EMA-MSH Hematology Tutorial on Hodgkin Lymphoma

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PET-CT Imaging; cornerstone in Hodgkin lymphoma treatment

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Disclosure of Interest Statement

- 1) I or one of my co-authors hold a position as an employee, consultant, assessor or advisor for a pharmaceutical, device or biotechnology company. **If yes, please specify name/position/company:**

  No

- 2) I or one of my co-authors receive support from a pharmaceutical, device or biotechnology company. **If yes, please specify name/position/company/which project and whether support is in kind or monetary:**

 **Yes, Roche, Gilead, Karyopharm, BMS; in kind support**

- 3) I or one of my co-authors hold property rights/patents for (radio)pharmaceuticals, medical devices or medical consulting firms. **If yes, please specify name/position/company:**

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  No

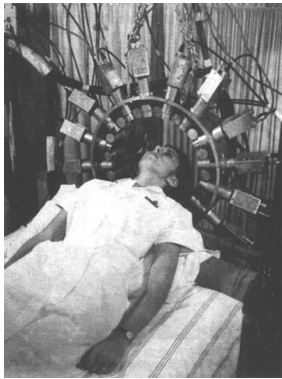# Treatment of Hodgkin lymphoma is very successful, but..
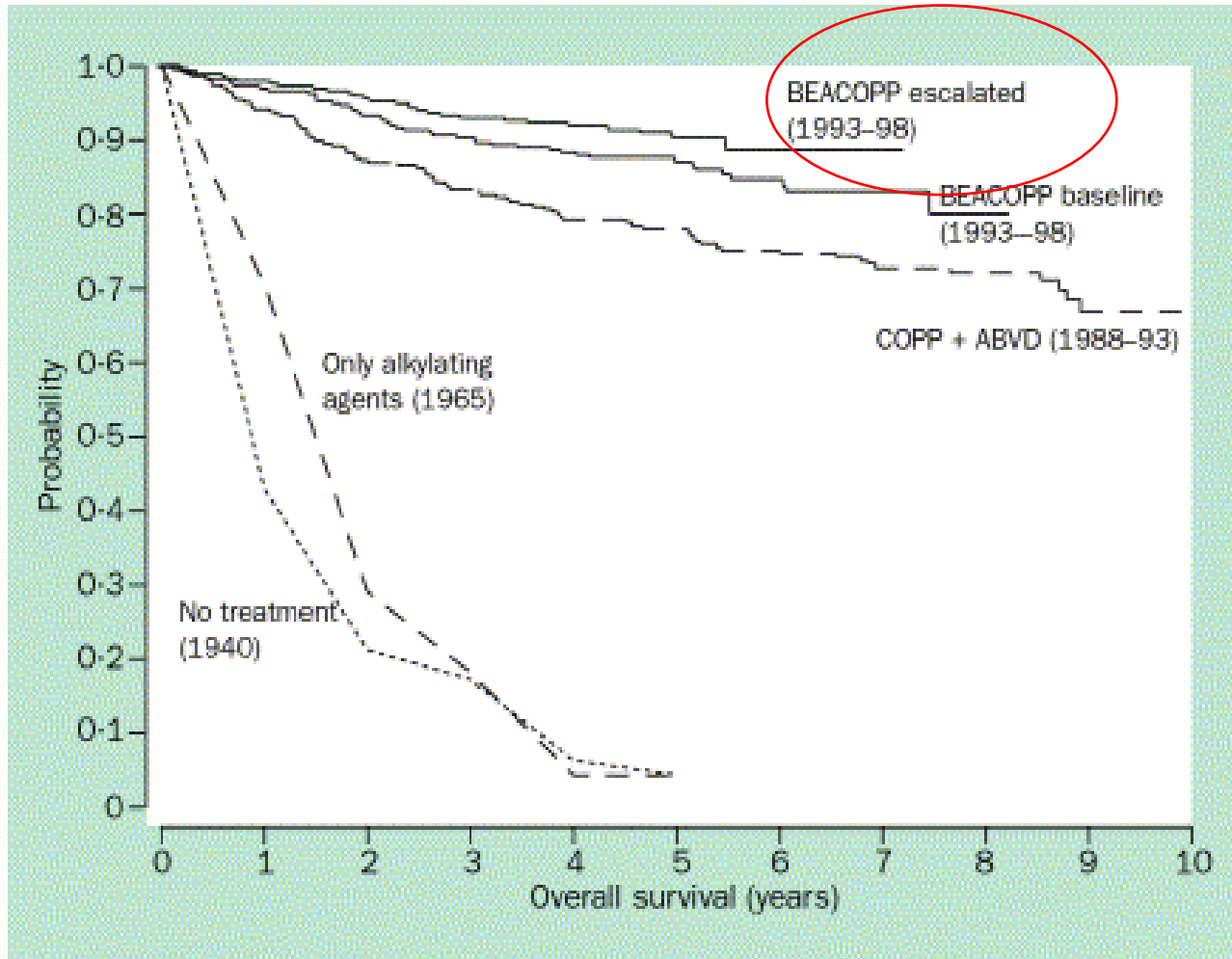
Overall Survival advanced stage Hodgkin lymfoom ~90% !

➢ Can it become even better?

➢ And with less toxicity and better quality of live afterwards?

➢ More personalized treatment ; PET-CT guided?!

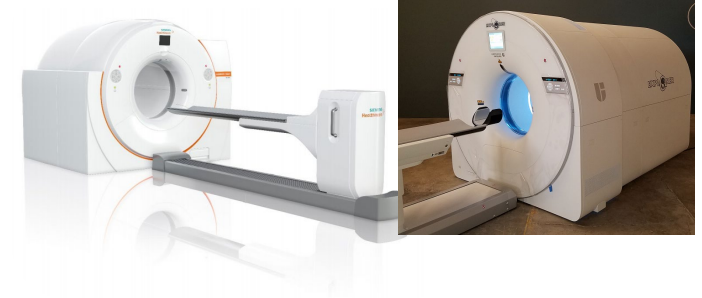# PET/CT technology over time – large steps
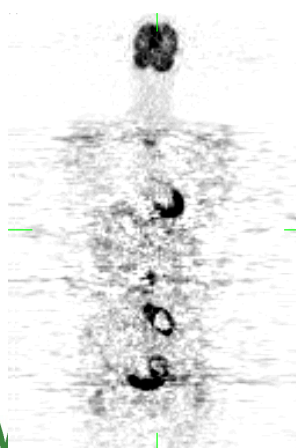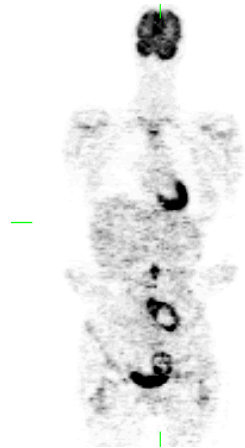
70's   90's   00's   2000's-10's   2020's
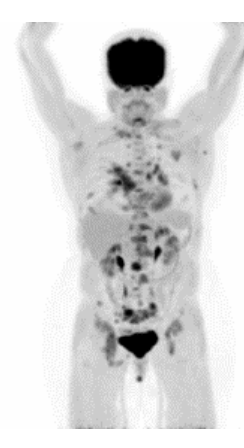

FBP   OSEM   TOF-OSEM   TOF-PSF-OSEM

FDG PET/CT in the management of Hodgkin lymphoma patients

FDG PET/CT plays a crucial role in

- staging

- restaging

- response assessment during treatment

- biopsy guidance

➢ PET/CT has become a cornerstone of patient care.

Barrington SF et al; J Clin Oncol 2014 Cheson BD et al; J Clin Oncol 2014

But how reliable is PET/CT for response assessment?

- Sensitivity is very high but residual disease less than 0.5 cm can be missed

- Specificity is not so very good; not every PET-positive abnormality is always residual Hodgkin lymphoma

  - So need for biopsy to confirm residual disease when possible

^{18}F-FDG PET/CT-scanning in Hodgkin lymphoma

- Scans should be reported using visual assessment

- Images scaled to a fixed SUV & colour table

- noting location of foci in nodal & extranodal sites

- distinguished from physiological uptake & other patterns of disease according to distribution and/or CT characteristics

Timing of PET-CT scans

At end of treatment

- 6-8 wks post chemotherapy ideally
  - minimum ≥3 wks

- ≥ 3 months after radiotherapy

During therapy ("interim-PET") at day just before next cycle

Hodgkin lymfoom stadium I-II

> Early stage *without* risk factors: 2-3x ABVD plus 20 Gy IS RT

> Early stage *with* risk factors

- 4 cycles of ABVD plus 30 Gy IS-RT

    - or HD17 schema:

- 2x BEACOPPesc plus 2x ABVD; **when PET negative**; no Radiotherapy !
  5yrs PFS 95.1 % vs 97.3% met RT

TABLE 1	Favourable prognosis stage I–II Hodgkin lymphoma
EORTC	**GHSG**
No large mediastinal adenopathy	No large mediastinal adenopathy
ESR <50 without B symptoms	ESR <50 without B symptoms
ESR <30 with B symptoms	ESR <30 with B symptoms
Age ≤50	No extranodal disease
1–3 lymph node sites involved	1–2 lymph node sites involved

Abbreviations: EORTC, European Organisation for the Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group.

TABLE 2	Unfavourable prognosis stage I–II Hodgkin lymphoma
EORTC	**GHSG**
Presence of one or more of the following:	Presence of one or more of the following:
Large mediastinal adenopathy	Large mediastinal adenopathy
ESR ≥50 without B symptoms	ESR ≥50 without B symptoms
ESR ≥30 with B symptoms	ESR ≥30 with B symptoms
Age >50	Extranodal disease
≥4 lymph node sites involved	≥3 lymph node sites involved

The GHSG considers stage IIB patients who have either large mediastinal adenopathy or extranodal disease as advanced stage and would not recommend treatment with early-stage unfavourable protocols.
Abbreviations: EORTC, European Organisation for the Research and Treatment of Cancer; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group.

HD17: Borchmann; Lancet Oncol 2021;22: 223-34

Interim-PET is reflecting chemo-sensitivity

Treatment of intermediate stage Hodgkin lymfoom: interim-PET guided

- Starting with ABVD: **PET2 +**　　　　-> escalation to 4 cycles of BEACOPPesc
　　　　　　　　　　　PET2 -　　　　-> de-escalation to 2 cycles of AVD plus 30 Gy

GHSG- HD 17 treatment scheme

- 2 cycles of BEACOPPesc plus 2 cycles op ABVD: **PET4 -**　　-> no radiotherapy

- Late effects of radiotherapy are serious; try to ommit mediastinal RT!

Interim-PET is reflecting chemo-sensitivity

Treatment of advanced Hodgkin lymfoom: interim-PET 2 guided

- Starting with ABVD: PET2 **+**   -> escalation to 4 cycles of BEACOPPesc

  PET2 **-**   de-escalation to 4 cycles of AVD (cf RATHL)

- Starting with BEACOPPesc: PET2 **-** -> de-escalation to 4 cycles instead of 6 cycles
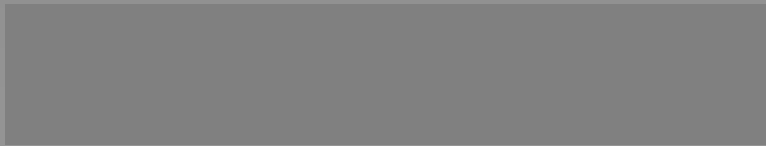
Visual assessment of FDG-PET-CT

Visual illusion:

Estimation of a focus depends on background activity

© Michel Meignan

➤ Definition of positive versus negative FDG-PET-CT?

FDG-uptake of involved lymph nodes related to mediatinal blood pool and liver uptake !

5 Point Scale (Deauville criteria)

DS 1. no uptake *in sites involved at baseline*

DS 2. uptake ≤ bloodpool *in sites involved at baseline*

DS 3. bloodpool < uptake ≤ liver[1] *in sites involved at baseline*

DS 4. moderately increased vs. liver *in sites involved at baseline*

DS 5. markedly[2] increased vs. liver *in sites involved at baseline*
        and/or new lesions estimated to represent lymphoma (!)

DSX[3] new uptake unlikely to be related to lymphoma

Interpretation of FDG PET-CT end of treatment

"Use visual assessment, with PET-CT images scaled to fixed SUV display and color table"

- Deauville scores 1 -3:   Complete Metabolic Response (CMR)

- Deauville score 4 of 5:   Partial Metabolic Response (PMR) or Stable disease
  /Progressive disease   → = treatment failure!

Barrington JCO 2014

Goal for treatment in 1st and 2nd line ?

- Aiming for Complete Metabolic Remission (=DS1-3: PET-negative) !
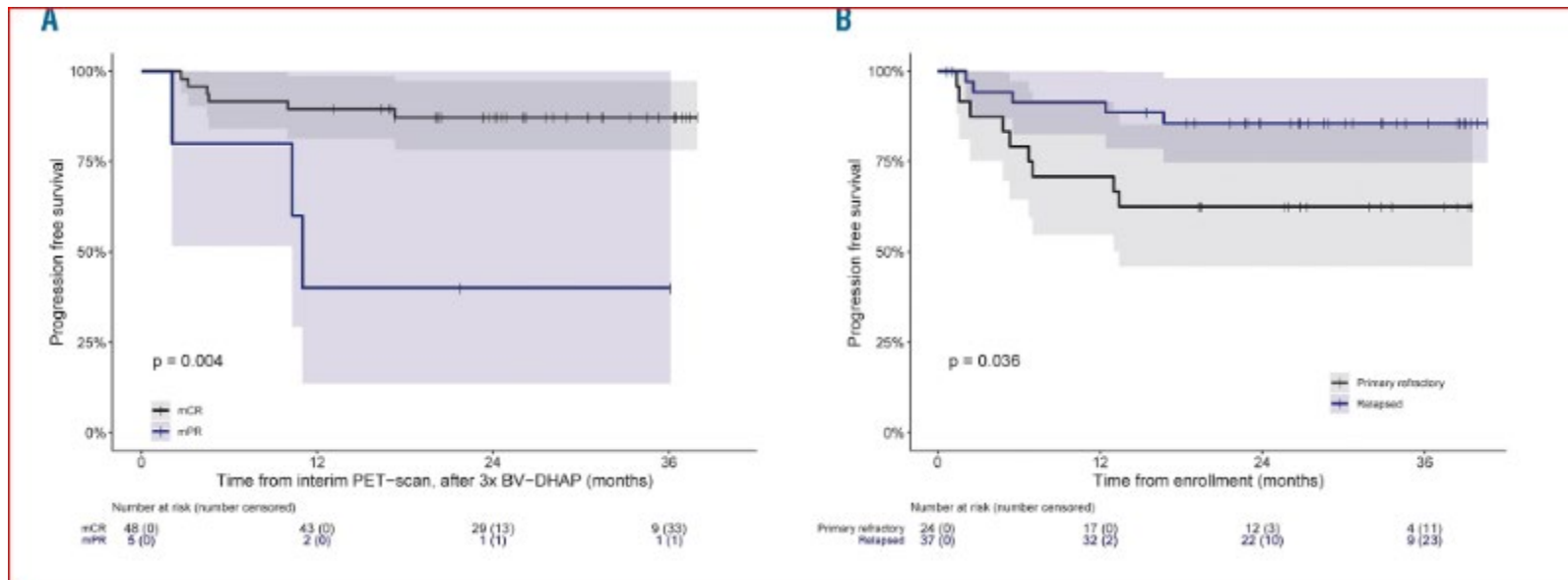
Transplant BraVe combining BV-DHAP before ASCT; Kersten MJ_ Haematologica 2021

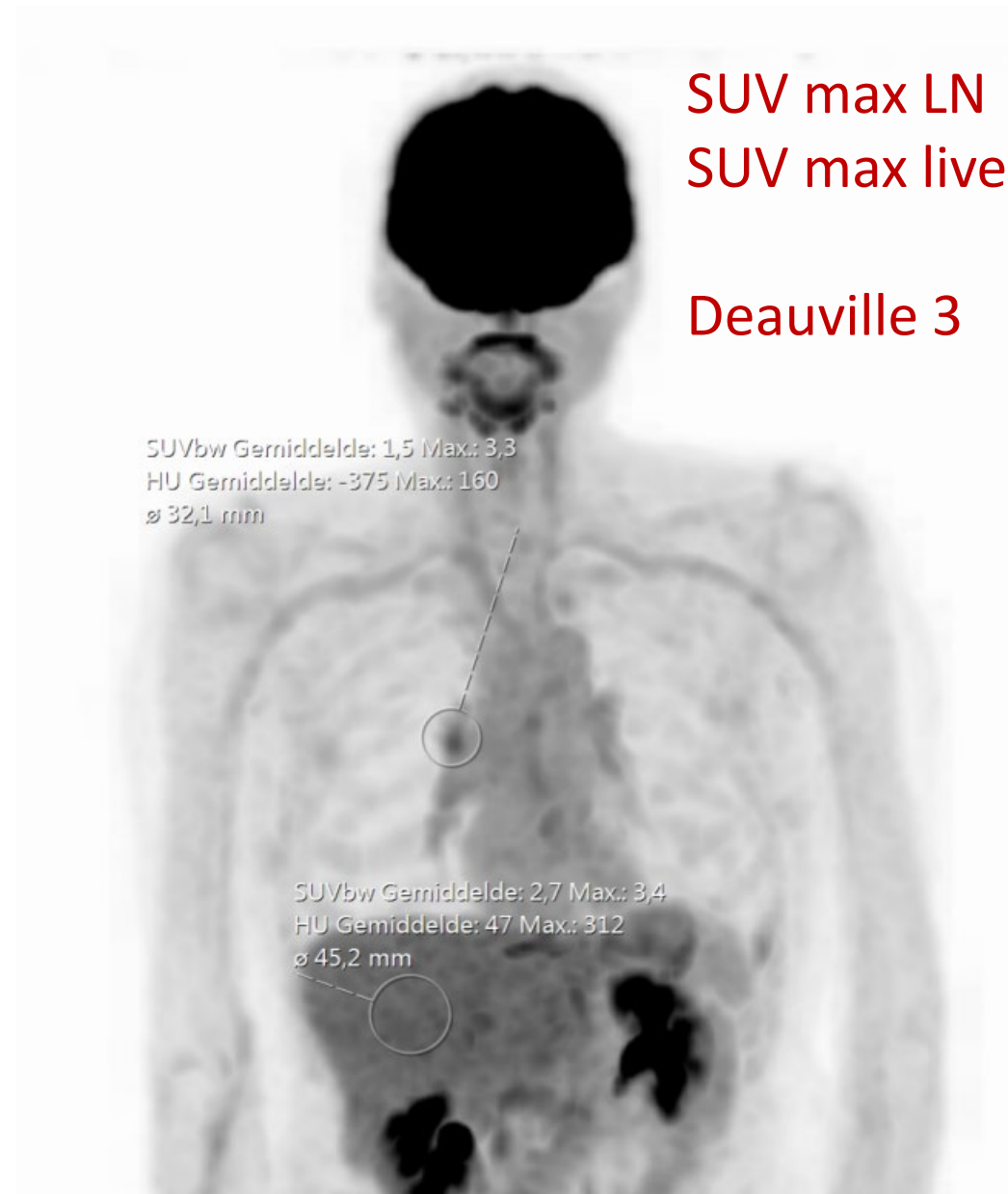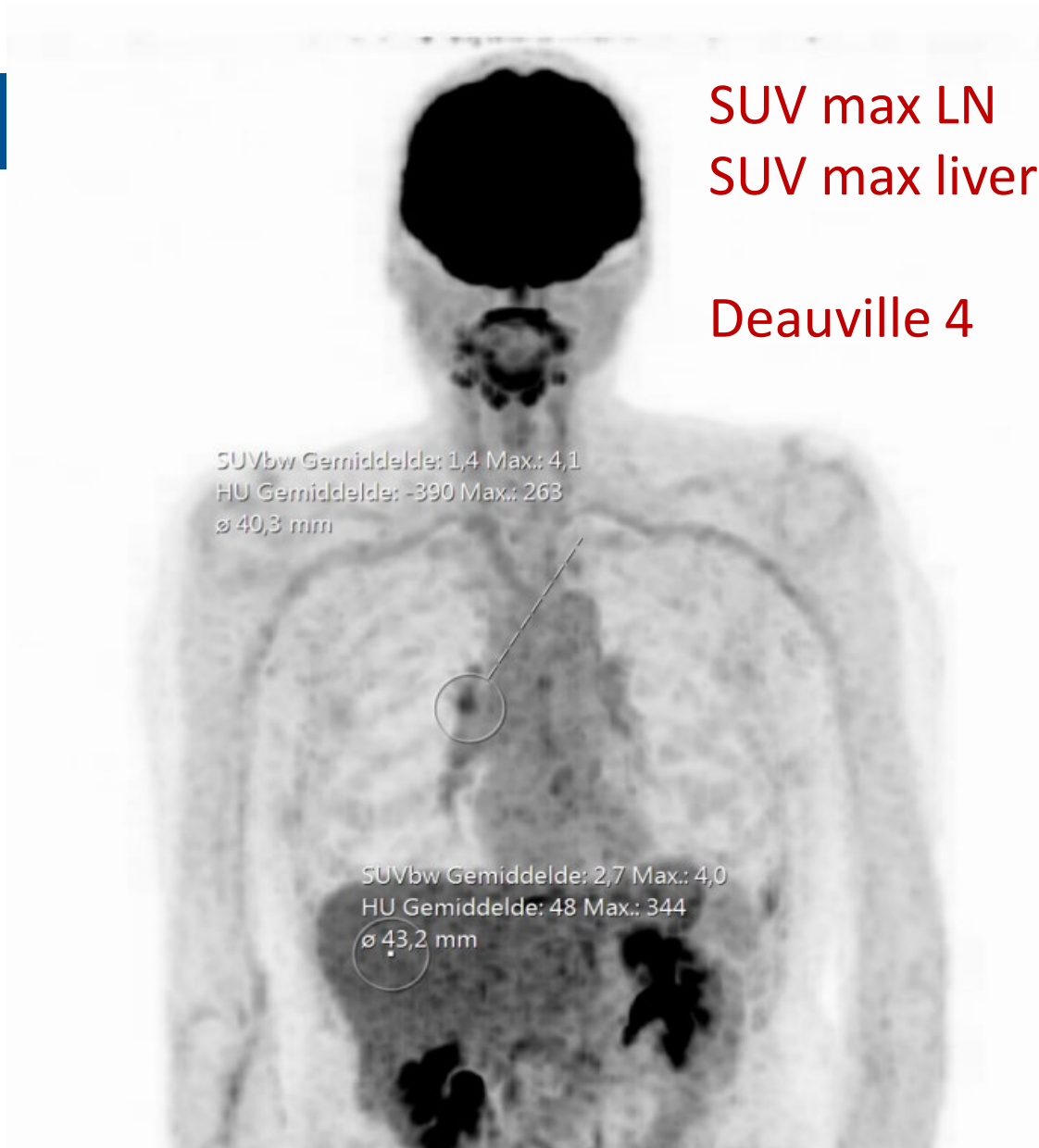# Deauville visual scoring versus quantification

Hodgkin lymphoma

Diagnosis

Interim-PET 2

End of Treatment

SUV max LN   4.1
SUV max liver 4.0

Deauville 4

SUVbw Gemiddelde: 1,4 Max.: 4,1
HU Gemiddelde: -390 Max.: 263
ø 40,3 mm

SUVbw Gemiddelde: 2,7 Max.: 4,0
HU Gemiddelde: 48 Max.: 344
ø 43,2 mm

SUV max LN   3.3
SUV max liver 3.5

Deauville 3

SUVbw Gemiddelde: 1,5 Max.: 3,3
HU Gemiddelde: -375 Max.: 160
ø 32,1 mm

SUVbw Gemiddelde: 2,7 Max.: 3,4
HU Gemiddelde: 47 Max.: 312
ø 45,2 mm
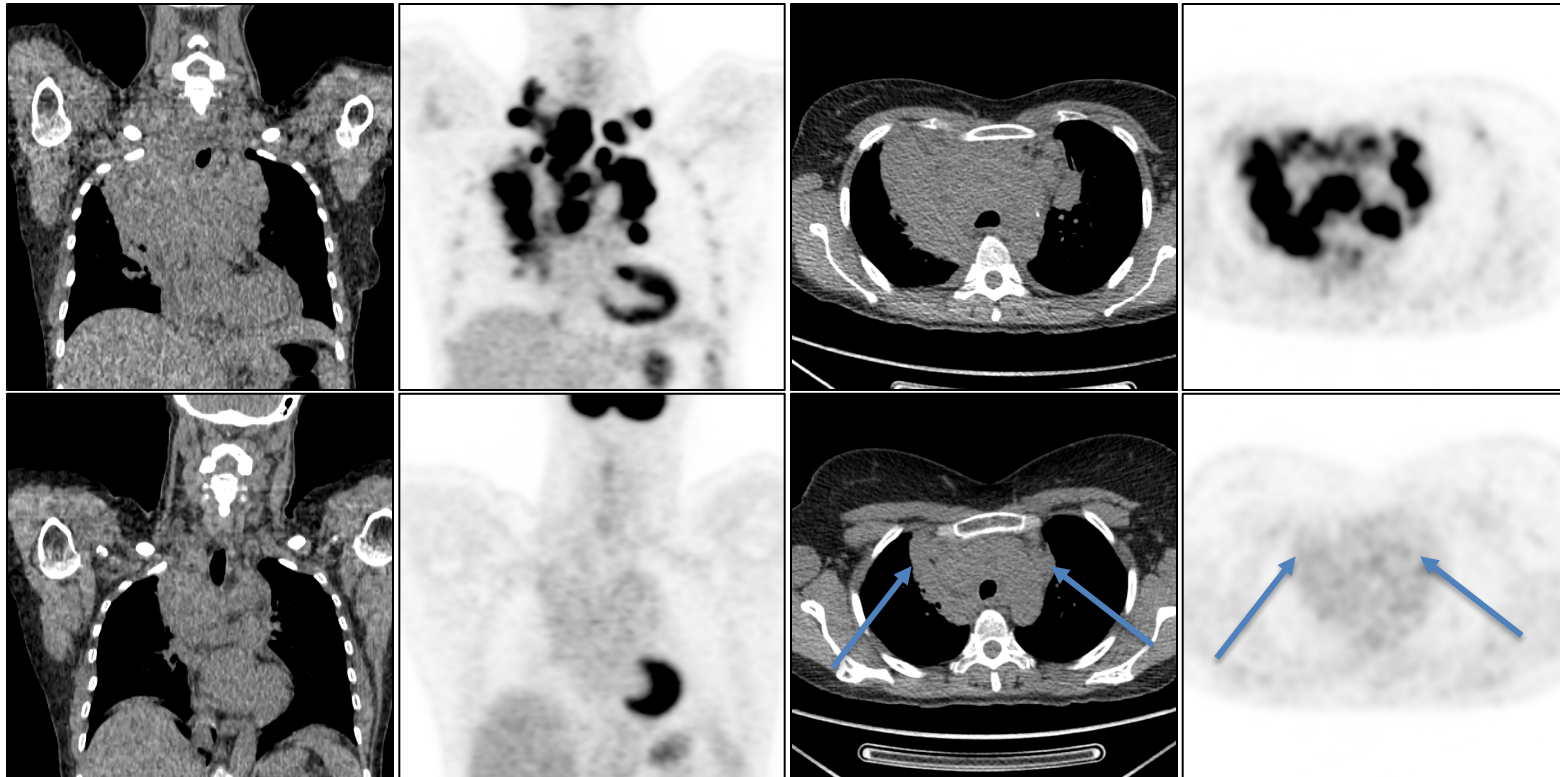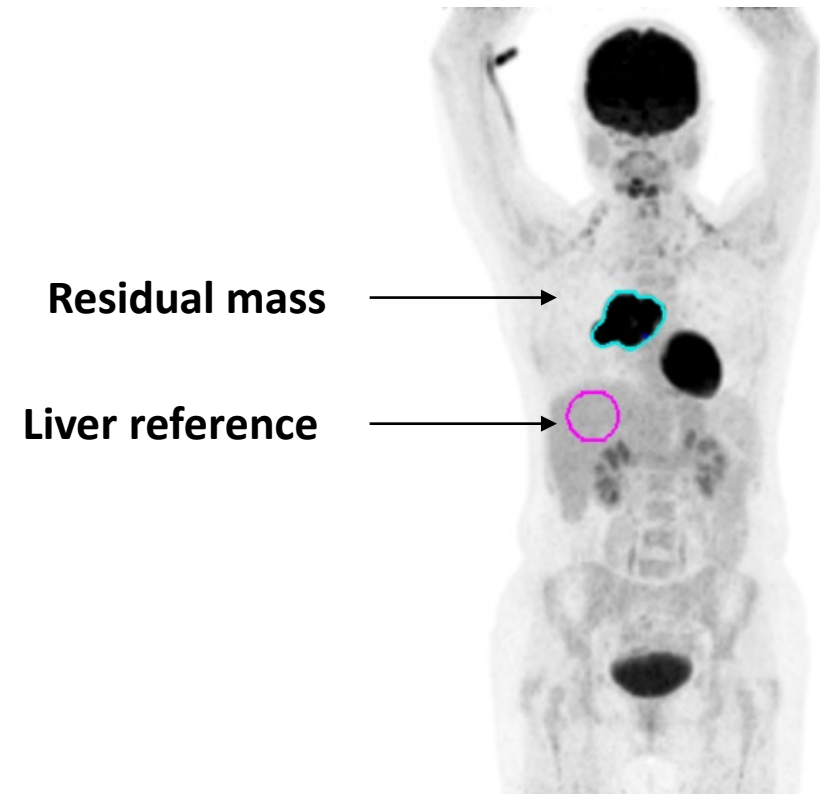
When 'interim' imaging is required, PET-CT is recommended as the best imaging modality to assess early response

Semiquantitative or visual assessment?

- **Semi-quantitative assessment is required to confirm the visual impression of uptake for response assessment using the Deauville Criteria (DC) (type1).**

Residual mass →

Liver reference →
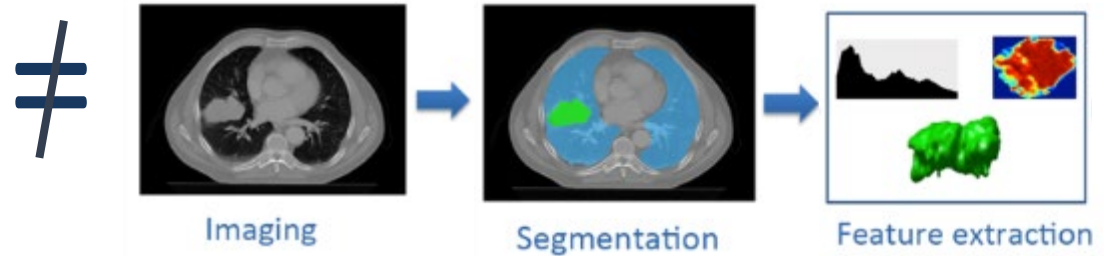
| Semiquantitative or visual assessment?

- Semi-quantitative assessment takes account of reference background
- Less user dependent and can be semi-automated
- Normalisation to reference reduces variability between centres
- Semi-quantitative assessment for D4 and D5 in Lugano 2014
- Allows for development of continuous scales with potential to refine optimal thresholds

What is Radiomics?

Human eye, subjective

Automated, more sensitive, quantitative
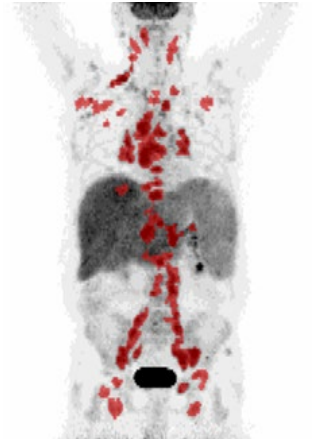

$\neq$

Imaging → Segmentation → Feature extraction

"Radiomics is the future of diagnostic imaging!"

$\neq$

Same difference

*Lambin P *et al*. Eur J Cancer. 2012; Aerts HJ *et al*. Nat Commun. 2014; Leijenaar et al. Acta Oncol *2018*

Radiomics

- Radiomics is a proces to analyse PET-Images in digital data

- Introduction of quantitative evaluation of (baseline) PET/CT images provided new functional indices such as metabolic tumor volume (MTV)

- Radiomics analysis has allowed the extraction of a wide variety of quantitative data that reflect **biological characteristics of disease** providing additional promising prognostic biomarkers in lymphomas.

- Use of Artificial Intelligence to analyse PET-data and predict outcome !
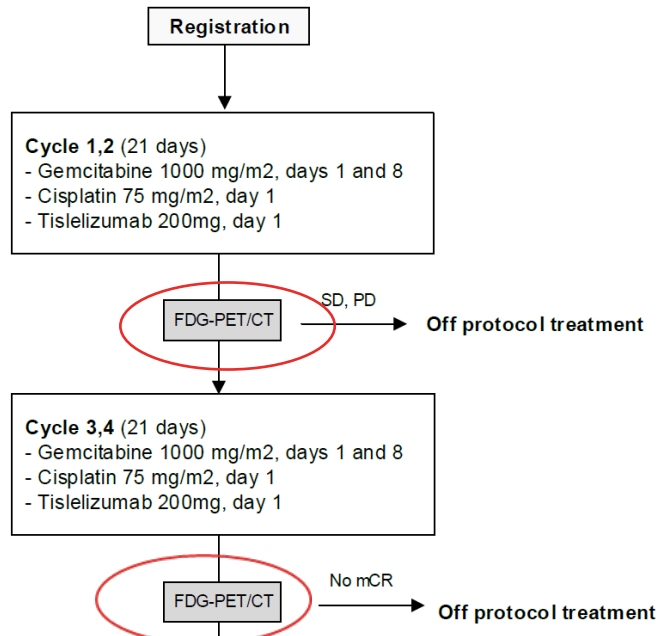
New trials in HL using check point inhibitors

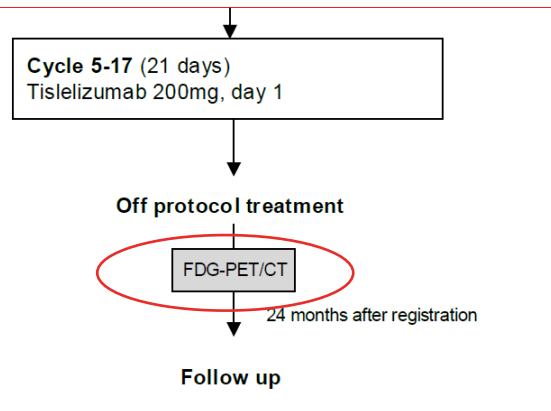HOVON 164 HL   Version 2.0, 22 MAR 2023

Tislelizumab plus Gemcitabine and Cisplatin for Relapsed or Refractory Hodgkin Lymphoma followed by Tislelizumab Consolidation in Patients in Metabolic Complete Remission (TIGERR-HL). An open label phase II trial.

Patients with classical Hodgkin lymphoma, 18-70 years of age, refractory to or in first relapse after first line multi-agent classical chemotherapy.

Registration

Cycle 1,2 (21 days)
- Gemcitabine 1000 mg/m2, days 1 and 8
- Cisplatin 75 mg/m2, day 1
- Tislelizumab 200mg, day 1

FDG-PET/CT → SD, PD → **Off protocol treatment**

Cycle 3,4 (21 days)
- Gemcitabine 1000 mg/m2, days 1 and 8
- Cisplatin 75 mg/m2, day 1
- Tislelizumab 200mg, day 1

FDG-PET/CT → No mCR → **Off protocol treatment**

Cycle 5-17 (21 days)
Tislelizumab 200mg, day 1

Off protocol treatment

FDG-PET/CT

24 months after registration

Follow up

Humanized, immunoglobulin G4 (IgG4)-variant
Binding to extracelluar domain of human PD-1

Phase-II single arm
Prim objective: 2yrsPFS

N=75 pts

- Omitting ASCT
- Outpatient treatment

Duration 12 mo

Checkpoint toxicity and efficay ?

Personalized medicine

Each patient PET-CT guided treatment!

➢ No over-treatment (toxicity)   and no undertreatment (risk for relapse)

- PET-CT assessment nowadays visual but will become quantitative

- Development of ct-DNA and TARC monitoring (liquid biopsies)

Conclusie:

Navigating increasingly individualised Hodgkin lymphoma treatments to optimally balance risks and benefits

Paul J. Bröckelmann[1,2,3,4] | Peter Borchmann[1,2]

Br J Haematol 2022;
Commentary on Guideline for the first-line management of Classical Hodgkin Lymphoma –A British Society for Haematology guideline. Br J Haematol. 2022;197:558-572.