFS 92.6% and 92.1%, respectively
- **BEST EVIDENCE: escBEACOPP x 6 + RT only for PET+ residual mass of ≥ 2.5 cm**

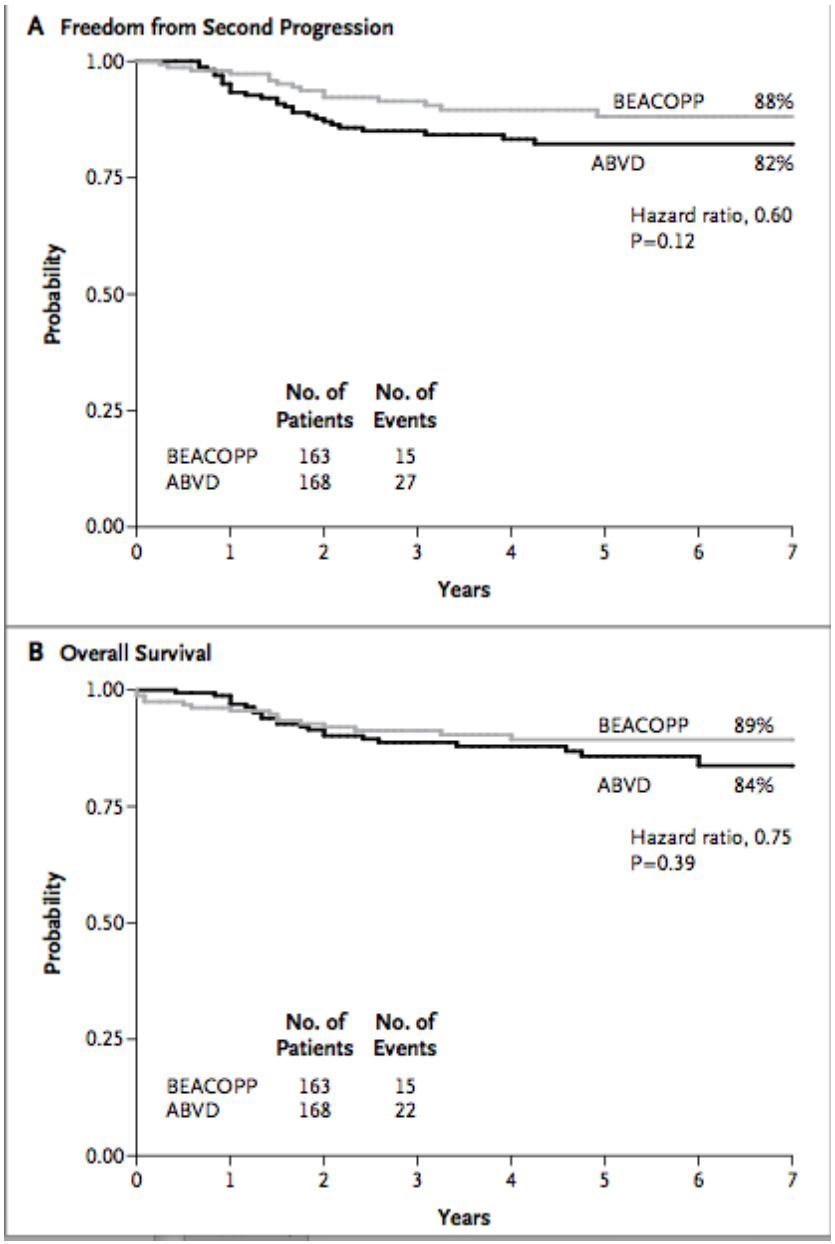
Andreas Engert, Blood 2011: a589

Italian trial of ABVD x 6-8 vs BEACOPP (4e + 4b) in advanced HL

- N = 331
- median f/u = 61 months
- severe heme toxicities ABVD 43% vs BEACOPP 81% (p<0.001)
- severe non-heme toxicities 7% vs 19%

Viviani *et al* NEJM 2011; 365: 203





Viviani *et al* NEJM 2011; 365: 203

Italian (GITIL) BEACOPP study

Table 2. Salvage Therapy and Outcome of Overall Intended Treatment.*

Variable	ABVD	BEACOPP
Salvage therapy		
Characteristics of patients		
No. undergoing salvage therapy	45	20
Induction failure, less than complete remission, or complete remission <12 mo — no. (%)	26 (58)	14 (70)
Complete remission ≥12 mo — no. (%)	19 (42)	6 (30)
Stage III or IV disease — no. (%)	24 (53)	13 (65)
Feasibility of salvage regimen — no. (%)		
Unable to start on protocol salvage therapy	6 (13)	5 (25)
Started on protocol salvage therapy	39 (87)	15 (75)
Induction therapy completed	39 (87)	15 (75)
Consolidation therapy completed	30 (67)	13 (65)
Complete response at end of salvage therapy — no. (% [95% CI])	23 (51 [26–66])	7 (35 [15–59])
Deaths — no. (%)	3 (7)	4 (20)
Hodgkin's lymphoma	0	1 (5)
Acute toxic effects	3 (7)	3 (15)
In continuous complete response as of cutoff date — no. (% [95% CI])	15 (33 [20–49])	3 (15 [3–38])
7-Year outcome of overall intended treatment after initial therapy, with or without salvage therapy†		
Freedom from first progression — % (95% CI)‡	73 (66–80)	85 (78–91)
Event-free survival — % (95% CI)§	71 (64–78)	78 (70–85)
Freedom from second progression — % (95% CI)¶	82 (76–88)	88 (82–94)
Overall survival — % (95% CI)‖	84 (77–91)	89 (84–95)

Viviani *et al* NEJM 2011; 365: 203

Conclusions from GITIL study

- BEACOPP better than ABVD in terms of FFFP (10% diff) but not in terms of OS after high dose salvage therapy (regimens are comparable in terms of OS)
- toxicity of BEACOPP more than ABVD
- no impact of IPS on outcomes (cut-off 3)
- Note: N in GITIL study much smaller than HD9 (331 vs 727) + 1/2 as long f/u and OS was only a secondary endpoint + need to follow longer to see if extra secondary mortality post-BEAM ASCT influences longterm OS

Viviani *et al* NEJM 2011; 365: 203

BEACOPP Meta-analysis

Figure 2. Forest plot of comparison: 1 Analysis of Overall Survival, outcome: 1.1 OS - all - same recruitment period between the 2 arms (HD9).

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GHSG HD14 (abstract)	0.02	0.32	805	818	24.2%	1.02 [0.54, 1.91]
GHSG HD9	-0.485	0.225	265	177	49.0%	0.62 [0.40, 0.96]
GSM-HD 2008 (abstract)	0.03	0.37	155	166	18.1%	1.03 [0.50, 2.13]
HD 2000	0.077	0.538	98	99	8.6%	1.08 [0.38, 3.10]
Total (95% CI)			**1323**	**1260**	**100.0%**	**0.80 [0.59, 1.09]**

Heterogeneity: Chi² = 2.71, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.40 (P = 0.16)

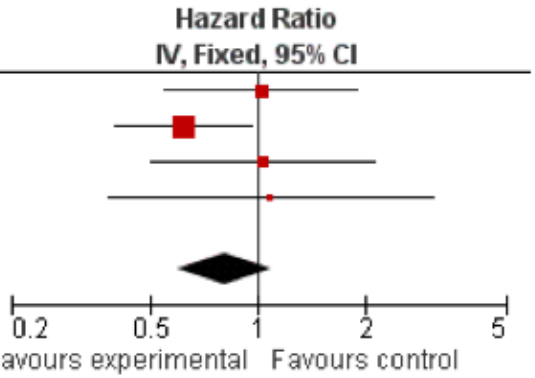
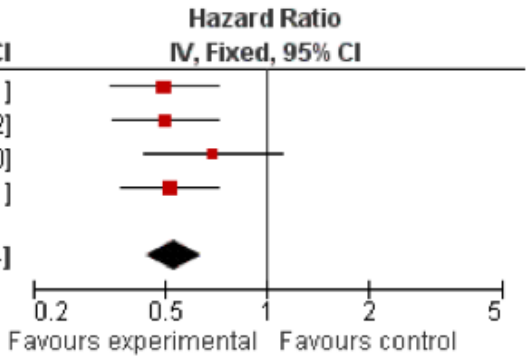


Figure 3. Forest plot of comparison: 2 Analysis of Progression Free Survival, outcome: 2.1 PFS - all - same recruitment period between the 2 arms (HD9).

Study or Subgroup	log[Hazard Ratio]	SE	Experimental Total	Control Total	Weight	Hazard Ratio IV, Fixed, 95% CI
GHSG HD14 (abstract)	-0.71	0.19	805	818	25.7%	0.49 [0.34, 0.71]
GHSG HD9	-0.7	0.188	265	177	26.2%	0.50 [0.34, 0.72]
GSM-HD 2008 (abstract)	-0.371	0.24	155	166	16.1%	0.69 [0.43, 1.10]
HD 2000	-0.669	0.17	98	99	32.1%	0.51 [0.37, 0.71]
Total (95% CI)			**1323**	**1260**	**100.0%**	**0.53 [0.44, 0.64]**

Heterogeneity: Chi² = 1.52, df = 3 (P = 0.68); I² = 0%
Test for overall effect: Z = 6.65 (P < 0.00001)



Bauer *et al* Cochrane Dat Sys Rev 2011; 8:CD007941

Fertility in male patients with advanced HL treated with BEACOPP

- 38 male pts in GHSG studies
-
-

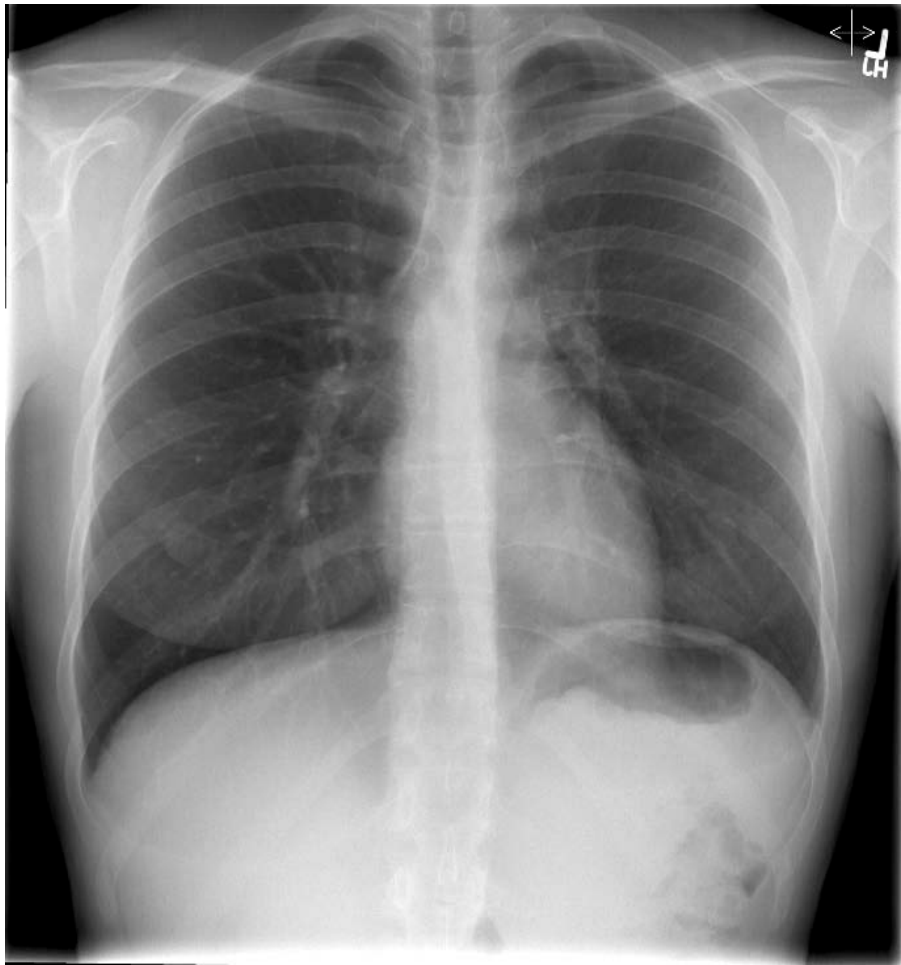
Treatment	Before treatment	After
Normozoospermia	6 (23%)	0 (0%)
Dysspermia	20 (77%)	4 (11%)
Azoospermia	0 (0%)	34 (89%)

- Azoospermia bBEACOPP vs escBEACOPP 93% vs 87%, p>.999
- After treatment 93% abN FSH, 57% abN testosterone, 21% abN LH

Sieniawski *et al* Ann Onc 2008; 19:1795

Case 3: Stage IVB HL

- Escalated BEACOPP Feb 8-May 31, 2010
  - Other meds: G-CSF, Kytril, Aprepitant, Septra, Valtrex
  - Tolerated well.
    - No febrile neutropenia
    - No treatment delay.
    - No dose reductions.
    - No organ toxicity.



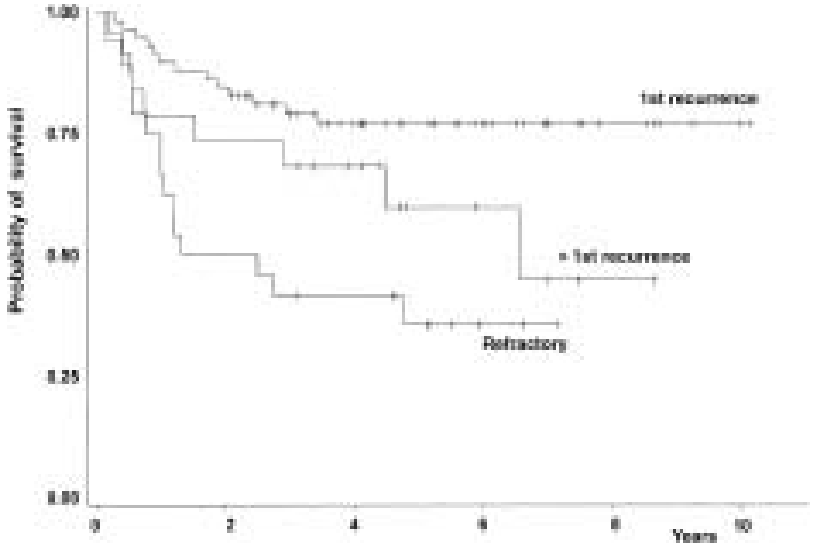
• recurrent LNs 14 months post-tx, awaiting bx

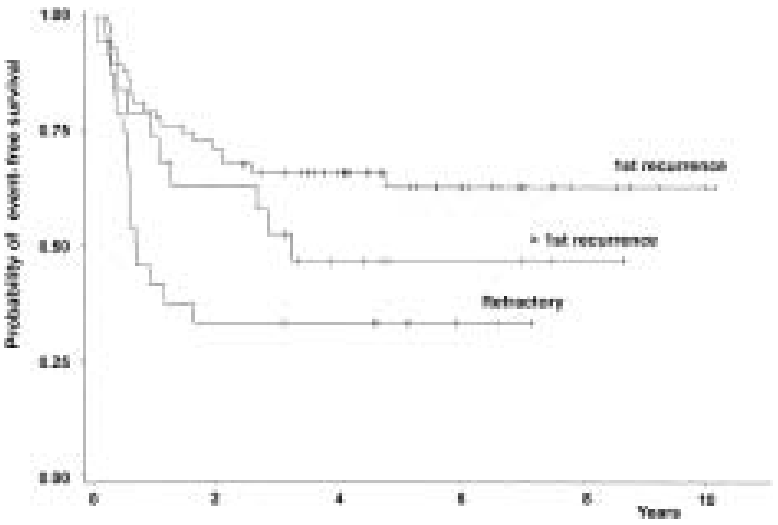
Treatment of relapsed/refractory Hodgkin lymphoma

Case 4: 36 y.o. woman Stage IVA HL

- Presented with groin nodes
  - Bilateral groin, (left 4.9x3.0cm + 4.4x2.2cm) + bilat external iliac, extensive aortocaval nodes
- 1 week post-diagnosis, develops skin nodules – biopsy proved NS HL
- WBC 13.2, Hgb 111, plts 545, alb 32, LDH normal, ESR 97
- Stage IVA nodular sclerosing HL with IPS 2 (stage + albumin)
- ABVD x 2 cycles with progression of abdominal pain and skin lesions
- diagnosis - Refractory HL

Treatment of relapsed/refractory HL





Overall survival

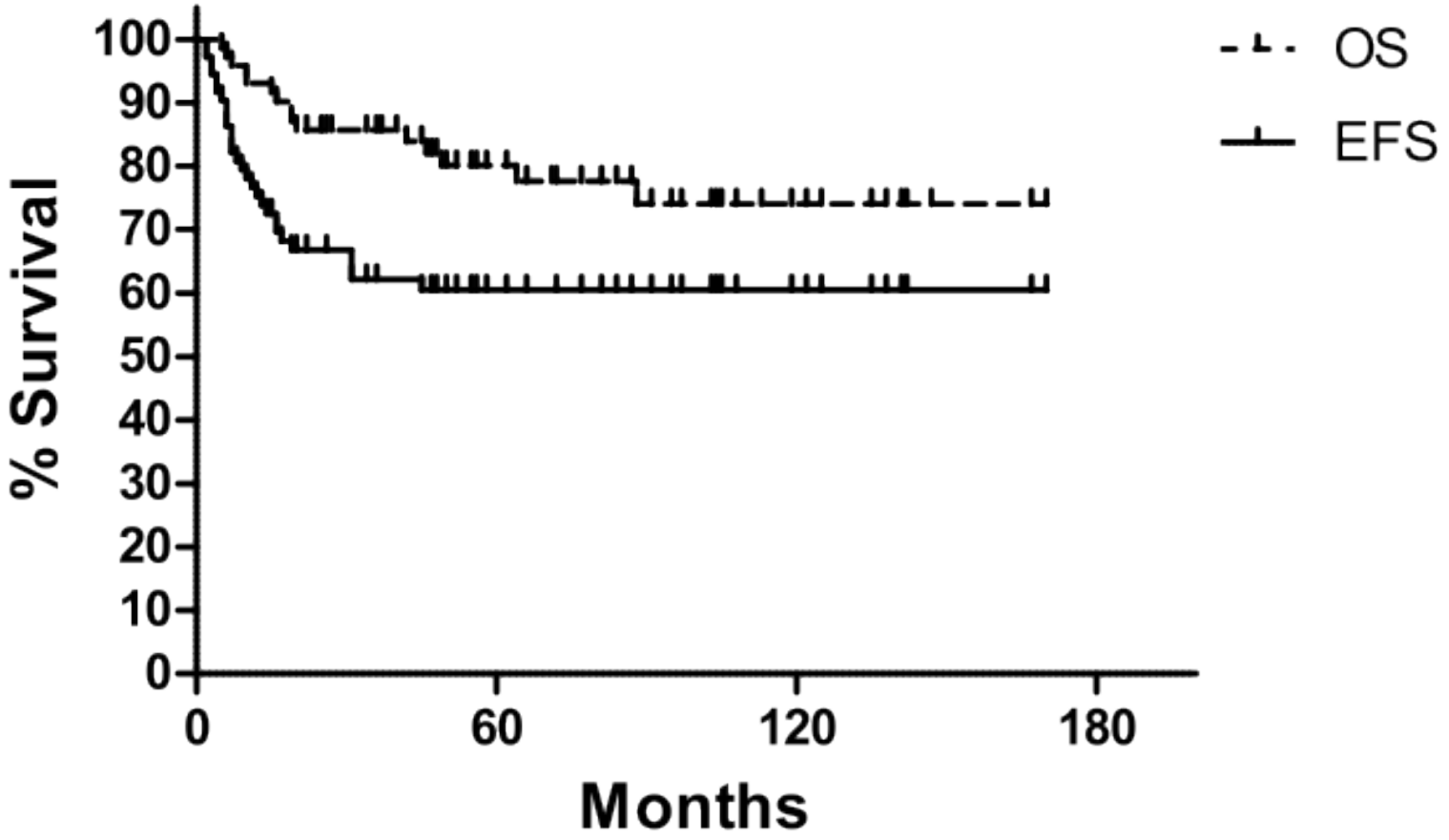
5 yr OS: 77% for 1st relapse
36% for refractory

Event-free survival

5 yr EFS: 63% for 1st relapse
33% for refractory

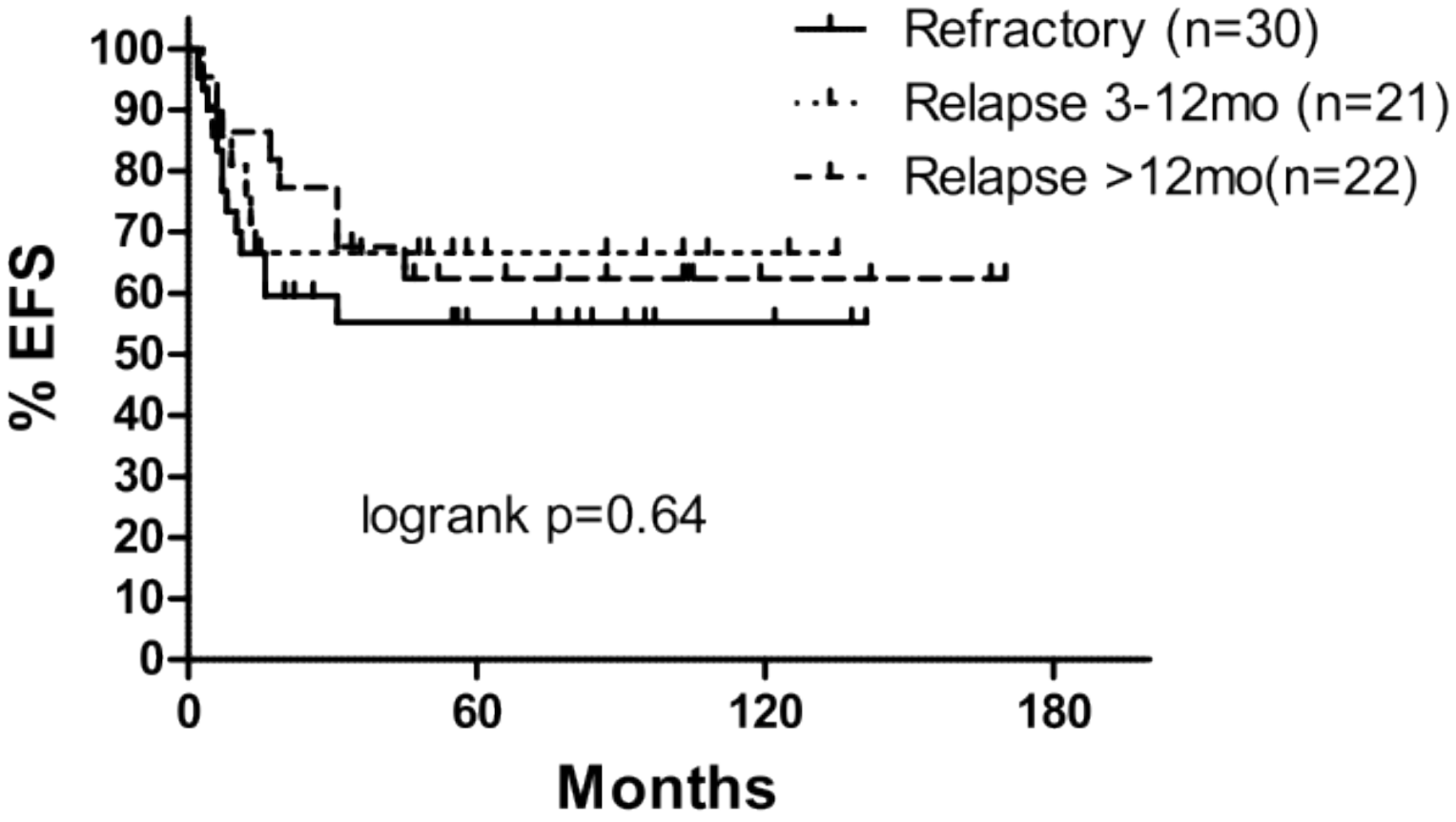
Tarella *et al* Cancer 2003;97:2748

DICEP then Melphalan/ASCT for Relapsed/Refractory Classical Hodgkin Lymphoma in Calgary (n=73)



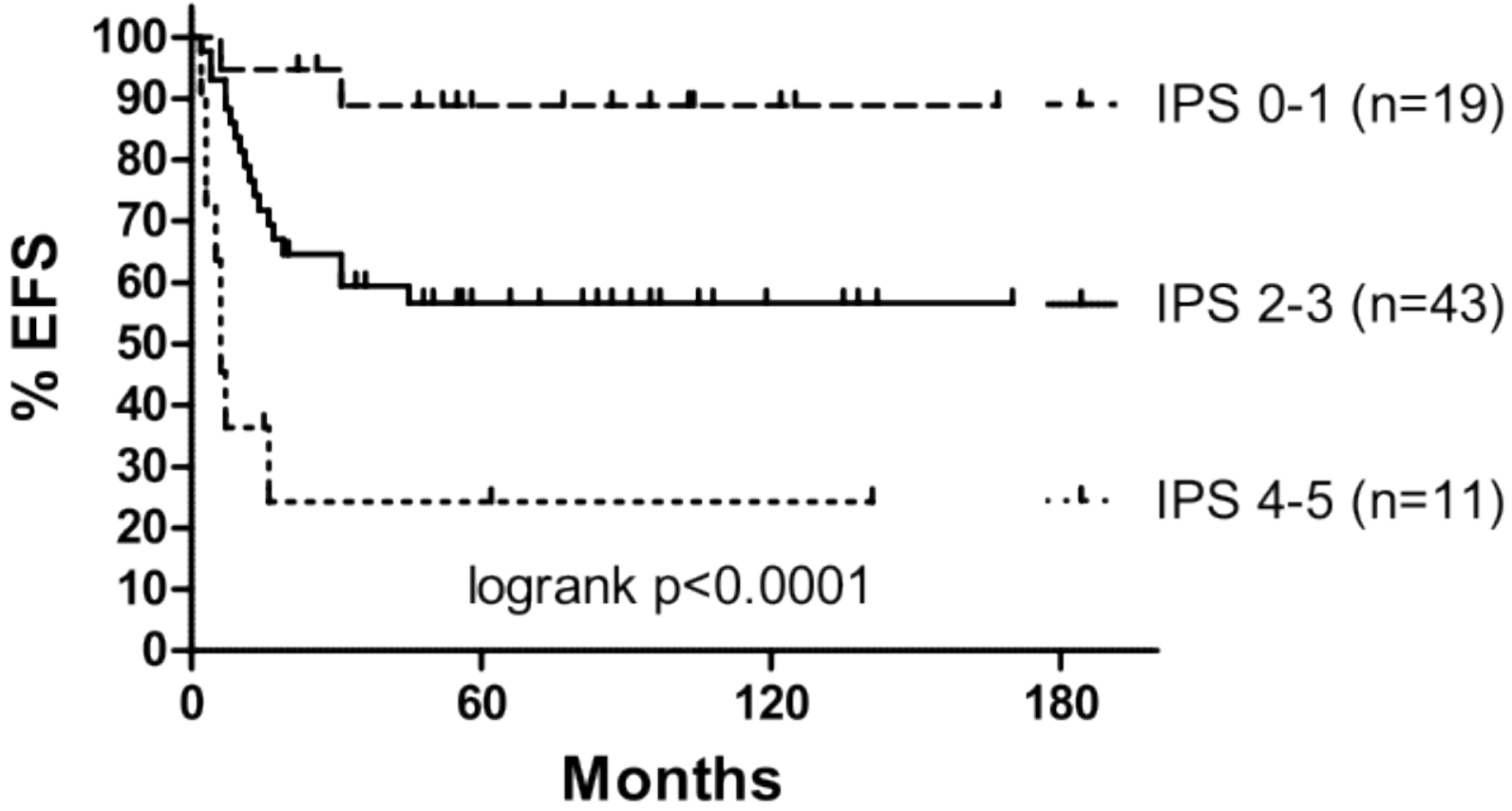
Stewart Oct 2010

DICEP then Melphalan/ASCT for Relapsed/Refractory Classical Hodgkin Lymphoma in Calgary (n=73)



Stewart Oct 2010

DICEP then Melphalan/ASCT for Relapsed/Refractory Classical Hodgkin Lymphoma in Calgary (n=73) by Relapse IPS



Stewart Oct 2010

Case 4: outcome

- Positive PET post-DICEP (ie no response to salvage chemotherapy)
- further progression after BEAM/ASCT (within 2 months)
- renal failure 2ndary to obstructive nephropathy (corrected with renal stents)
- Initially refused palliative RT for renal failure but agreed 1 month later
- Died 1 month later = 12 months from diagnosis

Novel salvage therapy options for relapsed/refractory HL

- Lenalidomide
  - N= 33
  - median prior therapies 4 (2-9)
  - 55% refractory to last therapy

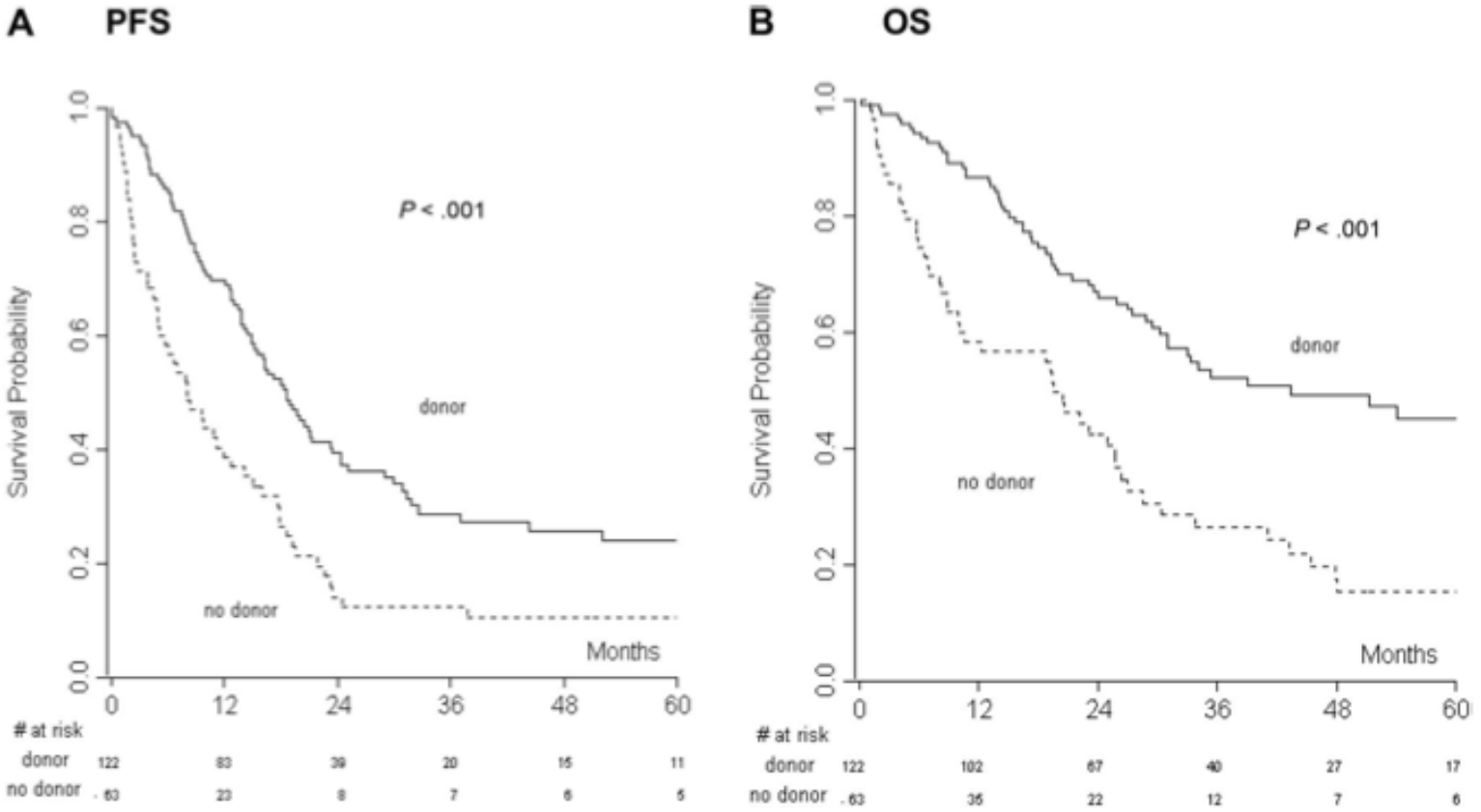
Table 2. Response rates for entire cohort (N = 38) and per protocol response evaluable patients (n = 36)

Type of response	Patients, n	Entire cohort, %	Response evaluable, %
CR	1	2.6%	2.8%
PR	6	15.7%	16.6%
SD > 6 months	5	13.2%	13.9%
ORR (CR + PR)	7	18.4%	19.4%
Cytostatic ORR (CR + PR + SD ≥ 6 mo)	12	31.6%	33.3%

Fehniger *et al* Blood 2011; 118:5119

Allo SCT for relapsed/refractory HL

- retrospective analysis of 185 patients having HLA typing after relapse post-ASCT
- 122 had a donor, 62 did not

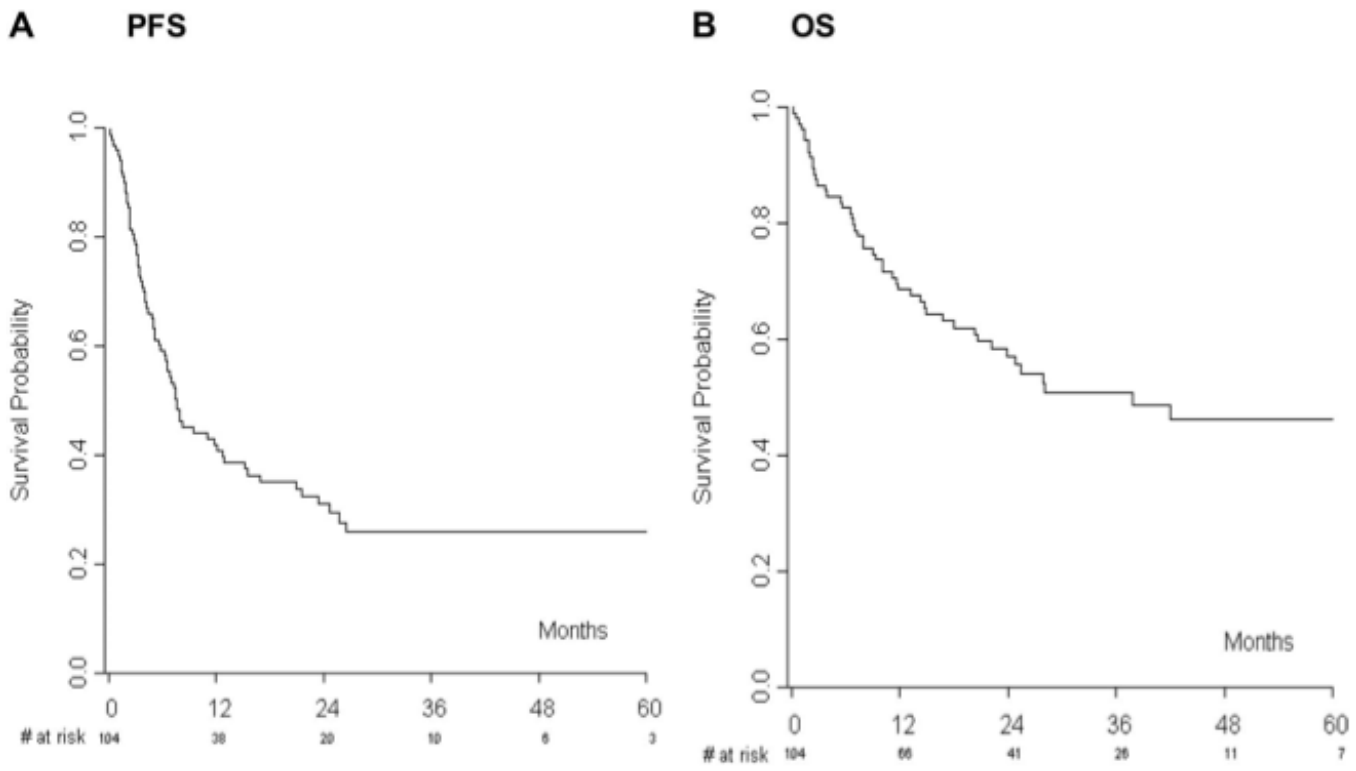


Sarina *et al* Blood 2010; 115:3671

Allo SCT

Table 4. Multivariable analysis

	PFS		OS	
Factor	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Intention to treatment, no donor versus donor	1.94 (1.38-2.73)	< .001	2.47 (1.68-3.64)	< .001
Time from autoSCT to relapse, less than 12 mo versus more than 12 mo	1.57 (1.06-2.31)	.023	1.90 (1.19-3.01)	.007



Sarina *et al* Blood 2010; 115:3671

QUESTIONS?