Incontri Bresciani di Radioterapia Oncologica – Edizione 2010
Brescia Meetings in Radiation Oncology – 2010 Edition

Hodgkin and Non Hodgkin Lymphomas:
a new Role for Radiation Therapy?

Brescia – May 14th, 2010

The Problem of Interpretation and Use of Response Evaluation for Treatment

Dr. Gabriele Simontacchi

Prof. Giampaolo Biti

Radiation Oncology Department,
Florence University
AOU Careggi - Firenze

Response evaluation in HDG

Report of a Committee Convened To Discuss the Evaluation and Staging of Patients with Hodgkin's Disease: Cotswolds Meeting

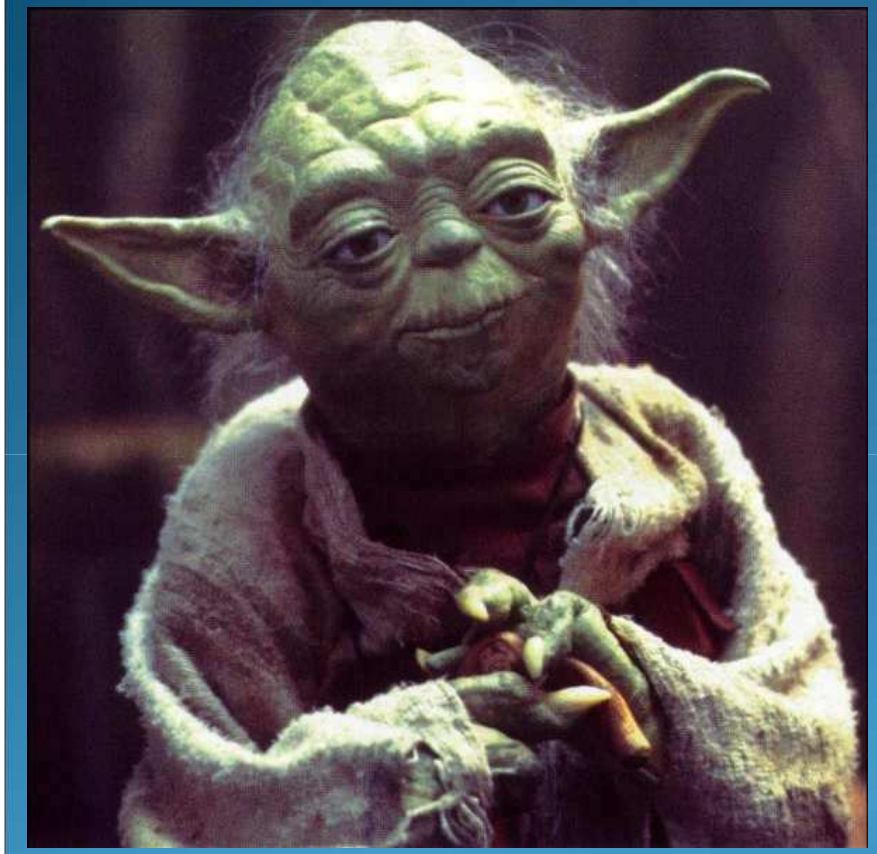
By T.A. Lister, D. Crowther, S.B. Sutcliffe, E. Glatstein, G.P. Canellos, R.C. Young, S.A. Rosenberg, C.A. Coltman, and M. Tubiana

JCO, 1989

Criteria for Reporting Response to Therapy

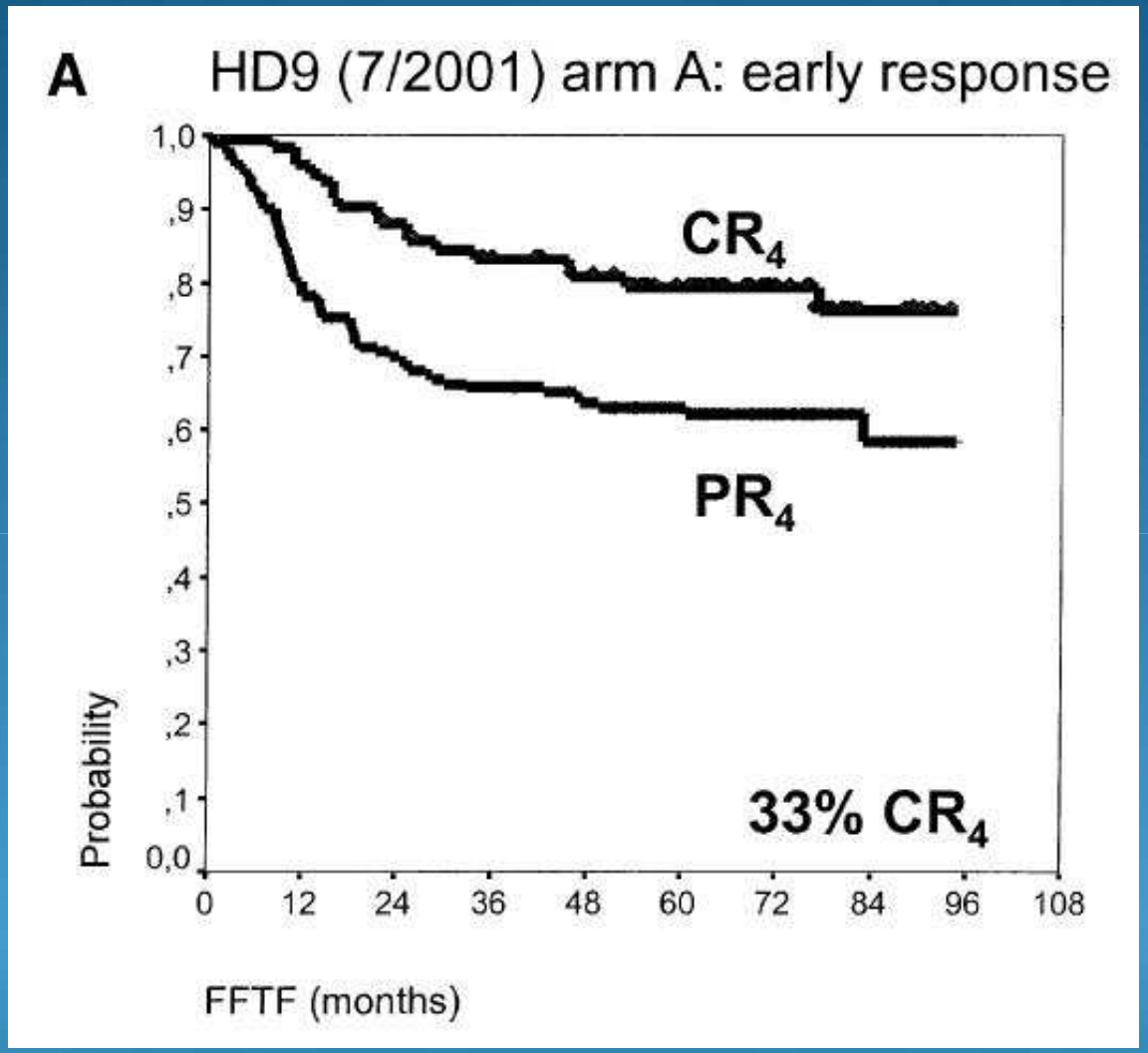
CR. The patient has no clinical, radiological, or other evidence of Hodgkin's disease. Changes consistent with the effects of previous therapy (ie, radiation fibrosis) may be present.

CR (unconfirmed/uncertain). This category (CR[u]) of response has been included to denote patients in whom remission status is unclear. The patient is in normal health with no clinical evidence of Hodgkin's disease but some radiological abnormality, not consistent with the effects of therapy, persists at a site of previous disease. Implicit in this designation is considerable uncertainty about the significance of such abnormalities, it being well known that abnormal widening of the mediastinum or architectural distortion of lymphographic studies may persist for many years without therapy and without evidence of recurrent Hodgkin's disease. Attempts to resolve



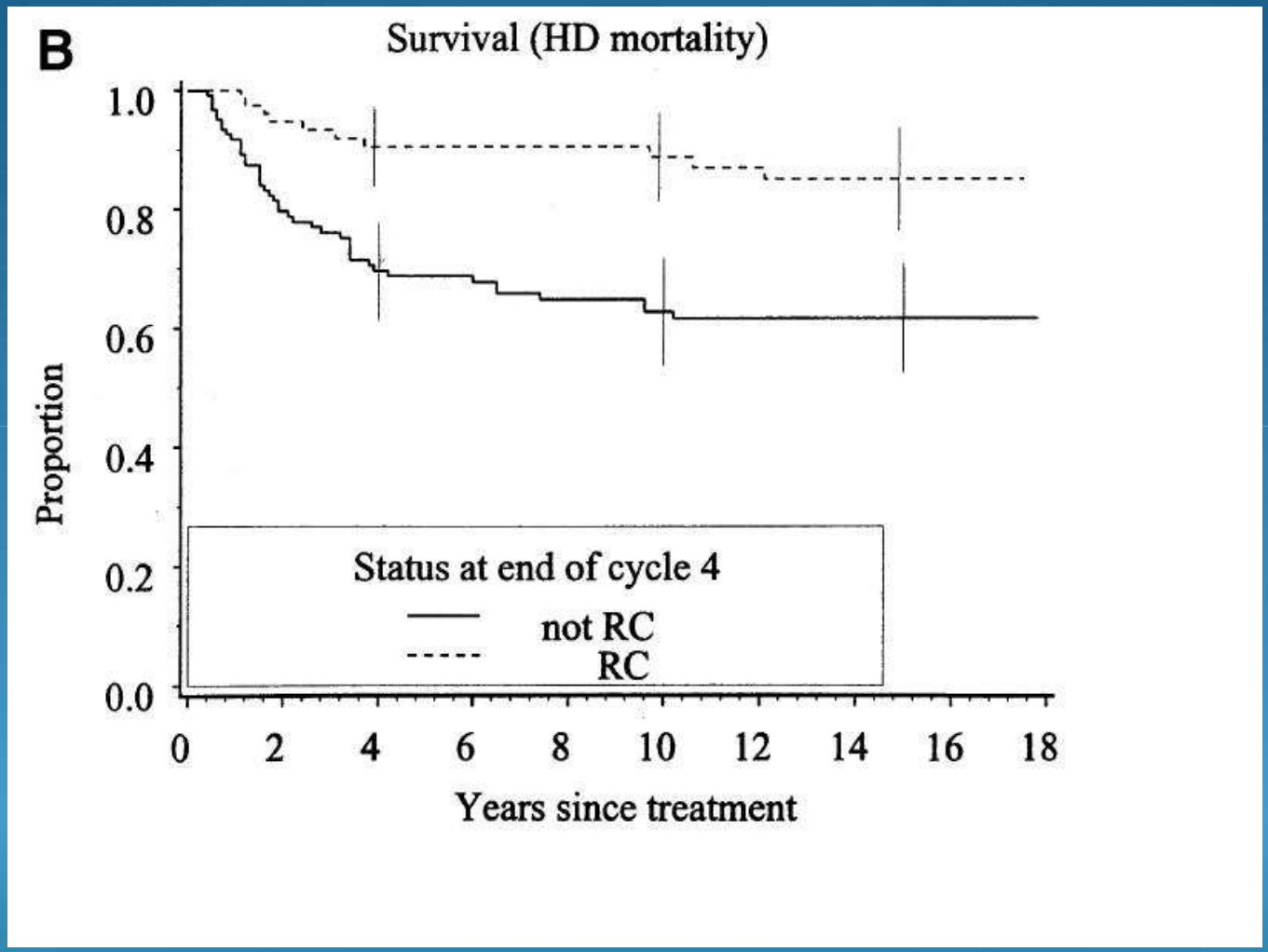
… our teachers used to tell us: "…in HL, early responder patients are likely to be cured…"

GHSG HD9 trial



Diehl, AnnOncol 1997

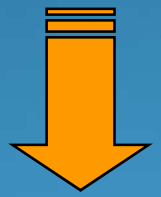
EORTC 1981-1986 trial



Carde, Blood 2000

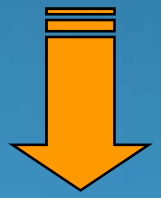
AIMS of research in Hodgkin's Lymphoma:

- **Improvement of (already) low relapse rate**



Identify non responder patients who could benefit from an alternative therapy protocol

- **Reduction of toxicity**



Identify patients who could benefit from a reduction of the treatment burden

18FDG-PET in Hodgkin Lymphoma

In the staging of Hodgkin Lymphoma, PET scan showed a sensitivity around 85-90% and specificity up to 95-100%, leading to a stage change from 8% up to 40% of patients

(Bangerter 1998, Partridge 2000, Jerusalem 2001, Weihrauch 2002)

Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma

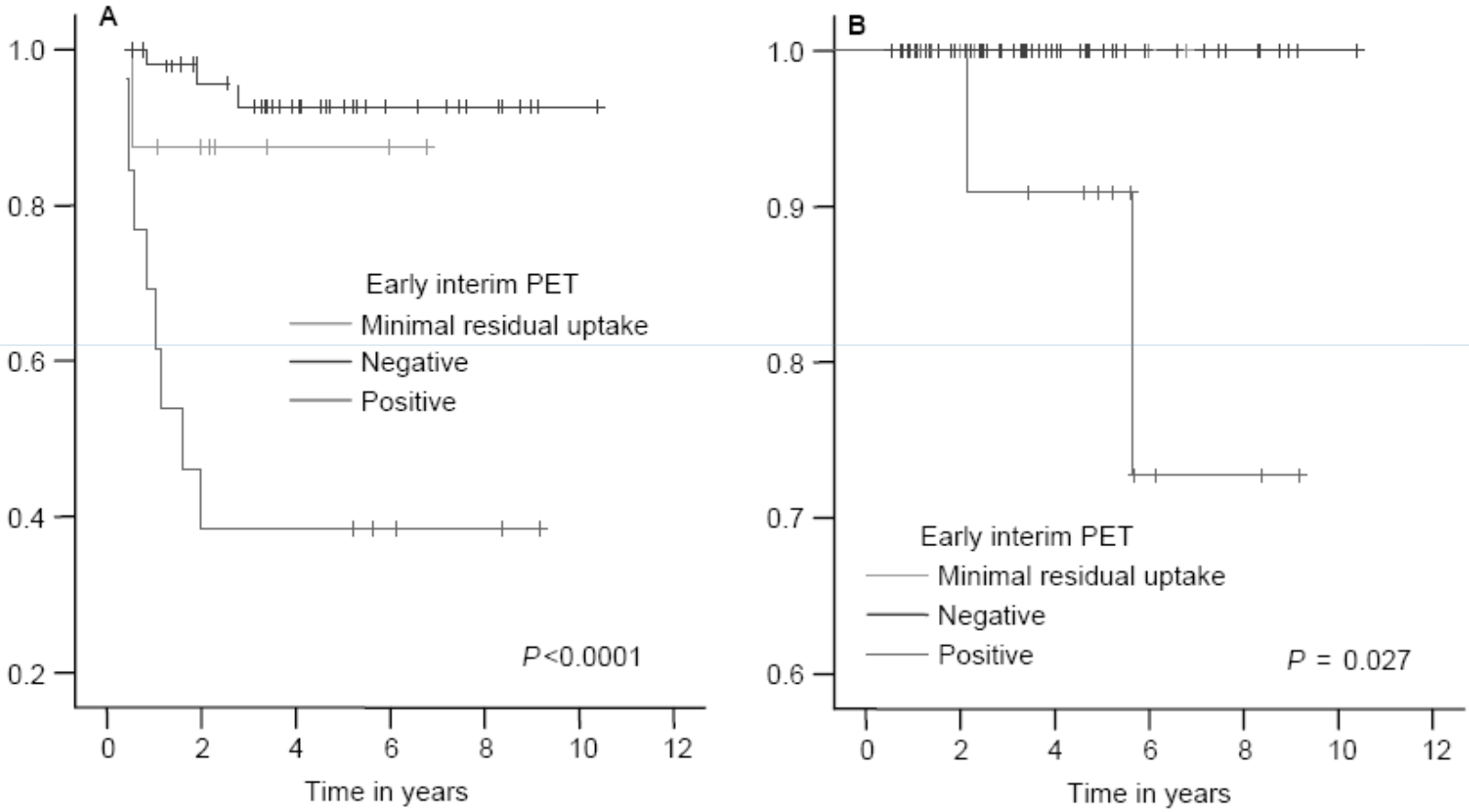


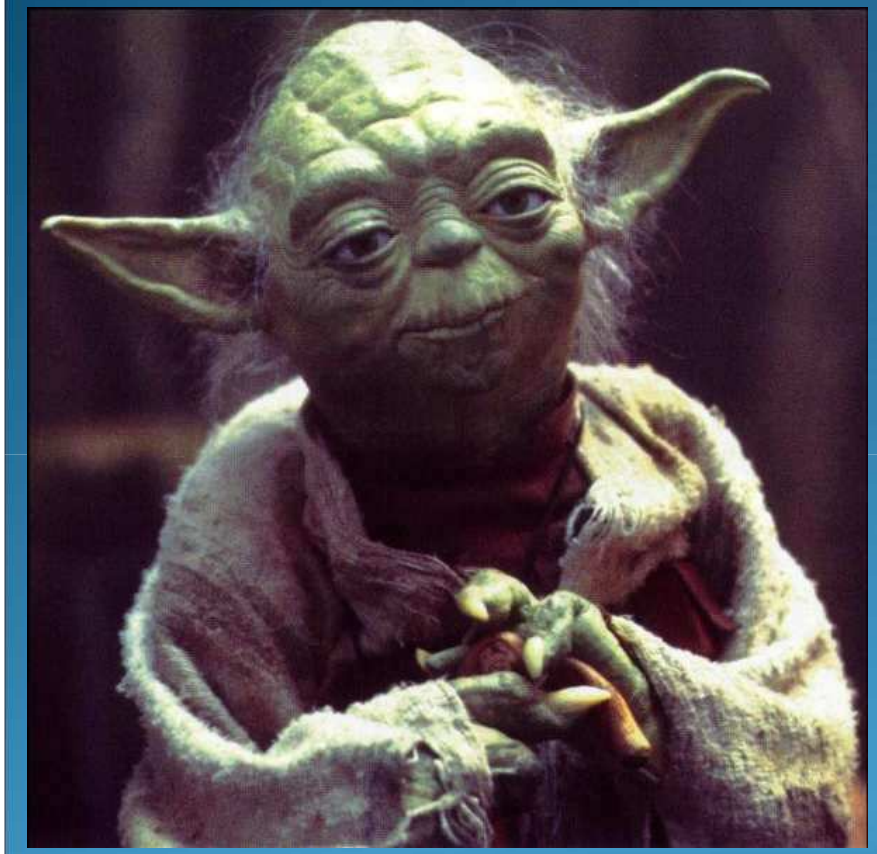
Figure 3. (A) Progression-free survival and (B) overall survival according to the outcome of early interim FDG-PET.

Hutchings, Ann Oncol 2005

Table 2. PET results during and after therapy

	PET-2 (after 2 cycles)	PET-4 (after 4 cycles)	PET-6 (after 6 cycles)
Positive	8	7 → 1	7
Minimal residual uptake	4	3 → 2	1 → 2
Negative	20	30	32

Zinzani, AnnOncol 2006



… our teachers used to tell us: "…in HL early responder patients are likely to be cured…"

PET could give a reliable idea of this "early response".

Can interim FDG-PET drive treatment decision in HL?

- Early stage with interim PET -
- Early stage with interim PET +
- Advanced stage with interim PET -
- Advanced stage with interim PET +

Can FDG-PET drive treatment decision in HL?

- **Early stage with interim PET -**
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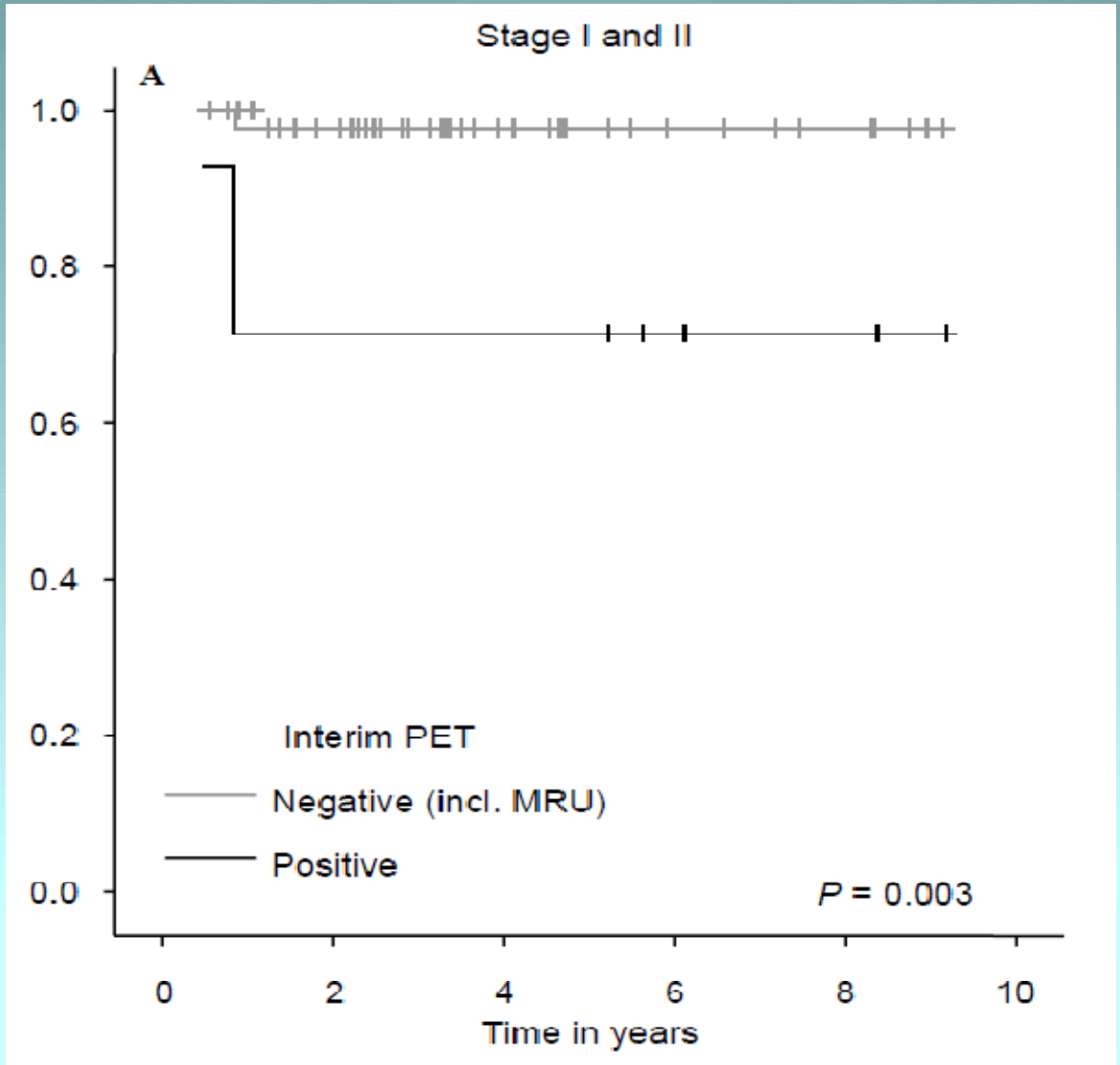
Early stage with interim PET -



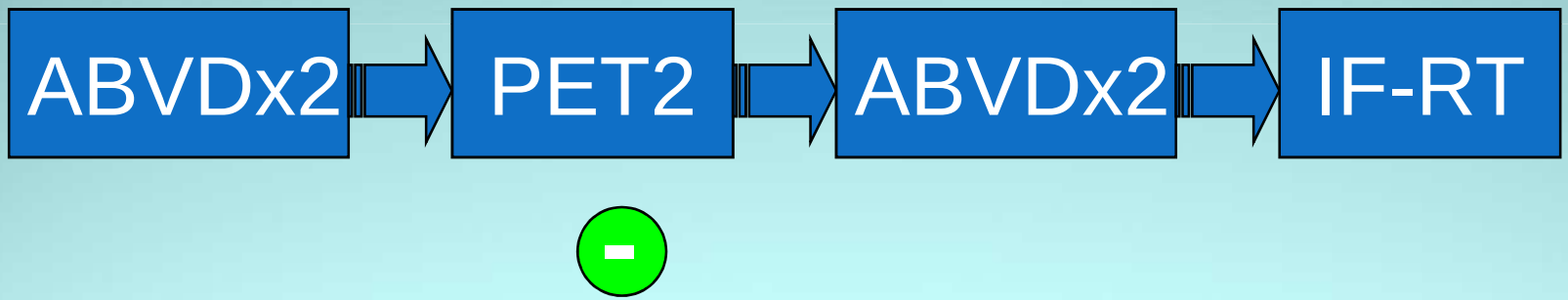
Hutchings, Ann Oncol 2005

Early stage with interim PET -

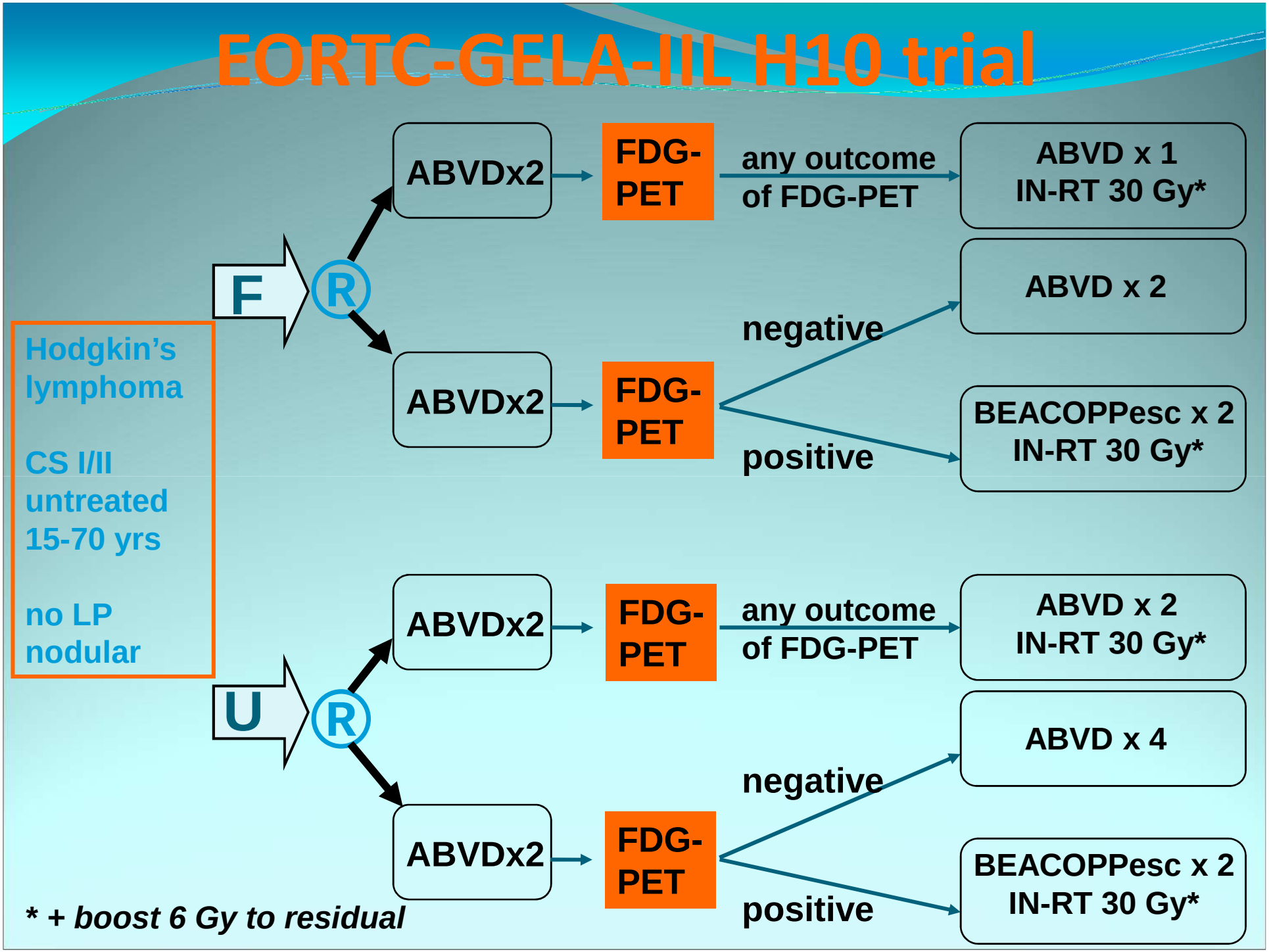
The negative predictive value of early interim FDG-PET is extremely high in early-stage patients. This is not particularly surprising, since early-stage HL generally has an excellent prognosis. We confirm the findings from Hutchings et al that the positive predictive value is very high in advanced-stage patients.[22] In the

Hutchings, Blood 2006

Early stage with interim PET-



EORTC-GELA-IIL H10 trial



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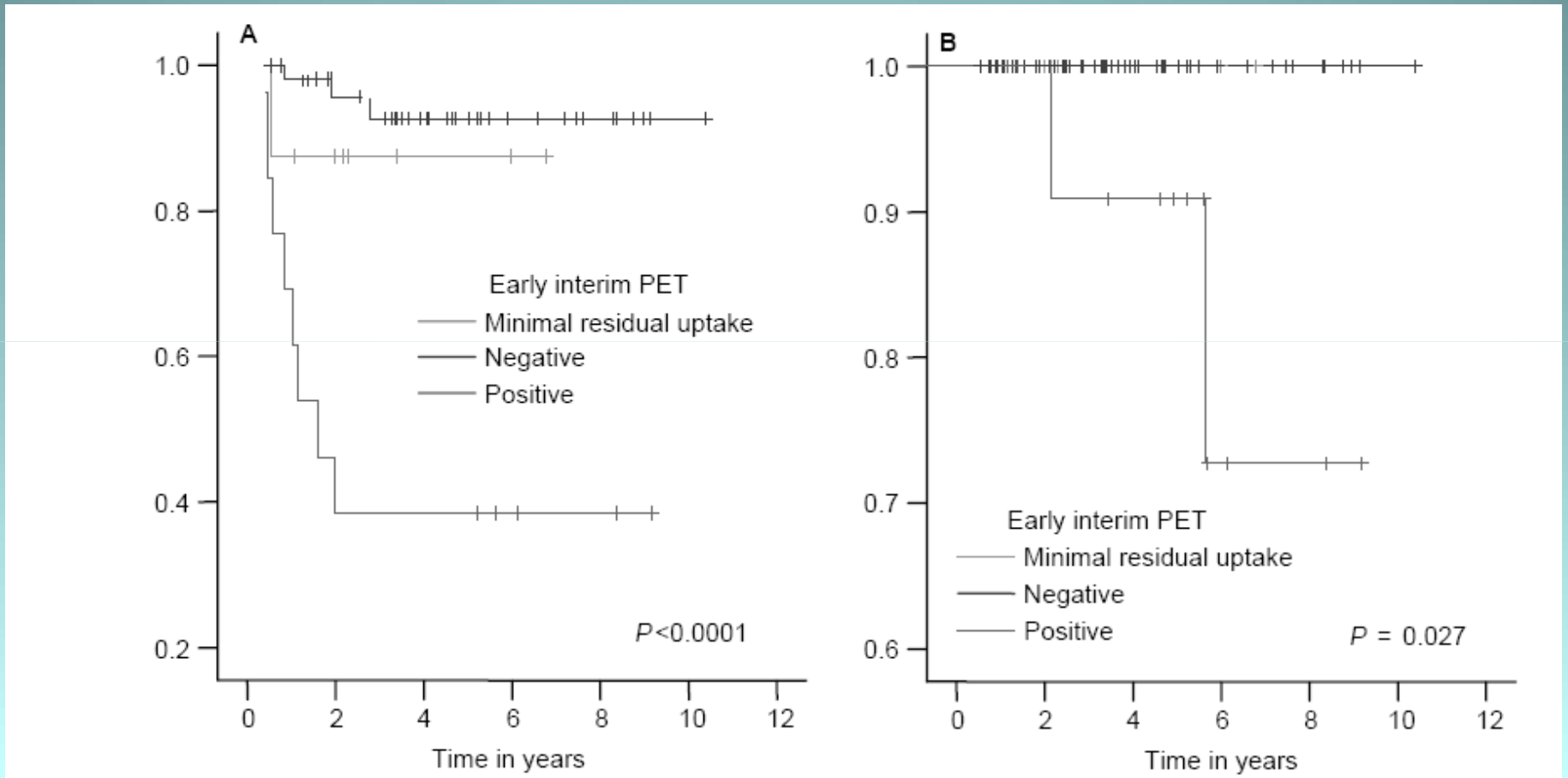
Early stage with interim PET +

Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma



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Hutchings, Ann Oncol 2005

Early stage with interim PET +

Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma

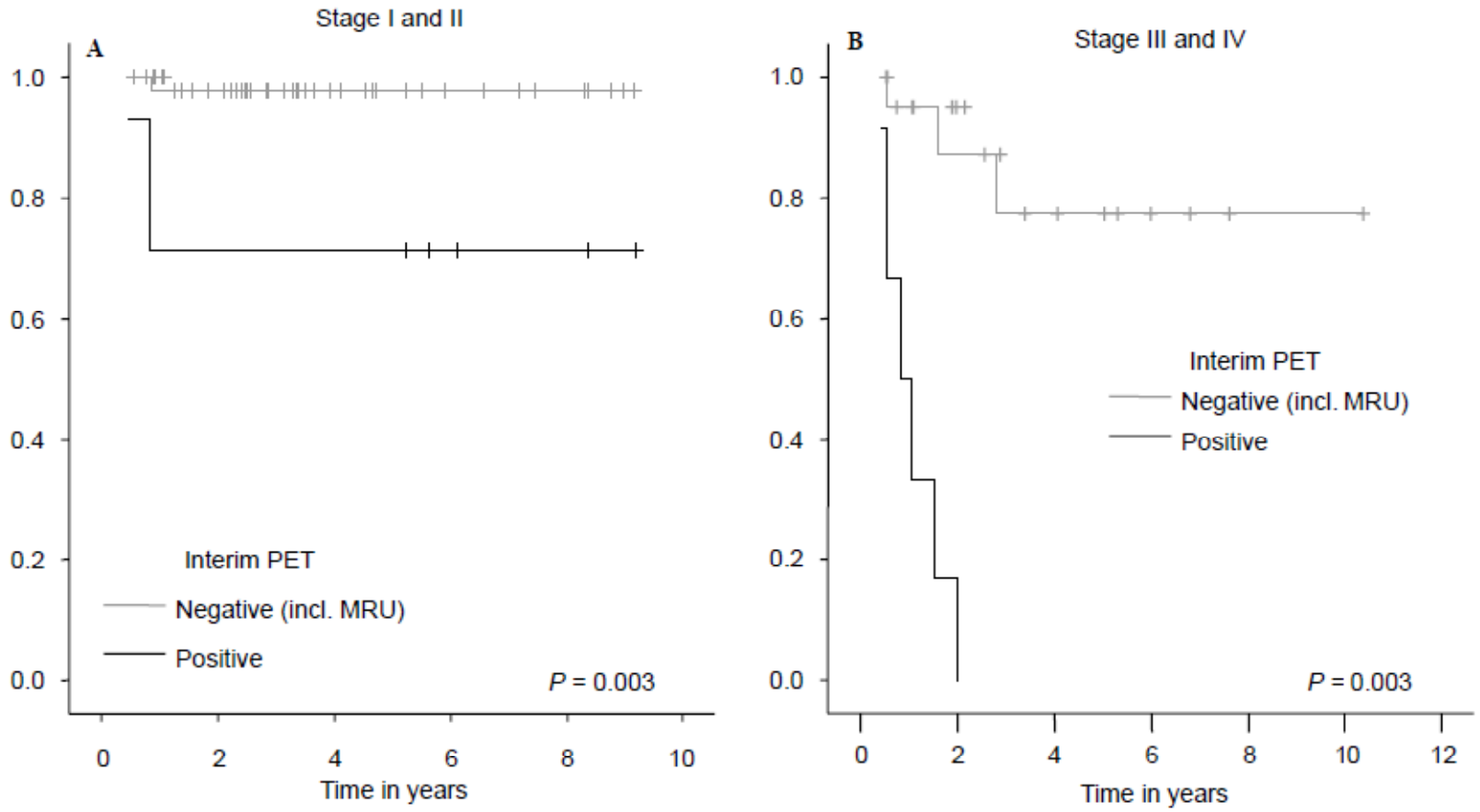


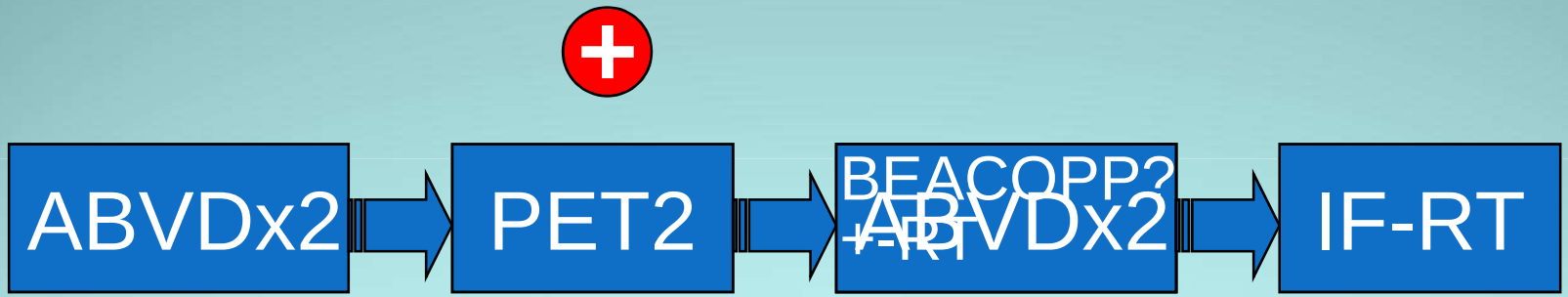
Figure 5. Progression-free survival according to the outcome of early interim FDG-PET for (**A**) stage I–II patients and (**B**) stage III–IV patients.

Hutchings, Ann Oncol 2005

Recidive secondo PET2 nei pazienti Early Stage

Author	Follow-up	PET2 +	Relapses in PET2 +	Relapses in PET2 -
Hutchings (Ann Oncol, 2005)	6-125 months (avg. 46,6)	7/57 (12,3%)	2/7 (28,5%)	1/50 (2%)
Hutchings (Blood, 2006)	6,1-40,8 months (avg. 23,4)	5/31 (16,1%)	1/5% (20%)	0/26 (0%)
Firenze-Brescia series (unpublished data)	6,1-70,8 months (avg. 32,8)	4/44 (9,1%)	1/4 (25%)	1/40 (2,5%)

Early stage with interim PET +



original article

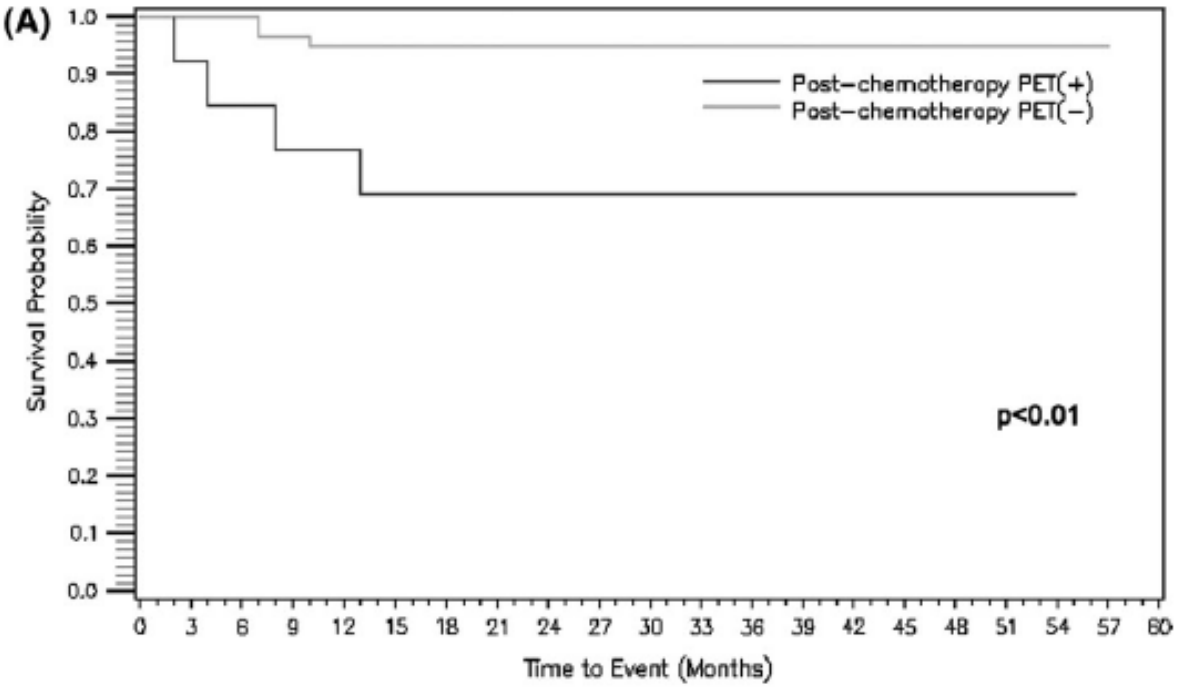
Annals of Oncology 20: 1848–1853, 2009
doi:10.1093/annonc/mdp071
Published online 18 June 2009

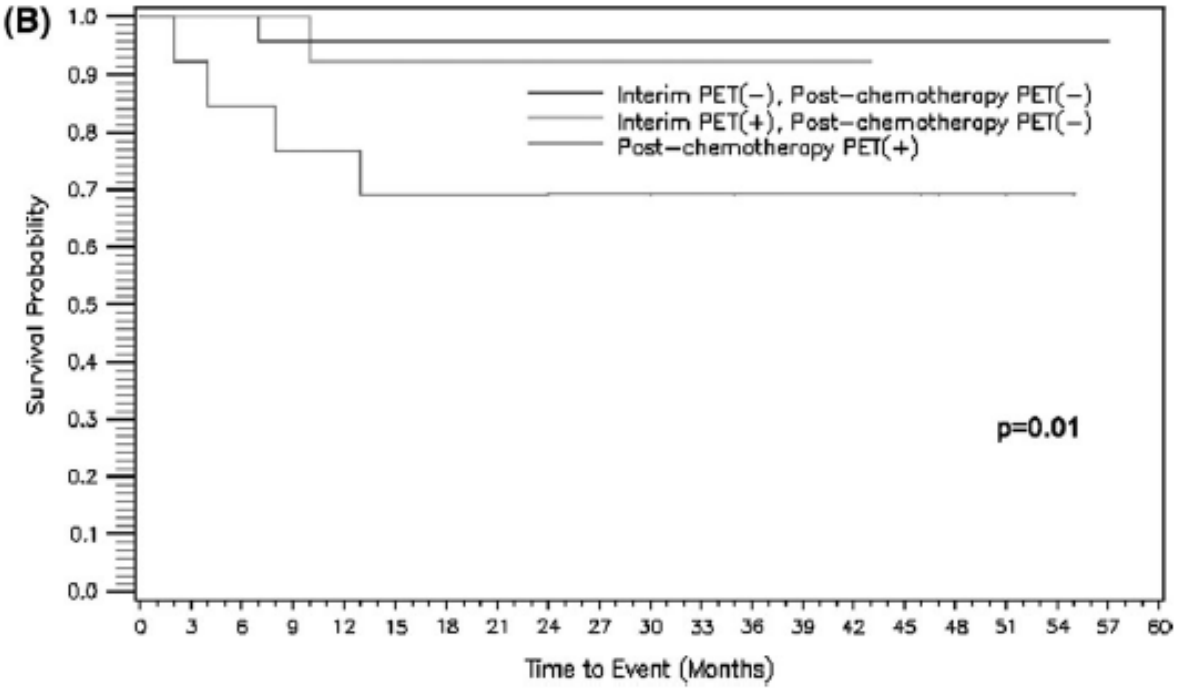
Prognostic significance of mid- and post-ABVD PET imaging in Hodgkin's lymphoma: the importance of involved-field radiotherapy

D. J. Sher[1]*, P. M. Mauch[1], A. Van Den Abbeele[2], A. S. LaCasce[3], J. Czerminski[1] & A. K. Ng[1]

[1]*Department of Radiation Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital; Departments of* [2]*Nuclear Medicine and* [3]*Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA*

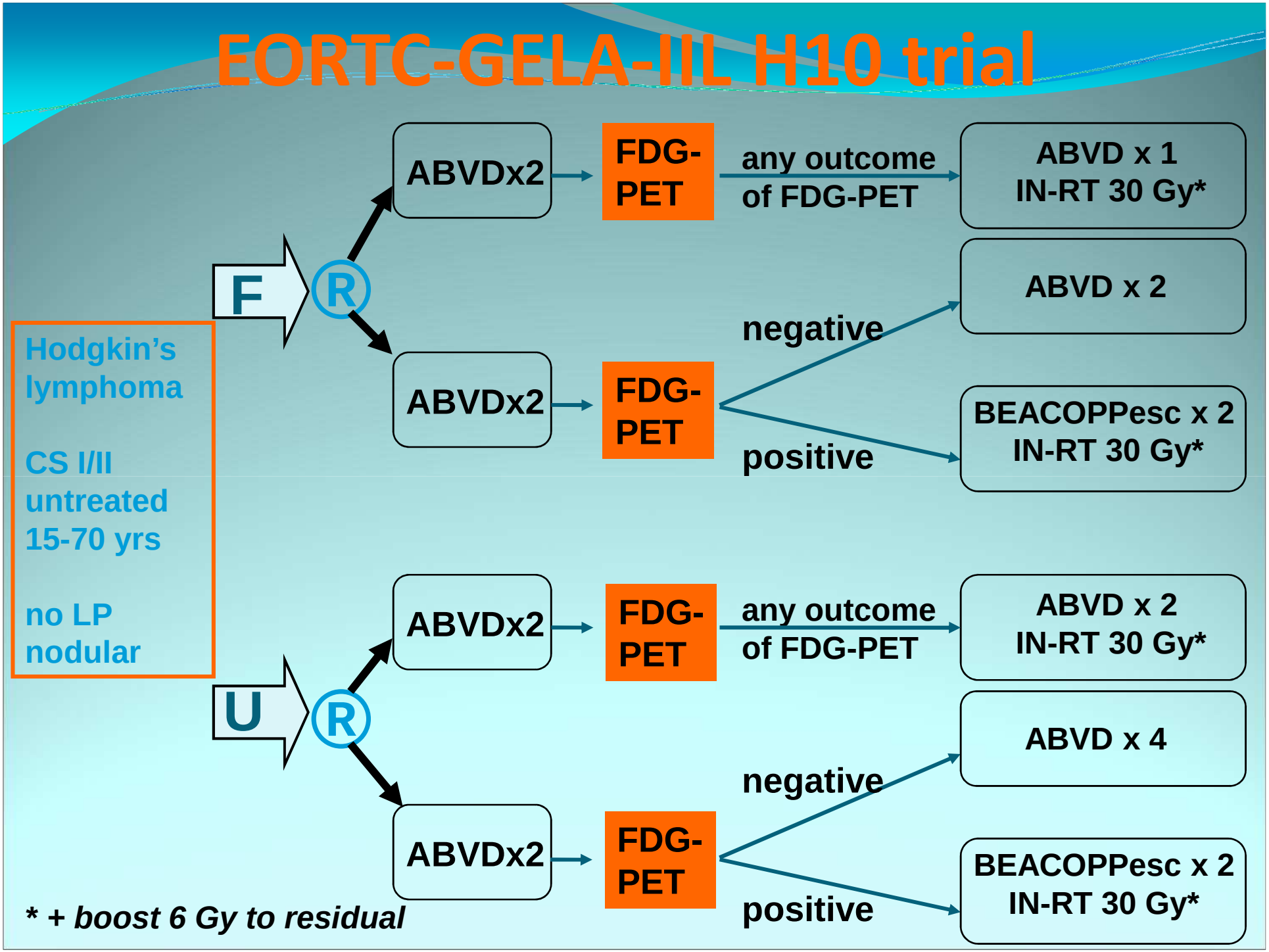
Received 24 February 2009; accepted 26 February 2009





Sher, AnnOncol 2009

EORTC-GELA-IIL H10 trial



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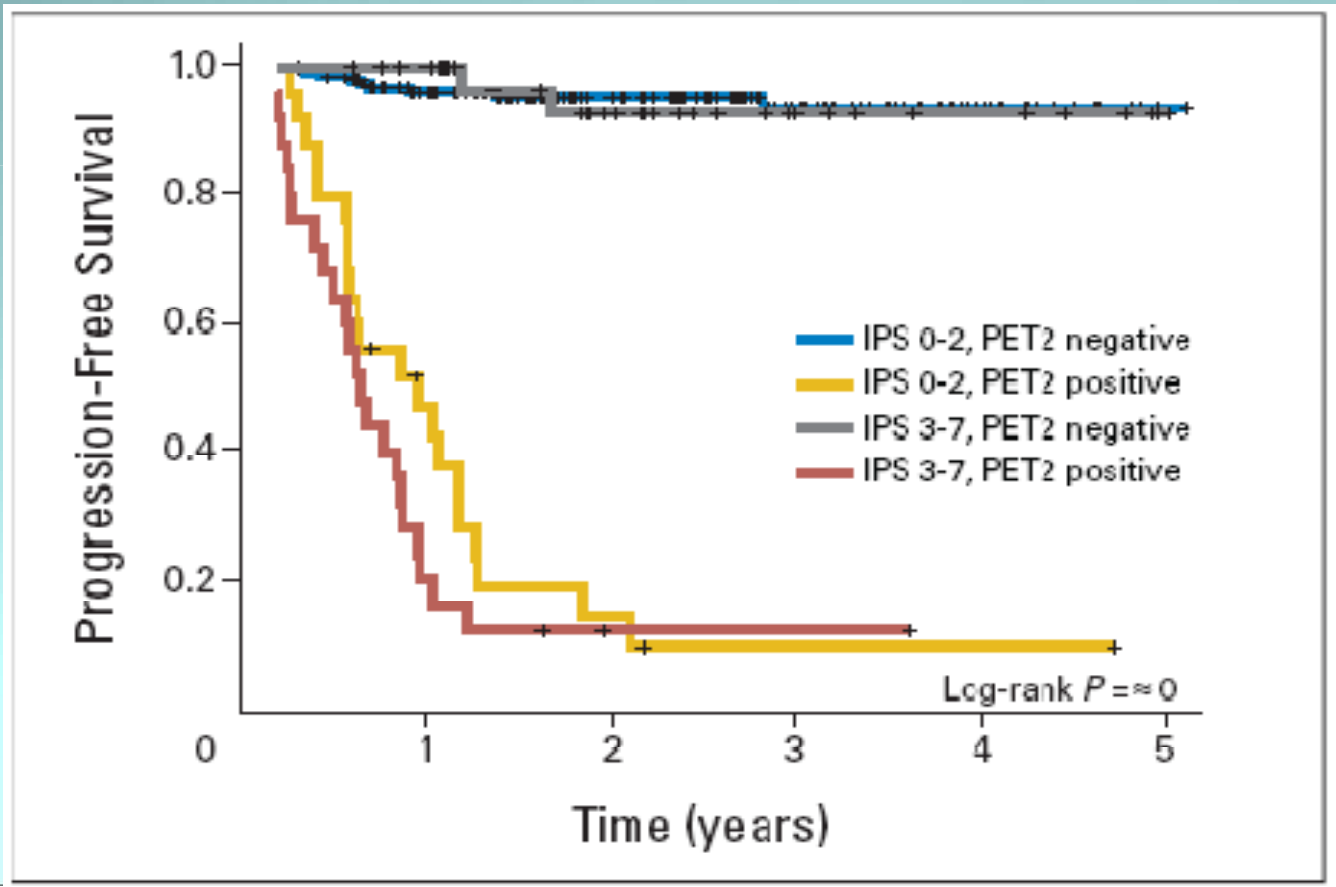
Early Interim 2-[^{18}F]Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography Is Prognostically Superior to International Prognostic Score in Advanced-Stage Hodgkin's Lymphoma: A Report From a Joint Italian-Danish Study



Gallamini,

JCO 2007

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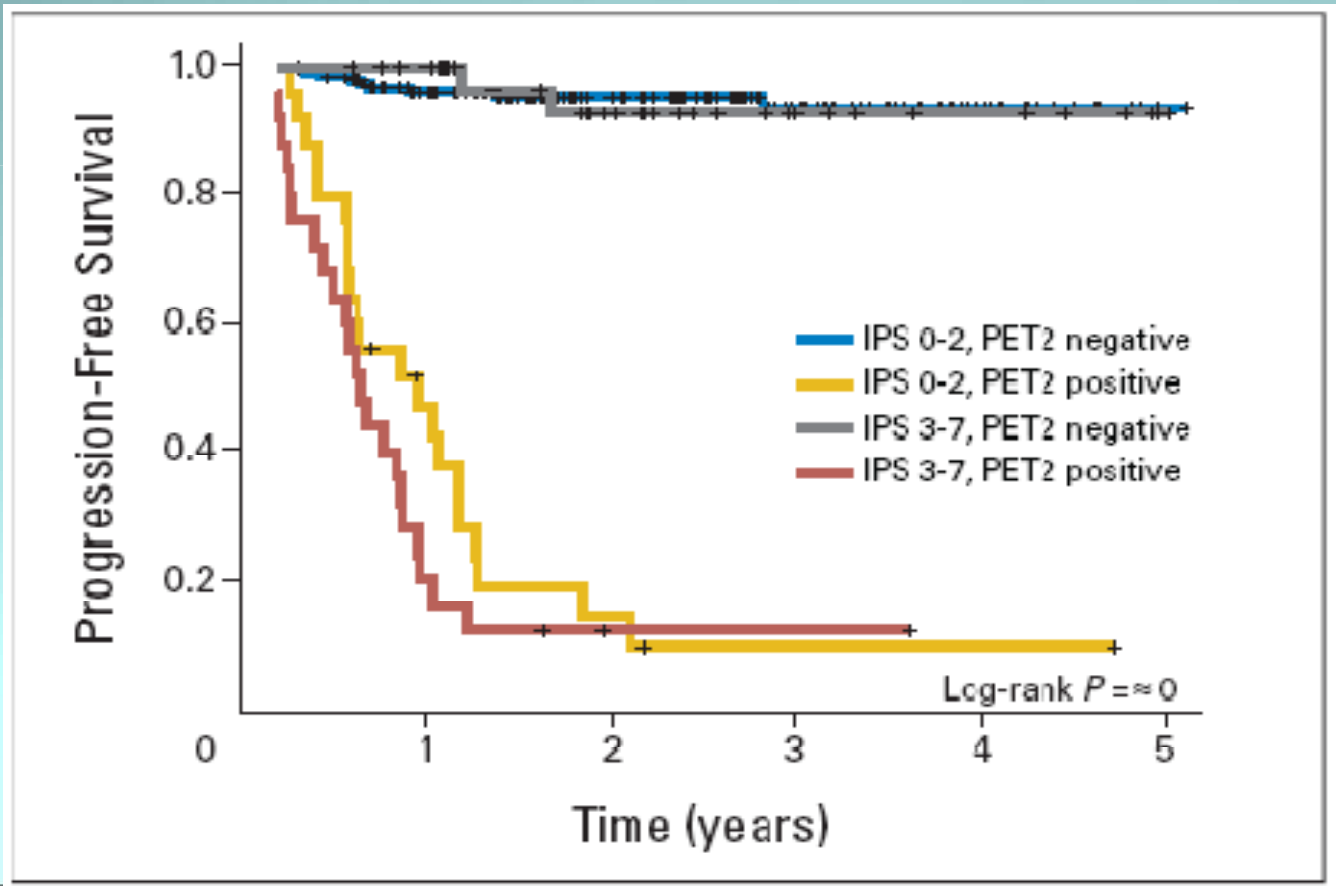


Gallamini,

JCO 2007

Advanced stage with interim PET +

Malignant Lymphomas • Research Paper

The predictive value of positron emission tomography scanning performed after two courses of standard therapy on treatment outcome in advanced stage Hodgkin's disease

6 ABVD + RT if mediastinal bulky or nodes >5cm

No influence of PET2 on treatment decision

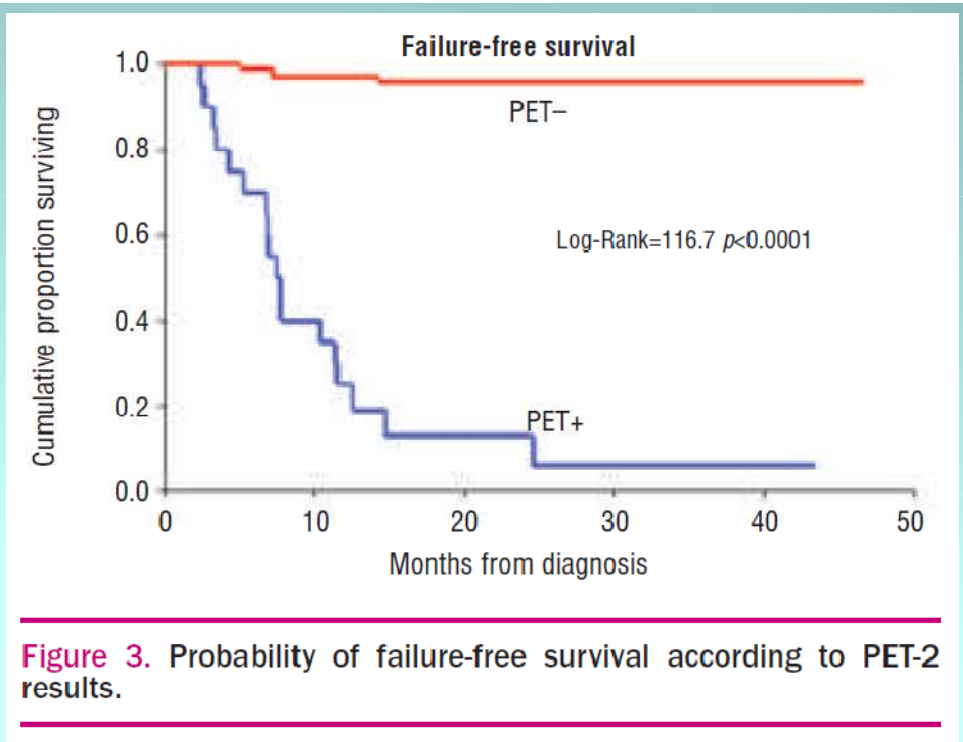
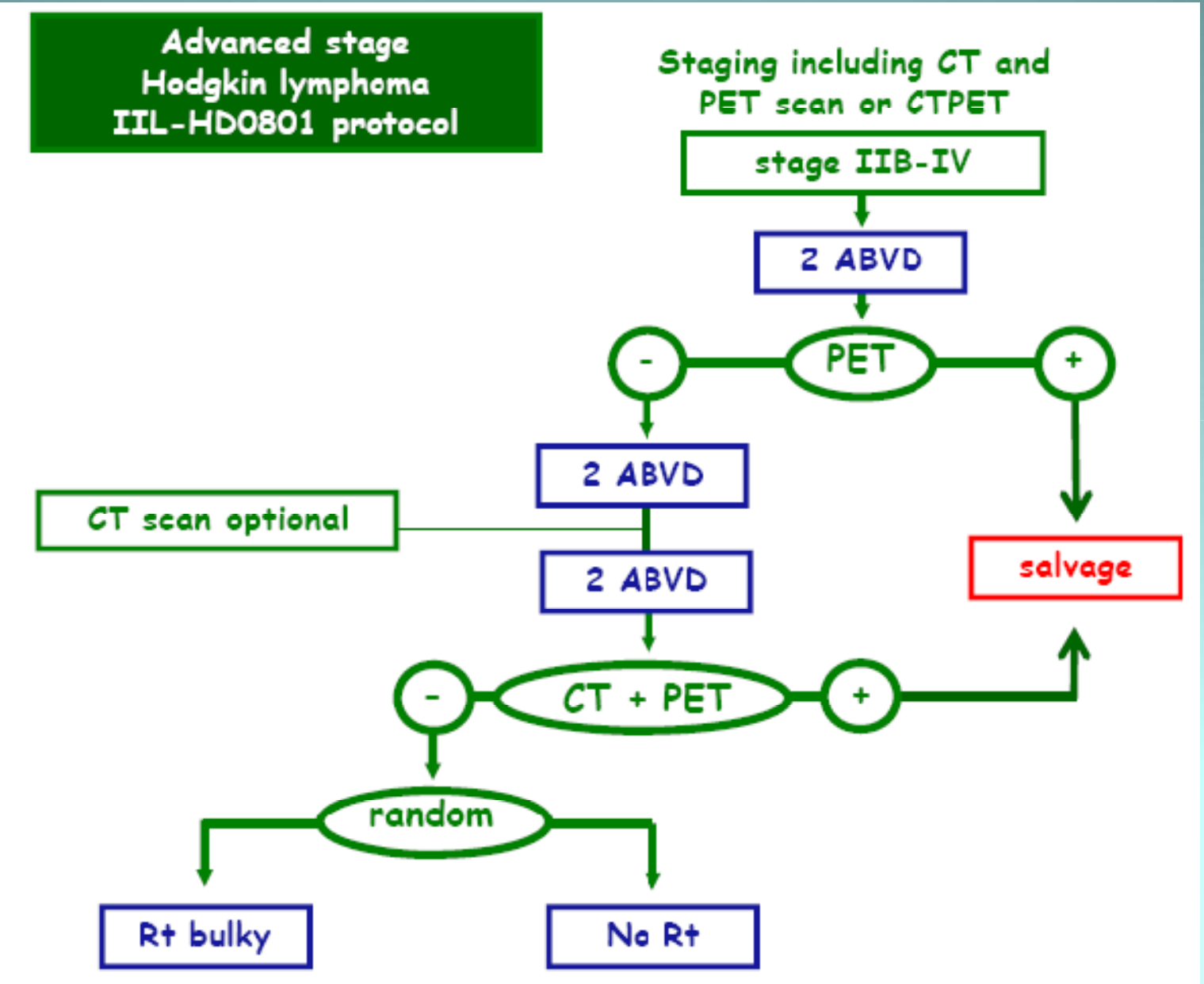


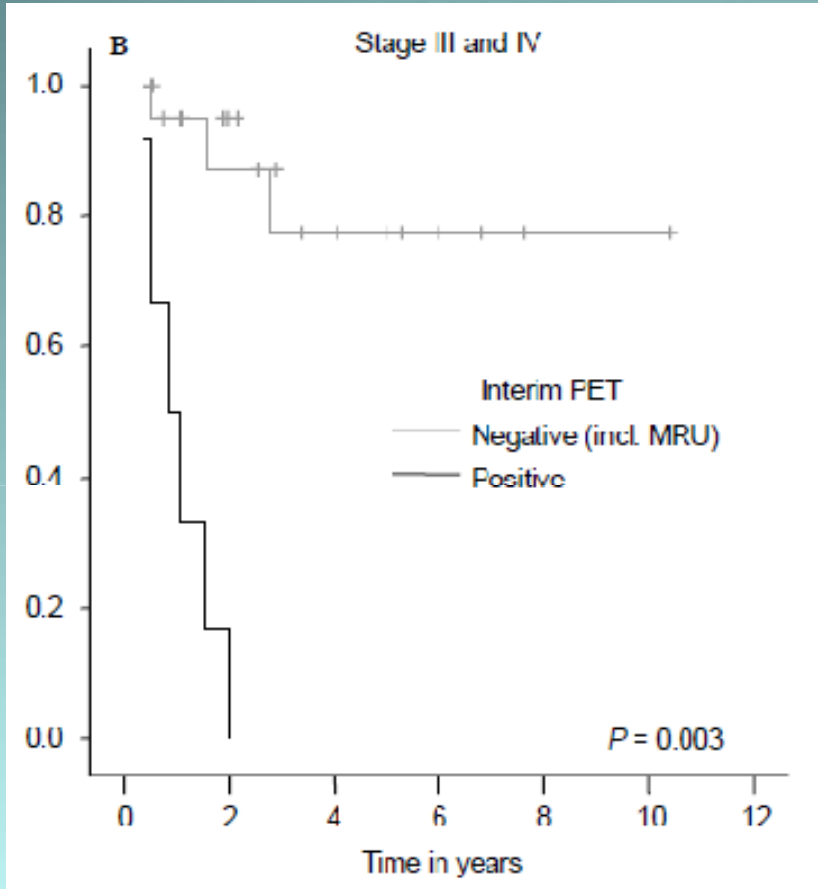
Figure 3. Probability of failure-free survival according to PET-2 results.

Gallamini, Haematol 2006

IIL trial H0108



Advanced stage with interim PET +



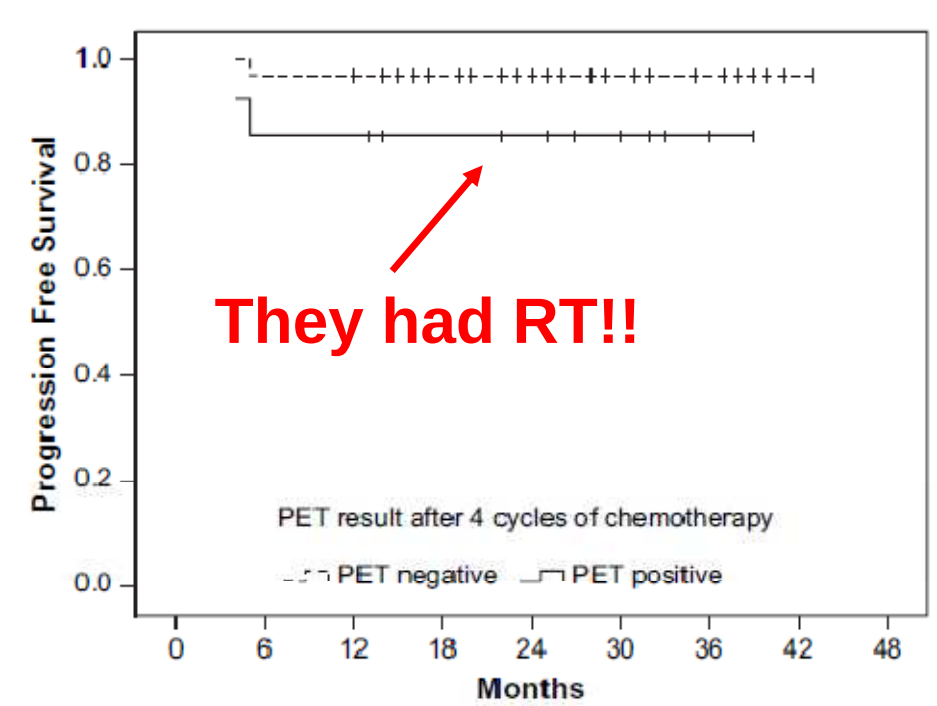


Figure 1. Positron emission tomography (PET) after four cycles of chemotherapy. Kaplan–Meier curves of PET-4-negative and -positive patients. No significant intergroup difference.

Hutchings, Ann Oncol 2005

Markova, Ann Oncol 2009

Positron emission tomography has a high negative predictive value for progression or early relapse for patients with residual disease after first-line chemotherapy in advanced-stage Hodgkin lymphoma

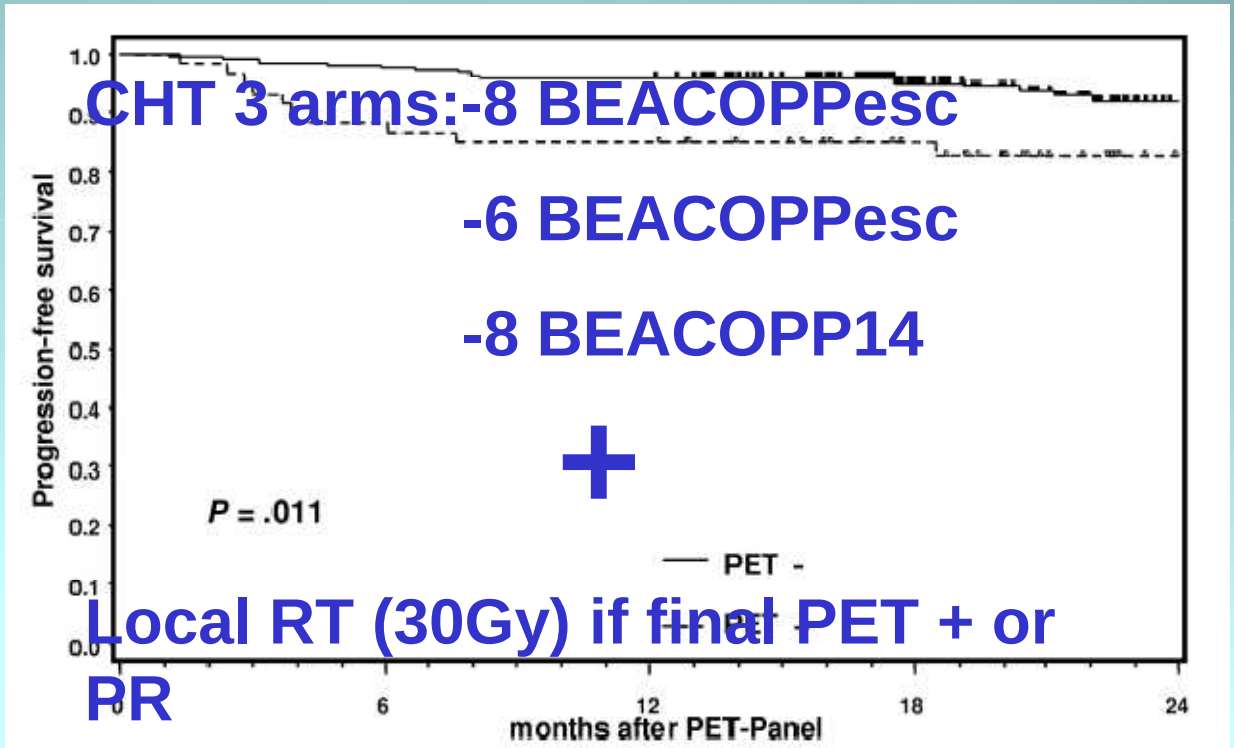
Carsten Kobe,[1] Markus Dietlein,[1] Jeremy Franklin,[2] Jana Markova,[3] Andreas Lohri,[4] Holger Amthauer,[5] Susanne Klutmann,[6] Wolfram H. Knapp,[7] Josee M. Zijlstra,[8] Andreas Bockisch,[9] Matthias Weckesser,[10] Reinhard Lorenz,[11] Mathias Schreckenberger,[12] Roland Bares,[13] Hans T. Eich,[14] Rolf-Peter Mueller,[14] Michael Fuchs,[2,15] Peter Borchmann,[2,15] Harald Schicha,[1] Volker Diehl,[2] and Andreas Engert[2,15]

Blood, 2008

GHSG

HD15

275 pts.



"…first randomized trial to prove a high NPV (94%) in HL"

VOLUME 25 · NUMBER 25 · SEPTEMBER 1 2007

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Impact of Positive Positron Emission Tomography on Prediction of Freedom From Progression After Stanford V Chemotherapy in Hodgkin's Disease

Ranjana Advani, Lauren Maeda, Philip Lavori, Andrew Quon, Richard Hoppe, Sheila Breslin, Saul A. Rosenberg, and Sandra J. Horning

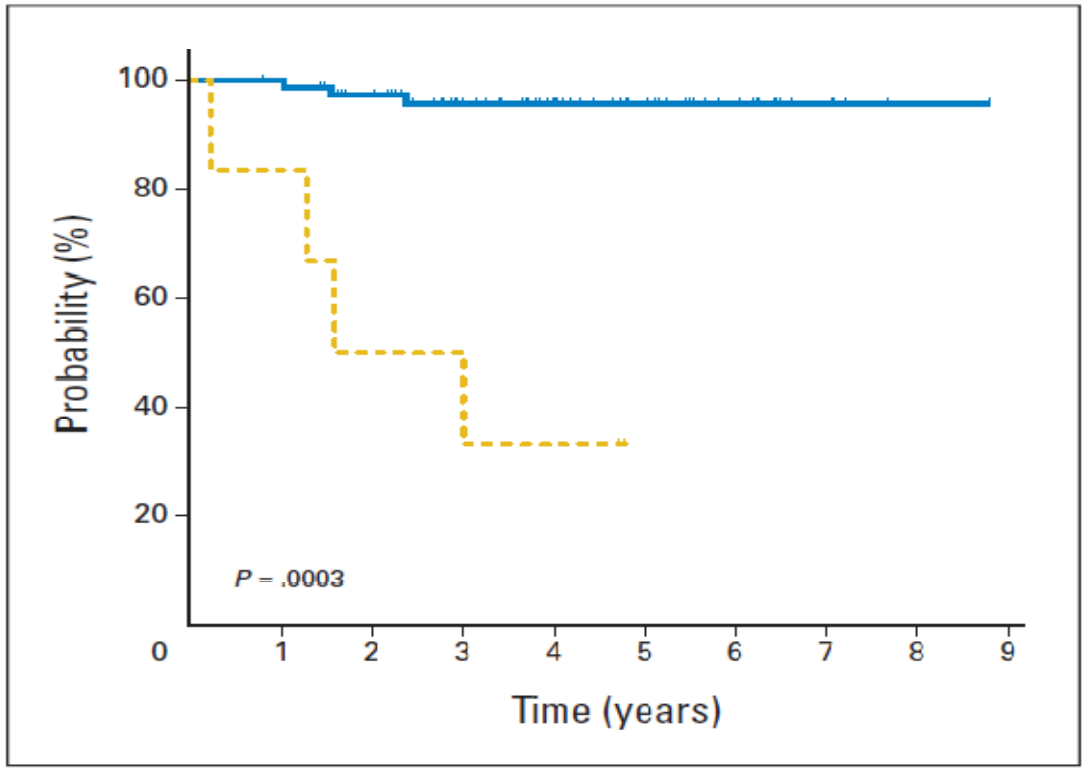
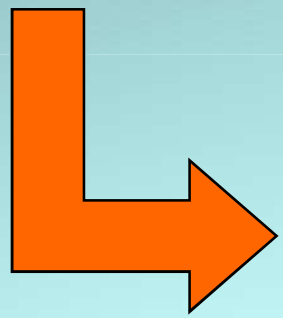


Fig 2. Freedom from progression in patients with positive [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) positron emission tomography (PET) scans after chemotherapy (– – –) versus negative [^{18}F]FDG-PET scans (——).

“…in our patient population, the addition of RT…did not overcome the adverse prognostic significance of 18FDG-PET positivity. These patients were resistant to RT in the doses that were used.”



“…18FDG-PET status after CHT may be useful in identifying a small subset of patients who might not benefit from RT and for whom treatment intensification could be considered.”

Advani, JCO 2007

4 out of 6 PET positive patients relapsed despite RT, but…

Table 2. Characteristics of Patients Who Experienced Relapse

Age (years)	Sex	Stage	CT Duration (weeks)	[18F]FDG-PET–Positive Sites		RT Site	Dose (Gy)	Sites of Relapse	Relationship to RT Field
				Pre CT	Post CT				
31	Male	IIBX	12	M, SC	None	M, SC	36	M, SC, PA	In and distant
31	Male	IIBX	12	M, SC	M	M, SC	36	Chest wall	In*
28	Female	IIAX	12	M, H	M	M, SC	36	M	In
29	Male	IVB	12	M, H, SC	None	M, SC	36	M	In
43	Male	IIA	8	M, H, SC	M	M, SC	20	M, H, S, O	In and distant
23	Male	IIA	8	M, H, SC	M	M, SC	30	M	In
22	Female	IIA	8	M, H, SC	None	M, SC	30	M	In

Abbreviations: CT, chemotherapy; [18F]FDG, [18F]fluorodeoxyglucose; PET, positron emission tomography; RT, radiation therapy; X, bulky mediastinal disease; M, mediastinum; SC, supraclavicular; PA, para-aortic; H, hilum; S, spleen; O, bone.
*Margin.

Advani, JCO 2007

CONCLUSIONS

❖**Early stage with interim PET –**

-Awaiting results of randomized trials to understand if we can avoid Radiotherapy

❖**Early stage with interim PET +**

-RT can cure most of these patients, the need for intensified CHT in under investigation

❖**Advanced stage with interim PET –**

-Standard is adequate

❖**Advanced stage with interim PET +**

-Could be interesting investigating the role of IF-RT against ABMT

VOLUME 25 · NUMBER 5 · FEBRUARY 10 2007

JOURNAL OF CLINICAL ONCOLOGY

SPECIAL ARTICLE

Revised Response Criteria for Malignant Lymphoma

Bruce D. Cheson, Beate Pfistner, Malik E. Juweid, Randy D. Gascoyne, Lena Specht, Sandra J. Horning, Bertrand Coiffier, Richard I. Fisher, Anton Hagenbeek, Emanuele Zucca, Steven T. Rosen, Sigrid Stroobants, T. Andrew Lister, Richard T. Hoppe, Martin Dreyling, Kensei Tobinai, Julie M. Vose, Joseph M. Connors, Massimo Federico, and Volker Diehl

From the Division of Hematology/ Oncology, Georgetown University Hospital, Washington, DC; University of

PET becomes a milestone in staging and response assessment

REVISED RESPONSE CRITERIA

CR

The designation of CR requires the following (Table 2):

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2a. Typically FDG-avid lymphoma: in patients with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

Inserire titolo articolo Cheson su revised criteria +

eventuali altre cose interessanti da articolo

Hodgkin lymphoma: Response assessment by Revised International Workshop Criteria

LIESELOT BREPOELS[1], SIGRID STROOBANTS[1], WALTER DE WEVER[2], KAROLINE SPAEPEN[1], PETER VANDENBERGHE[3], JOSE THOMAS[4], ANNE UYTTEBROECK[5], LUC MORTELMANS[1], CHRISTIANE DE WOLF-PEETERS[6], & GREGOR VERHOEF[7]

Inserire titolo articolo su applicazione Revised Criteria + scrivere su miglioramento predittività

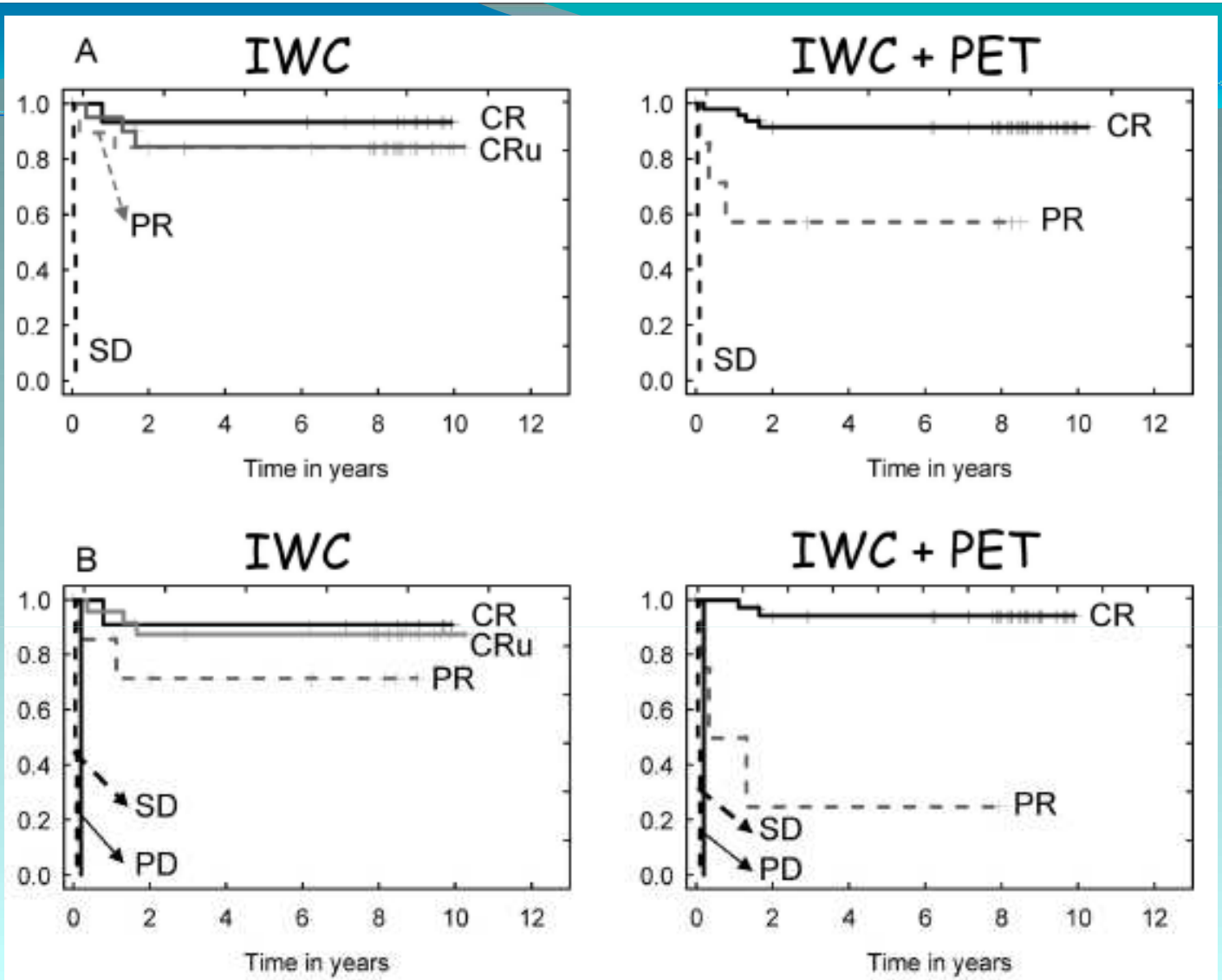
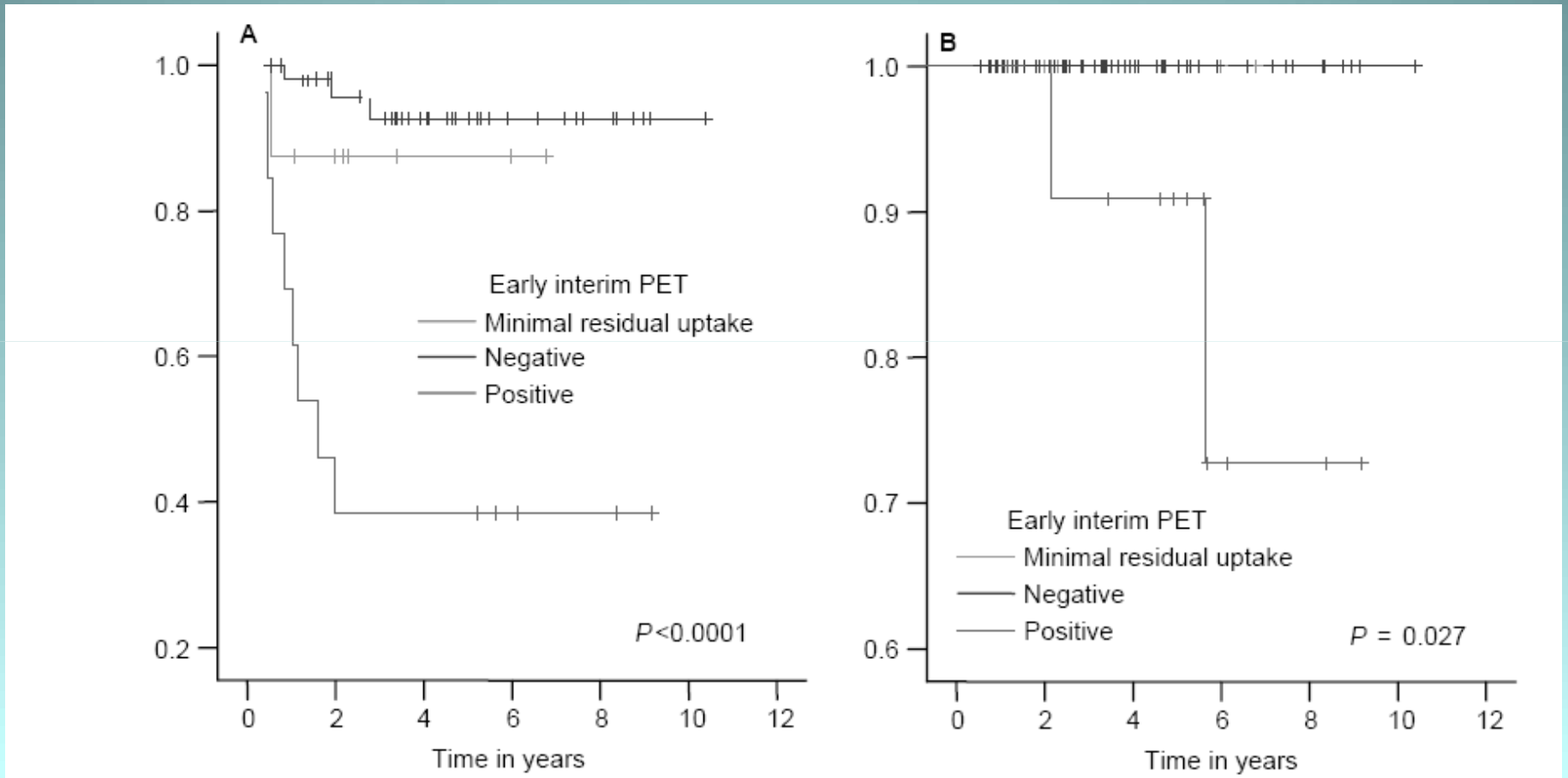


Figure 3. Kaplan–Meier curves of time-to-next treatment (TNT). Kaplan–Meier curves of TNT after first-line chemotherapy (A) and after completion of therapy (B) by International Workshop Criteria (IWC) and Integrated Response criteria (IWC+PET). CR, complete remission; CRu, unconfirmed complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Commento o spiegazione!!! + Cit.!!

Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma



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Hutchings, Ann Oncol 2005

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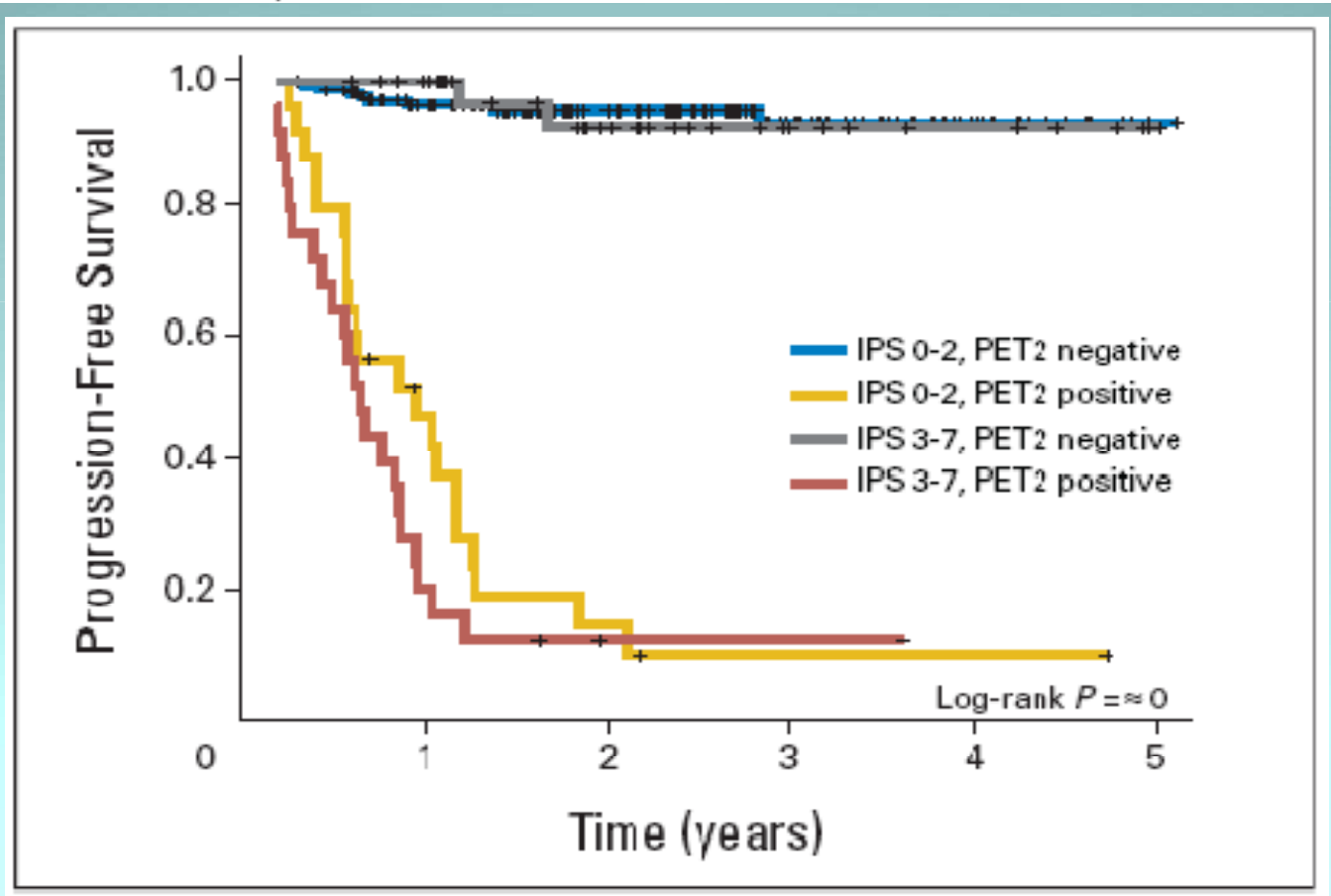
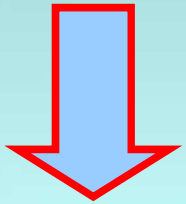


Gallamini, JCO 2007

+ Articolo Zinzani?!? + altri citati?!?

Articoli meta-analisi? Terasawa + Zjilstra
(cercare) da articoli di Juweid?!?



Emerge importanza del valore prognostico negativo, ma del positivo ci sono dubbi! (addirittura biopsia?!? e articolo su necessità di biopsia?!?)

The negative predictive value of early interim FDG-PET is extremely high in early-stage patients. This is not particularly surprising, since early-stage HL generally has an excellent prognosis. We confirm the findings from Hutchings et al that the positive predictive value is very high in advanced-stage patients.[22] In the

Hutchings, Blood 2006

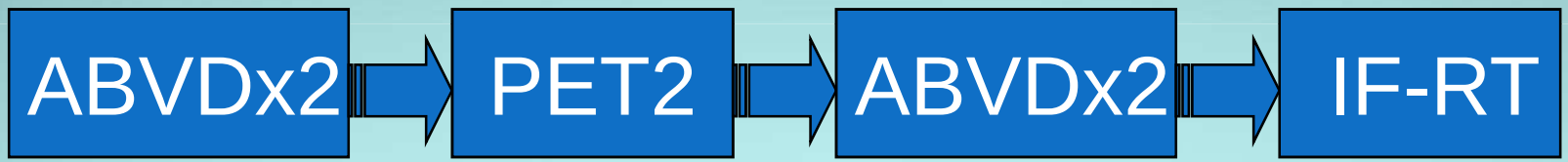
- Nei linfomi di Hodgkin la PET in fase di stadiazione ha mostrato una sensibilità nell'ordine dell'85-90% con una specificità quasi del 100%, in grado di portare ad un cambiamento di stadio dal 12% fino ad oltre il 40% dei pazienti.

(Bangerter 1998, Partridge 2000, Jerusalem 2001, Weihrauch 2002)

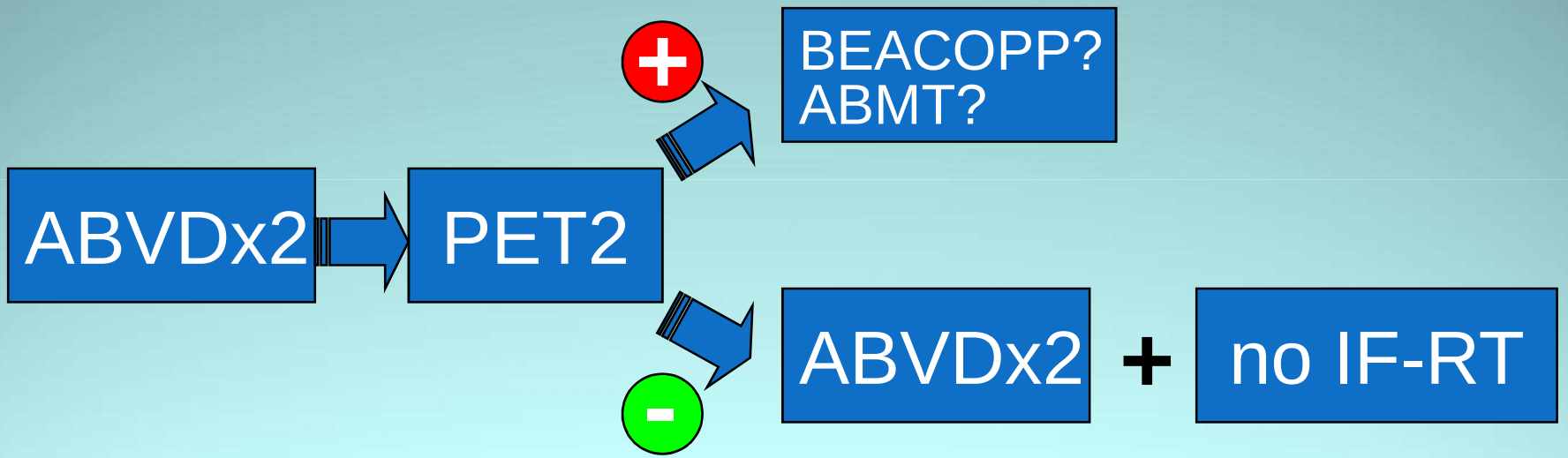
RUOLO DELLA “INTERIM PET”

Dimostrato ruolo importante negli stadi avanzati, in grado di modificare l’atteggiamento terapeutico (DFS a 2 anni 0-12% in PET2+), importante valore prognostico positivo

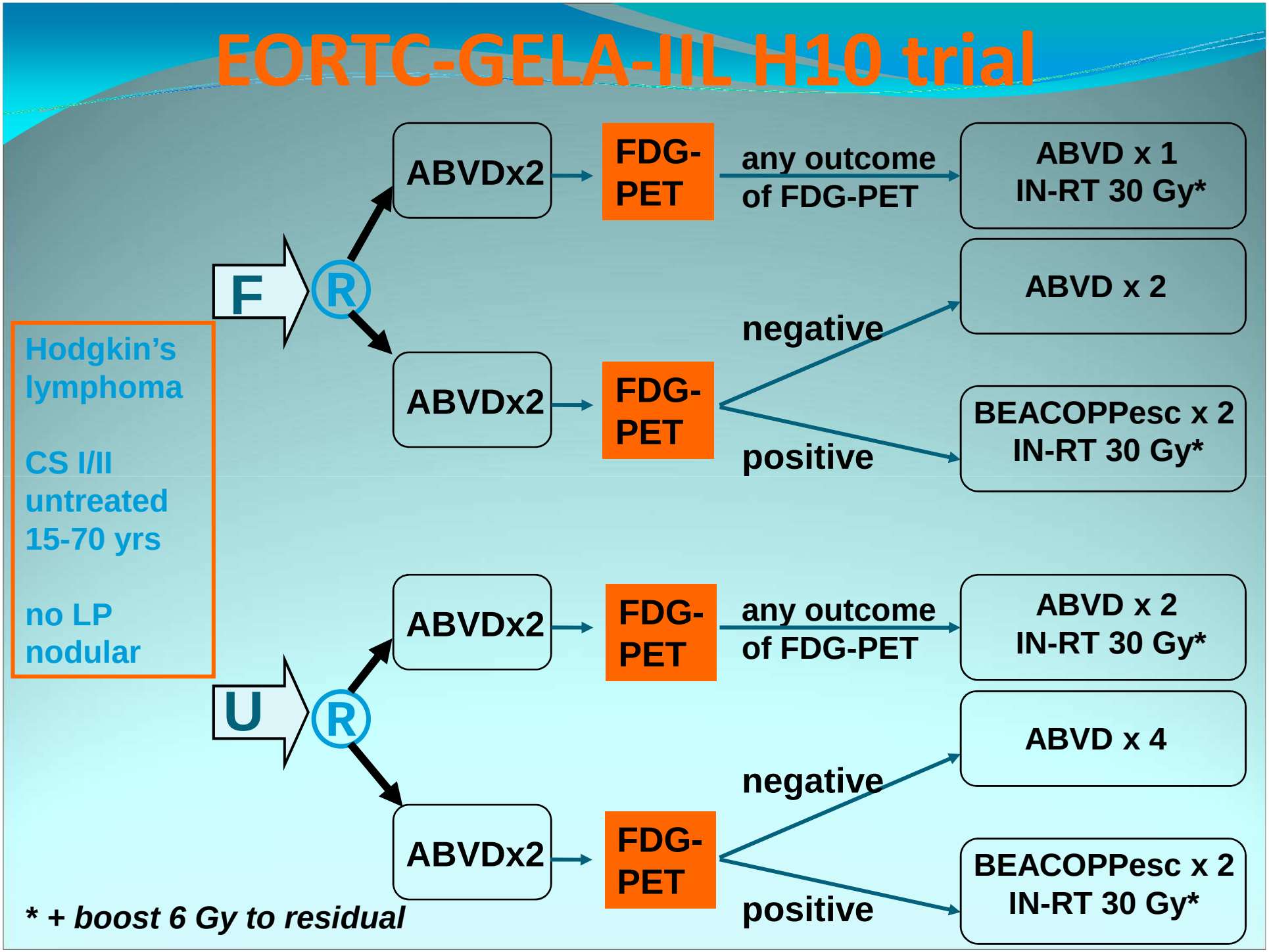
Ruolo della PET2 negli early stage?



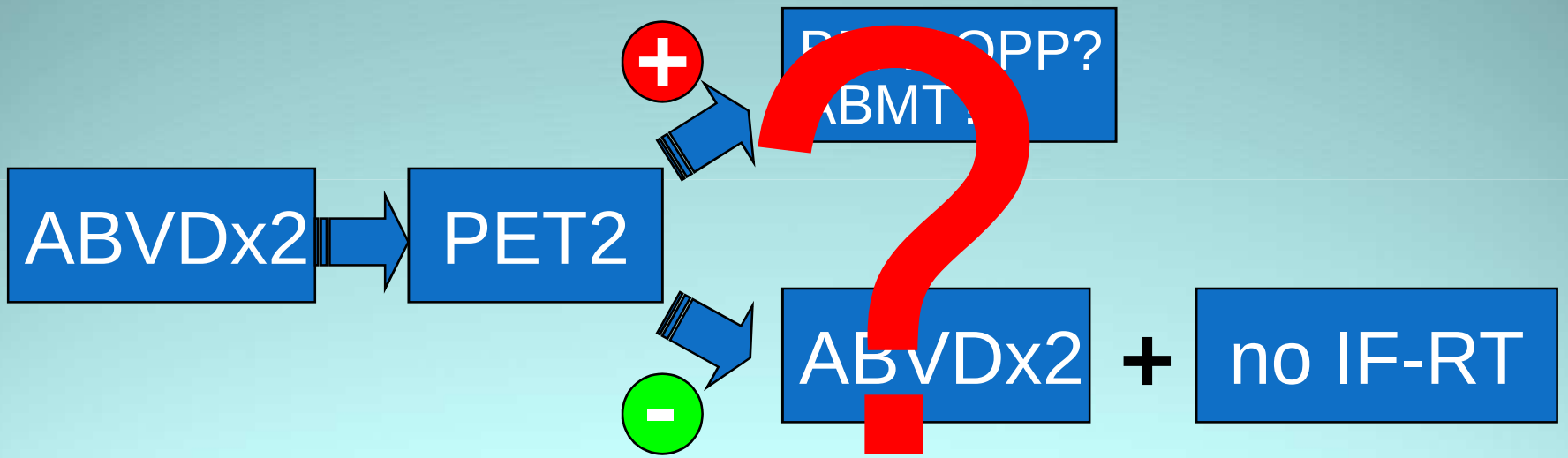
Ruolo della PET2 negli early stage?



EORTC-GELA-IIL H10 trial



Ruolo della PET2 negli early stage?



Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma

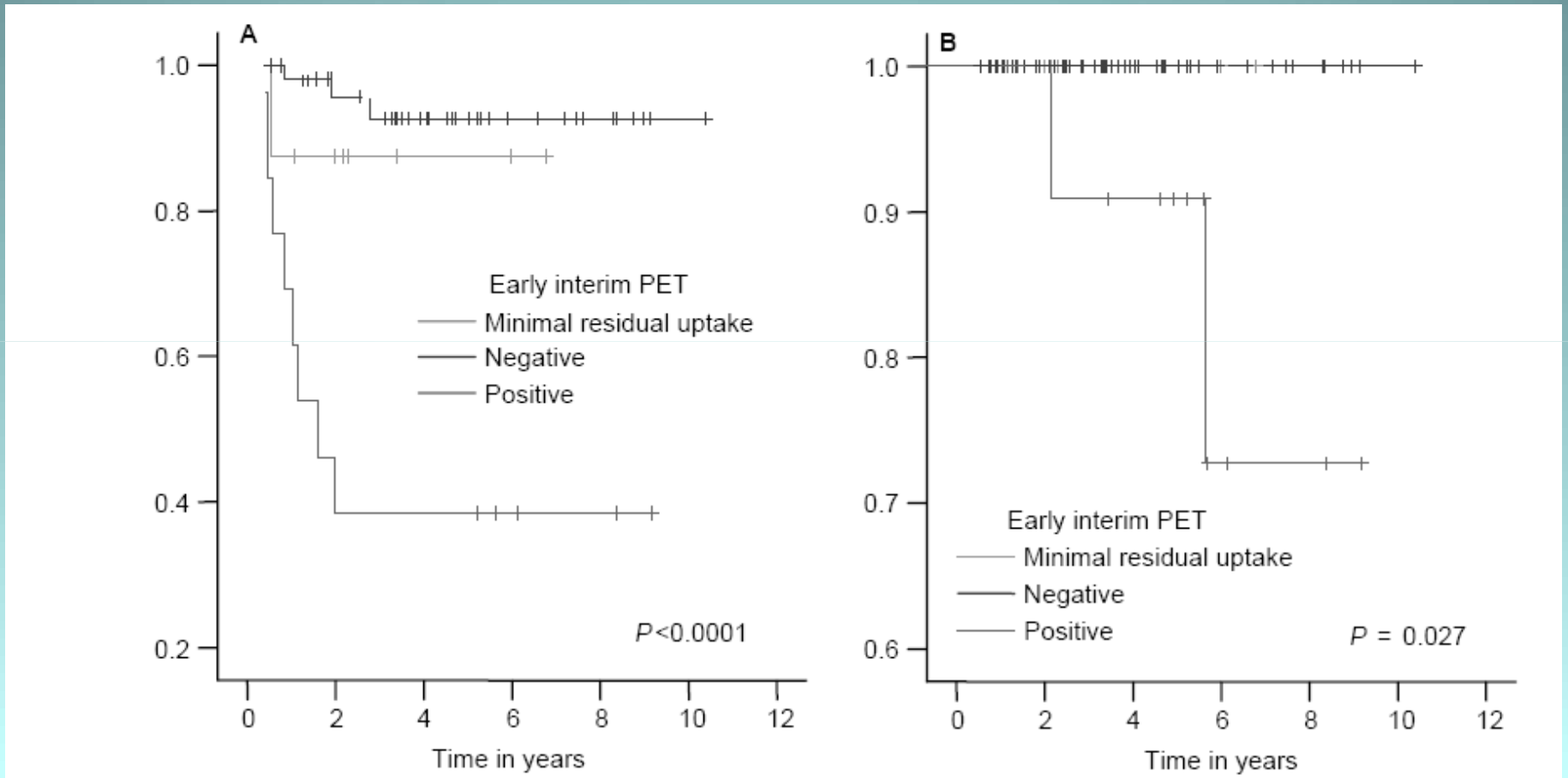


Figure 3. (A) Progression-free survival and (B) overall survival according to the outcome of early interim FDG-PET.

Hutchings, Ann Oncol 2005

Prognostic value of interim FDG-PET after two or three cycles of chemotherapy in Hodgkin lymphoma

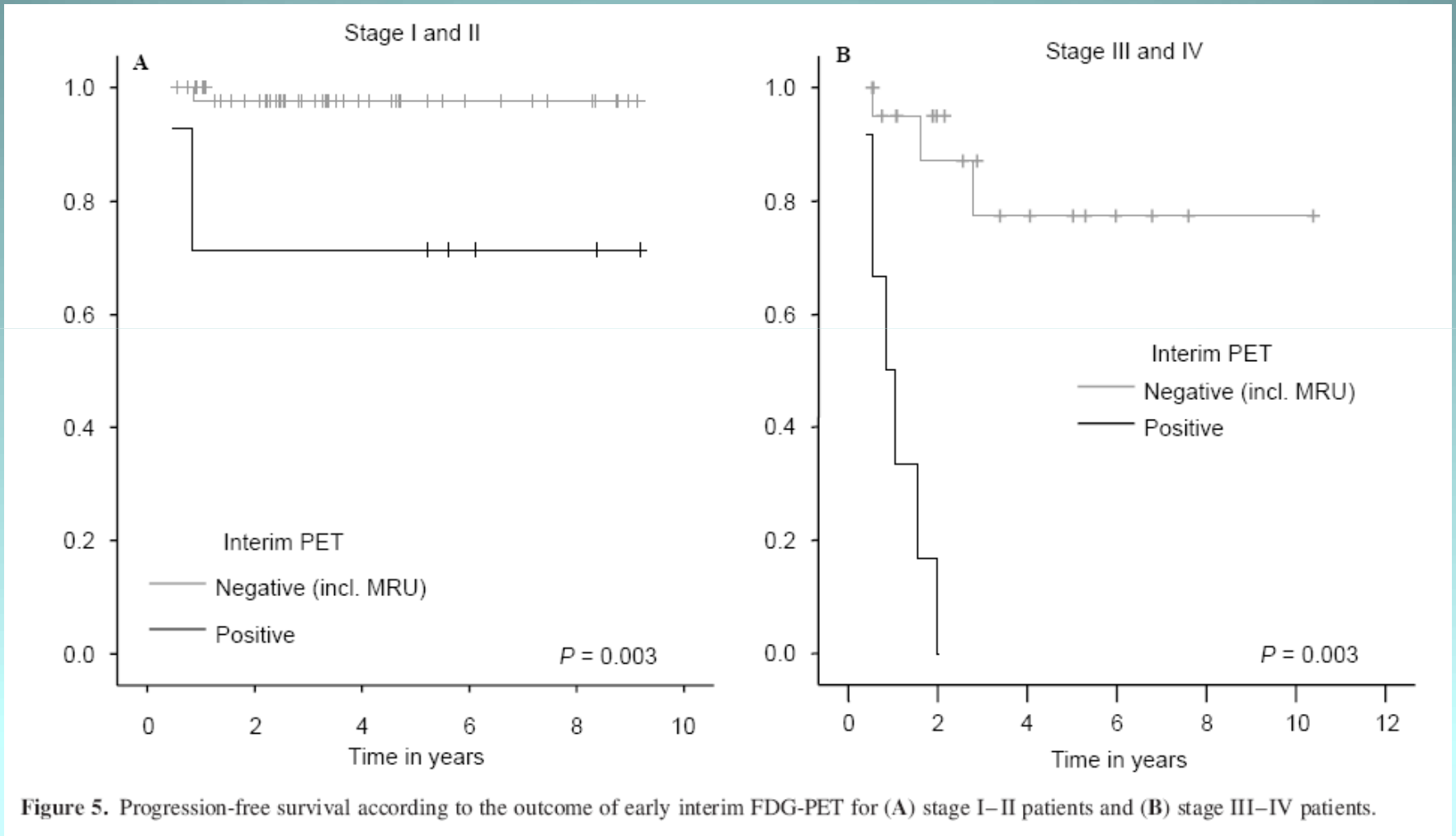


Figure 5. Progression-free survival according to the outcome of early interim FDG-PET for (**A**) stage I–II patients and (**B**) stage III–IV patients.

Hutchings, Ann Oncol 2005

The negative predictive value of early interim FDG-PET is extremely high in early-stage patients. This is not particularly surprising, since early-stage HL generally has an excellent prognosis. We confirm the findings from Hutchings et al that the positive predictive value is very high in advanced-stage patients.[22] In the

Hutchings, Blood 2006

CARATTERISTICHE DELLA CASISTICA

88 pazienti con LHDG in stadio I e II trattati presso le Radioterapie delle Università di Firenze e Brescia dal 2002 alla fine del 2008

Follow up	9-73 mesi (media 35,8)	
Sesso	M F	• (47,7%) 46 (52,3%)
Istologia	PL SN CM DL	10 (11,3%) 65 (74,2%) 8 (9,1%) 3 (3,4%)
Stadio	I II	12 (13,8%) 76 (86,4%)
Sintomi	A B	• (80,7%) 17 (19,3%)
Bulky	Sì No	20 (22,6%) 68 (77,3%)

CARATTERISTICHE DELLA CASISTICA

Volume RT	IF EF	69 (78,4%) 19 (21,6%)
Dose RT	30 Gy 36 Gy 40 Gy >40 Gy	28 (31,8%) 28 (31,8%) 28 (31,8%) 7 (8,0%)
Tipo CHT	ABVD VEPEB IGEV MAMA No CHT	• (85,2%) • (4,6%) 2 (2,2%) 1 (1,1%) 6 (6,8%)
PET 2	Sì No	• (50%) 44 (50%)

3 RECIDIVE:

- Recidiva mediastinica in area PET+ alla diagnosi ed irradiata (PET 2 e PET 4 positive)
- Recidiva su regione SPCL in area PET- alla diagnosi e non irradiata (no PET 2)
- Recidiva mediastinica in area PET+ alla diagnosi marginale al campo di trattamento (PET 2 negativa)

Recidive secondo PET2 nei pazienti Early Stage

Autore	Follow-up	PET2 positivi	Recidive nei PET2 positivi	Recidive nei PET2 negativi
Hutchings (Ann Oncol, 2005)	6-125 mesi (media 46,6)	7/57 (12,3%)	2/7 (28,5%)	1/50 (2%)
Hutchings (Blood, 2006)	6,1-40,8 mesi (media 23,4)	5/31 (16,1%)	1/5% (20%)	0/26 (0%)
Casistica FI-BS	6,1-70,8 mesi (media 32,8)	4/44 (9,1%)	1/4 (25%)	1/40 (2,5%)

CONCLUSIONI

- Elevato valore predittivo negativo della PET2 negli early stage
- Il 70-80% dei pazienti early stage PET2 positivi vengono comunque recuperati con una RT IF
- Al momento la PET2 + non sembra giustificare una modifica del normale iter terapeutico
- Necessari comunque i dati che emergeranno dagli studi attualmente in corso che utilizzano la PET per la stratificazione dei pazienti (EORTC H10, UK, etc.)