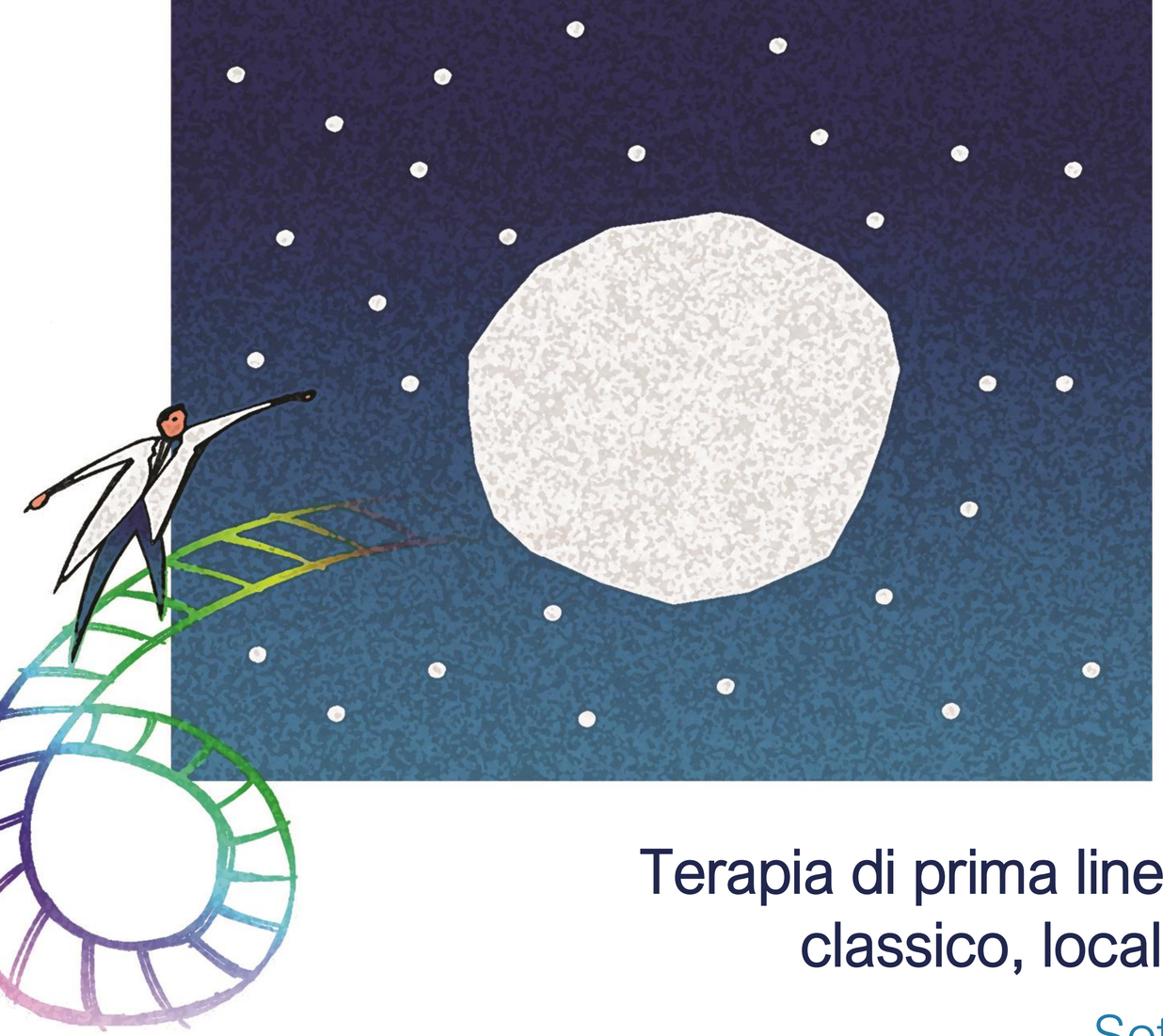


The young side of LYMPHOMA

gli under 40 a confronto

Pescara, Auditorium Petruzzi
11-12 ottobre 2024

Terapia di prima linea nel linfoma di Hodgkin classico, localizzato sfavorevole

Sottotitolo

Dott. Andrea Guerini – Università degli Studi di Brescia

Disclosures of Andrea Guerini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Definition of Unfavorable early-stage Hodgkin lymphoma

Table 2. Risk factor definitions in Hodgkin's lymphoma. Patients in CS I–II are staged unfavorable if at least one of the listed risk factors is present [34].

Risk Factors	GHSG	EORTC	NCIC/ECOG	NCCN
Large mediastinal mass	Yes [1], ratio ≥ 1/3	Yes, ratio ≥ 0.35	No	Yes, ratio > 1/3
Extranodal disease	Yes [1]	No	No	Yes
Nodal areas	Yes, ≥3 areas	Yes, ≥4 areas	Yes, ≥4 areas	Yes, ≥3 regions
ESR	Yes, ≥50 (A) or ≥30 (B)	Yes, ≥50 (A) or ≥30 (B)	Yes, ≥50	Yes, ≥50 (A)
B-symptoms	No	No	No	Yes
Bulk	No	No	No	Yes, >10 cm
Age	No	Yes, ≥50 years	Yes, ≥40 years	No
Histology other than LP/NS	No	No	Yes	No

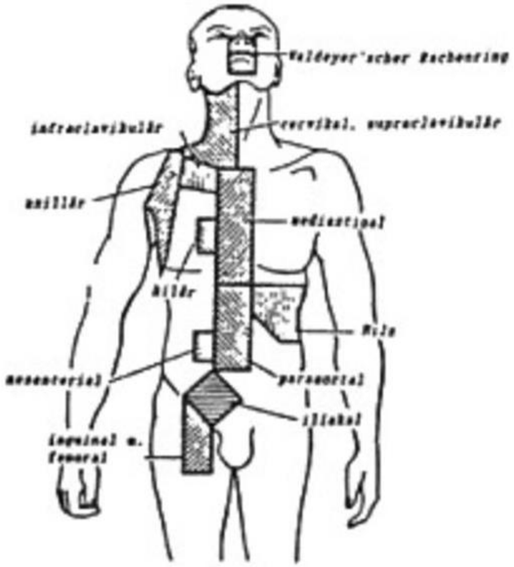


Table 1. PET-adapted therapeutic trials in early-stage HL

Study (median follow-up)	Patient population (N)	Risk factors at enrollment	PET negative	Treatment arms	PFS or FFTF	OS
UK RAPID[6] (5.0 years)	Stage IA or IIA (n=602)	Nonbulky	Deauville 1–2	PET neg: ABVD×3 PET neg: ABVD×3+30 Gy IFRT PET pos: ABVD×4+30 Gy IFRT	3-year 90.8% 3-year 94.6% 3-year 83%	3-year 99.0% 3-year 97.1%
CALGB 50604[8] (3.8 years)	Stage I or II (n=164)	Nonbulky	Deauville 1–3	PET neg: ABVD×4 PET pos: ABVD×2, eBEACOPP×2, 30 Gy IFRT	3-year PFS 91% 3-year PFS 66%	
EORTC[9] (4.5–5.1 years)	Stage I or II (n=1950)	Favorable (no risk factors) Unfavorable (any of the following) 1. Age ≥50 2. Bulk 3. >3 nodal sites 4. ESR ≥50 (or 30 if B-symptoms)	Deauville 1–2	(F) PET neg: ABVD×3+30 Gy INRT (F) PET neg: ABVD×4 (U) PET neg: ABVD×4+30 Gy INRT (U) PET neg: ABVD×6 (F/U) PET pos: ABVD×4+30 Gy INRT (F/U) PET pos: ABVD×2, eBEACOPP×2, 30 Gy INRT	5-year PFS 99% 5-year PFS 87.1% 5-year PFS 92.1% 5-year PFS 89.6% 5-year PFS 77.4% 5-year PFS 90.6%	5-year OS 100% 5-year OS 99.6% 5-year OS 96.7% 5-year OS 98.3% 5 year OS 89.3% 5 year OS 96.0%
GHSG HD16[10] (45 months)	Stage I or II (N=1150)	Favorable (none of the following risk factors): 1. Bulk 2. Extranodal sites 3. >2 nodal areas 4. ESR ≥50 (or 30 if B-symptoms)	Deauville 1–2	PET neg: ABVD×2+20 Gy IFRT PET neg: ABVD×2 PET pos: ABVD×2+20 Gy IFRT	5-year PFS 93.4% 5-year PFS 86.1% 5-year PFS 88.4%	5-year OS 98.1% 5-year OS 98.4% 5-year OS 97.9%
GHSG HD17[11] (46.2 months)	Stage I or II (N=1100)	Unfavorable (with one of the following risk factors): 1. Bulk 2. Extranodal sites 3. >2 nodal areas 4. ESR ≥50 (or 30 if B-symptoms)	Deauville 1–2	PET negative: eBEACOPP/ABVD×4+ 30 Gy IFRT PET neg: eBEACOPP/ABVD×4 PET pos: eBEACOPP/ABVD×4+30 Gy IFRT	5-year PFS 97.7% 5-year PFS 95.9% 5-year PFS 94.2%	5-year OS 98.7% 5-year OS 98.8% 5-year OS 99.2%

eBEACOPP, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; EN, XXX; F, favorable; FFTF, freedom from treatment failure; neg, negative; pos, positive; U, unfavorable.

UNFAVORABLE EARLY STAGE HOGKIN LYMPHOMA

BEFORE GHSG HD17

AFTER GHSG HD17

PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase 3 trial

www.thelancet.com/oncology Vol 22 February 2021

Peter Borchmann, Annette Plütschow, Carsten Kobe, Richard Greil, Julia Meissner, Max S Topp, Helmut Ostermann, Judith Dierlamm,

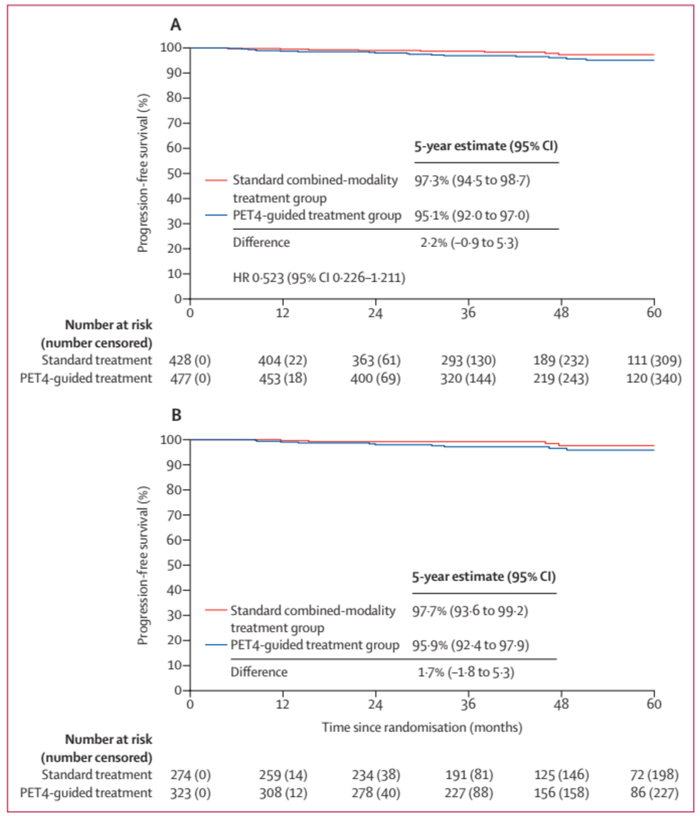


Figure 2: **Kaplan-Meier estimates of 5-year progression-free survival in the per-protocol analysis population (A) and in a subset of PET4-negative patients in the per-protocol analysis population (B)**
PET4=PET scan at the end of four cycles of chemotherapy.

St I/II U GHSG

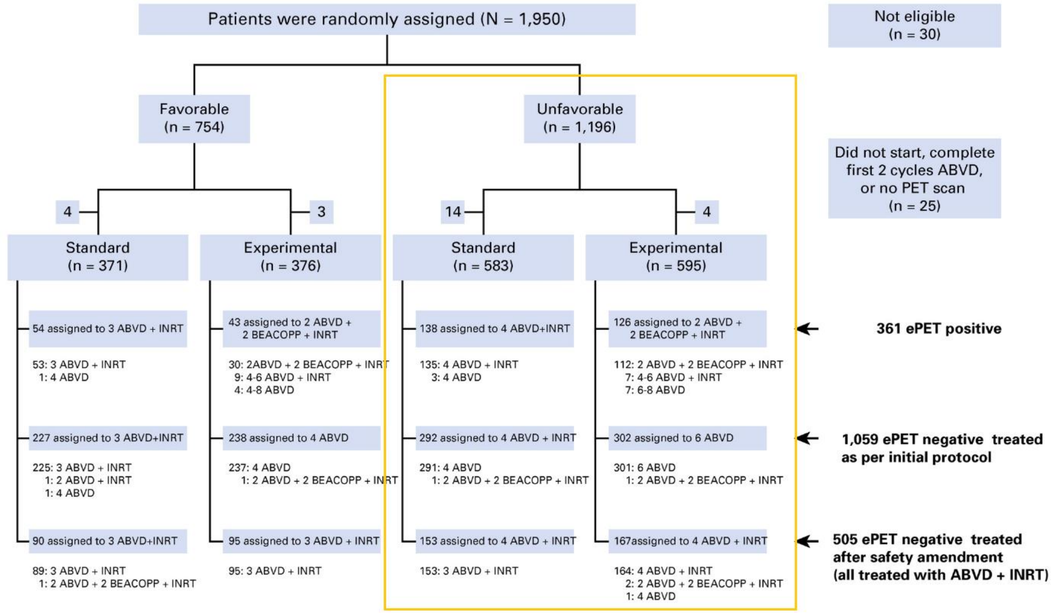
standard 2 + 2 + 30 Gy IFRT (n=548) VS

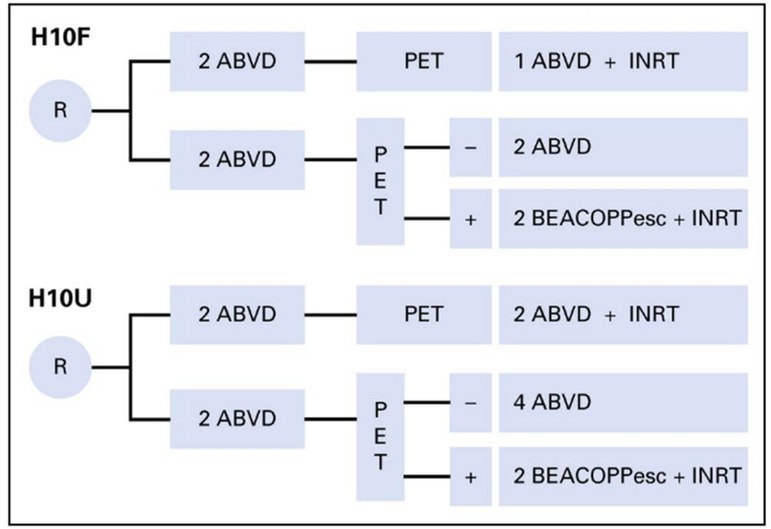
PET guided (n=552) 2+2 > PET > DS 1-2 stop
DS 3-5 INRT/ISRT

5y PFS 97.7% vs 95.9 (N.S.) pre-defined non-inferiority 8%

FREE ACCESS | ORIGINAL REPORTS | March 14, 2017
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Early Positron Emission Tomography Response–Adapted Treatment in Stage I and II Hodgkin Lymphoma: Final Results of the Randomized EORTC/LYSA/FIL H10 Trial





1950 St I-II 754 F vs 1196 U according to EORTC

U PET- 5-y PFS 92.1% 4 ABVD+ISRT vs 89.6% 6 ABVD
Noninferiority could not be demonstrated upper bound of 95% CI HR (2.50) exceeded the prespecified margin (2.10).

OPEN ACCESS | CLINICAL TRIAL UPDATES | November 15, 2023
Journal of Clinical Oncology®
An American Society of Clinical Oncology Journal

Long-Term Follow-Up of the Response-Adapted Intergroup EORTC/LYSA/FIL H10 Trial for Localized Hodgkin Lymphoma

Authors: Massimo Federico, MD, Catherine Fortpied, MSc, Yana Stepanishyna, MD, PhD, Manuel Gotti, MD, Richard van der Maazen, MD,

favorable (F) ePET-neg 10-y PFS 98.8% VS 85.4% (P < .0001) ABVD+INRT vs ABVD x 4

unfavorable (U) ePET-neg 10-y PFS 91.4% vs 86.5% (value for non-inferiority not reached)

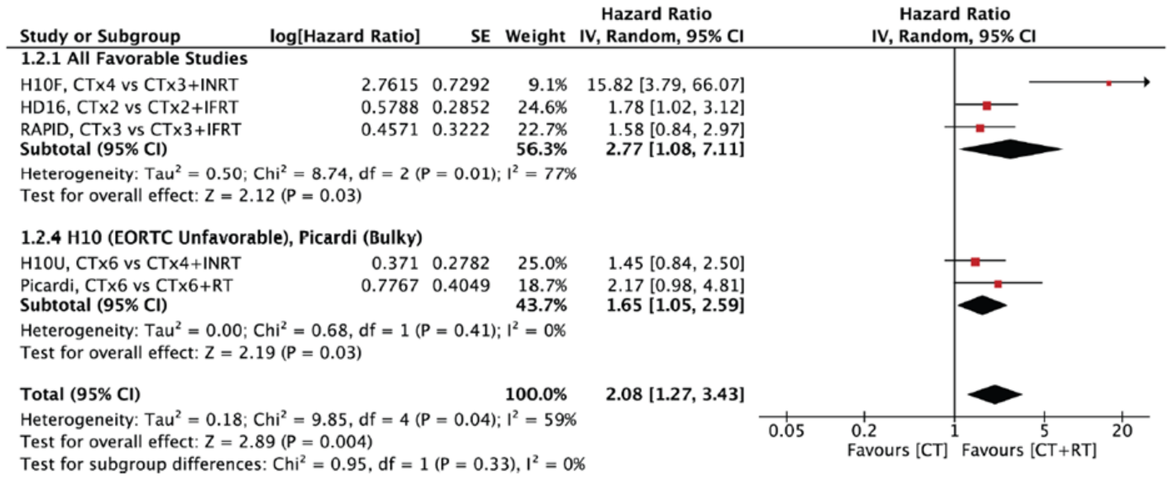
analyses performed in the ITT up to the safety amendment (n = 969)

U 20/ 22 relapses (91%) in the ABVD-only arm in previously involved nonirradiated sites

Leukemia & Lymphoma
Volume 61, 2020 - Issue 7

Consolidation radiotherapy following positron emission tomography complete response in early-stage Hodgkin lymphoma: a meta-analysis

Parvez Memet Shaikh, Fiori Alite, Novella Pugliese, Marco Picardi & John A. Vargo



EORTC/LYSA/FIL H10 + GHSG HD16 + UK-RAPID + Picardi

19502267 pts (RT: n=1136, control: n=1131). 1513 F 754 U

1951F+U recurrence 4.7% RT vs 11.2% no-RT p<.004

1952U 6.7% RT vs 12.0% p 0.03

Improvement larger in F than in U > in-field recurr 1.4% vs 9.5% F and 4.3% vs 9.7%

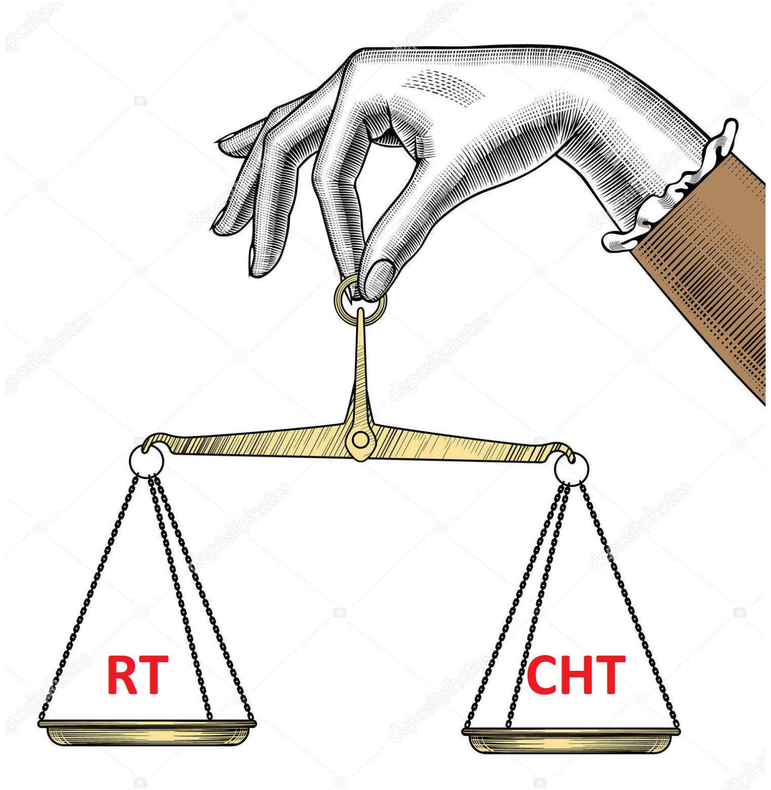
no difference in OS, toxicity, or development of second malignancy

Controversies in the management of unfavorable early-stage HL

- *Front line systemic treatment + number of cycles > eBEACOPP vs ABVD > varies across Institutions*
- *Clinical risk factors (e.g. comorbidities, mediastinal bulky, disease site and extension)*
- *Definition of PET negativity*
- *Brentuximab and check point inhibitors*
- *Modern RT techniques > impact on toxicity and SMN*

Controversies in the management of unfavorable early-stage HL

- *Front line systemic treatment + number of cycles > eBEACOPP vs ABVD > varies across Institutions*
- *eBEACOPP intensification > increased risk of side effects vs ABVD in HD14, risk of infertility? risk of SMNs?*
- *Loss of s.n. in PFS at 10 y for eBEACOPP intensification in H10*
- *ABVD x 6 > increased antracycline dose > risk of cardiotoxicity?*



Controversies in the management of unfavorable early-stage HL

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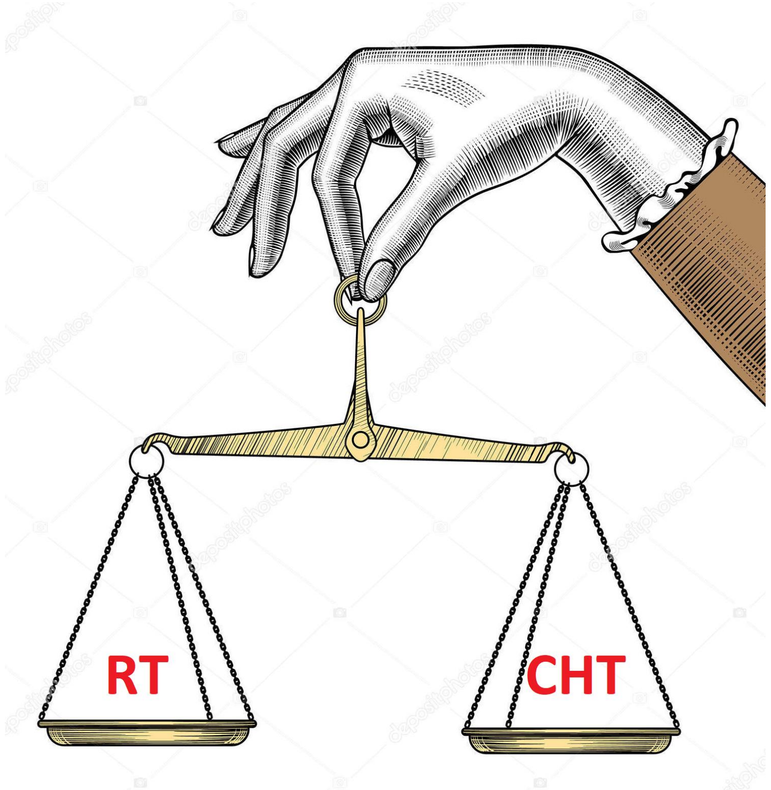
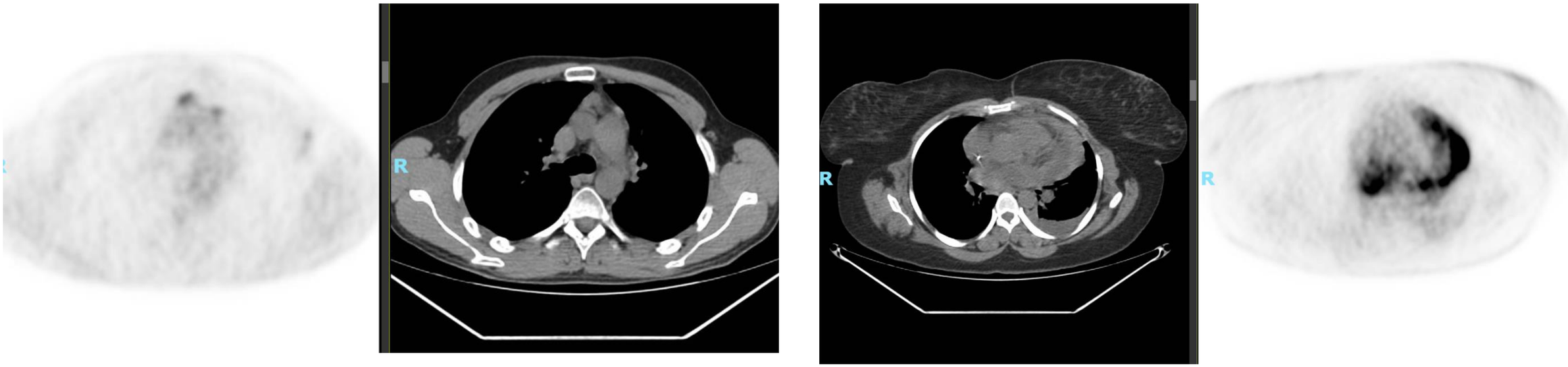


Controversies in the management of unfavorable early-stage HL

- *Clinical risk factors (e.g. comorbidities, mediastinal bulky, disease site and extension)*



45 yo male non-bulky upper mediastinum

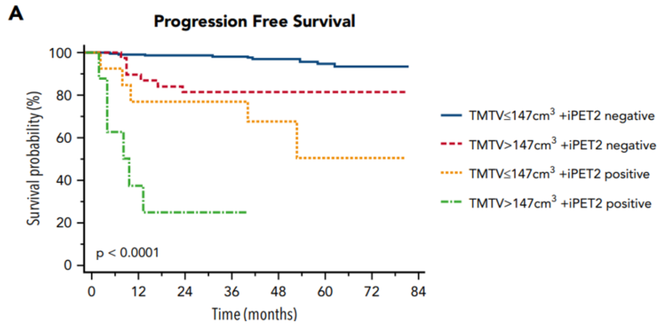
28 yo female bulky mediastinum

Controversies in the management of unfavorable early-stage HL

LYMPHOID NEOPLASIA

Prognostic value of baseline metabolic tumor volume in early-stage Hodgkin lymphoma in the standard arm of the H10 trial

Anne-Ségolène Cottereau,[1] Annibale Versari,[2] Annika Loft,[3] Olivier Casasnovas,[4] Monica Bellei,[5] Romain Ricci,[6] Stéphane Bardet,[7]



variable analysis including iPET2, TMTV was the only baseline prognosticator compared with the current staging systems proposed by the European Organization for Research and Treatment of Cancer/Groupe d'Etude des Lymphomes de l'Adulte, German Hodgkin Study Group, or National Comprehensive Cancer Network. TMTV and iPET2 were independently prognostic and, combined, identified 4 risk groups: low (TMTV≤147+DS1-3; 5-year PFS, 95%), low-

Deauville score versus ratio Deauville score in the interpretation of interim 18F-FDG PET-CT and in prediction of outcome in children with FDG-avid extra-nodal lymphomas

Hadeer Yousef Elhamady[1*], Hosna Mohamed Mostafa[2], Huda Fathy Elsayed[1],

Eur J Nucl Med Mol Imaging (2013) 40:1312–1320
DOI 10.1007/s00259-013-2435-6

ORIGINAL ARTICLE

An international confirmatory study of the prognostic value of early PET/CT in diffuse large B-cell lymphoma: comparison between Deauville criteria and ΔSUVmax

Emmanuel Itti · Michel Meignan · Alina Berriolo-Riedinger · Alberto Biggi ·

- Definition of PET negativity

> *All patients in the RAPID, HD16, and HD17 trials with a DS 3 received CMT*

> *CALGB 50604 inferior PFS of 77% in 22 patients with a DS 3 treated with CHT alone*

The conclusion that DS3 cases should be considered negative was arbitrary; in our study, as in the RAPID and HD17 trials, a conservative threshold was chosen to define negative PET findings, thus limiting the risk of undertreatment of patients with a negative PET2. We acknowledge that applying a different cutoff to define PET positivity would have resulted

all the technical issues, including advances in PET techniques and acquisition methods over the years, efforts have been made for such a retrospective review in the PET-

been the same. Our protocol clearly outlined that DS3 were to be considered positive, not negative, as proposed by Vassilakopoulos et al.[1]

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Controversies in the management of unfavorable early-stage HL

increased antracycline dose > risk of cardiotoxicity?

Article https://doi.org/10.1038/s41591-023-02514-1

Subsequent female breast cancer risk associated with anthracycline chemotherapy for childhood cancer

Accepted: 26 July 2023
Published online: 11 September 2023
Check for updates

Yuehan Wang[1], Cécile M. Ronckers[1,2,3], Flora E. van Leeuwen[4], Chaya S. Moskowitz[5], Wendy Leisenring[6], Gregory T. Armstrong[7],

tions for survivors treated with anthracyclines. In this study, we pooled individual patient data of 17,903 survivors from six well-established studies, of whom 782 (4.4%) developed a SBC, and analyzed dose-dependent effects of individual anthracycline agents on developing SBC and interactions with chest radiotherapy. A dose-dependent increased SBC risk was seen for doxorubicin (hazard ratio (HR) per 100 mg m^{-2}: 1.24, 95% confidence interval (CI): 1.18–1.31), with more than twofold increased risk for survivors treated with ≥200 mg m^{-2} cumulative doxorubicin dose versus no doxorubicin (HR: 2.50 for 200–299 mg m^{-2}, HR: 2.33 for 300–399 mg m^{-2} and HR: 2.78 for ≥400 mg m^{-2}). For daunorubicin, the associations were not statistically significant. Epirubicin was associated with increased SBC risk (yes/no, HR: 3.25, 95% CI: 1.59–6.63). For patients treated with

associations were not statistically significant. Epirubicin was associated with increased SBC risk (yes/no, HR: 3.25, 95% CI: 1.59–6.63). For patients treated with or without chest irradiation, HRs per 100 mg m^{-2} of doxorubicin were 1.11 (95% CI: 1.02–1.21) and 1.26 (95% CI: 1.17–1.36), respectively. Our findings support that early initiation of SBC surveillance may be reasonable for survivors who received ≥200 mg m^{-2} cumulative doxorubicin dose and should be considered in SBC surveillance guidelines for survivors and future treatment protocols.

			SBC (n)		HR	95% CI	HR	95% CI
Cumulative doxorubicin dose (mg m^{-2})								
0	11,170	62.4	431	55.1	1.0	Ref.		
<100	912	5.1	16	2.0	1.76	0.88–3.51		
100–199	1,795	10.0	69	8.8	1.77	1.30–2.42		
200–299	1,026	5.7	67	8.6	2.50	1.85–3.40	-	
300–399	1,012	5.7	64	8.2	2.33	1.68–3.23		
≥400	779	4.4	58	7.4	2.78	1.99–3.88		
Unknown	1,209	6.8	77	9.8				
Chest radiotherapy field and dose								
No chest radiotherapy	13,004	72.6	250	32.0	1.0	Ref.	1.0	Ref.
High-dose mantle (≥36 Gy; median: 40 Gy, IQR: 39–44 Gy)	698	3.9	238	30.4	8.99	7.00–11.53	9.12	7.09–11.75
Low-dose mantle (<36 Gy; median: 26 Gy, IQR: 21–30 Gy)	524	2.9	93	11.9	4.72	3.48–6.41	5.23	3.86–7.09
Mediastinal (median: 26 Gy, IQR: 21–36 Gy)	469	2.6	33	4.2	1.65	1.02–2.67	1.71	1.06–2.78
TBI (median: 12 Gy, IQR: 11–13 Gy)	371	2.1	22	2.8	7.05	4.11–12.10	7.18	4.18–12.33
Whole lung (median: 16 Gy, IQR: 12–23 Gy)	184	1.0	23	2.9	7.58	4.68–12.27	8.00	4.94–12.95
Other (median: 28 Gy, IQR: 21–36 Gy)	1,316	7.4	63	8.1	2.61	1.87–3.64	2.68	1.91–3.75

Controversies in the management of unfavorable early-stage HL

increased antracycline dose > risk of cardiotoxicity?

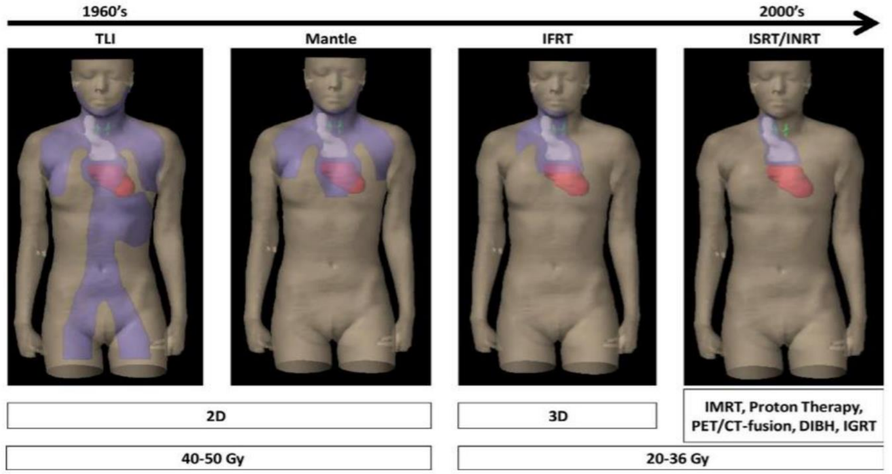
Original Reports | Hematologic Malignancy

Doxorubicin Exposure and Breast Cancer Risk in Survivors of Adolescent and Adult Hodgkin Lymphoma

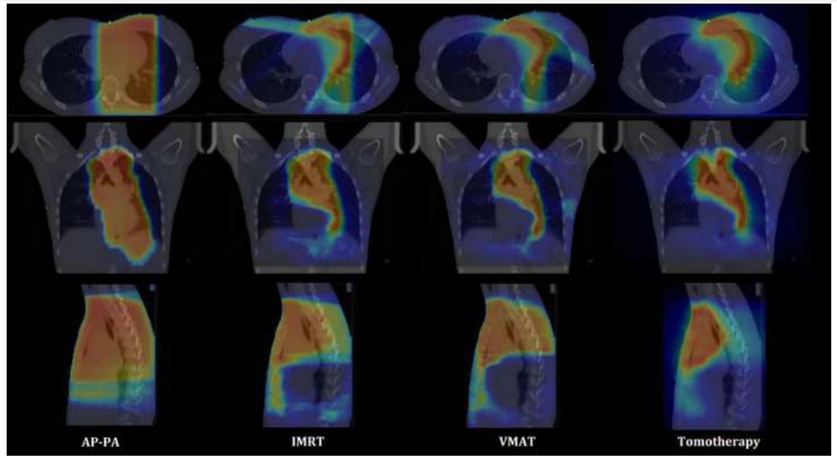
Suzanne I.M. Neppelenbroek, MD[1]; Yvonne M. Geurts, MSc[1]; Berthe M.P. Aleman, MD, PhD[2]; Pieternella J. Lugtenburg, MD, PhD[3]; Saskia E. Rademakers, MD, PhD[4]; Roel J. de Weijer, MANP[5]; Maaike G.A. Schippers, MD[6]; Bastiaan D.P. Ta, MD[7]; Wouter J. Plattel, MD, PhD[8];

RESULTS After a median follow-up of 21.6 years (IQR, 15.8-27.1 years), 252 women had developed invasive BC or ductal carcinoma in situ. The 30-year cumulative incidence was 20.8% (95% CI, 18.2 to 23.4). Survivors treated with a cumulative doxorubicin dose of >200 mg/m² had a 1.5-fold increased BC risk (95% CI, 1.08 to 2.1), compared with survivors not treated with doxorubicin. BC risk increased 1.18-fold (95% CI, 1.05 to 1.32) per additional 100 mg/m² doxorubicin (P_{trend} = .004). The risk increase associated with doxorubicin (yes *v* no) was not modified by age at first treatment (hazard ratio [HR]$_{age <21 years}$, 1.5 [95% CI, 0.9 to 2.6]; HR$_{age ≥21 years}$, 1.3 [95% CI, 0.9 to 1.9) or chest RT (HR$_{without mantle/axillary field RT}$, 1.9 [95% CI, 1.06 to 3.3]; HR$_{with mantle/axillary field RT}$, 1.2 [95% CI, 0.8 to 1.8]).

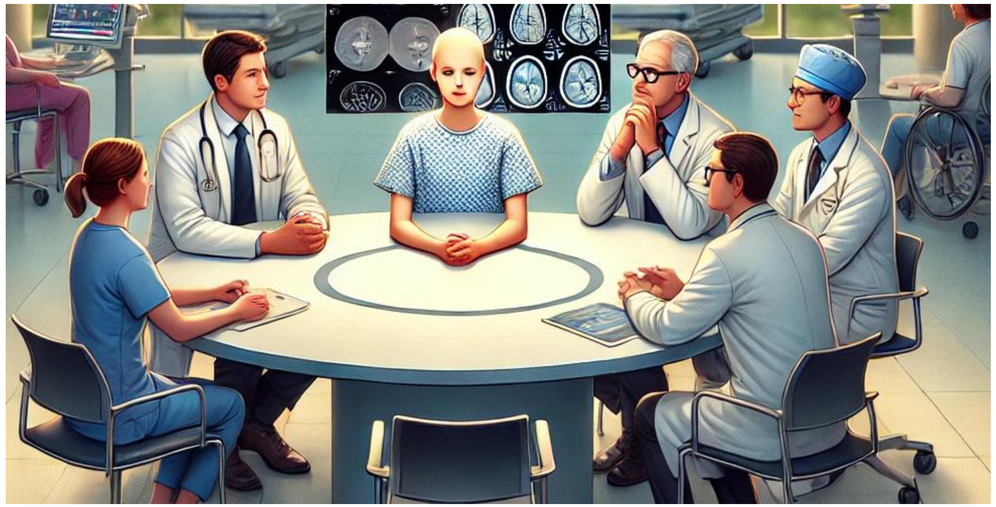
Doxorubicin dose, mg/m²[a]					
No doxorubicin	851 (43.3)	141		1.0 (ref)	
1-200	448 (22.8)	38		1.4 (0.9 to 2.0)	
201-700	621 (31.6)	71		1.5 (1.08 to 2.1)	
Unknown dose	44 (2.2)	2		–	
Doxorubicin dose (continuous)					
No doxorubicin	851 (43.3)	141			1.0 (ref)
Doxorubicin dose (per 100 mg/m²)	1,069 (54.4)	109			1.18 (1.05 to 1.32)
Unknown doxorubicin dose	44 (2.2)	2			–
Chest radiotherapy[b]					
No chest RT	388 (19.8)	23	1.0 (ref)	1.0 (ref)	1.0 (ref)
Mediastinum, not including axilla	609 (31.0)	45	1.0 (0.6 to 1.8)	1.0 (0.6 to 1.8)	1.1 (0.6 to 1.9)
Mantle field or RT including axillary field(s)	932 (47.5)	176	2.1 (1.3 to 3.3)	2.1 (1.3 to 3.4)	2.1 (1.3 to 3.4)
Unspecified RT fields	35 (1.8)	8	2.8 (1.2 to 6.5)	3.1 (1.3 to 7.2)	3.2 (1.3 to 7.4)



Int J Radiation Oncol Biol Phys, Vol. 111, No. 4, pp. 841–850, 2021



Patient tailored and patient centered treatment

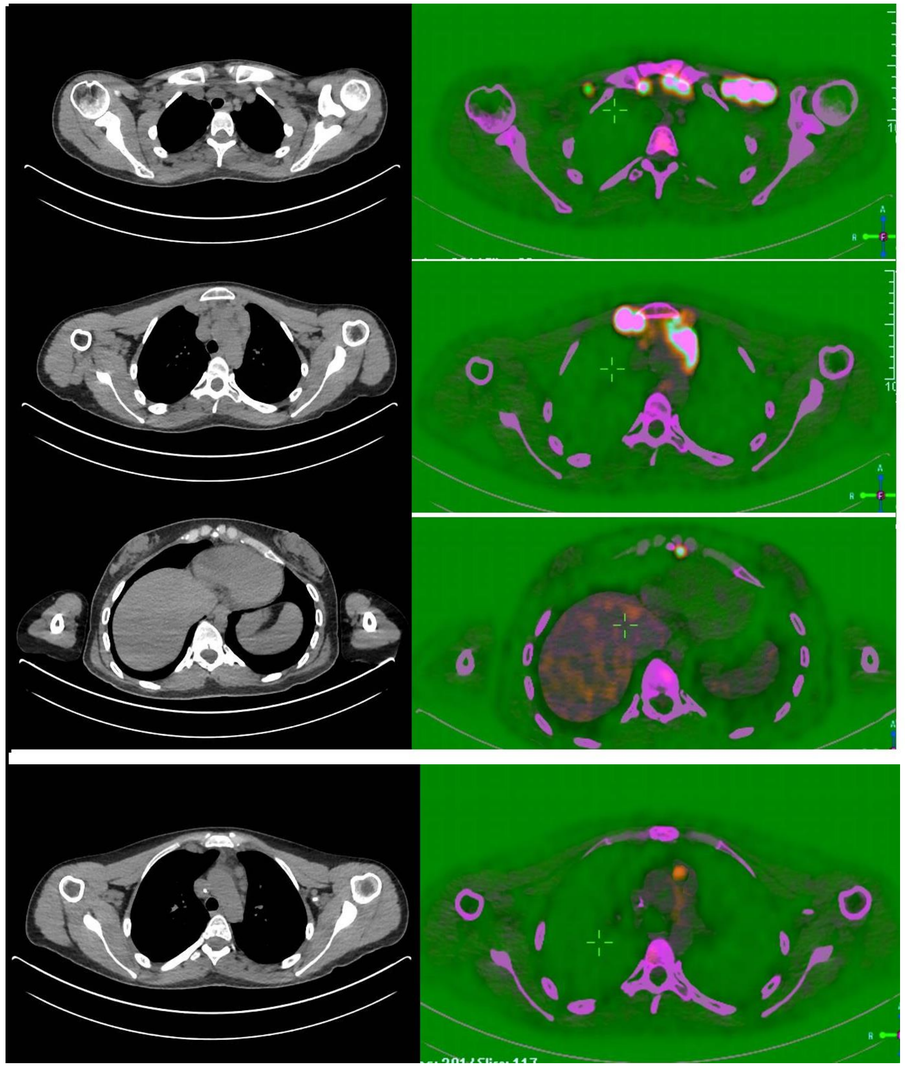


GHSG HD 17

33 (10%) of 318 PET4-negative in standard CMT refused RT

7 (2%) of 333 PET4-negative in PET-guided requested RT

Case report



Female 29 yo

Bilateral neck swelling > CT scan + PET-SC

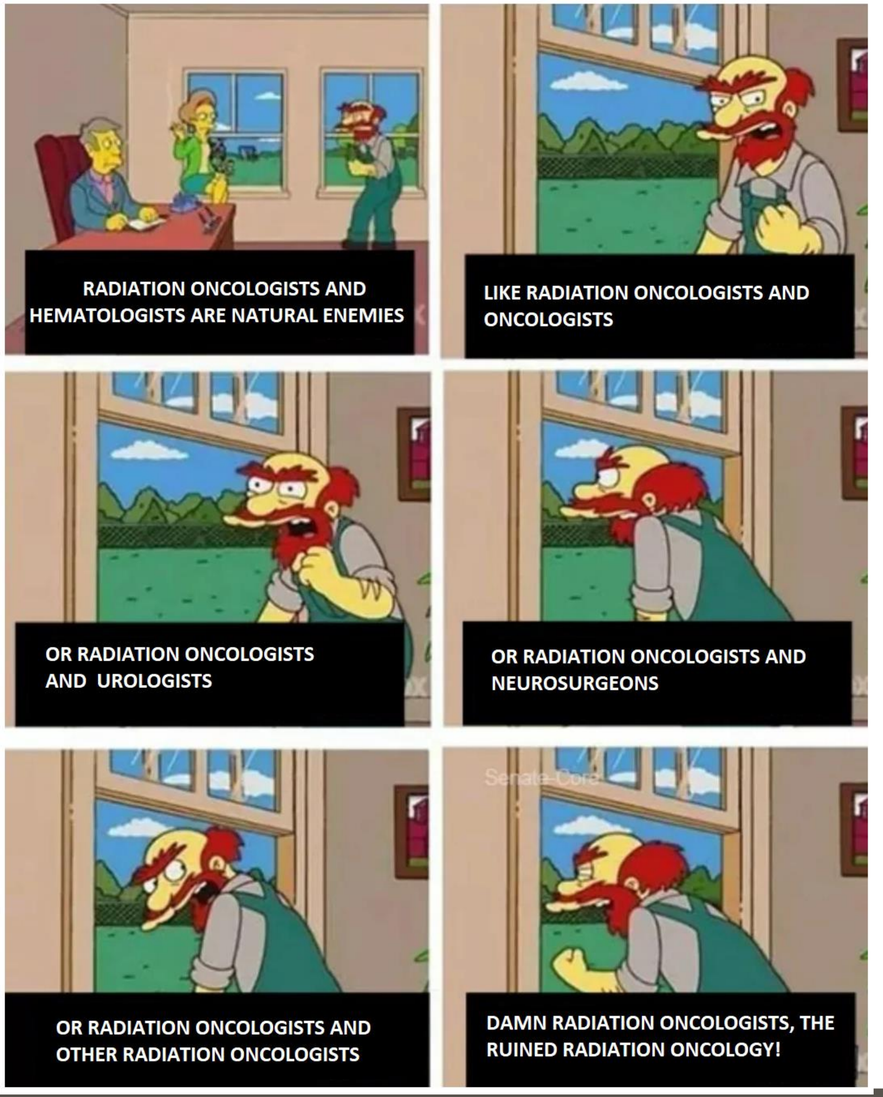
- *Level IV-V bilateral (SUVmax 12.9) + bilateral infraclavicular/retro-pectoral (SUVmax 14.9) + mediastinal and cardiophrenic (SUVmax 13.3).*

Level IV biopsy > NSCHL negative bone marrow biopsy ESR = 52

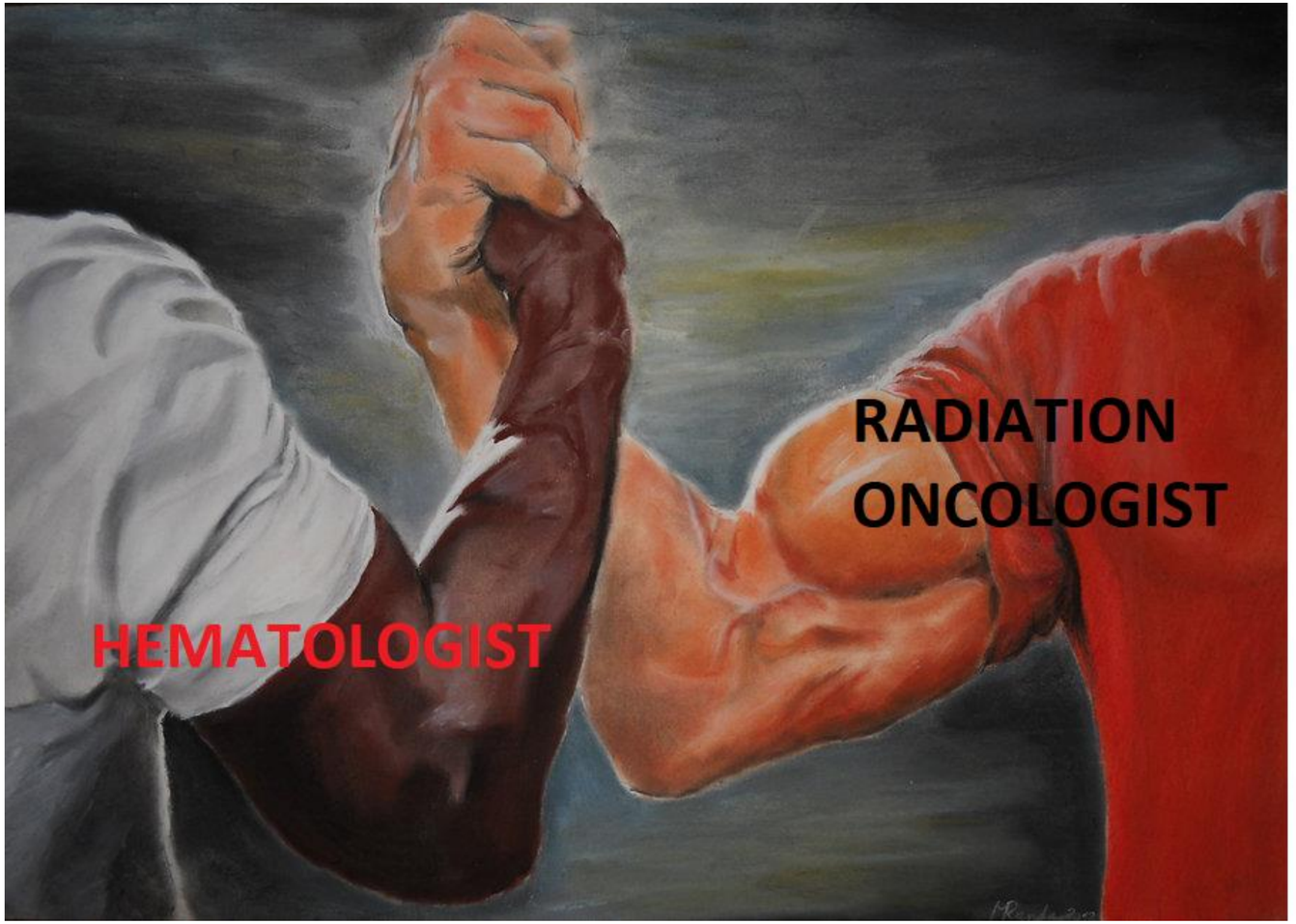
- *Stage IIA unfavourable non-bulky*

05/24 ABVD > PET 2 mediastinal Deauville 3

Multidisciplinary management



Multidisciplinary management



Multidisciplinary management