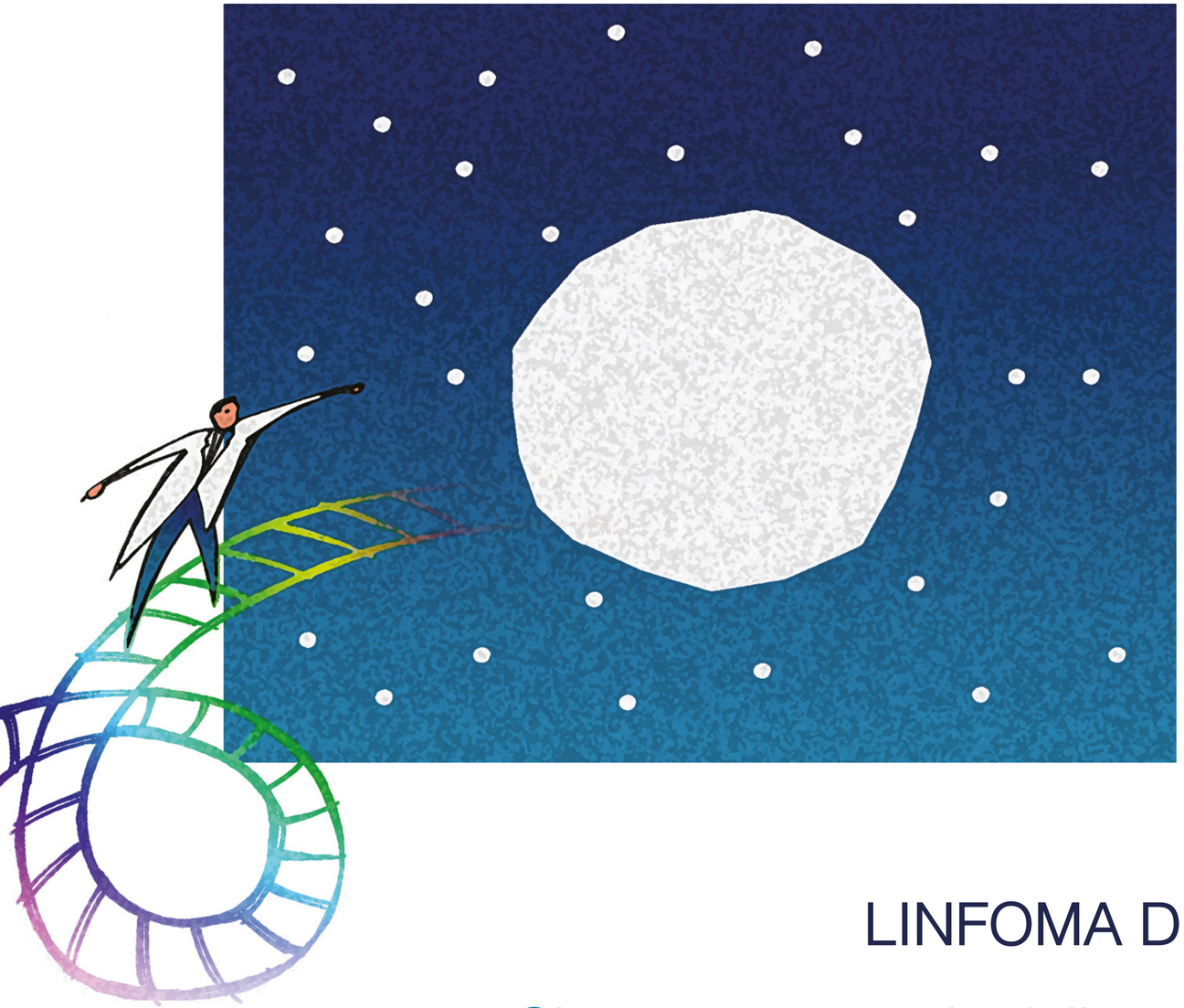


The young side of

LYMPHOMA

gli under 40 a confronto

Milano, 14-15 aprile 2023

LINFOMA DI HODGKIN

C’è ancora un ruolo della radioterapia nel paziente con linfoma di Hodgkin recidivato/refrattario

Mario Levis

Disclosures of Mario Levis

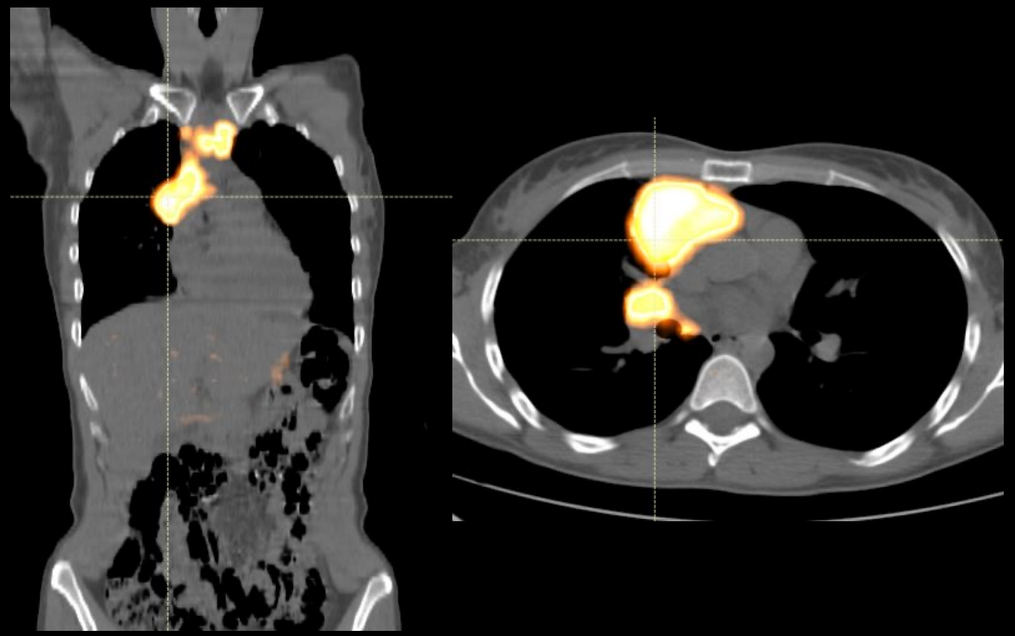
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

NOTHING TO DISCLOSE

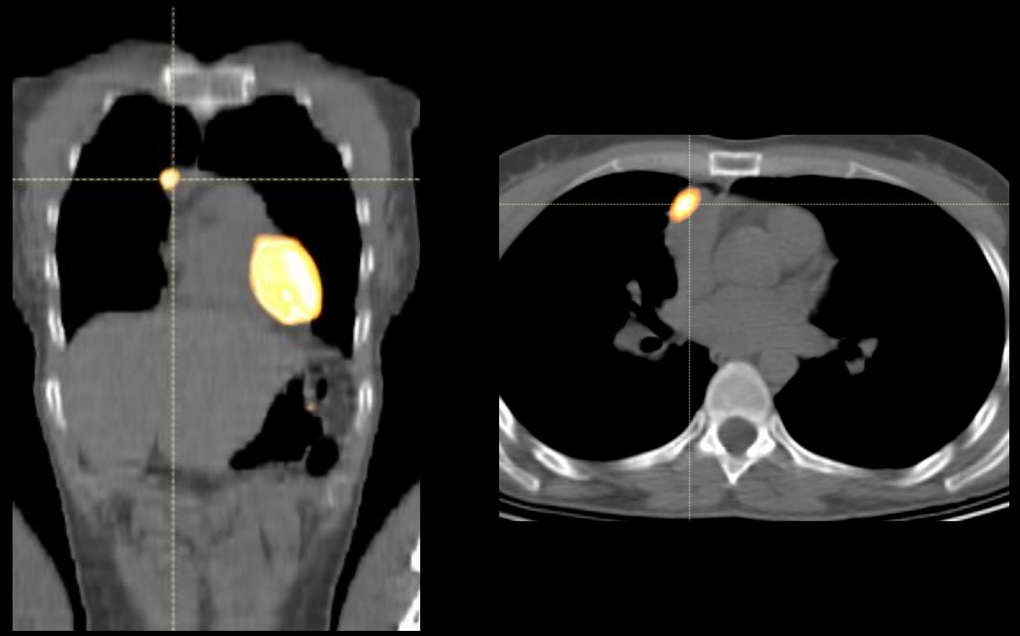
Clinical Case

- Female patient
- 38 years
- December 2019: diagnosis of cHL, stage IIB (X?)
- Therapy program: ABVD x 6 (with PET evaluation after 2 cycles)
- PET2: PR (focal residual uptake in the mediastinum), DS4 → continued with ABVD
- PET6: SD, DS4

Baseline



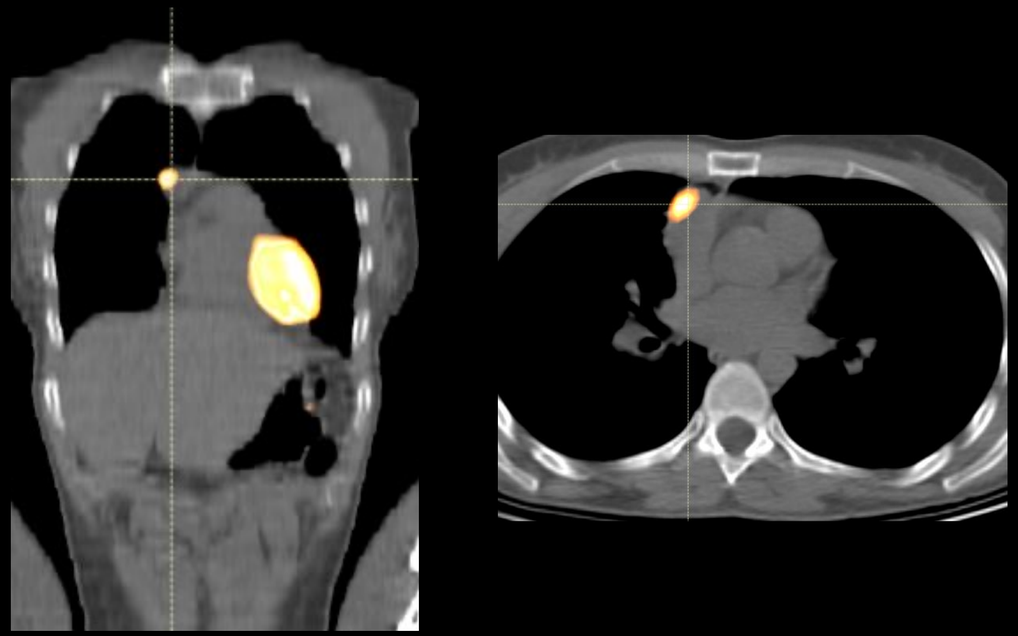
PET2 and PET6



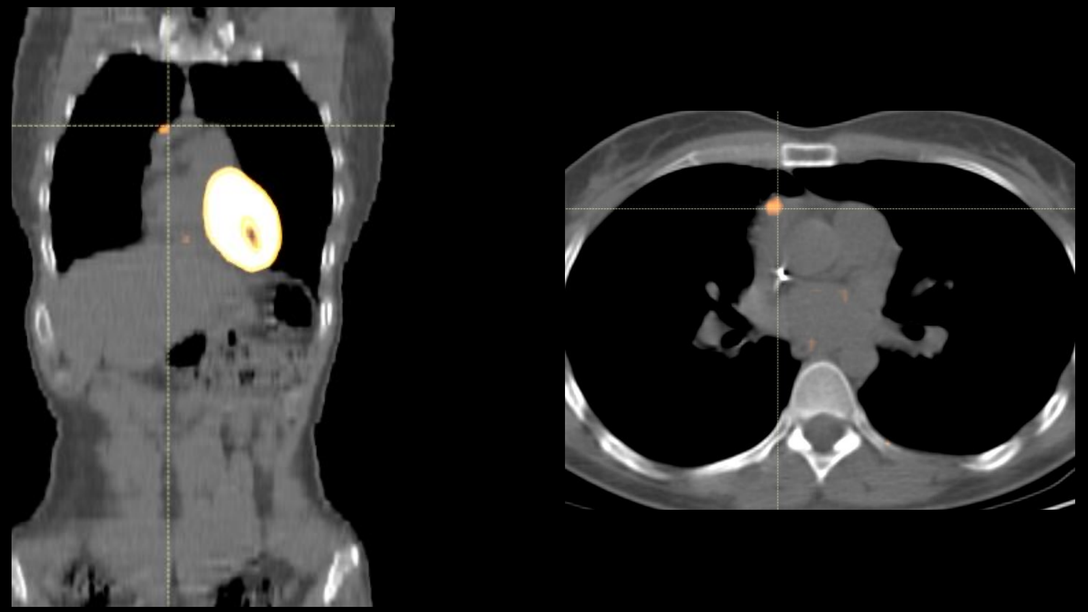
Clinical Case

- July 2020: salvage chemotherapy with BEGEV
- PET after 2 BEGEV: PR, with residual uptake in the mediastinum (SUVmax 2.8, liver uptake 2.3, DS 4)
- Interruption of BEGEV → start of Brentuximab Vedotin (September 2020)
- PET after 4 BV: SD (DS4)

Before BEGEV

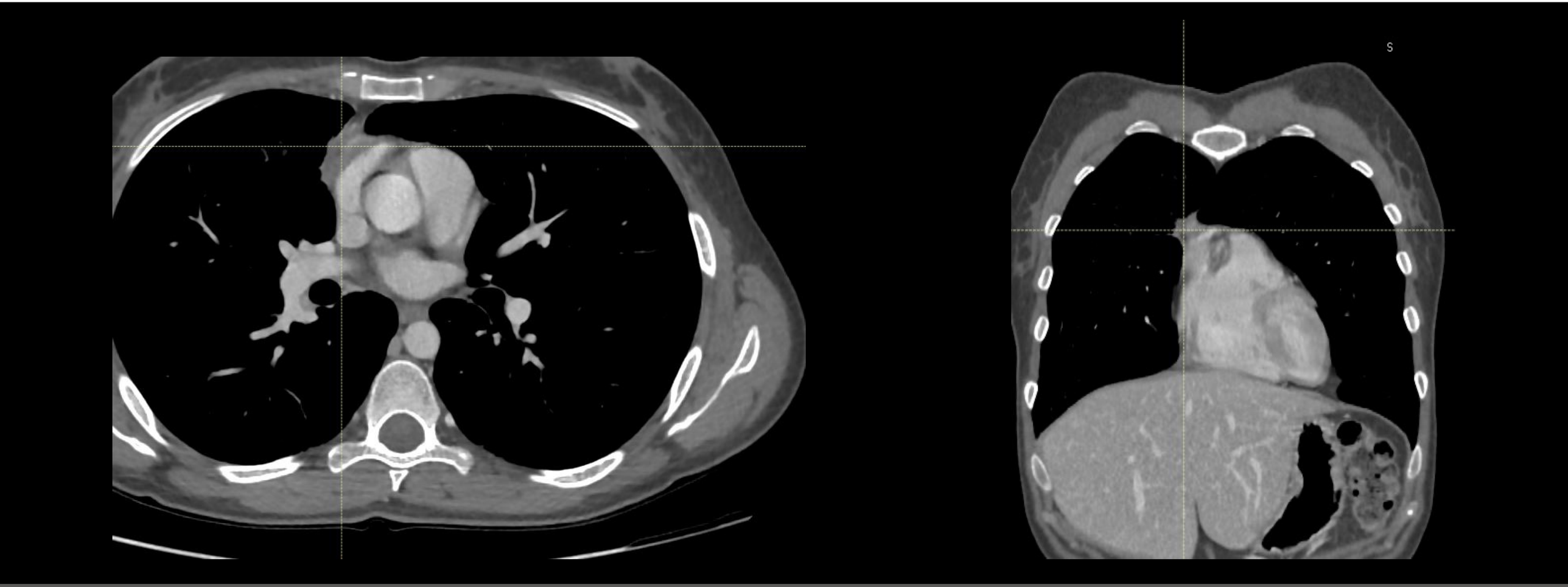


After 2 BEGEV and 4 BV



Clinical Case

- Contrast Enhanced CT scan: residual mediastinal mass, located in close proximity to the right atrium in the same region of baseline disease → radiological finding highly suspicious for residual disease.

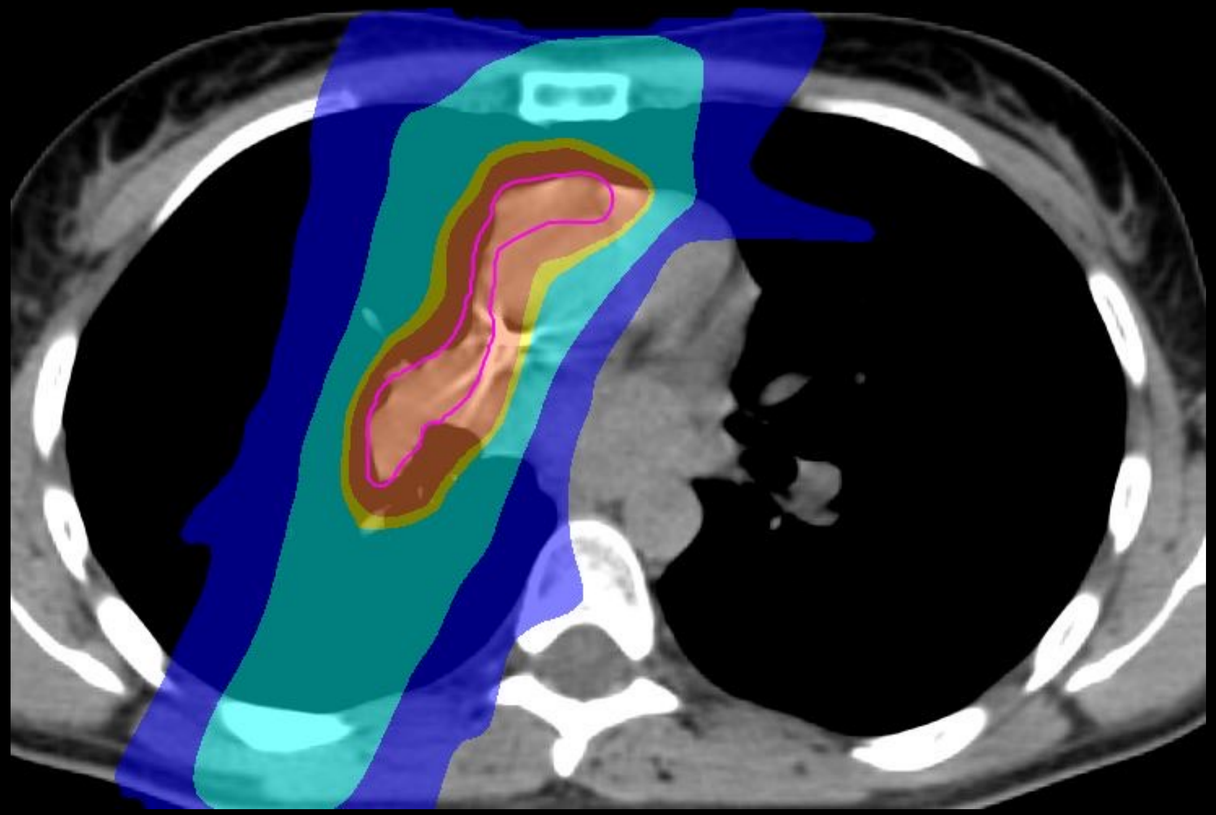


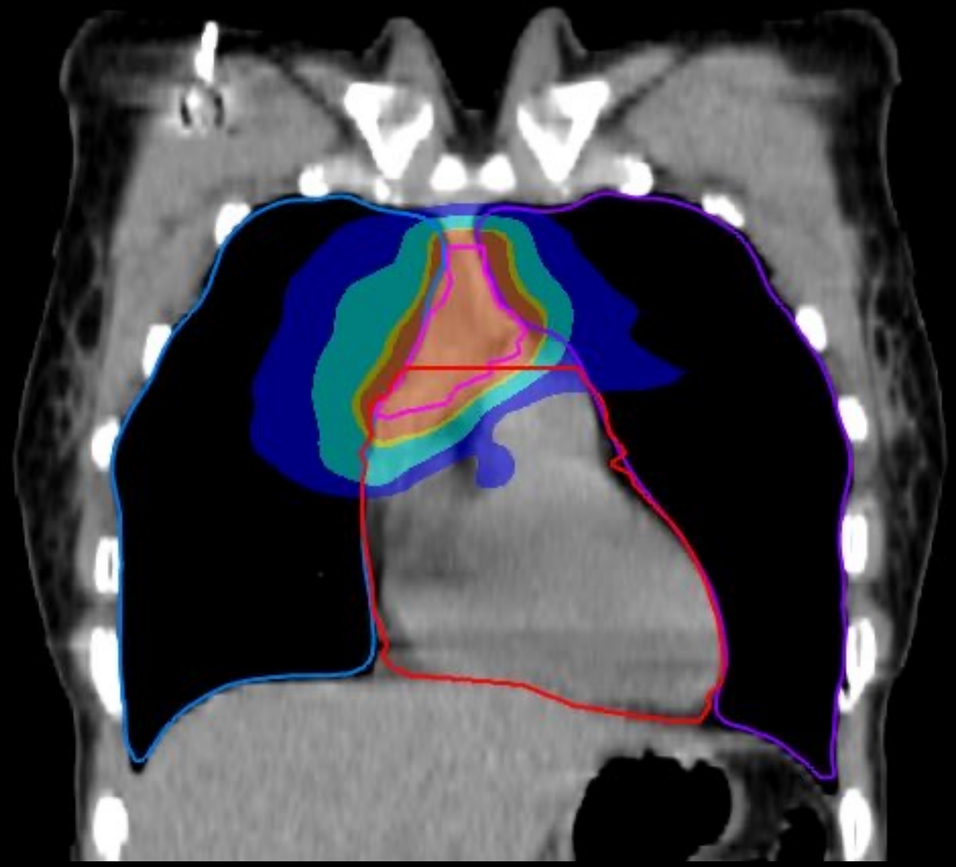
What to do now ?

- Continue BV
- Involved Site RT followed by ASCT
- PD-1 inhibitor
- ASCT (eventually followed by ISRT or by BV)

Clinical Case

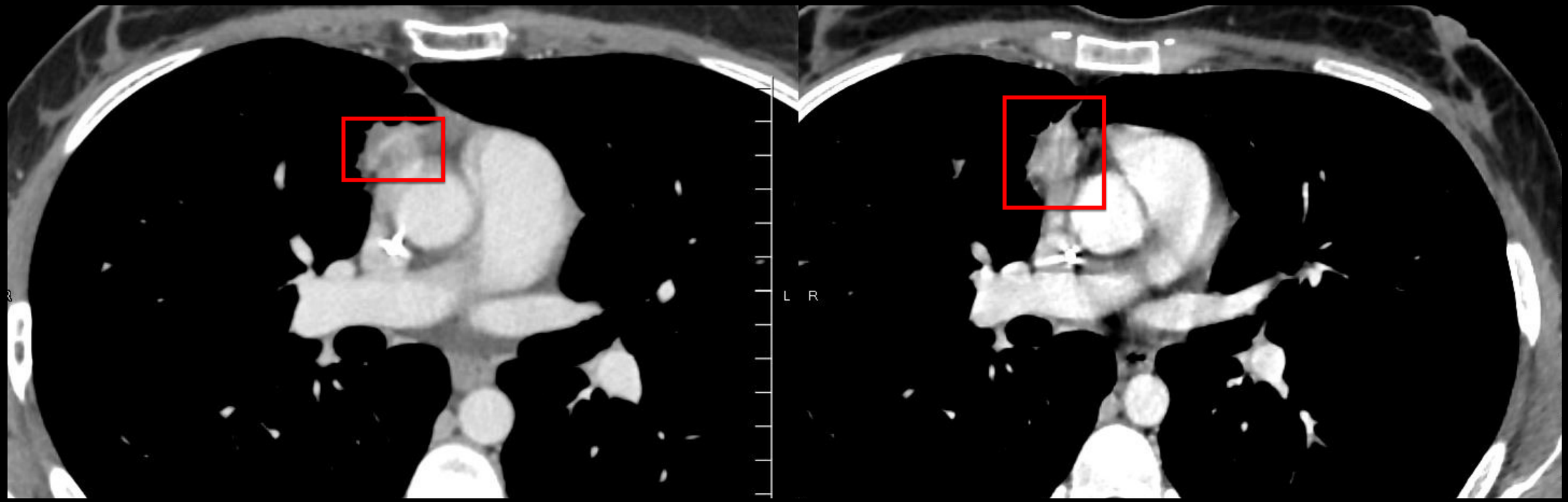
- January/February 2021: The patient was referred for ISRT with 30 Gy in 15 fractions with the aim of achieving a better response before ASCT





Clinical Case

- Restaging with CT scan 1 month after ISRT: reduction of the mediastinal mass



Clinical Case

- June 2021: FEAM + ASCT
- Complication after ASCT: bilateral pneumonia complicated by septic shock (G4), requiring CPAP and adrenaline.
- Complete pulmonary recovery after 6 months and several lines of antibiotic therapy
- PET scan (January 2022): CMR
- Last follow up visit: November 2022: complete remission

Role of Peritransplant (pre/post ASCT) Radiotherapy in R/R HL

- The role of radiotherapy (RT) is controversial in this setting.

- Unfortunately, the role of RT before or after ASCT has never been addressed by prospective randomized trials, due to the heterogeneity of presentations, salvage programs and uncertainties in selection criteria

Retrospective studies focusing on peritransplant RT in R/R HL

Study	N° pts N° receiving RT (%)	RT timing	RT dose	Results
Mundt et al. *(IJROBP 1995)*	54 pts 20 received RT (37%)	7 pre-ASCT 13 post-ASCT	Median 36 Gy (range 19.8 - 45.6 Gy)	**3 years PFS in post-HDCT SD or PR** NO-RT: 12.1% IFRT: 40% p = 0.04
Poen et al. *(IJROBP 1996)*	100 pts 24 received RT (24%)	18 pre-ASCT 6 post-ASCT	Median 30 Gy (range 12.5 - 45 Gy)	**3 years OS in Stage I-III pts:** NO-RT: 60% IFRT: 85% p = 0.16
Wendland et al. *(AJCO 2006)*	65 pts 21 received RT (32%)	6 pre-ASCT 15 post-ASCT	Median 28.8 Gy (range 21 – 43.2 Gy)	**5 years OS:** NO-RT: 55.6% IFRT: 73.3% p = 0.16
Kahn et al. *(IJROBP 2011)*	92 pts 46 received RT (50%)	38 pre-ASCT 8 post-ASCT	Median 30 Gy (range 21 - 45 Gy)	**DFS benefit** for patients receiving **IFRT to bulky sites**
Biswas et al. *(Radiother Oncol 2012)*	62 pts 32 received RT (52%)	32 post-ASCT	Median 30.6 Gy (range 6.0 – 44.2 Gy)	**3 years OS:** NO-RT: 40% IFRT: 69.6% p = 0.05
Eroglu et al. *(AJCO 2015)*	45 pts 20 received RT (44%)	16 pre-ASCT 4 post-ASCT	Median 30 Gy (range 25 - 44 Gy)	**5 years OS in Stage I-II pts:** NO-RT: 48% IFRT: 81% p = 0.045
Milgrom et al. *(Cancer 2016)*	189 pts 22 received RT (12%)	1 pre-ASCT 21 post-ASCT	Median 36 Gy (range 25.2 – 41.4 Gy)	**NO PFS/OS differences** **IFRT provided higher LC rates**
Levis et al. *(CLML 2017)*	73 pts 21 received RT (29%)	6 pre-ASCT 15 post-ASCT	Median 30 Gy (range 25.2 – 43.2 Gy)	**3 years OS in PET+/Stage I-II pts** NO-RT: 62.3% IFRT: 91.7% p = 0.14

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CLINICAL INVESTIGATION

Peritransplant Radiation Therapy in Patients With Refractory or Relapsed Hodgkin Lymphoma Undergoing Autologous Stem Cell Transplant: Long-Term Results of a Retrospective Study of the Fondazione Italiana Linfomi

Mario Levis, MD, PhD,* Belinda A. Campbell, MBBS, MMed, FRANZCR,†,‡,§ Fabio Matrone, MD,‖ Lavinia Grapulin, MD,¶ Anna Di Russo , MD,# Michela Buglione, MD,** Ilenia Iamundo De Cumis , MD,†† Gabriele Simontacchi, MD,‡‡ Patrizia Ciammella, MD,§§ Alessandro Magli, MD,‖‖ Giuliana Pascale, MD,¶¶ Sofia Meregalli, MD,## Michael MacManus, MD,†,‡ Giuseppe Fanetti, MD,‖ Francesca De Felice, MD,¶ Gabriella Furfaro, MSc,* Giovannino Ciccone, MD,*** and Umberto Ricardi, MD*

Table 1 - Patients characteristics

Variable		Patients (131) N (%)
Gender	male female	68 (52%) 63 (48%)
Age	Median (range)	32 (18-70)
ECOG PS	0 ≥1 N.A.	87 (66%) 35 (27%) 9 (7%)
Relapse Interval after 1st line	Early (≤ 6 months) Late (> 6months)	52 (40%) 79 (60%)
Stage at relapse	Stage I-II Stage III-IV N.A.	92 (72%) 36 (28%) 3
Bulky at relapse	NO YES	118 (92%) 10 (8%) 3
Site of relapse	Same site(s) Different site(s) Both N.A.	96 (75%) 11 (9%) 21 (16%) 3
PET status before ASCT	CR PR/SD PD N.A.	50 (42%) 53 (44%) 17 (14%) 11
RT timing	before ASCT after ASCT	32 (24%) 99 (76%)
Number of irradiated sites	1 2 3 4 5 N.A.	60 (47%) 35 (27%) 26 (20%) 5 (4%) 2 (2%) 3
Follow up time (median)	Median (in months)	60

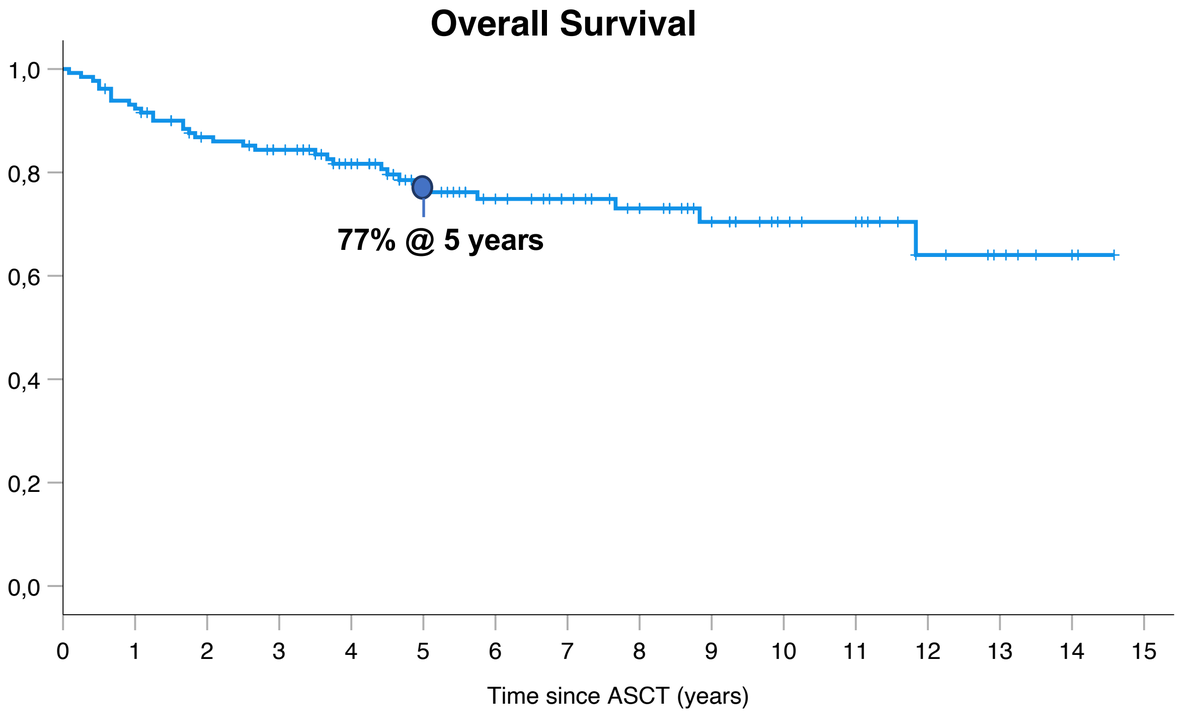
40%
Had an early relapse/refractory disease

72%
Had limited stage disease (Stage I-II) at relapse

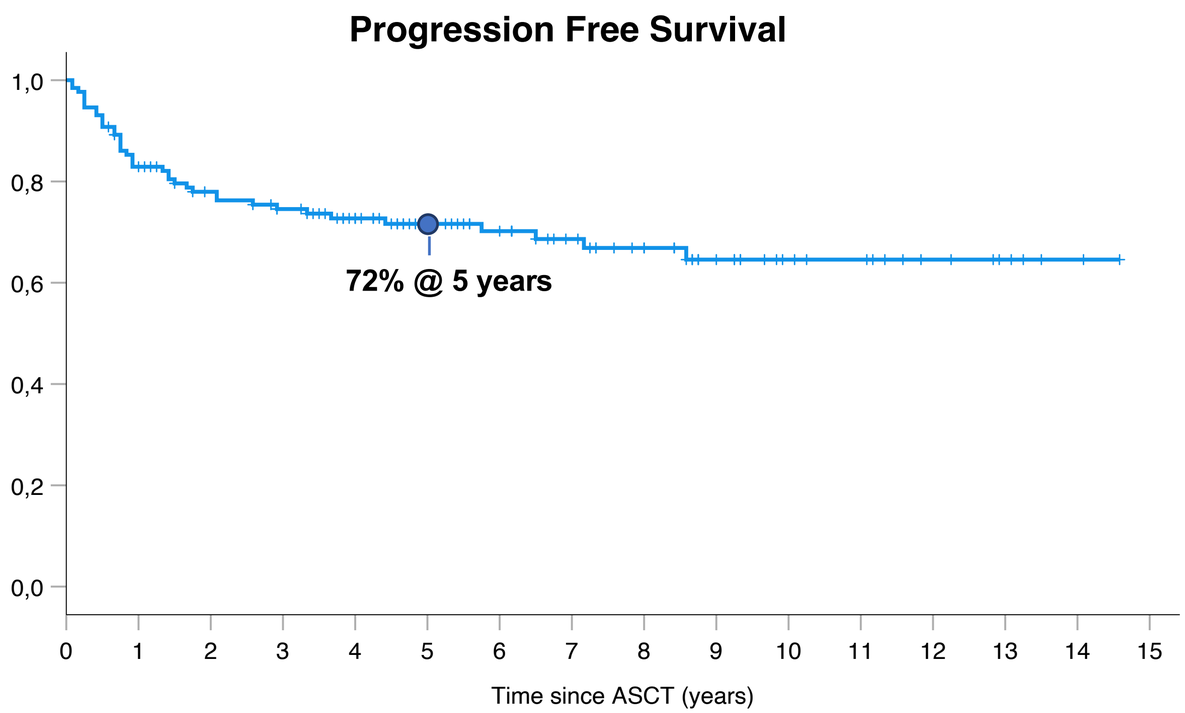
54%
did not achieve CMR before ASCT

76%
Received IFRT after ASCT

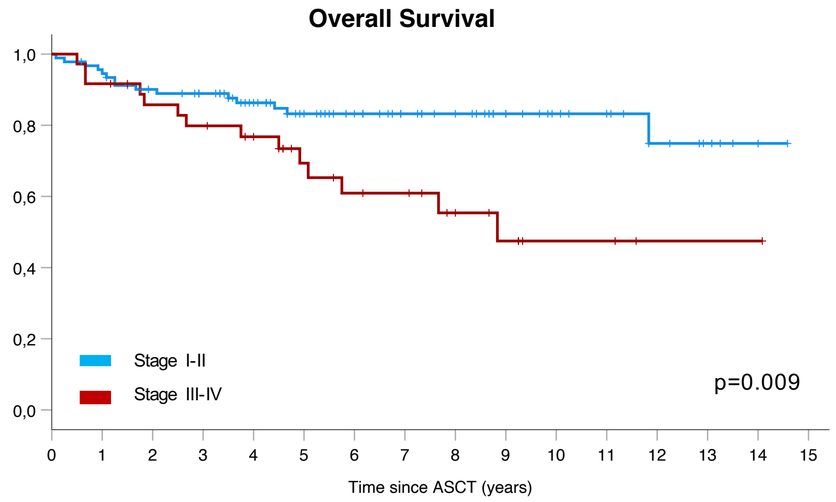
A


Overall Survival
1,0
0,8
0,6
0,4
0,2
0,0
77% @ 5 years
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since ASCT (years)

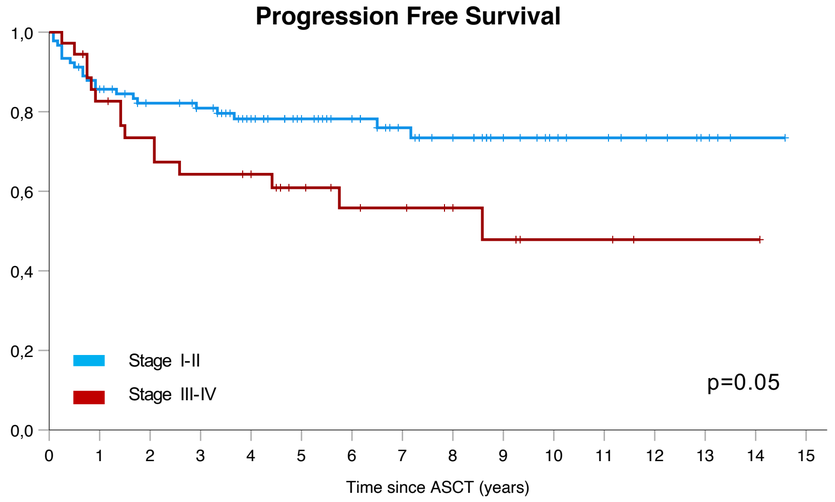
B


Progression Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
72% @ 5 years
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since ASCT (years)

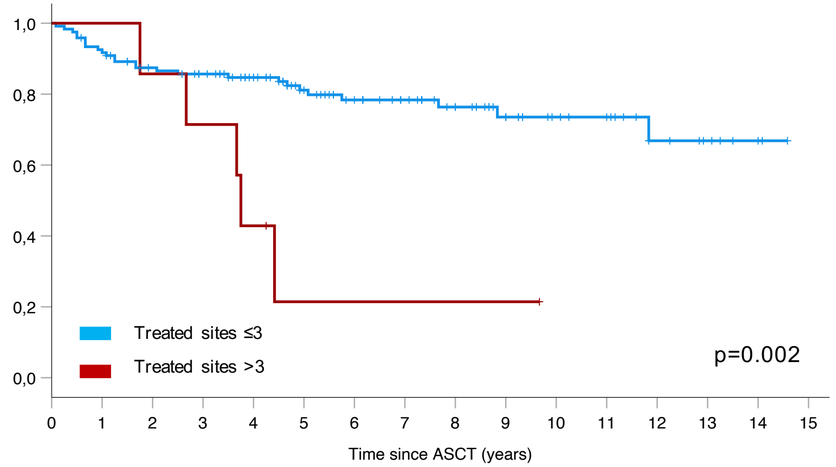
A


Overall Survival
1,0
0,8
0,6
0,4
0,2
0,0
Stage I-II
Stage III-IV
p=0.009
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since ASCT (years)

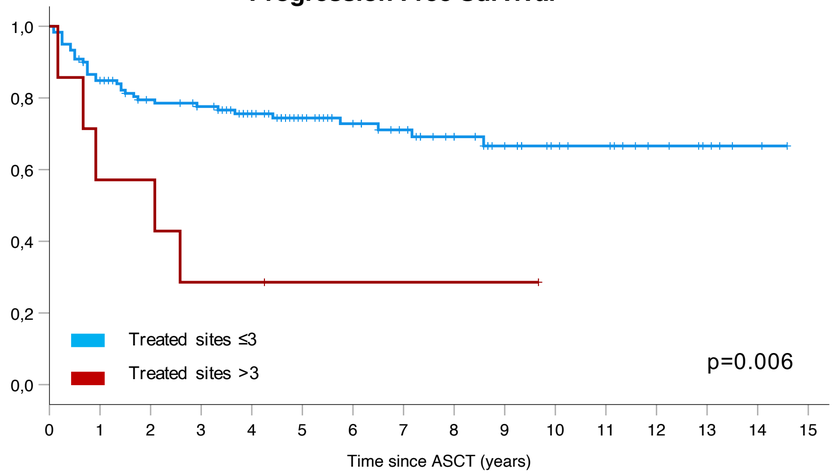
B


Progression Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Stage I-II
Stage III-IV
p=0.05
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since ASCT (years)

C

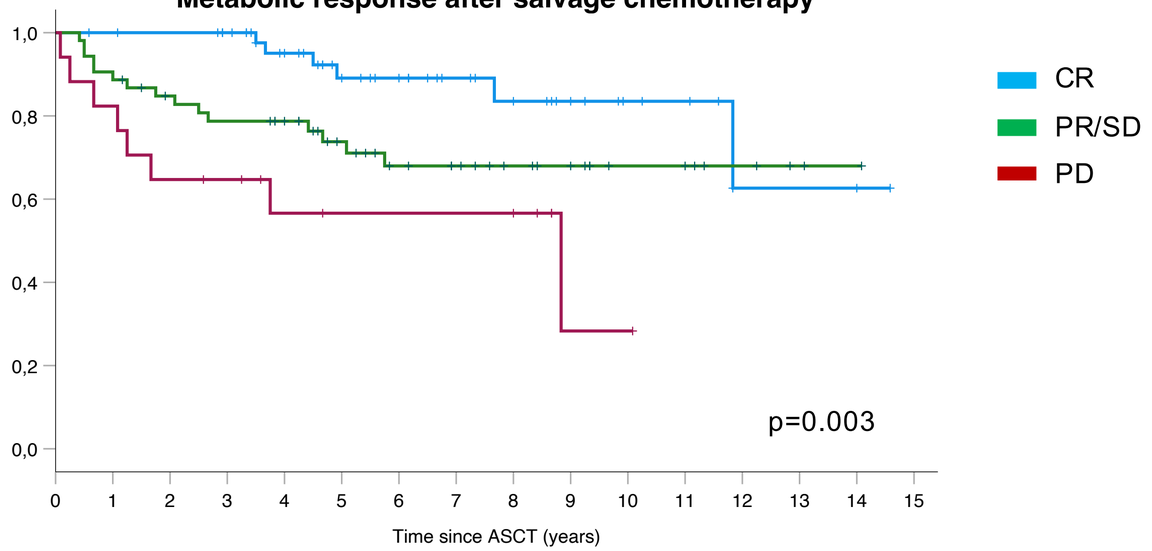

Overall Survival
1,0
0,8
0,6
0,4
0,2
0,0
Treated sites ≤3
Treated sites >3
p=0.002
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since ASCT (years)

D

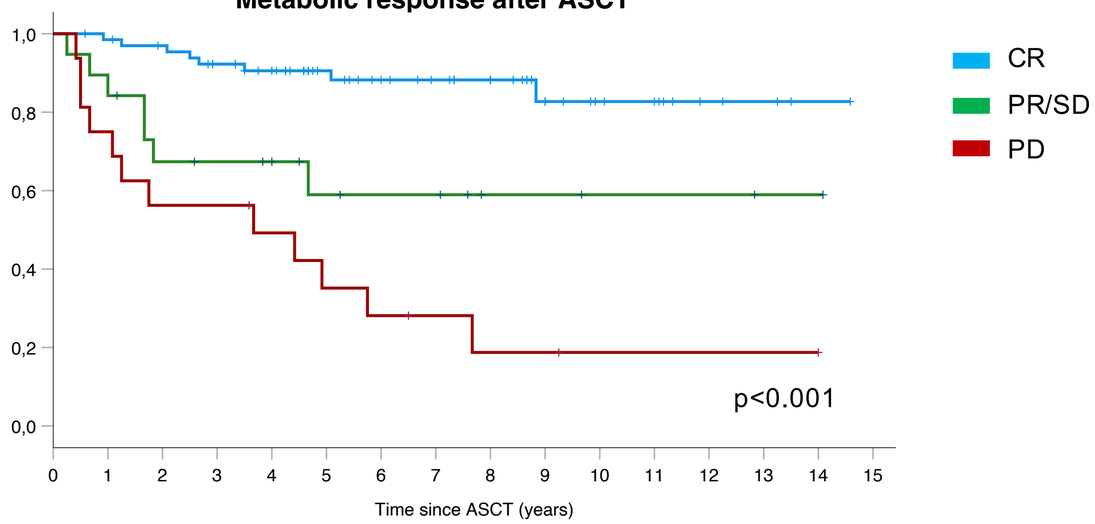

Progression Free Survival
1,0
0,8
0,6
0,4
0,2
0,0
Treated sites ≤3
Treated sites >3
p=0.006
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
Time since ASCT (years)

Overall survival according to PET status

A

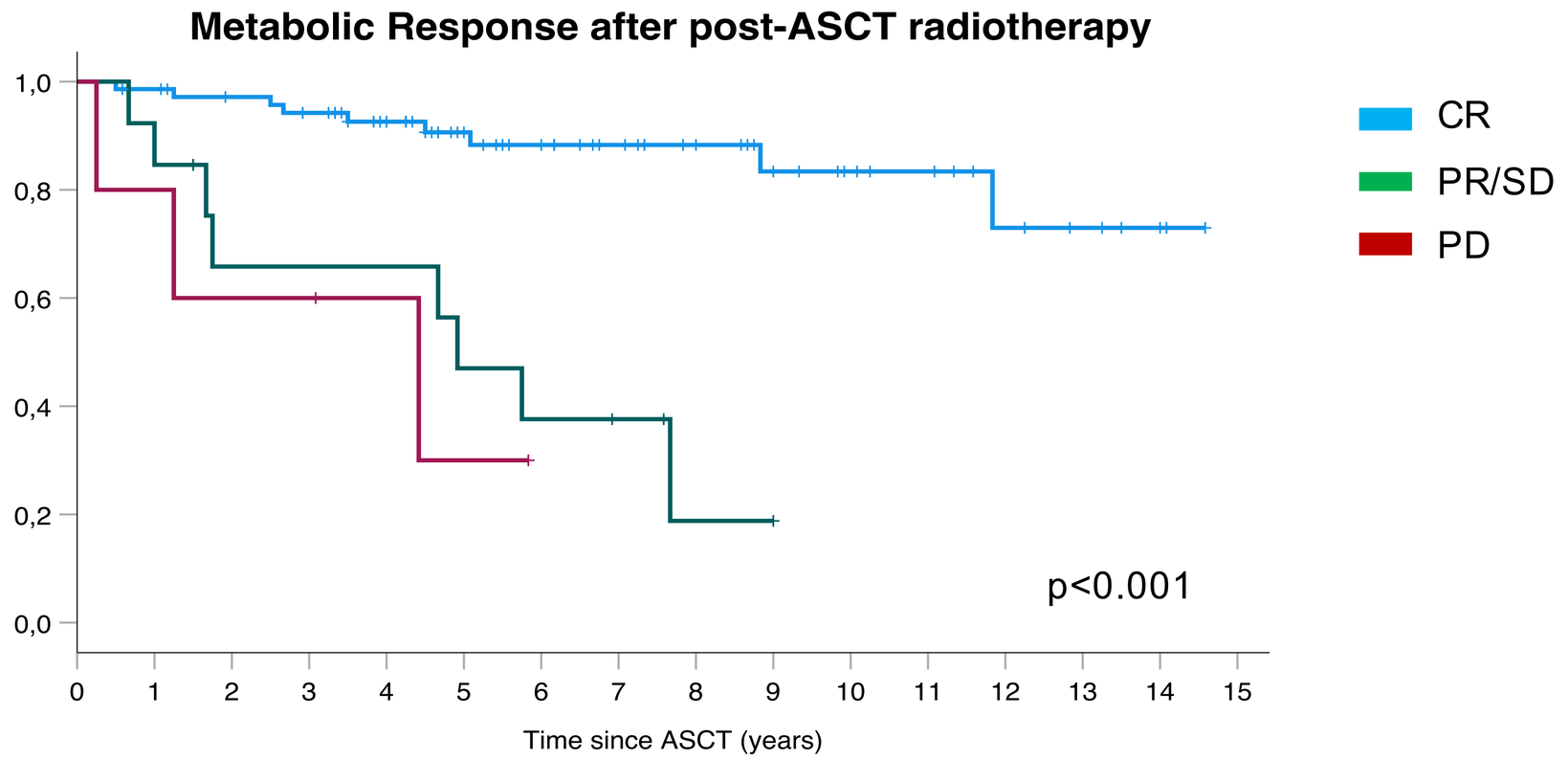


B



Incomplete responders after peritransplant RT have a dismal prognosis

C

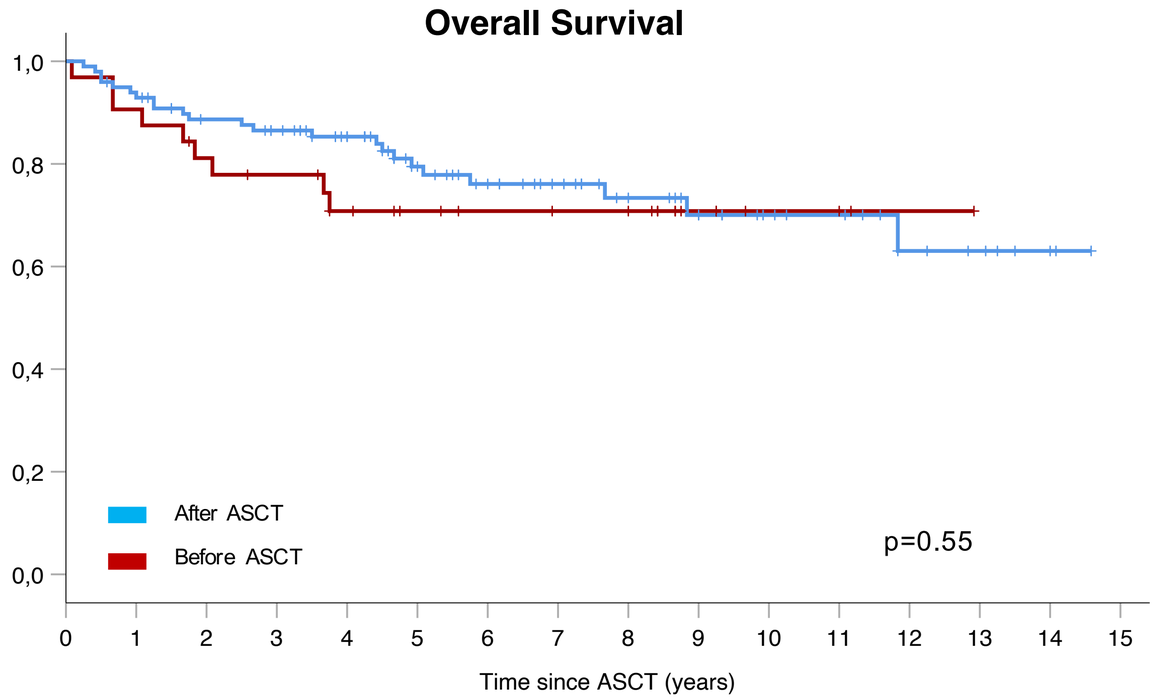


Which is the best timing for peritransplant RT ?

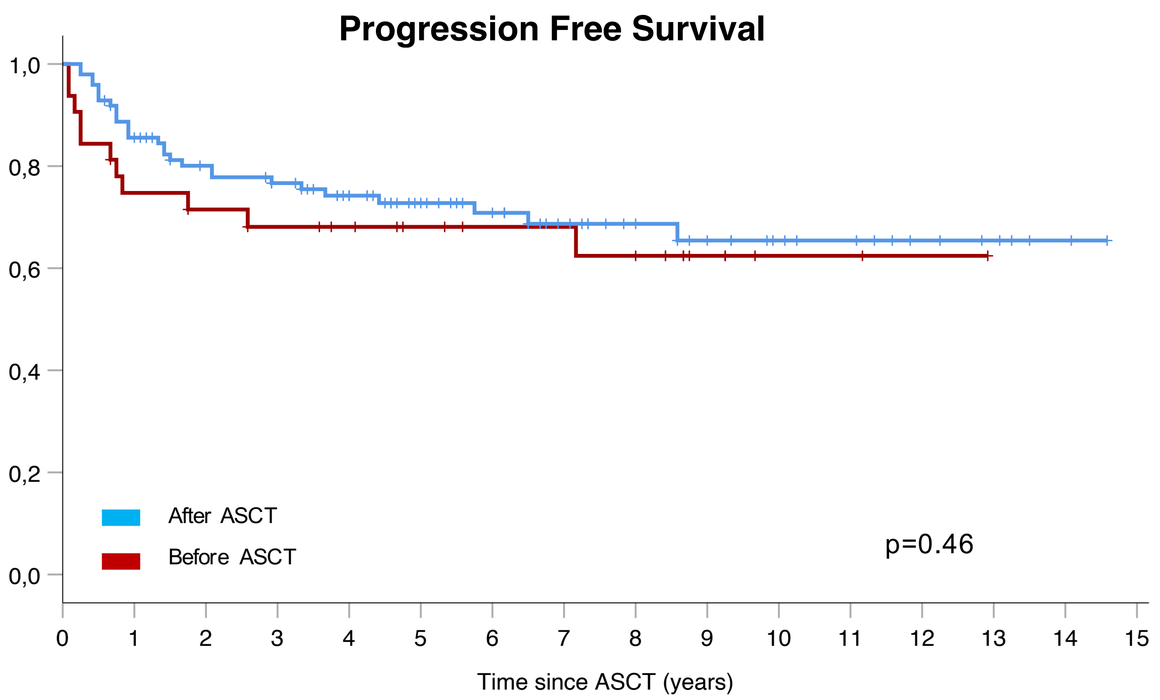
- Before ASCT
- After ASCT
- The timing of RT is not relevant as it does not affect the final outcome
- It depends on several clinical factors

Timing of peritransplant RT has no impact on the outcomes

A



B



Comparison with literature data

Chemo + RT

OS @ 3 years		
Study	N° pts receiving RT	Best arm
Stanford (1996)	24	85%
MDACC (2016)	22	78%
Duke/Rochester (2012)	32	82%
Utah (2006)	21	73%
FIL study (2023) *	131	83%

** single arm*

Chemo alone

OS @ 3 years		
Study	N° pts	Best arm
GHSG (2002)	161	68%
IIL/FIL (2003)	102	64% (5 years)
Aethera (2015)	**329**	**84%**
BEGEV (2016)	59	78%

What is the rate of complete metabolic response (CMR) achieved by RT in patients with incomplete metabolic response before radiation?

- <5%
- 10-15%
- 25%
- 50%

Metabolic response to peri-transplant RT

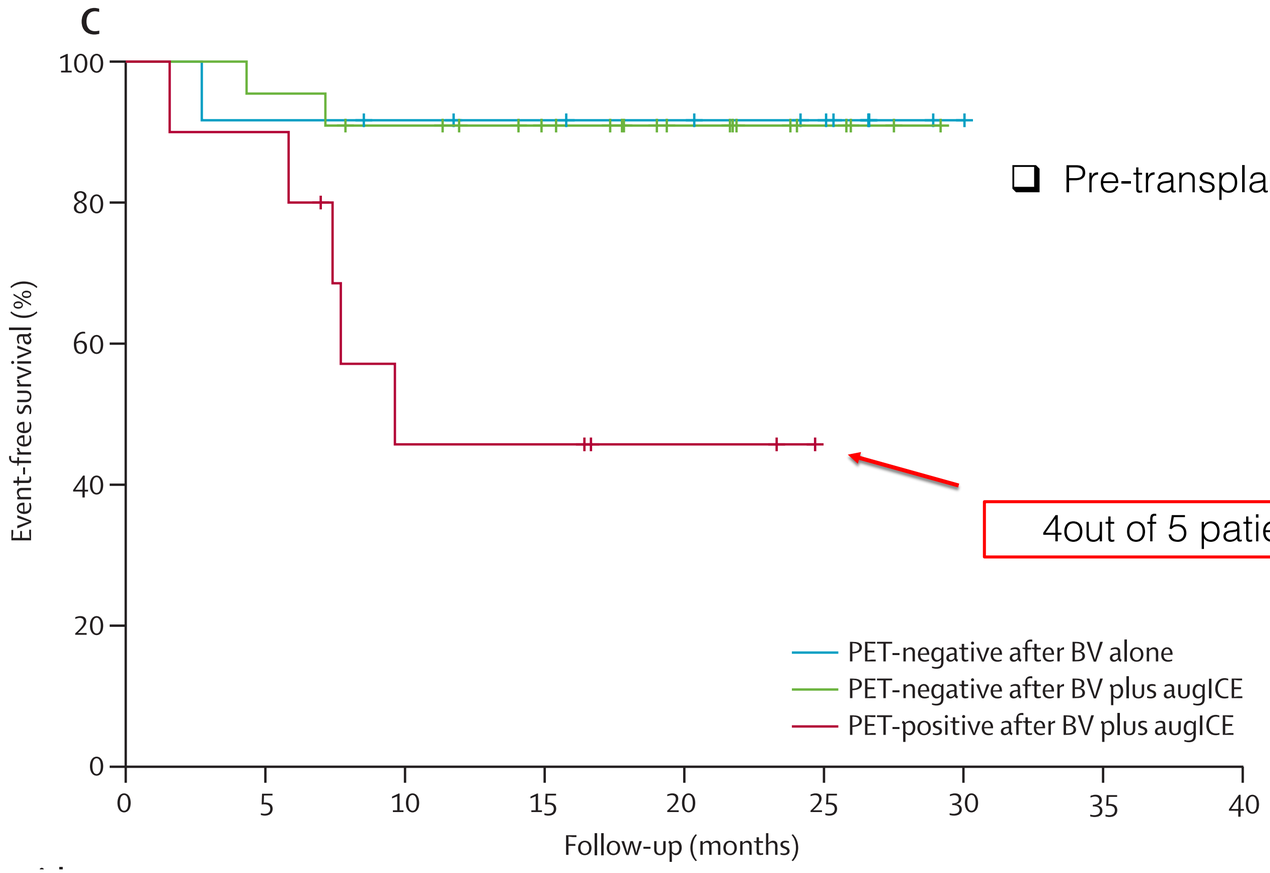
RT timing	Overall improvement in Metabolic response (ORR) after RT	Complete metabolic response (CMR) after RT
Before ASCT	9/14 (**64**%)	6/14 (**43**%)
After ASCT	16/24 (**67**%)	12/24 (**50**%)

Metabolic response to “modern” drugs

Drug	Overall Response Rate (ORR)	Complete Metabolic Response (CMR)
Brentuximab Vedotin *(Younes et al 2012)*	76/102 (**75**%)	35/102 (**34**%)
Nivolumab *(CheckMate 205)*	168/243 (**69**%)	40/243 (**16**%)
Pembrolizumab *(Keynote 087)*	145/210 (**69**%)	47/210 (**22**%)

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study

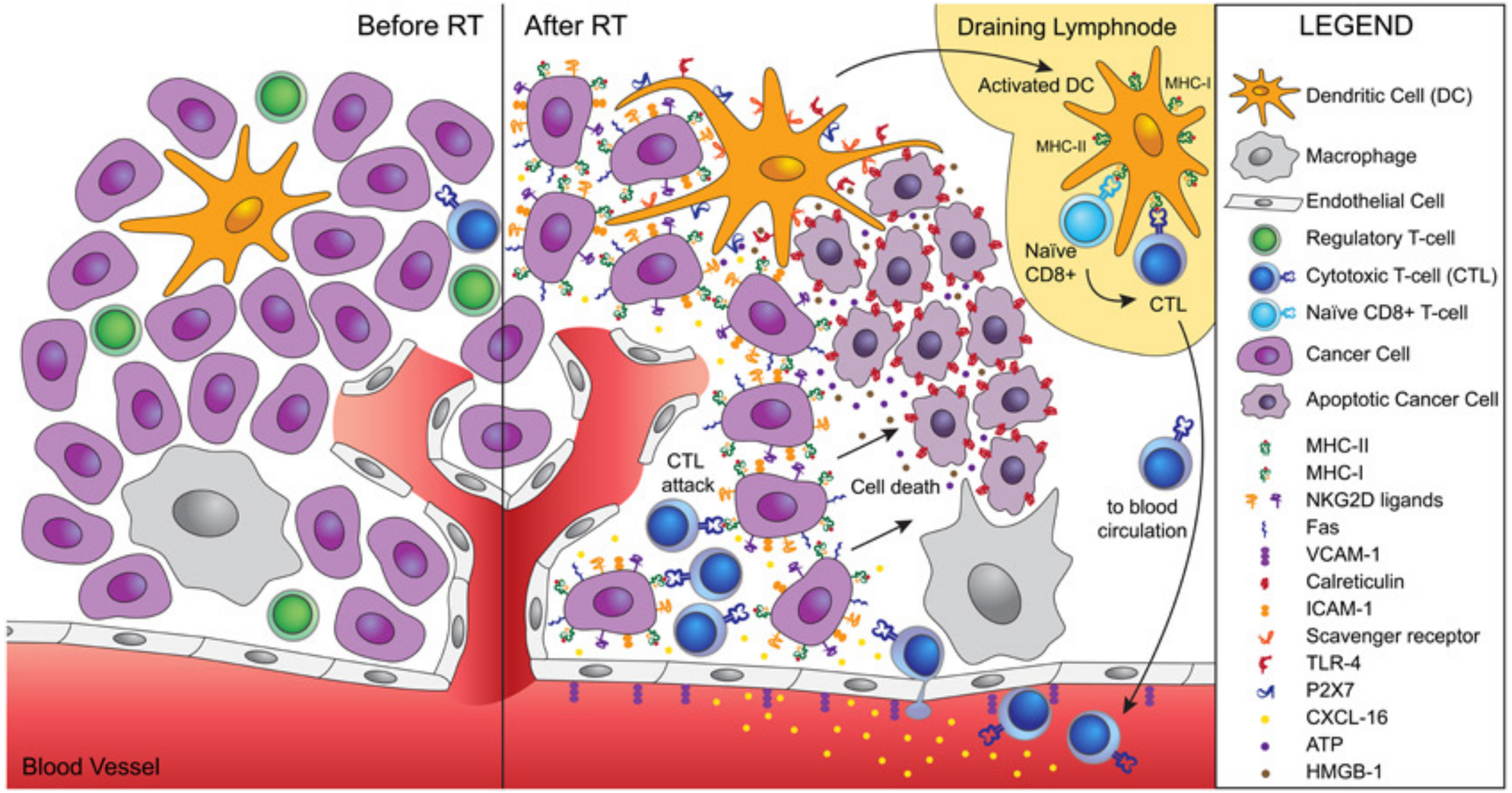
Novel Agents… Integration with RT Might Be Effective For Selected Patients



- Pre-transplant RT given to 38% patients

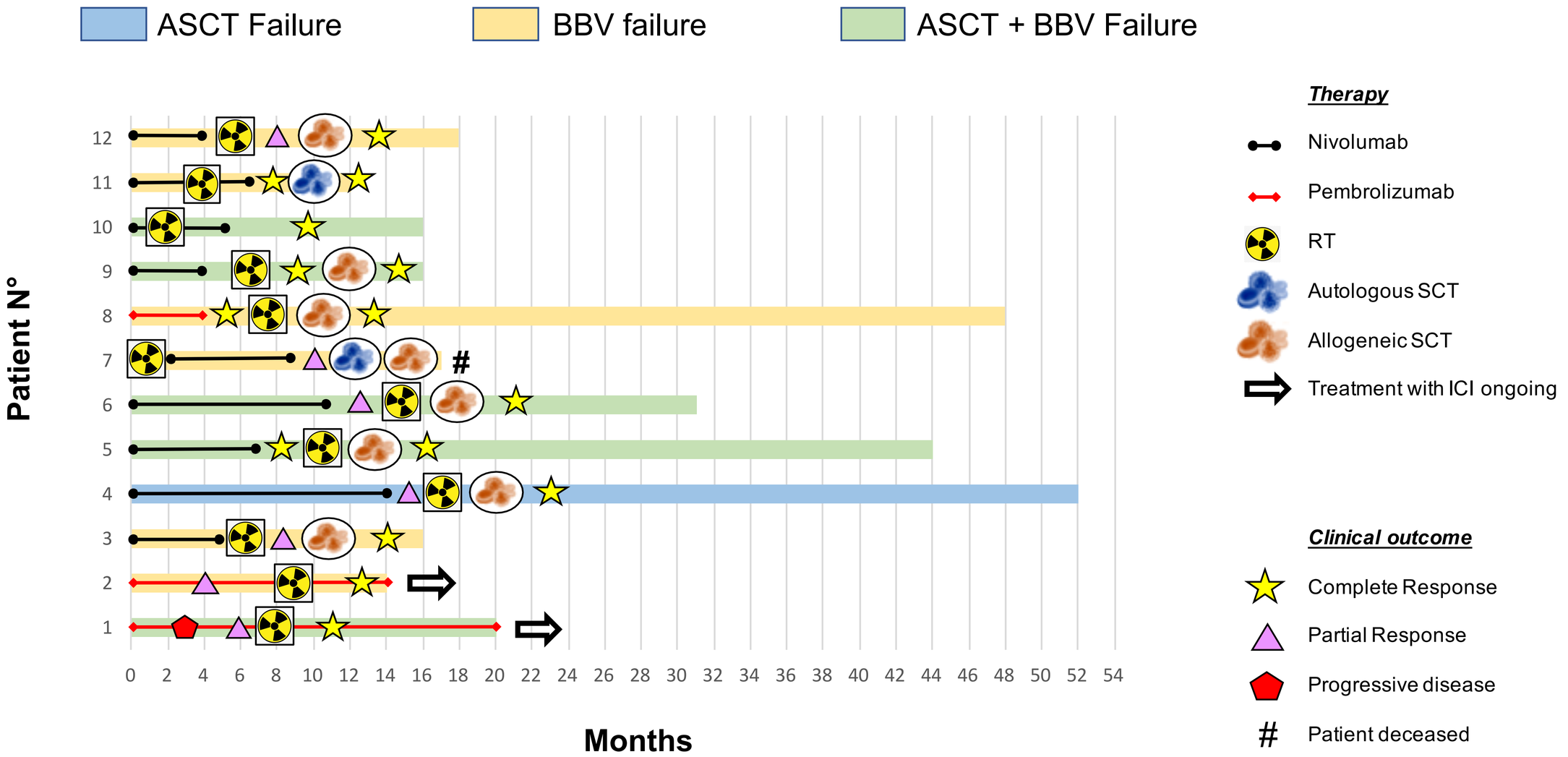
4out of 5 patients in remission received RT

Future perspectives: Combination of PD-1 inhibitors and RT
The potential effect of RT on the Tumor Micro Environment

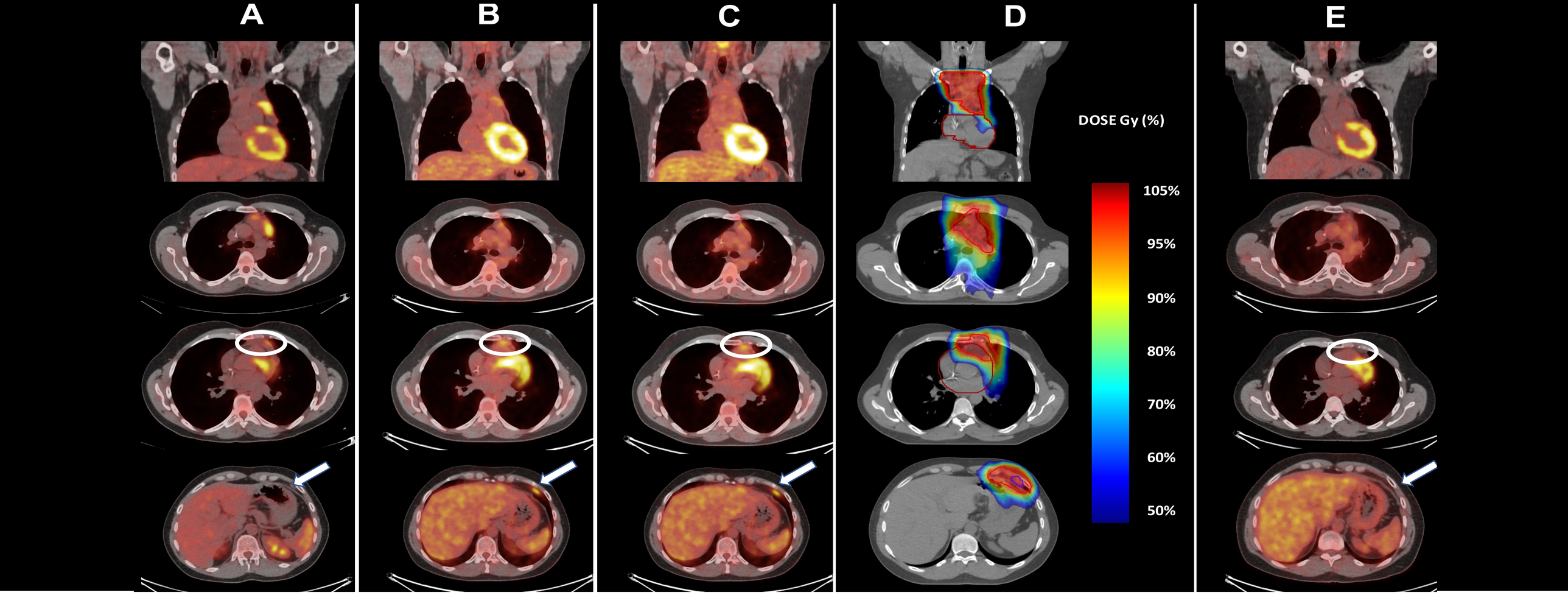


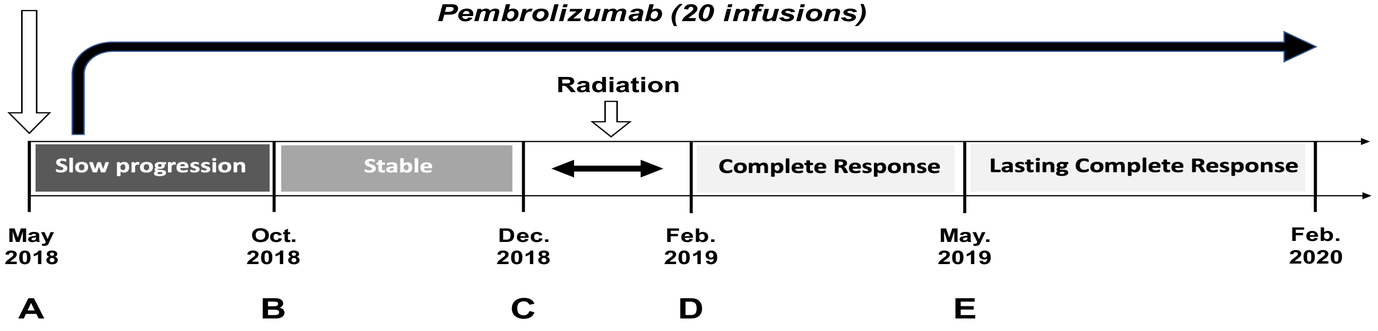
- RT can enhance TIL repertoir
- RT can lead to adaptive upregulation of PD-L1
- RT upregulates MHC expression and may increase neoantigen repertoire
- RT modifies tumour metabolism and may synergise with ICIs and metabolic inhibitors

De Maria & Formenti, Front Oncol 2012
Kordbacheh T et al, Annals Oncol 2018



CR rate: 58% **ORR: 100%**


A
B
C
D
E
DOSE Gy (%)
105%
95%
90%
80%
70%
60%
50%
May 2018
October 2018
December 2018
January 2019
May 2019


Pembrolizumab (20 infusions)
Radiation
Slow progression
Stable
Complete Response
Lasting Complete Response
May 2018
Oct. 2018
Dec. 2018
Feb. 2019
May. 2019
Feb. 2020
A
B
C
D
E

RT demand in the treatment of Hodgkin lymphoma

100
90
80
70
60
50
40
30
20
10
0

1970
1980
2000
2010
2020

RT as "single agent" has the potential to cure lymphomas

The combination of Chemotherapy with (less) RT, increases the chances for a lymphoma patient to get cured

RT Is the most effective single agent in the treatment of most type of lymphomas

RT Is the main cause of long term complication in lymphoma survivors and should be omitted whenever possible

Novel agents will more and more often replace RT, without compromising patients outcomes

Radiation has the potential to cure selected R/R patients in combination with novel agents

Let’s fight together against…

RADIOPHOBIA VULGARIS !