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REGION

Role of PET in staging and treatment of lymphoma

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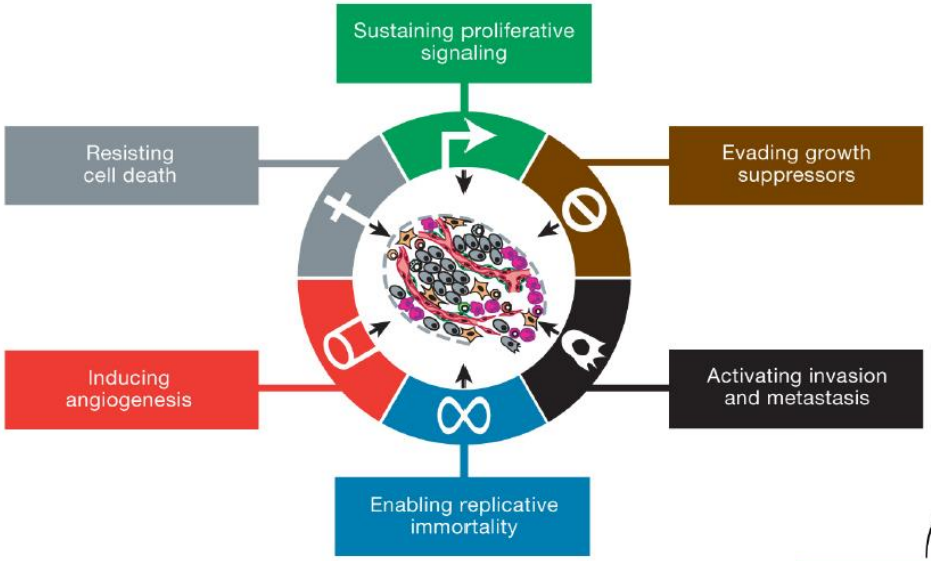
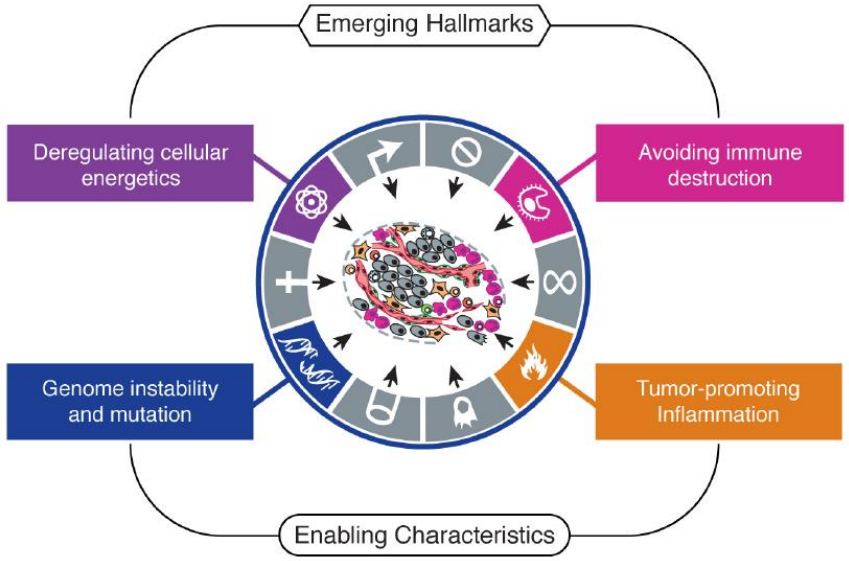
GLOBAL EXCELLENCE IN HEALTH

The hallmarks of cancer

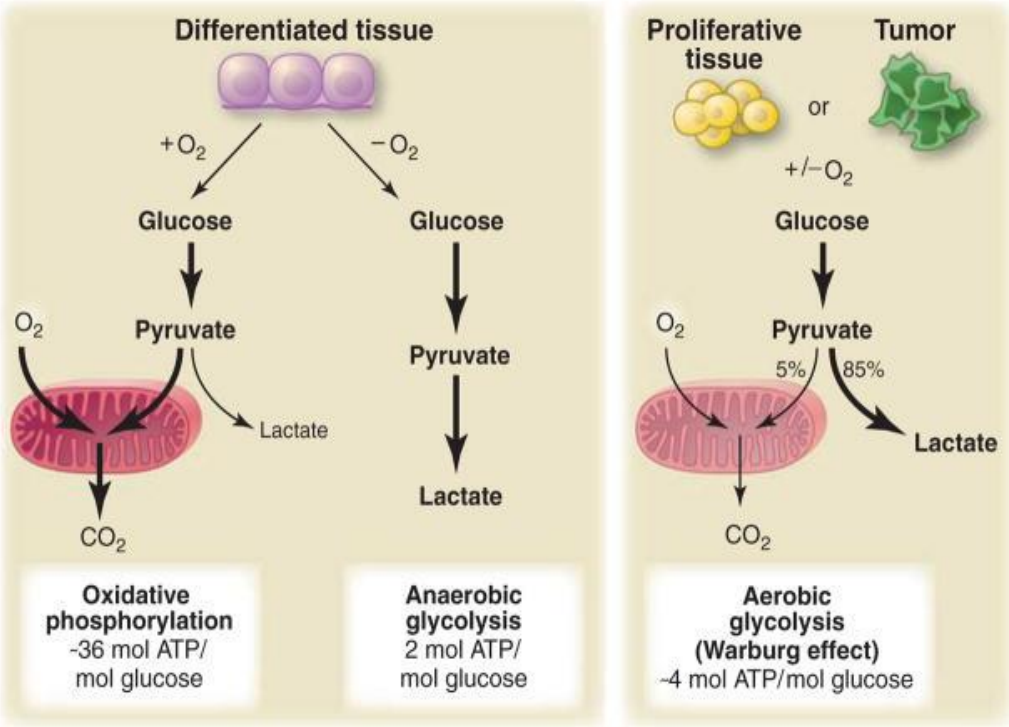
Hanahan & Weinberg, Cell 2000 + 2011



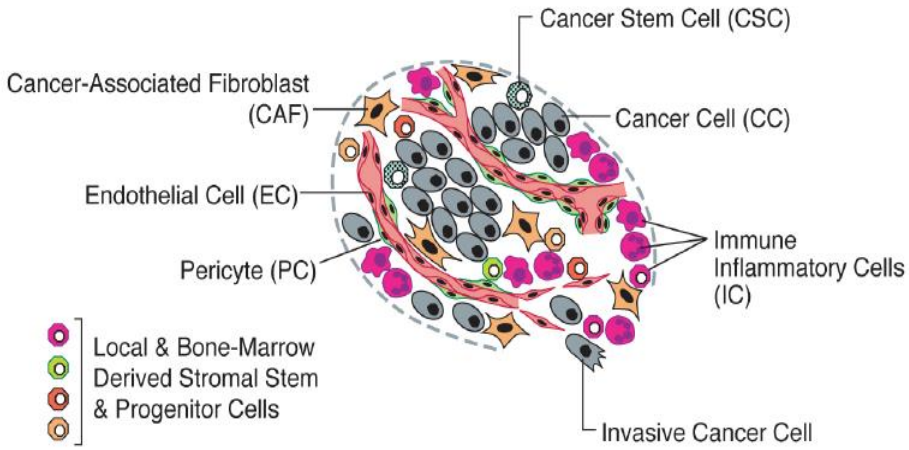


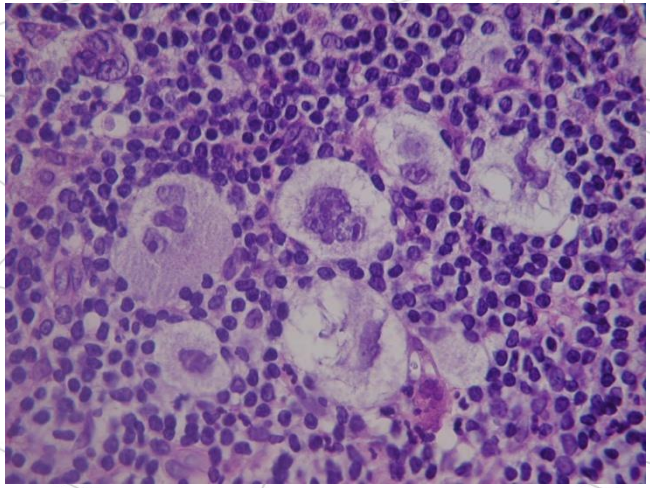
Deregulating cellular energetics

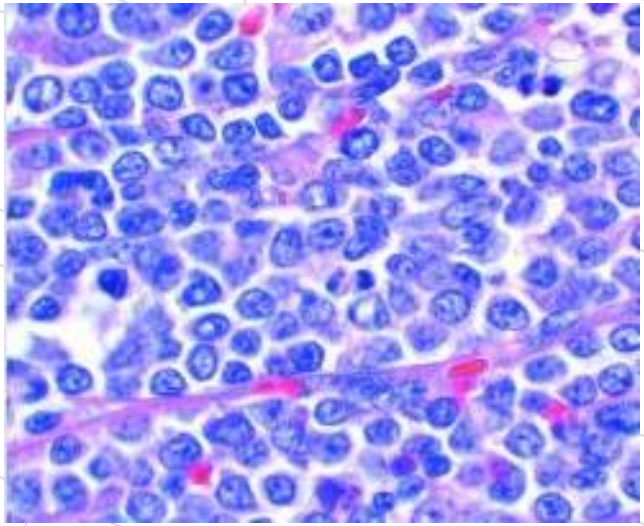
- Cancer cells can limit their energy metabolism largely to glycolysis, even in the presence of oxygen (”aerobic glycolysis”)
- Rapidly growing tumours have glycolytic rates up to 200 x that of the normal tissues
- Lower efficiency of energy production, but upregulation of glucose transporters (GLUT1)
- Visualized by FDG-PET



Tumour microenvironment







The ”reverse Warburg effect”:
Induced by the cancer cells by oxidative stress in adjacent stromal cells, promoting aerobic glycolysis under normoxic conditions

FDG-PET for staging of lymphomas

FDG-PET/CT should be used for staging in clinical practice and clinical trials, but it is not routinely recommended in lymphomas with low FDG avidity

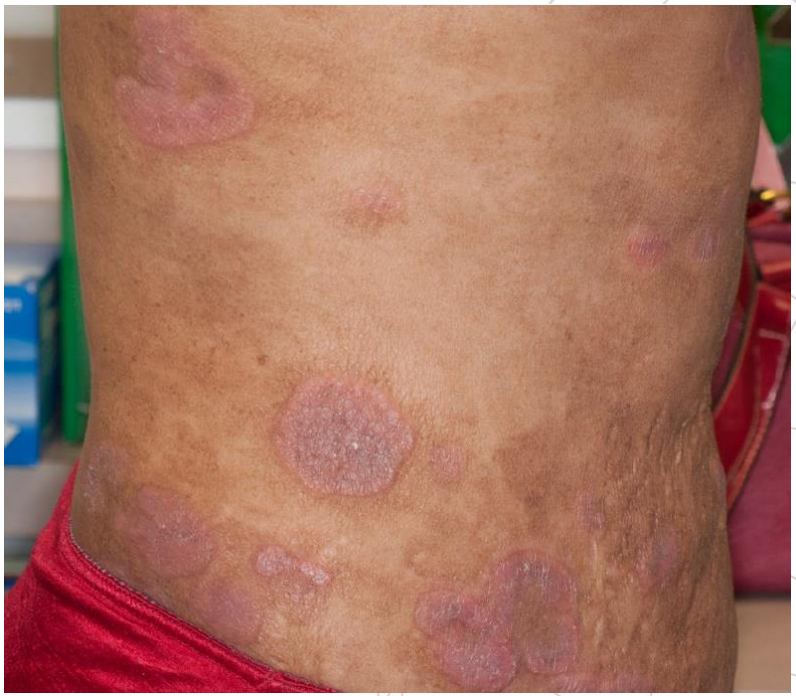
Barrington S et al. JCO 2014; 32: 3048-58

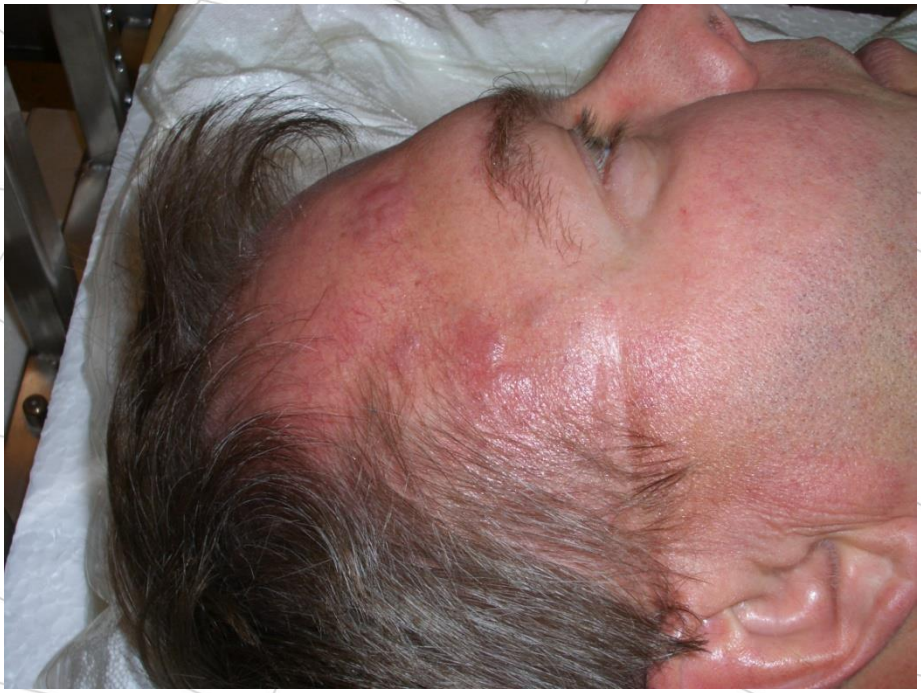
Table 2. FDG Avidity According to WHO Classification

Histology	No. of Patients	FDG Avid (%)
HL	489	97-100
DLBCL	446	97-100
FL	622	91-100
Mantle-cell lymphoma	83	100
Burkitt's lymphoma	24	100
Marginal zone lymphoma, nodal	14	100
Lymphoblastic lymphoma	6	100
Anaplastic large T-cell lymphoma	37	94-100*
NK/T-cell lymphoma	80	83-100
Angioimmunoblastic T-cell lymphoma	31	78-100
Peripheral T-cell lymphoma	93	86-98
MALT marginal zone lymphoma	227	54-81
Small lymphocytic lymphoma	49	47-83
Enteropathy-type T-cell lymphoma	20	67-100
Marginal zone lymphoma, splenic	13	53-67
Marginal zone lymphoma, unspecified	12	67
Mycosis fungoides	24	83-100
Sezary syndrome	8	100†
Primary cutaneous anaplastic large T-cell lymphoma	14	40-60
Lymphomatoid papulosis	2	50
Subcutaneous panniculitis-like T-cell lymphoma	7	71
Cutaneous B-cell lymphoma	2	0

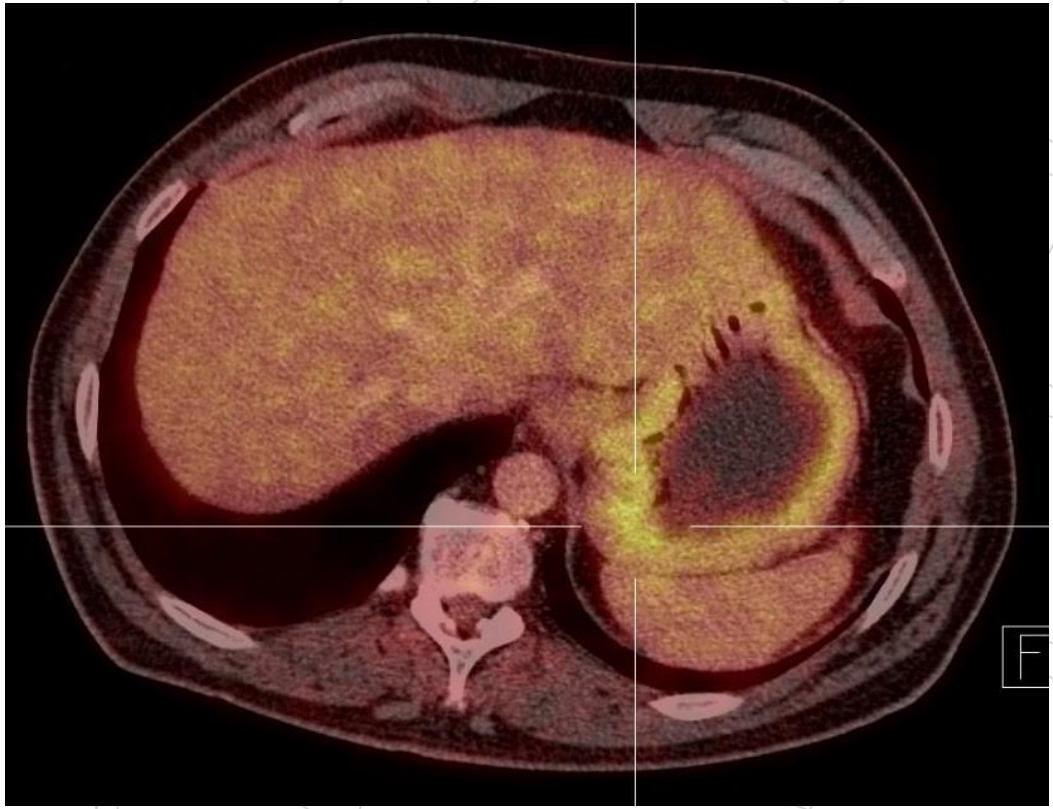
Different extranodal sites may show more or less ”avidity”, caused primarily by diffuse and low volume disease

- Cutaneous lymphomas often do not show up in cutaneous sites



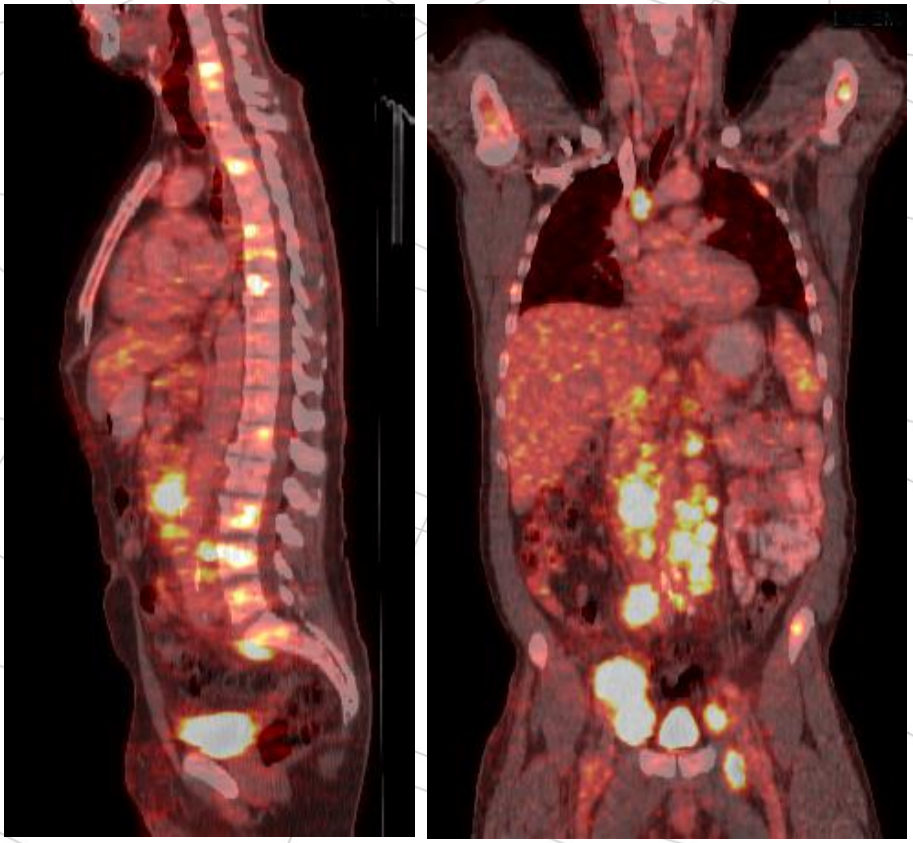


- Indolent lymphomas in the wall of hollow organs often do not show up



Bone marrow involvement

- PET is highly sensitive for focal involvement, and obviates the need for biopsy in HL (El-Galaly T. JCO 2012; 30: 4508-14)
- PET is less sensitive for diffuse involvement (typically in indolent lymphomas)

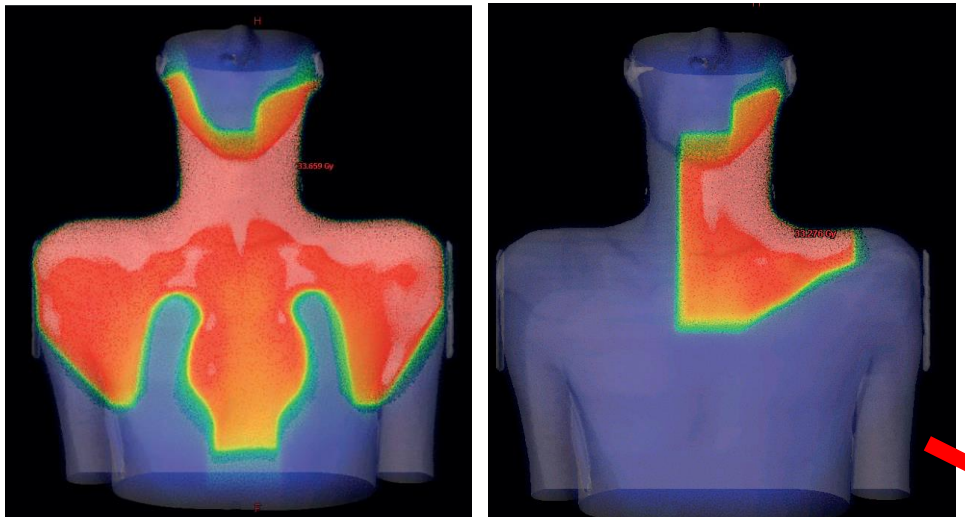


FDG-PET improves the accuracy of staging (i.e. anatomic definition of extent and location)

- Change in stage in 10-30 % of patients, most often upstaging, and may lead to changes i management strategy
- Ensures that fewer patients are undertreated or overtreated
- Particularly important if radiotherapy is an option (localized vs. disseminated disease)
- Ensures inclusion of all involved sites if radiotherapy is given
- May identify optimal biopsy site if discordant histology or transformation is suspected
- Facilitates response evaluation with PET after therapy

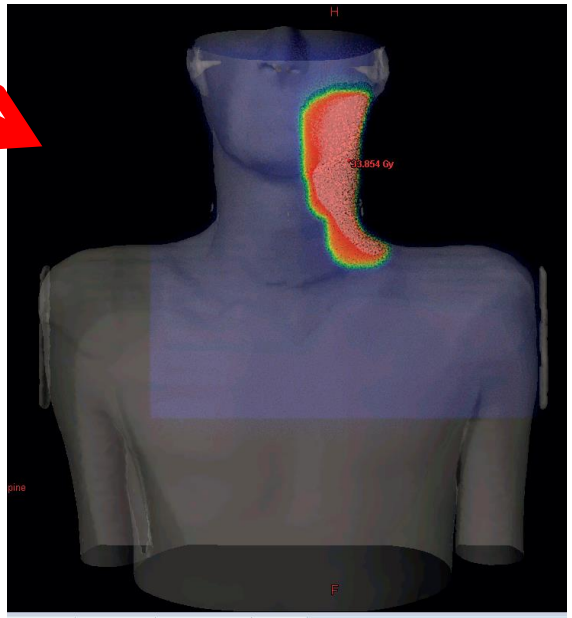
FDG-PET for early prediction and treatment modification

Mantle field (EFRT) or involved field (IFRT)



Based on:
- 2 D planning
- Regions
- Bony landmarks defining fields
- ”Fixed” margins

Involved site (ISRT) or involved node (INRT)

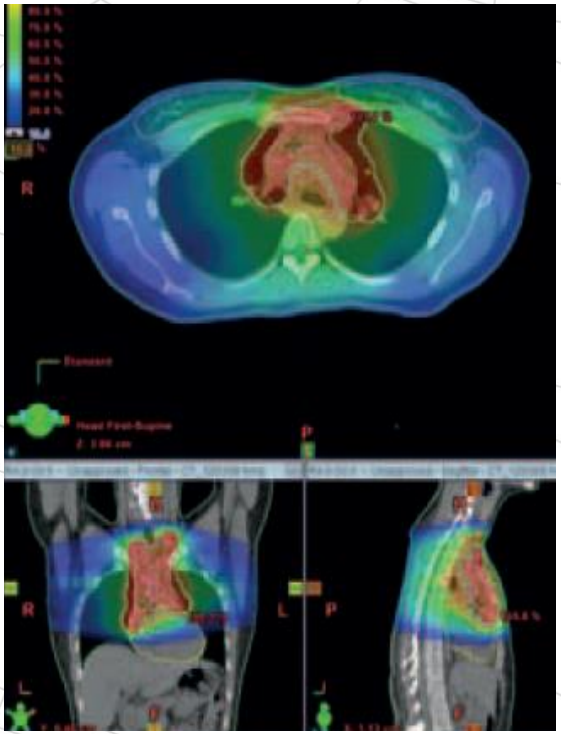


Based on:
- 3 D planning
- Actual lymphoma involvement
- Contouring of volumes (GTV, CTV, PTV)
- Margins (GTV→CTV) based on clinical judgement and (CTV→PTV) based on internal and setup uncertainties

Highly conformal radiotherapy

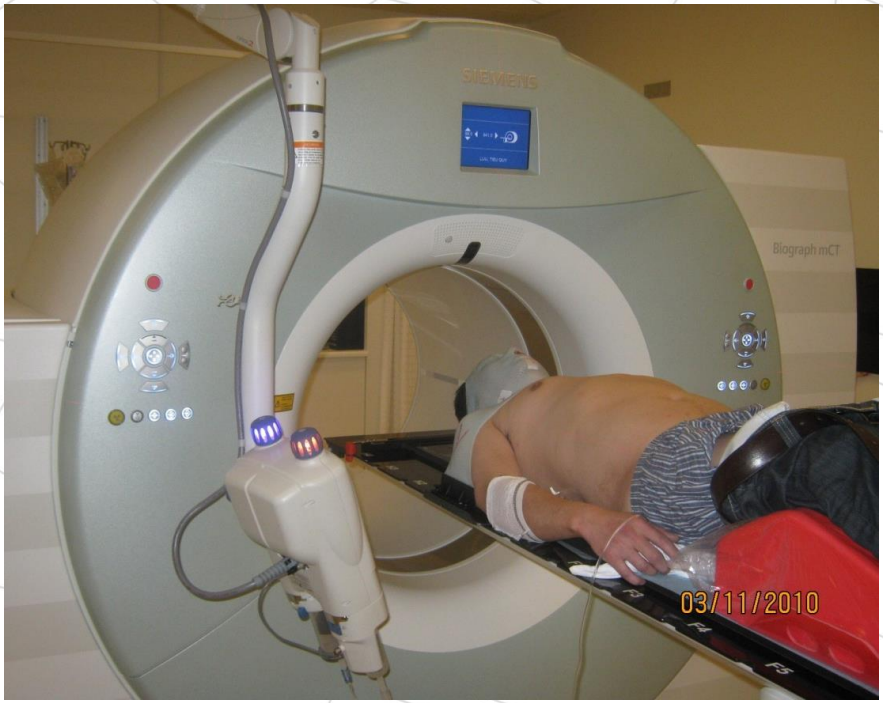
(3D conformal, intensity modulated radiotherapy IMRT, volumetric arc therapy VMAT)

- High dose volume conforms almost precisely to the target we contour
- Very steep dose gradients around the target
- Precise target definition is crucial
- If we contour too small we will miss lymphoma and jeopardize the patient's chance of cure
- If we contour too large unnecessary radiation will be given to normal structures



PET/CT improves accuracy of staging and target volume definition in FDG-avid lymphomas

- Pre-chemo PET/CT acquired with the patient in treatment position on a flat table top and with involvement of radiation oncology
- Post-chemo planning CT
- Diagnostic i.v. contrast enhanced CT is essential (PET/CT can be done with contrast with no interference with the attenuation correction)
- Oral contrast for abdominal and pelvic involvement
- 4D-CT imaging helpful for determining ITV



PET changes target volume in 30-60 % of patients compared to CT

- Terezakis et al. IJROBP 2014; 89: 376-83
- 89 pts. With PET+ lymphoma
- Treatment volume was contoured on CT and on PET/CT by 3 radiation oncologists and 3 nuclear medicine physicians

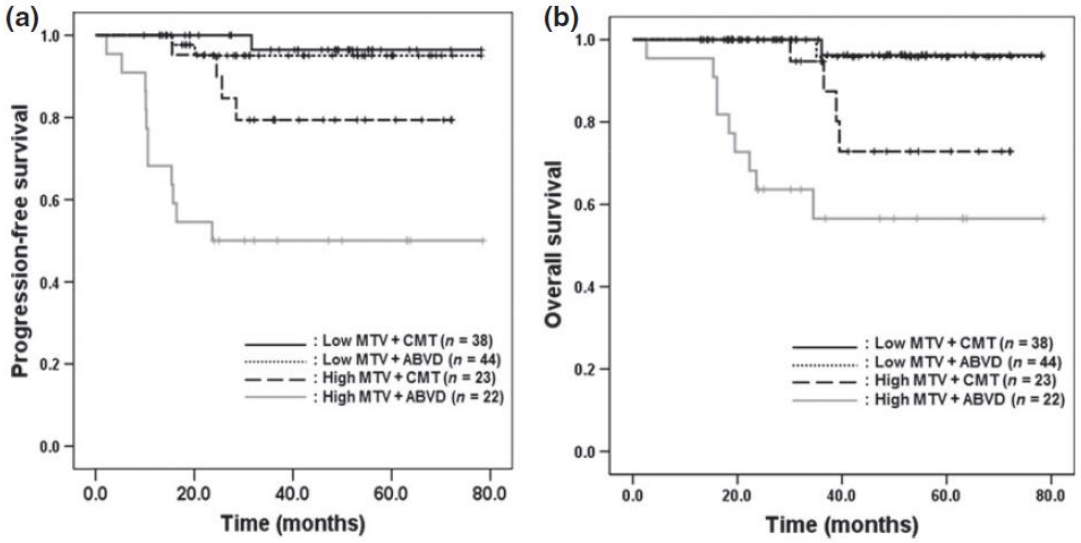
Table 2 PET/CT GTV alteration relative to CT-based treatment planning

GTV-RO		GTV-NMP	
Change	n	Change	n
Increase in GTV			
>5%-10%	5	>5%-10%	2
>10%-20%	12	>10%-20%	5
>20%-50%	17	>20%-50%	16
>50%	4	>50%	4
Total increase	38	Total increase	27
Decrease in GTV			
>5%-10%	6	>5%-10%	5
>10%-20%	7	>10%-20%	7
>20%-50%	12	>20%-50%	10
>50%	16	>50%	30
Total decrease	41	Total decrease	52
Change in GTV			
±5%	10	±5%	10

Abbreviations: CT = computed tomography; GTV = gross tumor volume; NMP = nuclear medicine physicians; PET = positron emission tomography; RO = radiation oncologists.

PET is prognostic

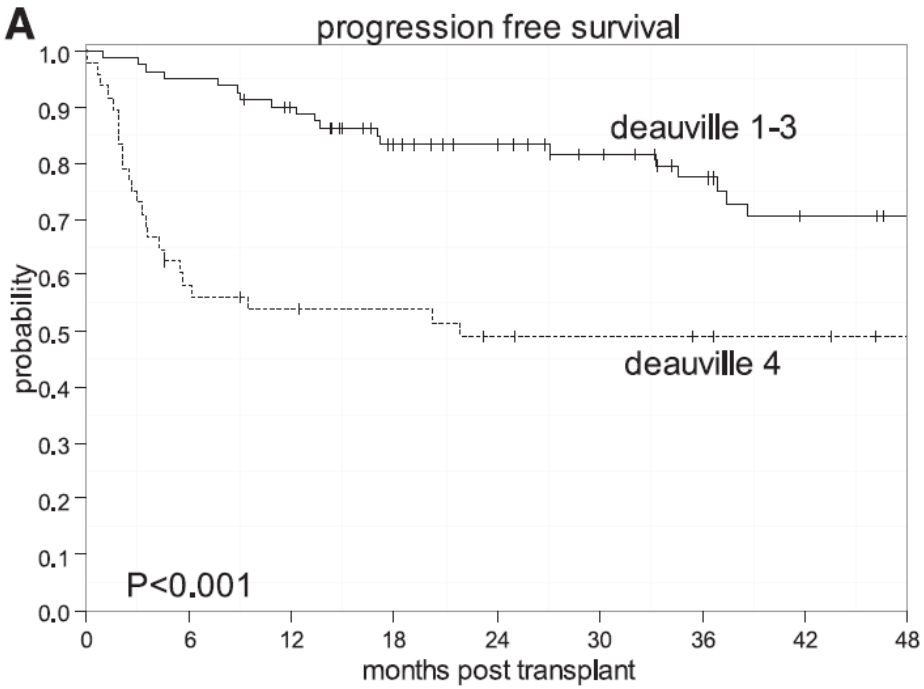
- An early interim PET-scan (typically after 2 cycles of chemotherapy) is highly predictive of outcome in most lymphoma types
- Prognostication up front before any therapy would be even better
- It has been demonstrated that the total tumour burden is the most important prognostic factor in HL in the pre-PET era (Specht L, Gobbi PG)
- Total tumour burden on CT is highly correlated with metabolic tumour volume (MTV) on PET/CT, which could be generated semi-automatically from PET images (Meignan, Berkowitz)
- MTV is prognostic in several lymphoma types (Song M-K. Cancer Sci 2013; 104: 1656-61)
- ΔSUV is being explored

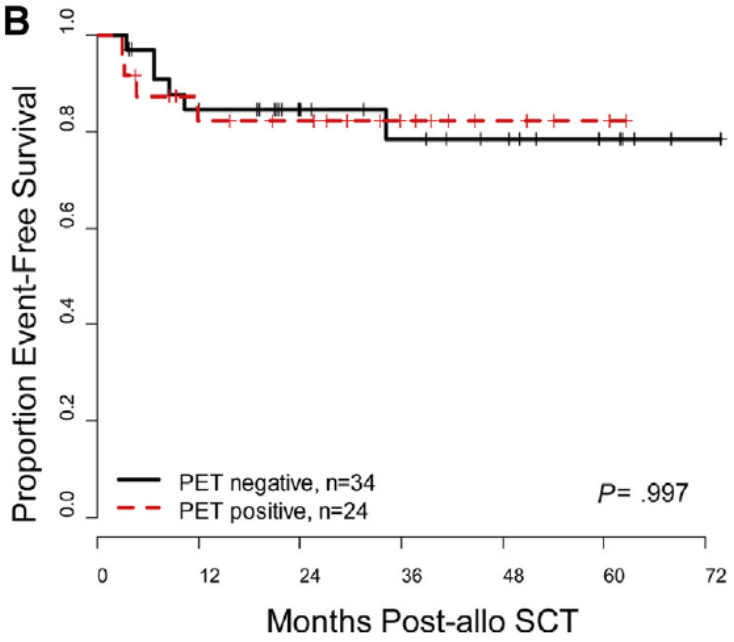


Is PET predictive?
Should treatment be modified according to iPET?

- Up till now no randomized evidence to support it
- Should not be done outside clinical trials
- In the EORTC H10 trial the final analysis of the patients who were PET+ after 2 cycles of ABVD has shown improved outcome with switch to BEACOPPesc
  (Raemaekers J, presented in Lugano 2013)

PET is prognostic pre-HDT-ASCT (left) but not pre-NMA-allo-SCT (right)





Sauter CS et al. Blood 2015; 125: 2579-81

Sauter CS et al. Biol Blood Marrow Transplant 2014; 20: 881-4

FDG-PET for response evaluation

Response evaluation

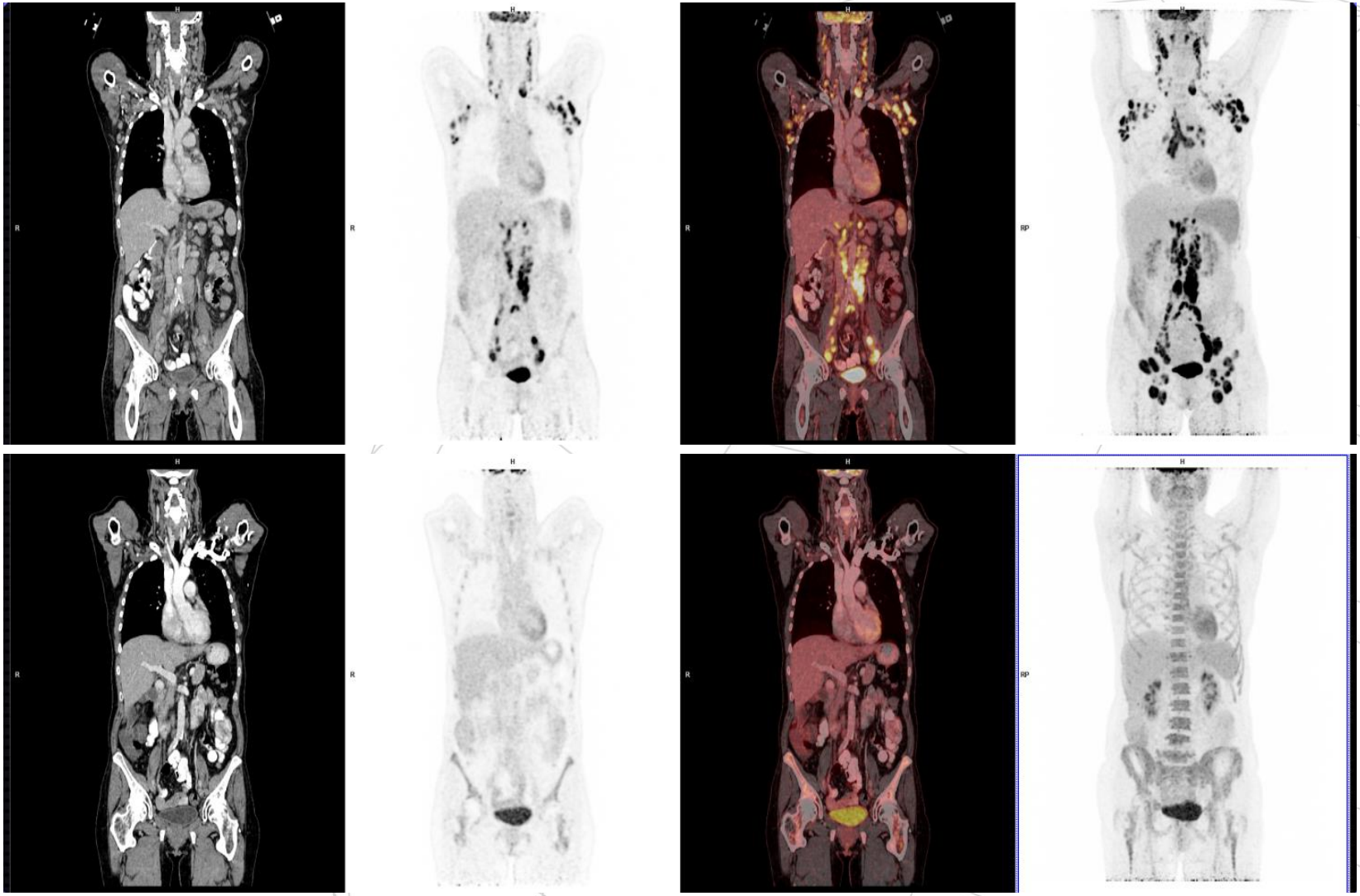
Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification

Bruce D. Cheson, Richard I. Fisher, Sally F. Barrington, Franco Cavalli, Lawrence H. Schwartz, Emanuele Zucca, and T. Andrew Lister

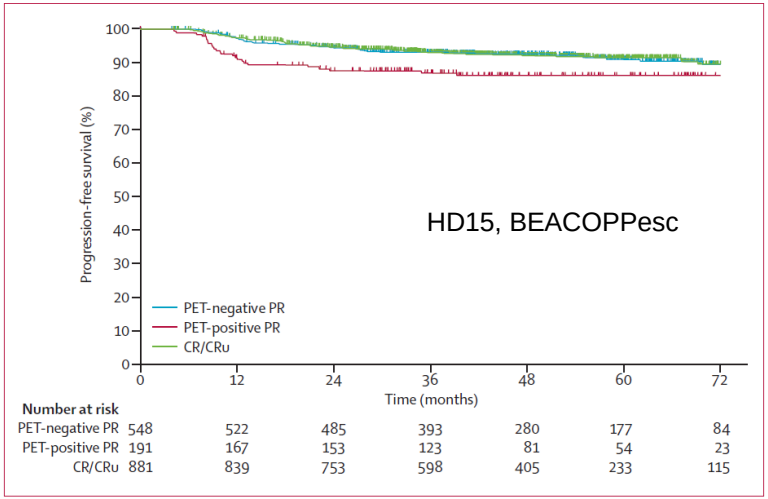
JCO 2014; 32: 3059-67

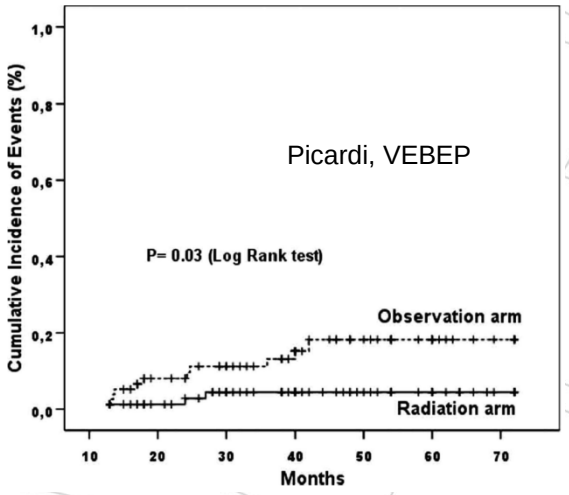
- PET/CT should be used in FDG-avid histologies
- Deauville criteria:
  - 1. No uptake
  - 2. Uptake ≤ mediastinum
  - 3. Uptake > mediastinum but ≤ liver
  - 4. Uptake moderately higher than liver
  - 5. Uptake markedly higher than liver and/or new lesions
  - X. New areas of uptake unlikely to be related to lymphoma
- A complete metabolic response even with persistent mass is considered CR

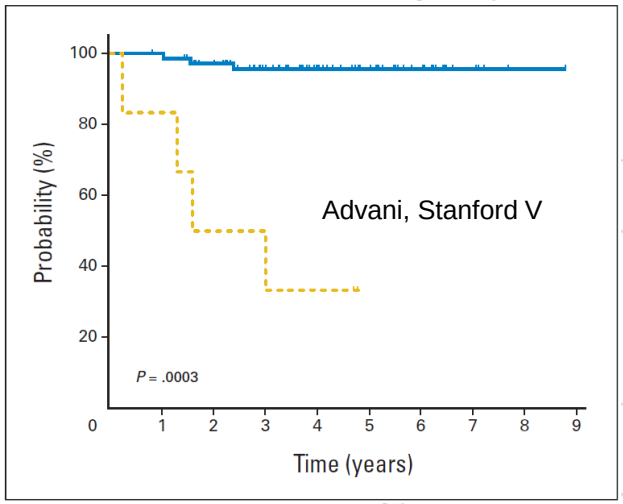
Lymphoma patient, FDG-PET/CT before and after 4 cycles of chemotherapy

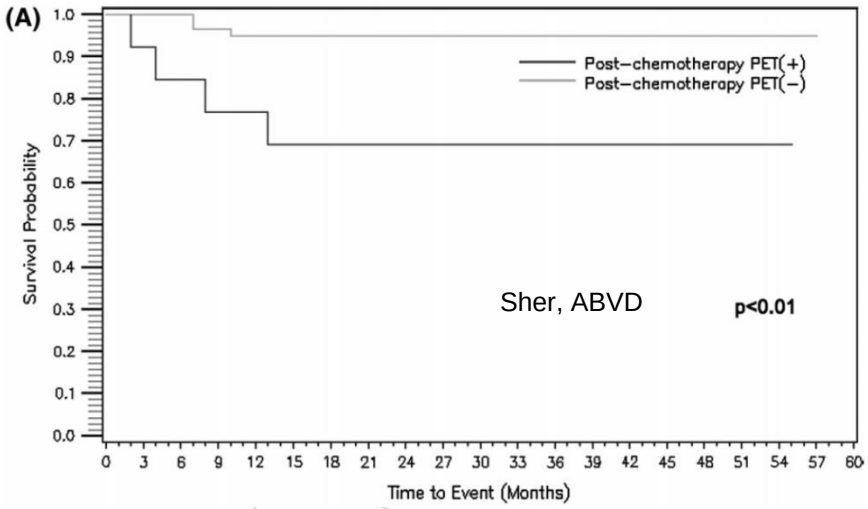


What does it mean to be PET+/- after chemotherapy?

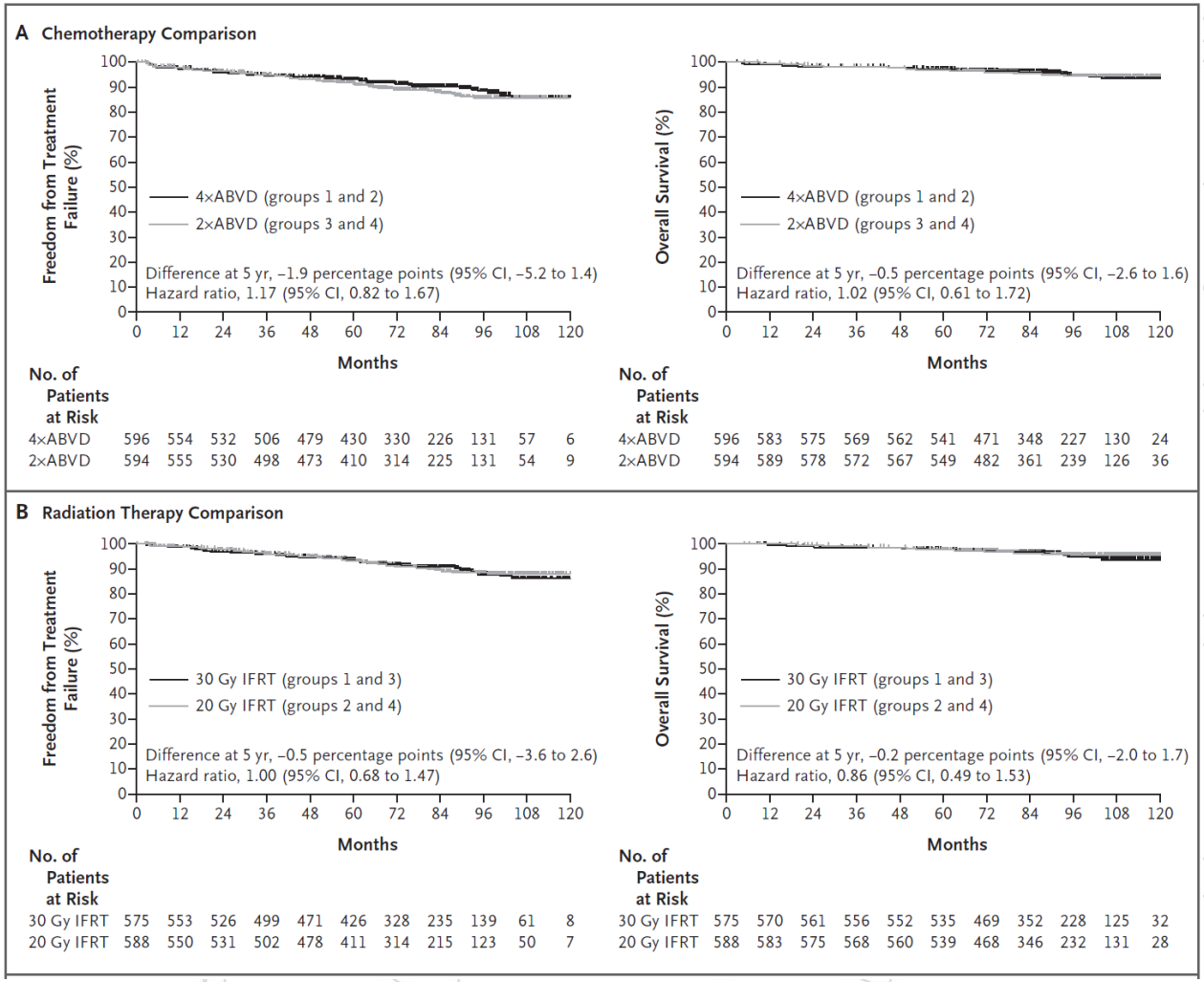








What is the negative predictive value of FDG-PET?

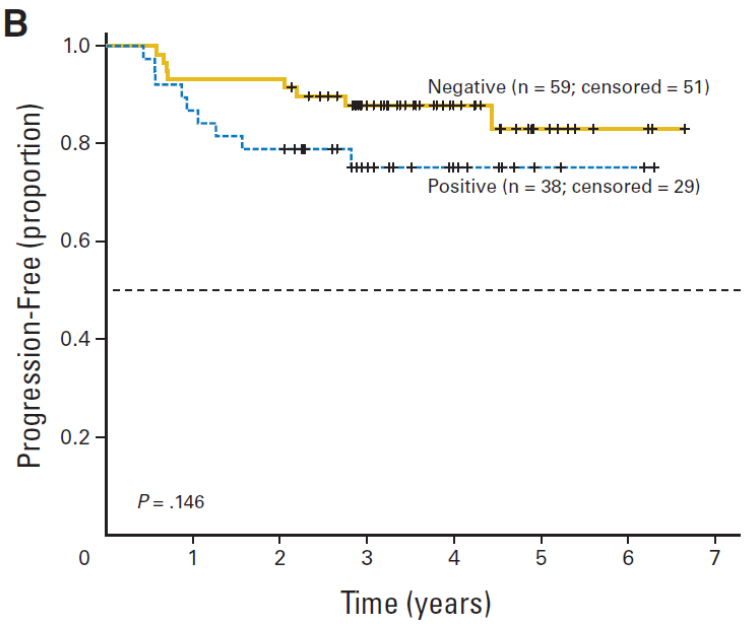


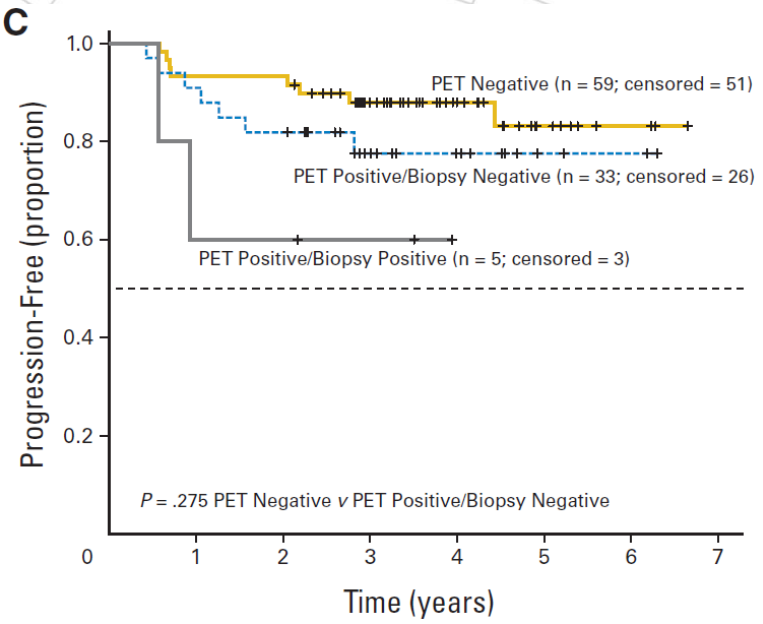
Engert A. N Engl J Med 2010; 363: 640-52

DLBCL

- FDG-PET did not predict outcome in high risk pts after 4 x R-CHOP14
- PET+ were biopsied, 33/38 were negative, all showed inflammation, no correlation with SUV

Moskowitz CH et al. JCO 2010; 28: 1896-1903





No indication for PET in routine follow-up

Thank you for your attention