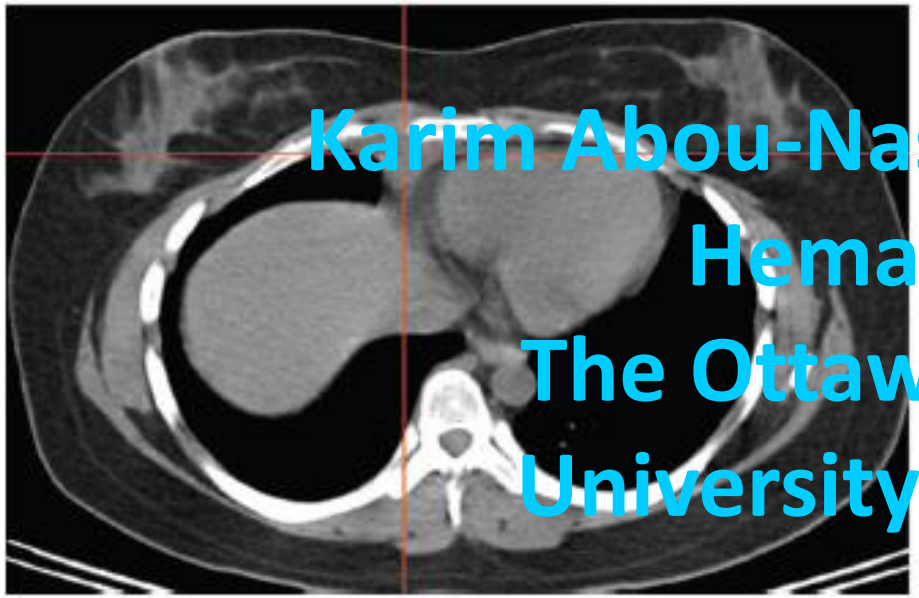
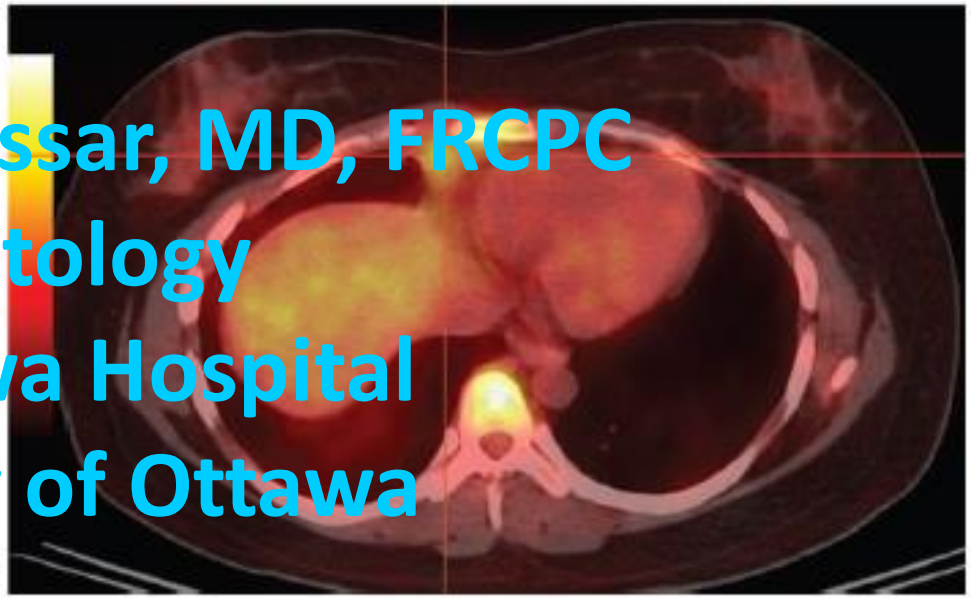
The roles of PET scan in lymphoma





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PET scan - History

- Introduced in the late 1950s at University of Pennsylvania
- Further developed at Washington University School of Medicine and Massachusetts General Hospital
- Development of labelled 2-fluorodeoxy-D-glucose (2FDG) contributed to the development of PET imaging (1970)

PET scan – Basic principles

- The tracer is chemically incorporated into a biologically active molecule.
- To conduct the scan, a short-lived radioactive tracer isotope is injected into the patient (usually into blood circulation).
- There is a waiting period while the active molecule becomes concentrated in tissues of interest; then the subject is placed in the imaging scanner.

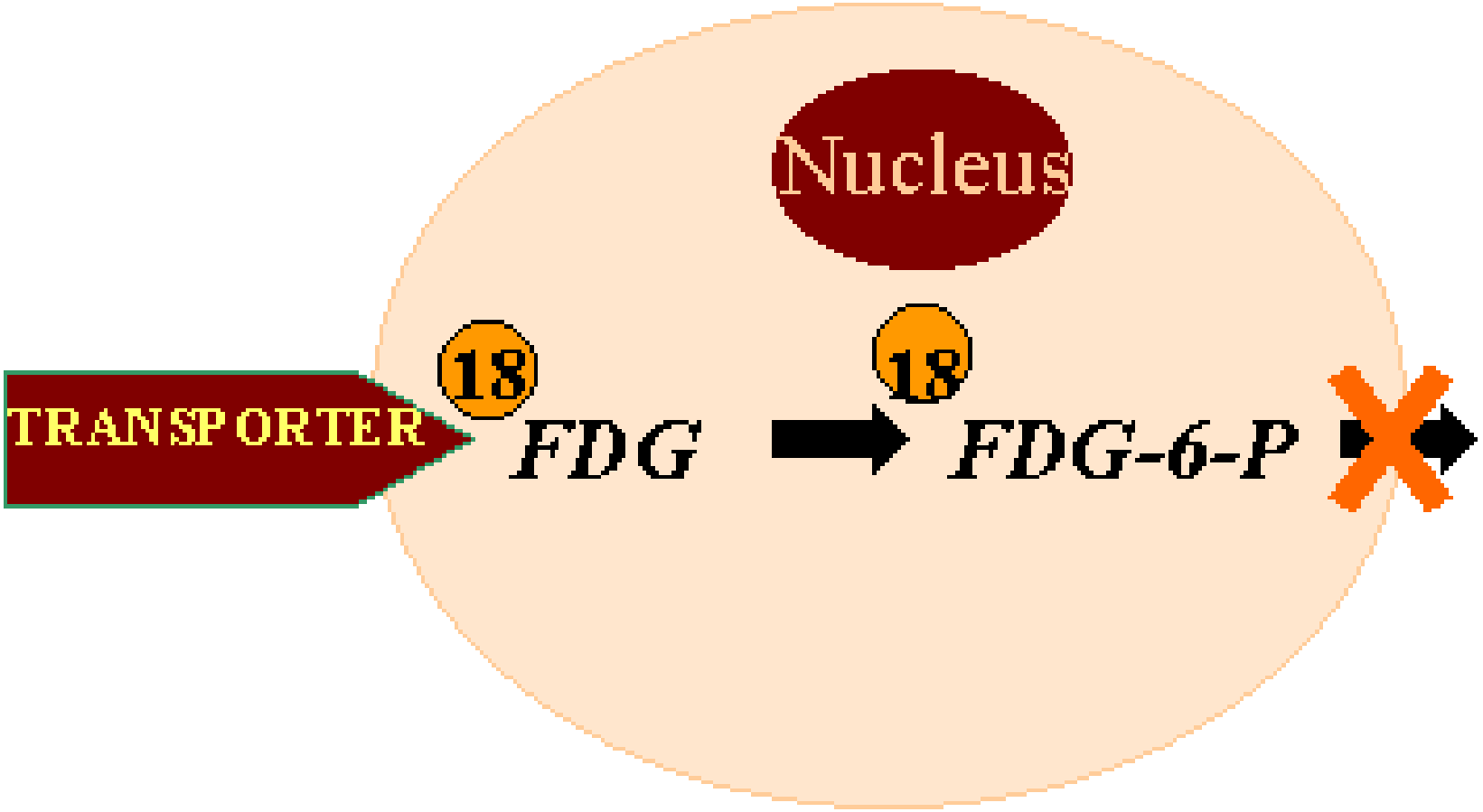
Radionuclides

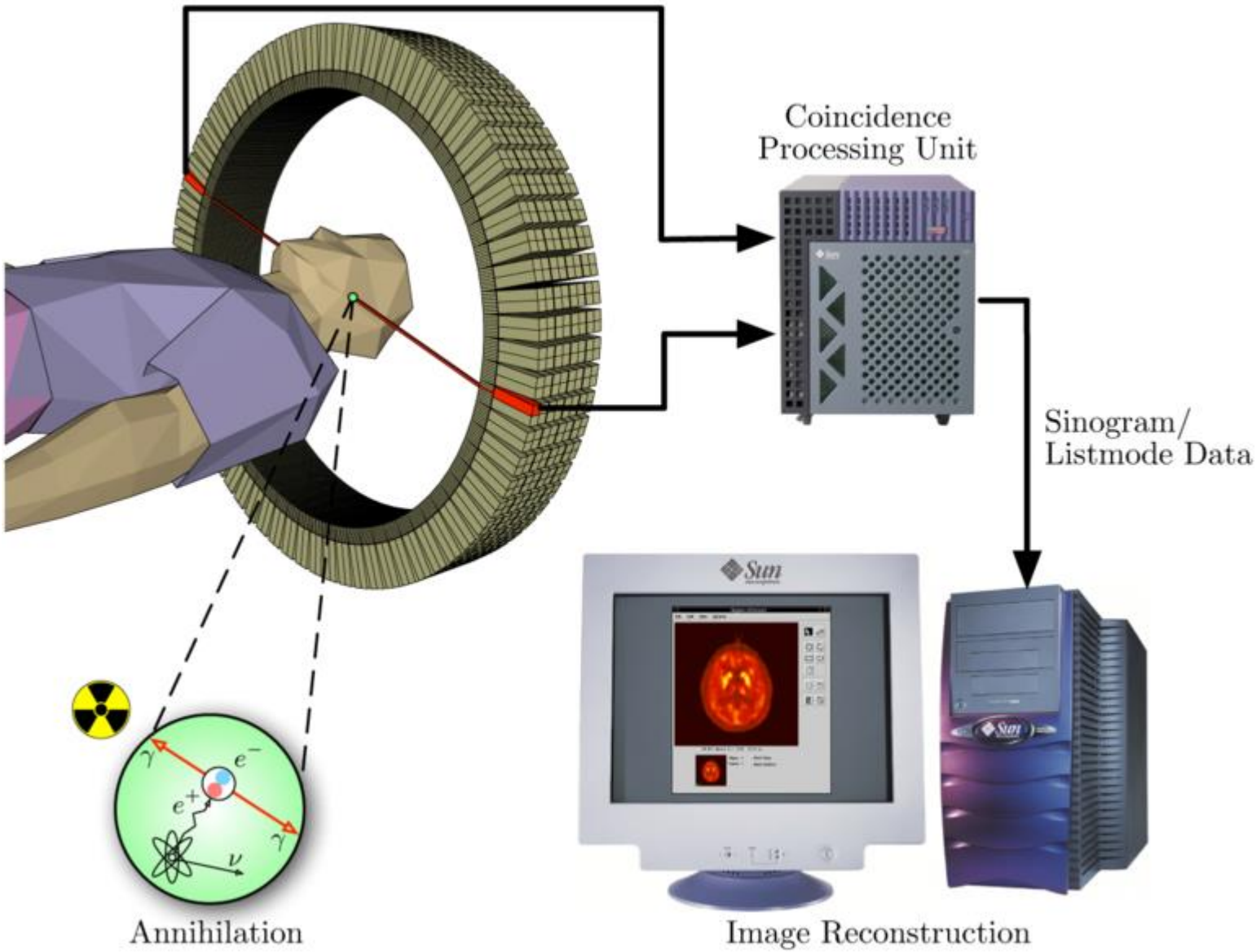
- The most commonly used radiotracer in clinical PET scanning is Fluorodeoxyglucose, an analogue of glucose that is labeled with fluorine-18

- Has a half-life of 110 minutes and can be transported a reasonable distance before use

- This tracer is a glucose analog that is taken up by glucose-using cells and phosphorylated by hexokinase (whose mitochondrial form is greatly elevated in rapidly growing malignant tumours).

2-fluorodeoxy-D-glucose (2FDG)



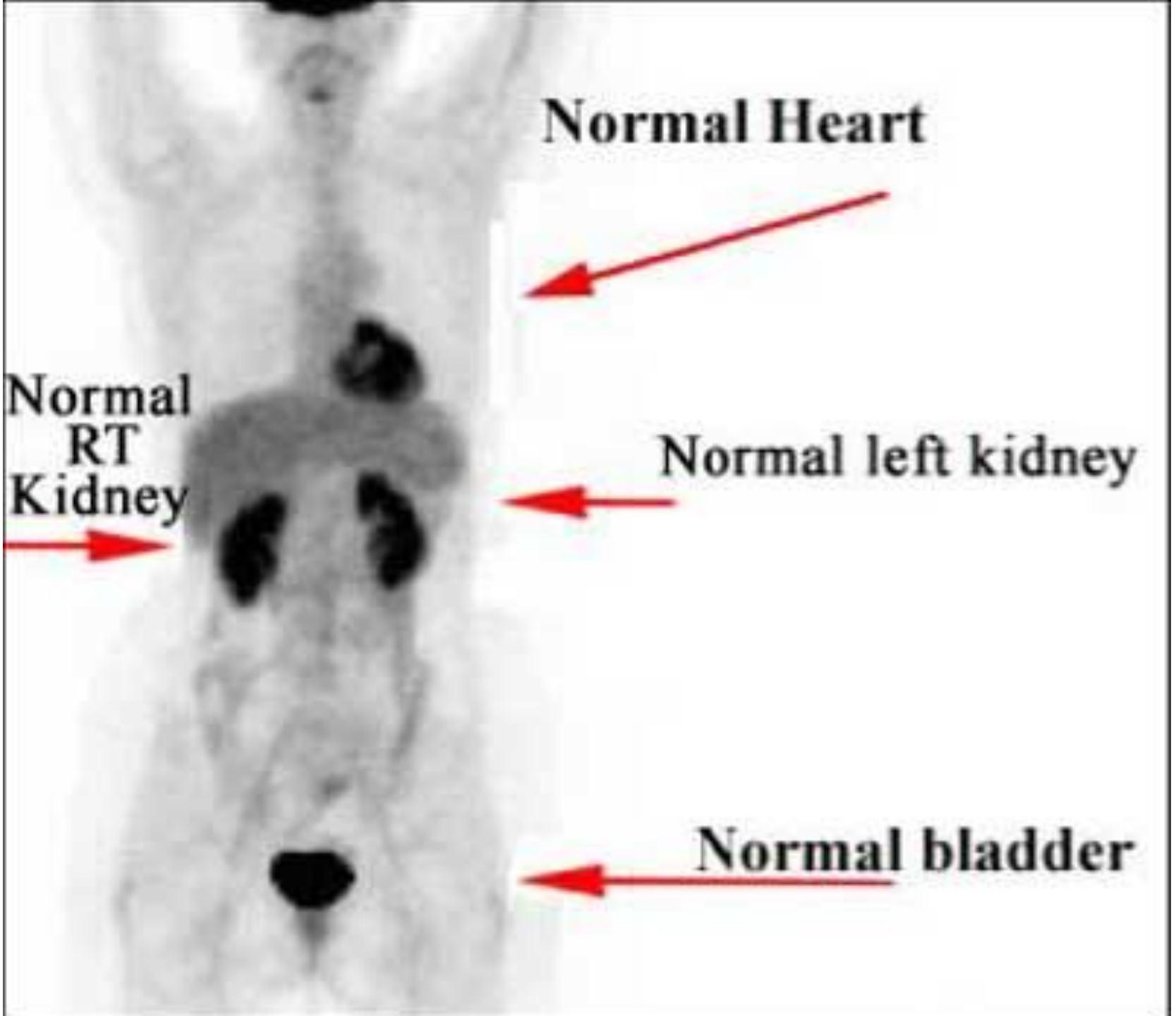

Coincidence
Processing Unit
Sinogram/
Listmode Data
Annihilation
Image Reconstruction

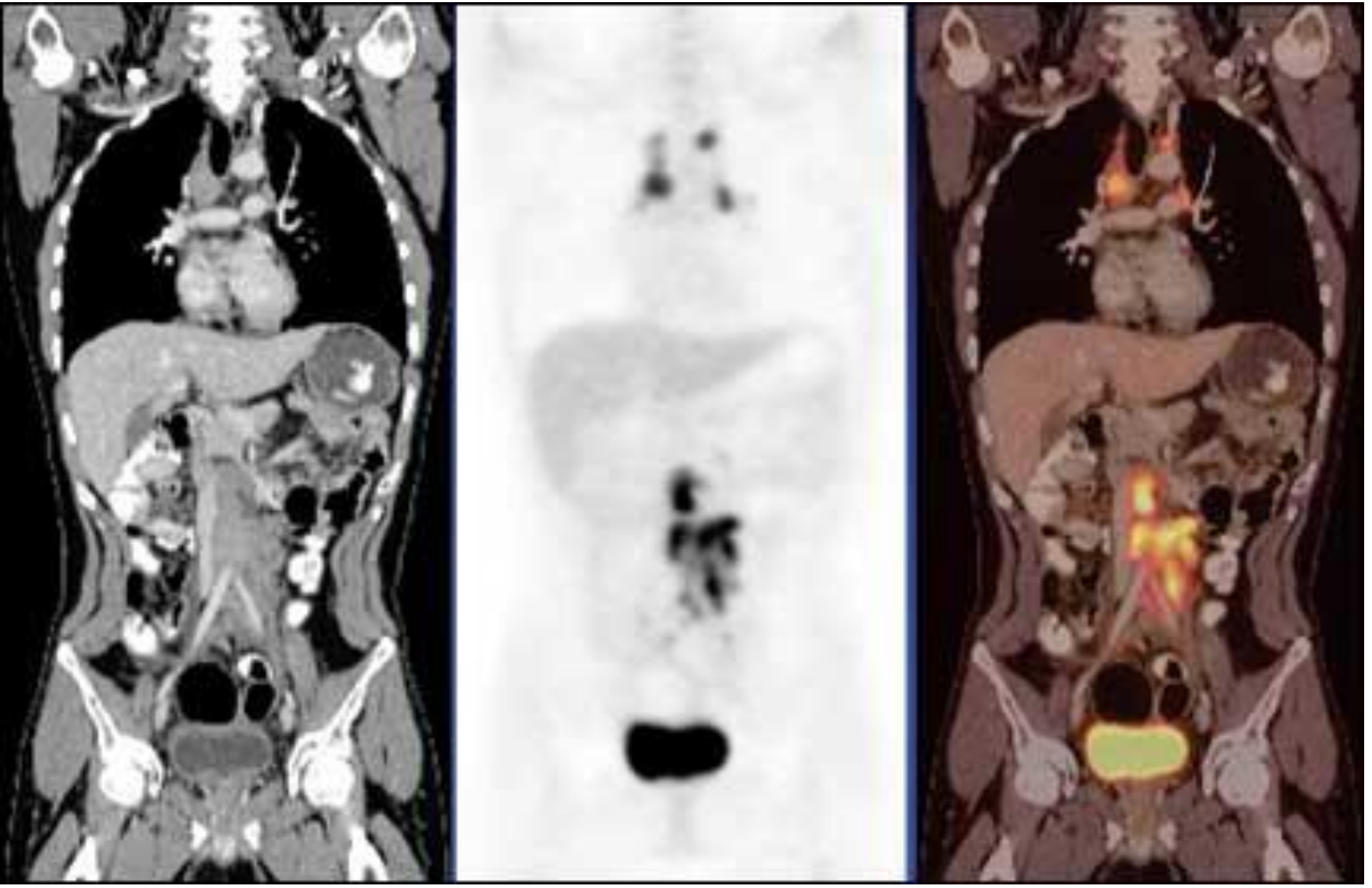
PET scan – Basic principles

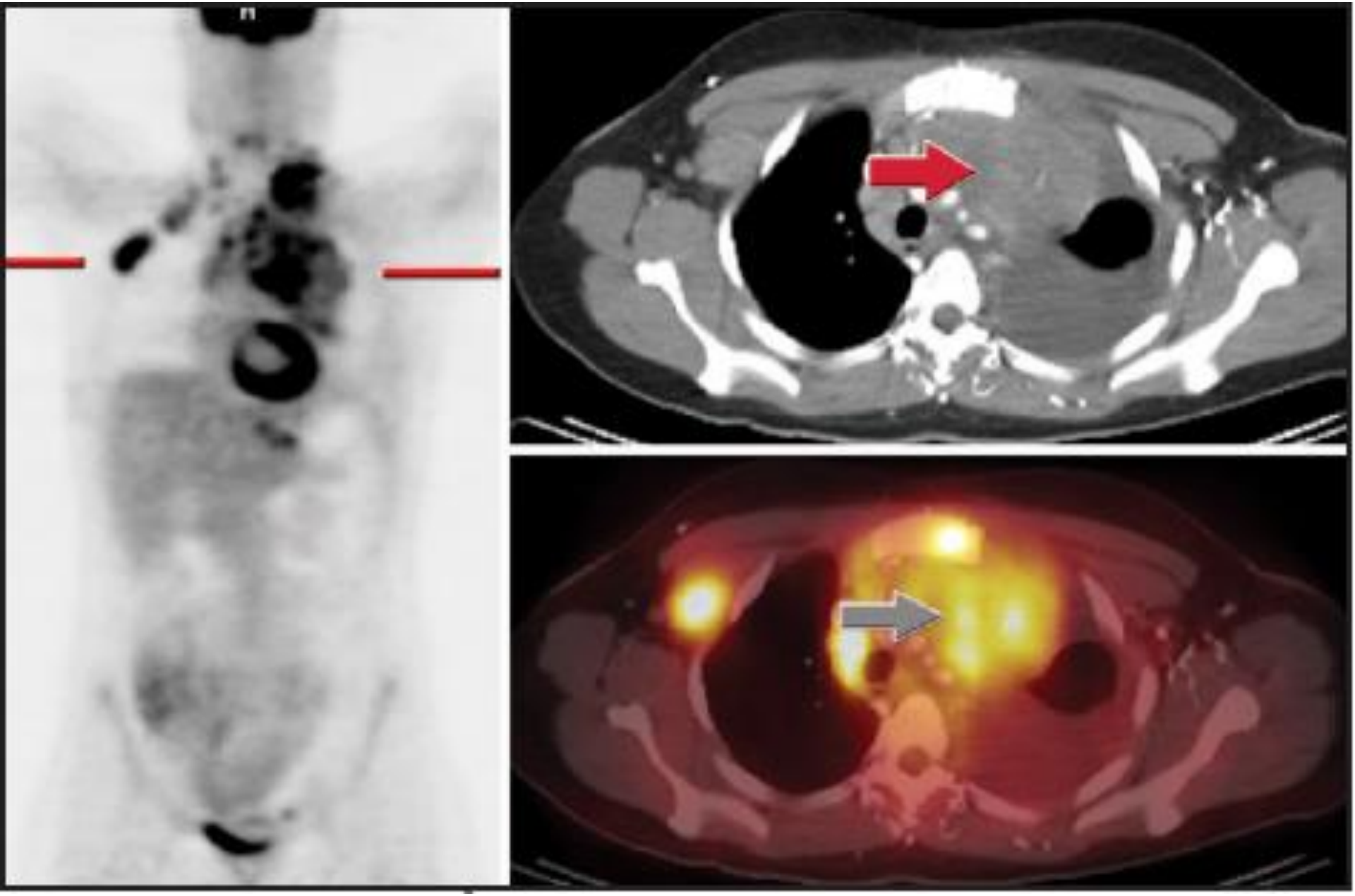
- As the radioisotope undergoes positron emission decay (also known as positive beta decay), it emits a positron, an antiparticle of the electron with opposite charge. The emitted positron travels in tissue for a short distance (typically less than 1 mm, but dependent on the isotope[10]), during which time it loses kinetic energy, until it decelerates to a point where it can interact with an electron.[11] The encounter annihilates both electron and positron, producing a pair of annihilation (gamma) photons moving in approximately opposite directions

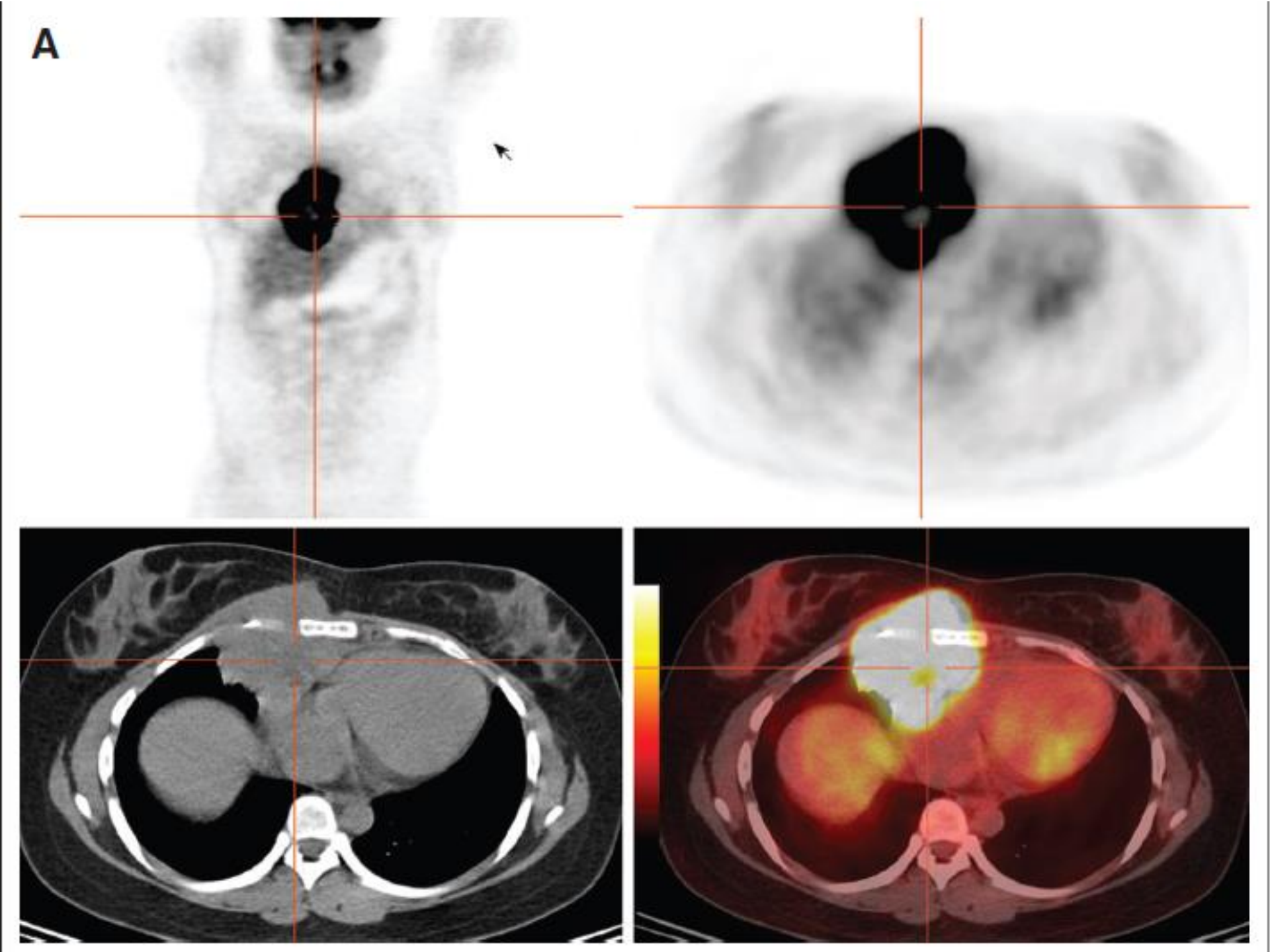
PET scan – Basic principles

- Because the oxygen atom that is replaced by F-18 to generate FDG is required for the next step in glucose metabolism in all cells, no further reactions occur in FDG.
- Most tissues (with the notable exception of liver and kidneys) cannot remove the phosphate added by hexkoinase. This means that FDG is trapped in any cell that takes it up, until it decays, since phosphorlayted sugars, due to their ionic charge, cannot exit from the cell.
- This results in intense radiolabeling of tissues with high glucose uptake, such as the brain, the liver, and most cancers


Normal Heart
Normal
RT
Kidney
Normal left kidney
Normal bladder



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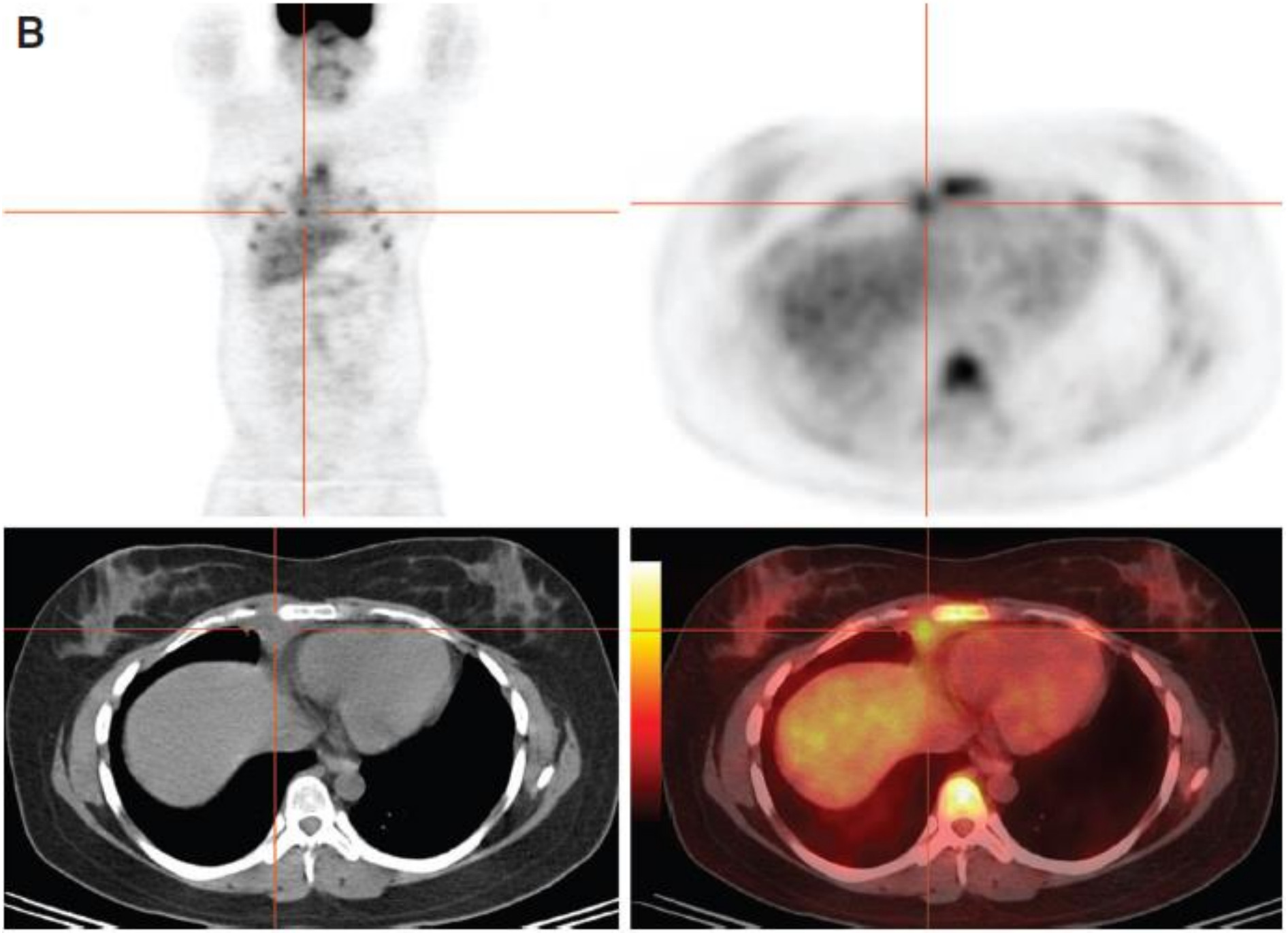
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PET Scan principles - Summary

- **FDG accumulates in tumor cells in proportion to the glycolytic metabolic rate**
- **Cancer cells generate energy by anaerobic/glycolytic metabolism, while benign cells use aerobic metabolism**
- **Glycolysis is inefficient: cancer cells increase their metabolic rate to obtain enough energy for rapid replication**
- **Biochemical changes in tumors precede morphologic changes, FDG-PET provides a sensitive means to evaluate response to therapy**

PET Scan principles - Summary

- **FDG-PET can detect infiltration of disease in normal size nodes**
- **FDG-PET accumulates in all types of lymphomas regardless of histologic grade or subtype**
- **Level of FDG uptake (SUV's-standard uptake values) may be significantly lower in low-grade NHL compared to aggressive NHL and HD**

PET Scans – Potential applications in lymphoma

- **Initial staging**
- **Midtreatment restaging**
- **Posttreatment restaging**
- **Prior to stem cell transplantation**
- **Detection of histological transformation**
- **Surveillance**

Initial Staging

Can PET replace CT for staging of lymphoma?

- PET/CT has consistently greater sensitivity compared to CT for staging
- Upstaging rate 20% for HL and NHL
  - Mostly stages I/II
- Downstaging < 10%
- Changes in therapy in 15%
  - Mostly increases in # of cycles of RT field

Can PET replace CT for staging of lymphoma?

Table 1. Sensitivity/Specificity of PET *v* CT in HL/NHL Staging

Study	No. of Patients	Modality	Sensitivity (%)	Specificity (%)
Newman[13]	16	PET	100	100
		CT	91	100
Thill[14]	27	PET	100	NA
		CT	77	
Buchman[16]	52	PET (N)	99.2	100
		CT (N)	83.2	99.8
		PET (E)	100	99.4
		CT (E)	80.8	99.4
Schaefer[17]	60	PET/CT	94	100
		CT	88	86
Hutchings[18]	99	PET/CT (N)	92.2	99.3
		CT	82.6	98.9

Can PET replace CT for staging of lymphoma?

Table 2. PET in Lymphoma Staging

Study	No. of Patients With HL	No. of Patients With NHL	Upstage (%)	Downstage (%)	Change in Therapy (%)
Bangerter[20]	44		12	2	14
Partridge[23]	44		40.9	< 10	25
Buchman[16]	27	25	8	0	8
Jerusalem[21]	33		1	1	1
Weihrauch[24]	22		18	0	5
Wirth[25]	19	31	14	0	18
Munker[26]	73		29	3	< 1
Raanani[27]			32	15	45
Hutchings[18]	99		17	5	7
Rigacci[22]	186		14	1	7
Pelosi[19]	30		10		7
Pelosi[19]		35	11.4		9

Can PET replace CT for staging of lymphoma?

- FDG avidity of low grade NHL is variable
  - FL is the most FDG avid of low grade NHL
- FDG avidity of T-cell NHL is heterogenous

Table 1. PET scan results by WHO classification

Histology	Positive	Negative	Total	% Positive
LBCL	51	0	51 (29.7%)	100
FL	41	1	42 (24.4%)	98
HL	46	1	47 (27.3%)	98
MZL	8	4	12 (7.0%)	67
MCL	7	0	7 (4.1%)	100
ALCL	2	0	2 (1.2%)	100
PTCL	2	3	5 (2.9%)	40
CBCL	0	2	2 (1.2%)	0
MF	1	0	1 (0.6%)	100
BL	1	0	1 (0.6%)	100
SLL	1	0	1 (0.6%)	100
T/NK	1	0	1 (0.6%)	100
Total	161	11	172	94

ALCL indicates anaplastic large cell lymphoma; PTCL, peripheral T-cell lymphoma; CBCL, cutaneous B-cell lymphoma; MF, mycosis fungoides; BL, Burkitt lymphoma; SLL, small lymphocytic lymphoma; and T/NK, T/natural killer cell lymphoma.

Table. Positive rate of FDG-PET in T/NK-cell neoplasms

Histology	All lesions			
	Positive	Negative	Total	%Positive (95% CI)
PTCLu	10	1	11	91 (59–100)
ENKL	8	0	8	100 (63–100)
C-ALCL	3	2	5	60 (15–95)
AILT	4	0	4	100 (40–100)
ALCL	3	0	3	100 (29–100)
MF/SS	1	2	3	33 (1–91)
Others**	7	0	7	100 (59–100)
Total	36	5	41	88 (74–96)

**Others include precursor T lymphoblastic lymphoma, T-cell prolymphocytic leukemia, T-cell large granular lymphocytic leukemia, aggressive natural killer cell leukemia, adult T-cell leukemia/lymphoma and subcutaneous panniculitis-like T-cell lymphoma.

Abbreviations: CI, confidence interval; PTCLu, peripheral T-cell lymphoma, unspecified; ENKL, extranodal natural killer/T-cell lymphoma, nasal type; C-ALCL, primary cutaneous anaplastic large cell lymphoma; AILT, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; MF/SS, mycosis fungoides and Sezary syndrome.

Annals of Oncology 18: 1685 -1690, 2007

Can PET replace CT for staging of lymphoma?

- DLBCL – Yes
- HL – Yes
- Low grade NHL – No
- T cell NHL – No/variable

PET scan for midtreatment restaging

PET for midtreatment restaging in lymphoma

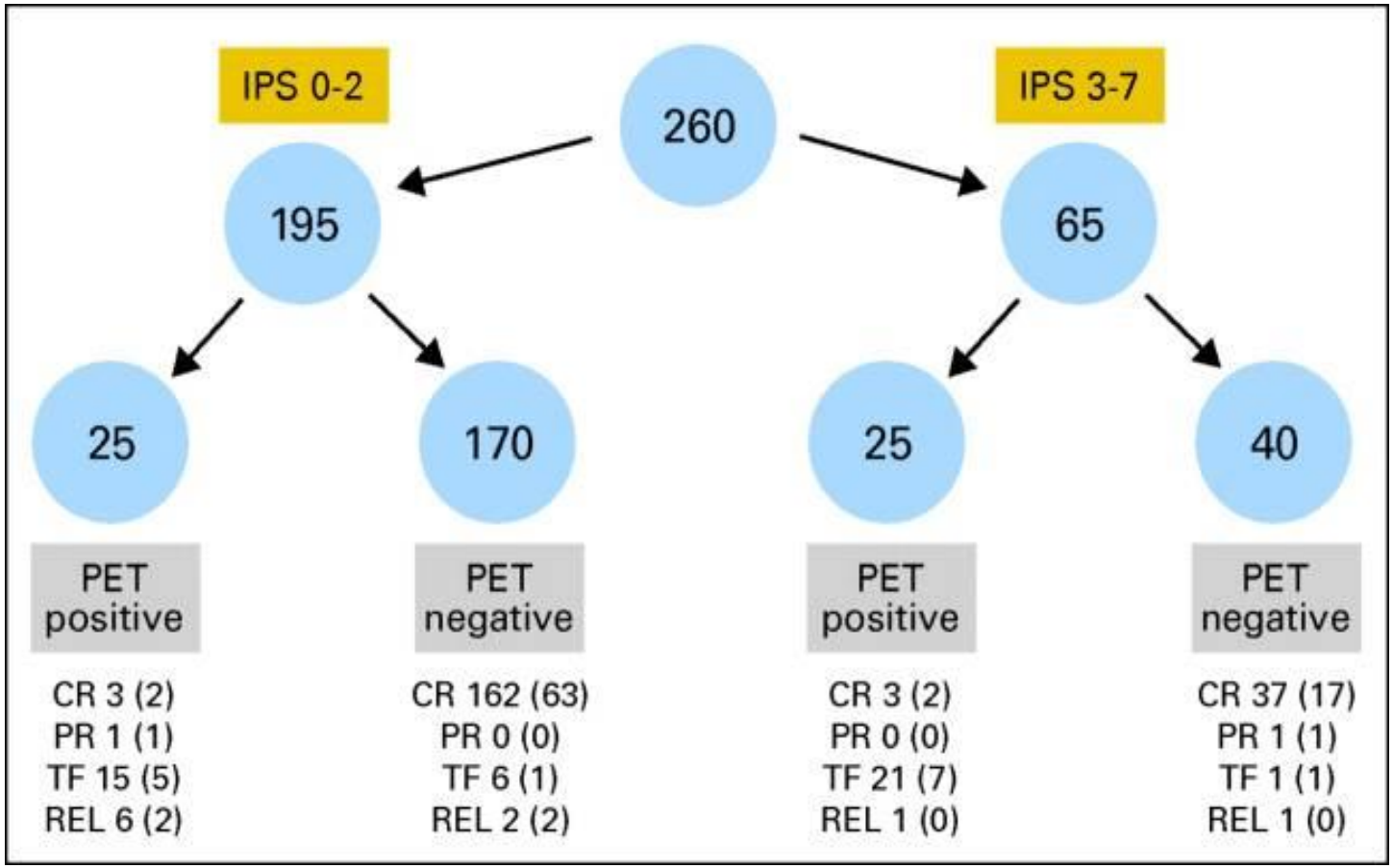
Table 5. Interim PET in HL and DLCBL

Study	No. of Patients With HL	No. of Patients With NHL	Cycles of Therapy	PET Negative (%)	PFS/EFS (%)	PET Positive (%)	PFS/EFS (%)
Jerusalem[65]		28	2-3	82	100	18	30
Spaepen[66]		47	3-4	47	84	53	0
Haioun[67]		90	2	60	82	40	43
Mikhaeel[69]		121	2-3	41.3	93	43	30
Kostakoglu[73]	23		1	74	100	26	12.5
		24		58	100	42	
Zinzani[74]		91	Various	61.5	89	38.5	17
Safar[75]		112	2	63	81	37	41
Cashen[50]		50	2-3	30	85	30	75
Gigli[49]		42	3	67	90	33	55
Micallef[76]		76	2	79	73	21	60
Pregno[77]		82	2	67	84	33	74
Hutchings[70]	85		2-3	72	94	13	38
Hutchings[71]	77		2	79	95	21	31
Zinzani[72]	40		2	80	97	20	12
Gallamini[79]	260		2	81	95	19	14
Markova[78]	50		4	72	100	28	86

PET for midtreatment restaging in lymphoma

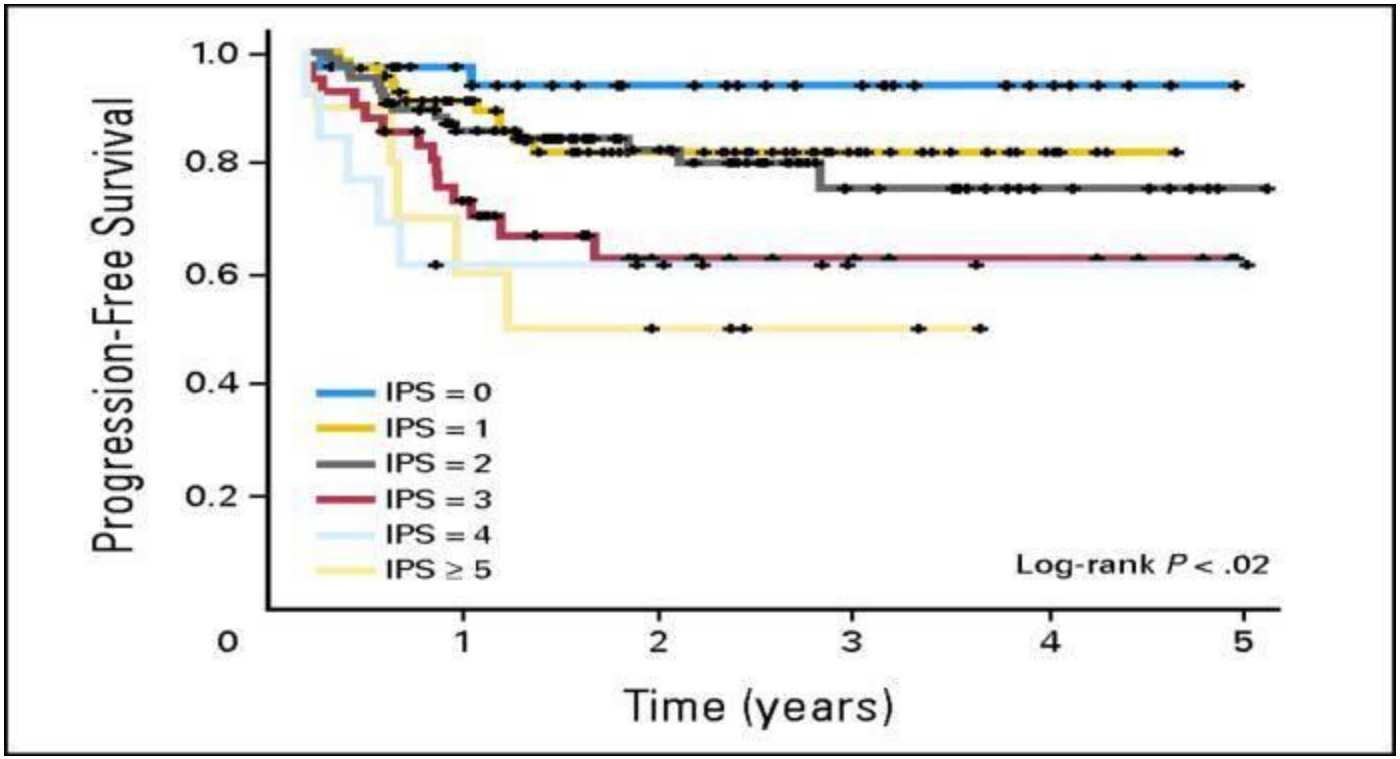
- In aggressive NHL, studies looking at the usefulness of mid-treatment PET in predicting long term outcomes post treatment have given mixed results.
- Many studies suggest no advantage ot midtreatment PET compared to post treatment PET
  - Up to 2/3 patients with positive midtreatment PET will become negative posttreatment

PET after 2 cycles of ABVD as a prognostic tool in HL



Gallamini et al. JCO 25:3746-52, 2007

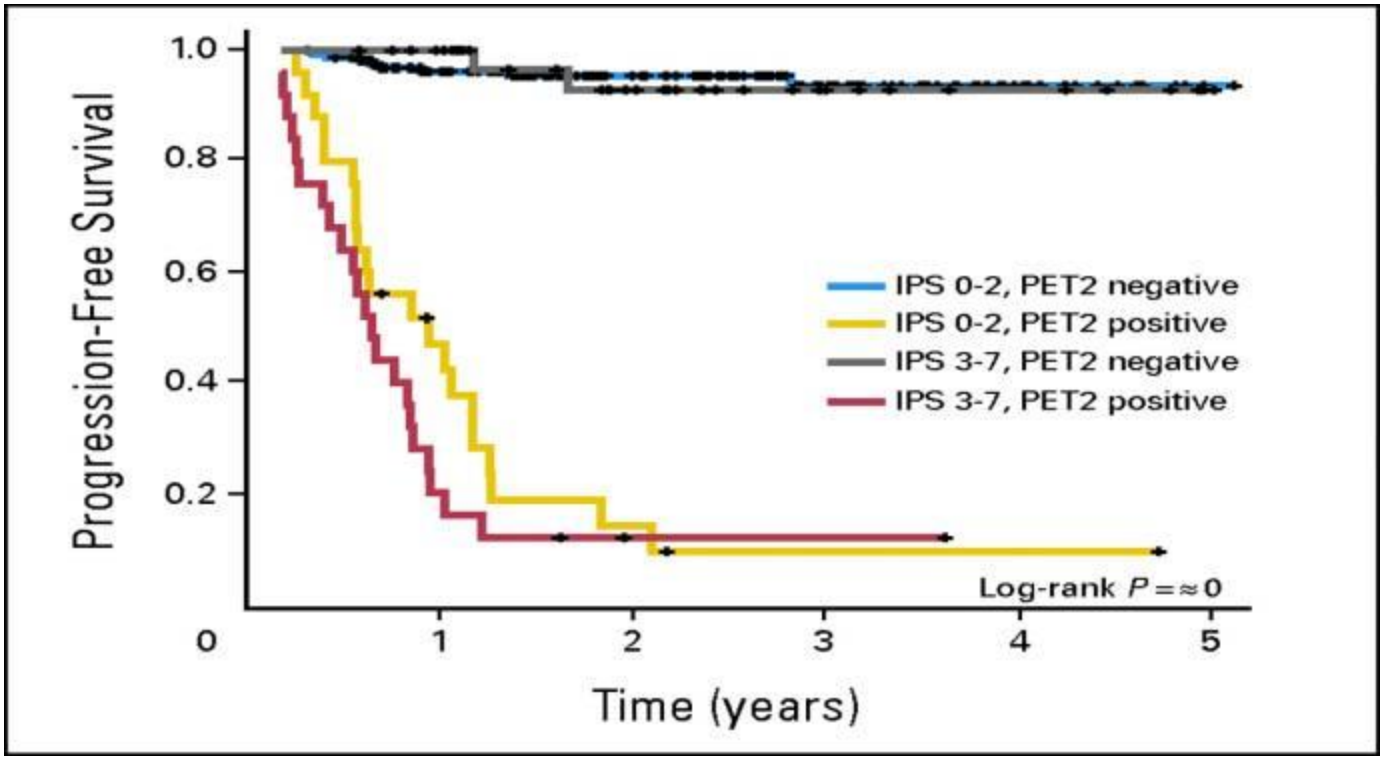
IPS as a Predictor of PFS



- PFS by IPS score

Gallamini et al. JCO 25:3746-52, 2007

Interim PET as a Predictor of PFS



- PFS separated by IPS and PET2 status

Gallamini et al. JCO 25:3746-52, 2007

PET for midtreatment restaging in lymphoma

- BOTTOM LINE:
  - The evidence does not support interim scanning outside of a clinical trial
  - To date, there is no direct evidence that altering therapy on the basis of interim PET findings improves patient outcome.

PET for posttreatment restaging

PET for restaging of lymphoma after therapy

Table 4. PET(CT) in Restaging of Lymphoma

Study	No. of Patients	PPV (%)	NPV (%)
NHL			
Bangerter[20]	89	90	98
Jerusalem[42]	35	42.9	100
Zinzani[47]	31	92.9	100
Mikhaeel[44]	45	60	100
Naumann[48]	15	85.7	88.2
Spaepen[45]	93	70.3	100
Cashen[50]	50	80	92
Gigli[49]	42	75	94
HL			
Spaepen[46]	60	100	91
Engert[51]	728	NA	94.6
Cerci[52]	130	92.3	100

PET for restaging of lymphoma after therapy

Table 4. PET(CT) in Restaging of Lymphoma

Study	No. of Patients	PPV (%)	NPV (%)
NHL			
Bangerter[20]	89	90	98
Jerusalem[42]	35	42.9	100
[illegible][47]	[illegible]	92.9	100
[illegible]	[illegible]	60	100
[illegible]	[illegible]	85.7	88.2
[illegible]	[illegible]	70.3	100
[illegible]	[illegible]	80	92
Gigli[49]	42	75	94
HL			
Spaepen[46]	60	100	91
Engert[51]	728	NA	94.6
Cerci[52]	130	92.3	100

Due to false positive results

PET for restaging of lymphoma after therapy

Table 4. PET(CT) in Restaging of Lymphoma

Study	No. of Patients	PPV (%)	NPV (%)
NHL			
		90	98
		42.9	100
		92.9	100
		60	100
		[illegible]	88.2
		70.3	100
		80	92
		75	94
[illegible]	[illegible]	100	91
Engert[51]	728	NA	94.6
Cerci[52]	130	92.3	100

Due to inability to detect microscopic disease

Assessment of Residual Bulky Tumor Using FDG-PET in Patients with Advanced-Stage Hodgkin Lymphoma After Completion of Chemotherapy: Final Report of the GHSG HD15 Trial

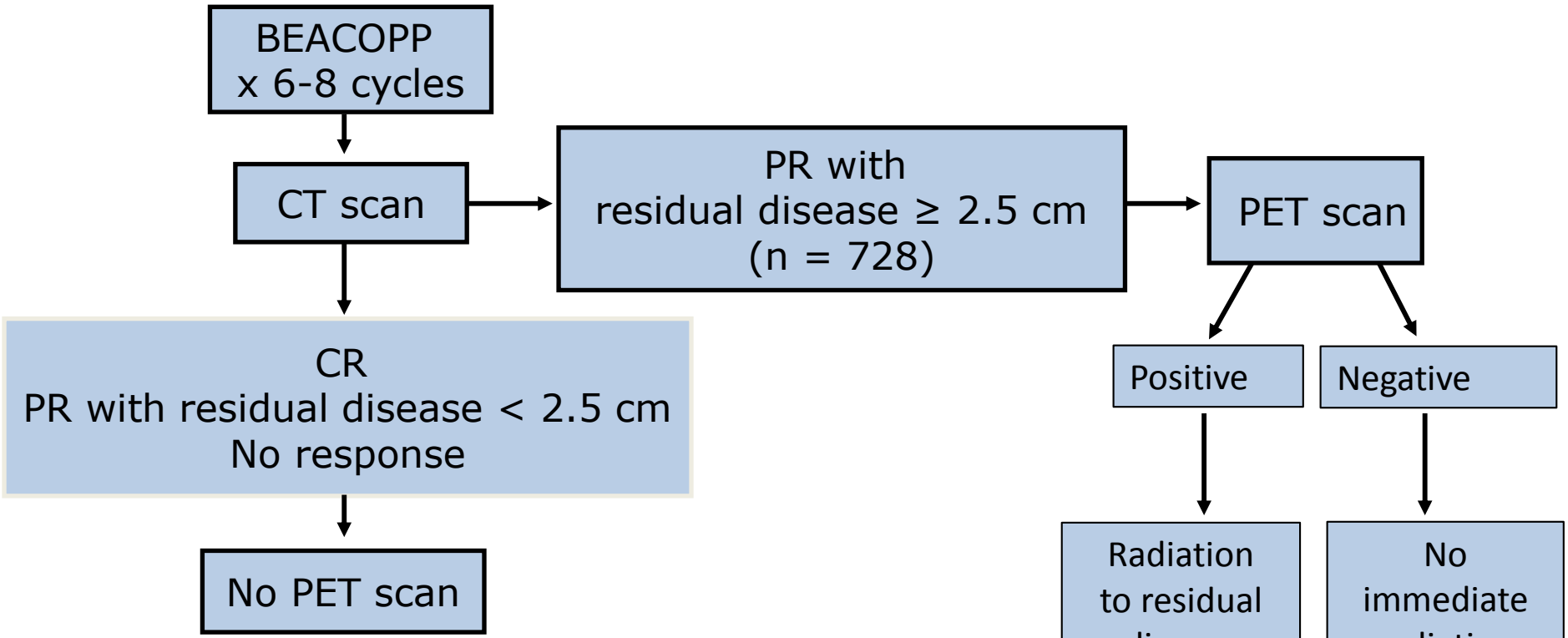
Engert A et al.

Proc ASH 2010;Abstract 764.

Study Schema

Eligibility (N = 2,137)

Advanced-stage Hodgkin lymphoma



Engert A et al. *Proc ASH* 2010;Abstract 764.

Results (from Abstract)

Patients with PR and Residual Disease ≥ 2.5 cm (n = 728)	
PET Negative	74.2%
PET Positive	25.8%

	PET Negative	PET Positive[1]
Negative Prognostic Value	94.6%	—
Lack of Progression Events[2] at 3 Years	92.1%	86.1%

[1] Patients with PET-positive disease received immediate radiation.
[2] Radiation counted as a progression event in PET-negative patients.

Engert A et al. *Proc ASH* 2010;Abstract 764.

Results (from Abstract)

	Current Trial	Earlier Trials
Radiation after BEACOPP	11%	71%

In addition, there was no difference in PFS or overall survival as compared to earlier trials in advanced-stage HL.

Engert A et al. *Proc ASH* 2010;Abstract 764.

Author Conclusion

- Patients with a negative PET scan after BEACOPP do not need additional radiation therapy.
  - 94.6% negative prognostic value of negative PET

Engert A et al. *Proc ASH* 2010;Abstract 764.

PET for restaging of lymphoma after therapy

- FDG-PET is helpful in restaging DLBCL and HL after therapy where a residual mass > 2cm remains.

- FDG-PET less relevant in low-grade NHL where an immediate change of treatment is usually not critical

PET scan for lymphoma surveillance post-therapy

Surveillance PET scans

- 80% or more of relapses are detected by patient or MD based on history and physical examination.
- False positive rate of surveillance PET up to 33%.
- PET identifies unsuspected early relapses in only 10% of cases of HL
- Routine surveillance PET in HL has been associated with a cost of 100 000$ for each event.

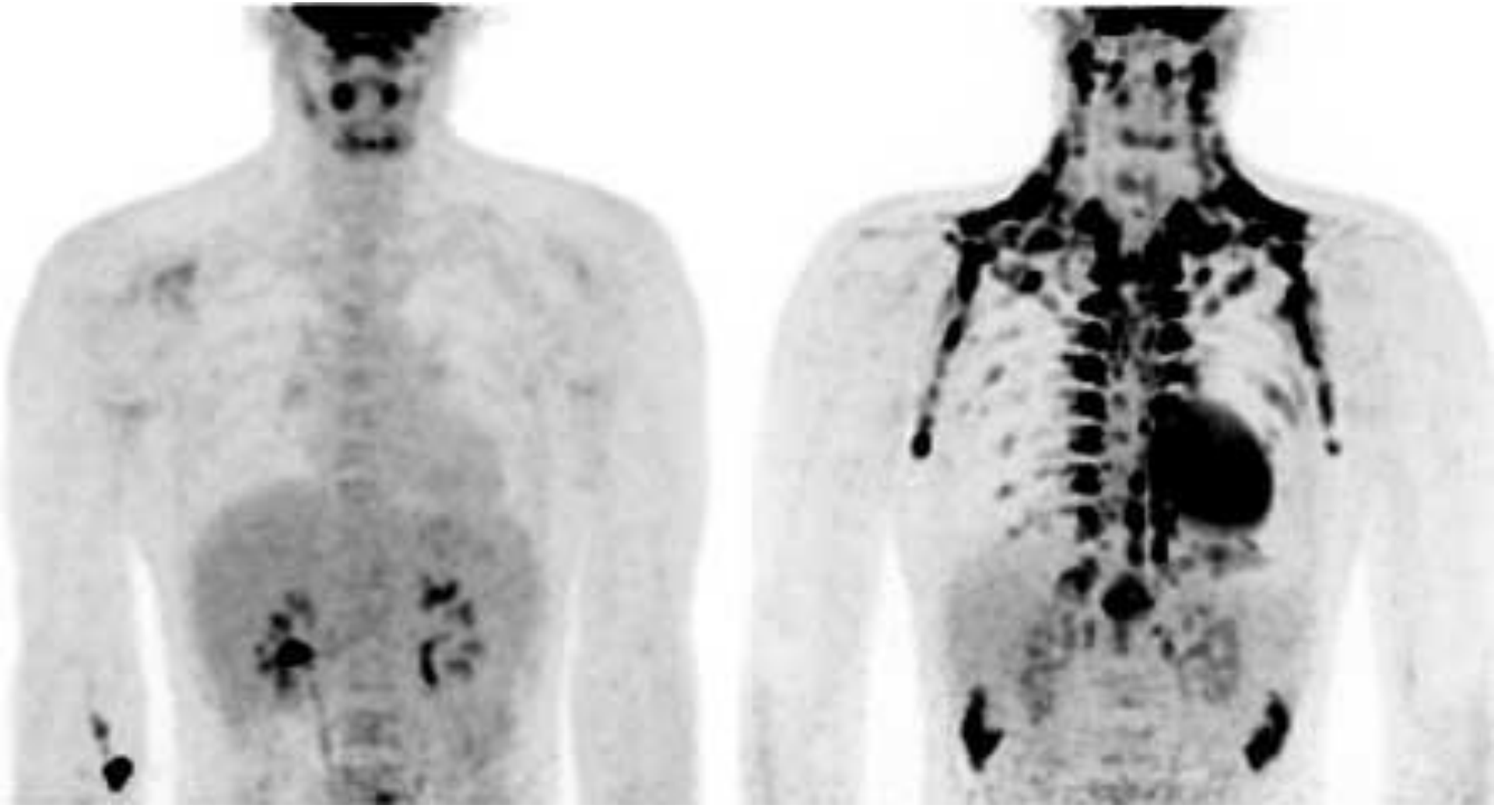
Table 6. Guidelines for Conduct of FDG-PET Scans

Parameter	Recommendations
Patient preparation	Fast overnight, or at least 6 hours Hydrate with > 500 mL post-FDG injection Mild sedation as needed
Blood glucose	Not to exceed 200 mg/dL **11.1 mmol/L**
Patient imaging	60 ± 10 minutes after FDG injection
Timing of PET scan	Pretreatment scans required if post-treatment to be performed, within 2 weeks of therapy Post-treatment scans at least 6-8 weeks after chemo(immuno)therapy
FDG dose	3.5-8 MBq/kg body weight, minimum 185 MBq
Acquisition	Base of skull to mid-thigh unless other areas of concern

Current issues with PET scans

- Methodologic limitations
  - Brown fat
  - Diabetes
- Standardization in reporting
  - Mediastinal blood pool as baseline
  - Concordance rates as low as 70% between radiologists. May be better with PET/CT

PET scan and brown fat



Current issues with PET scans

- False positives
  - Brown fat
  - Infection
  - Inflammation
  - Tumor necrosis
  - Thymic hyperplasia
  - GCSF
  - Rituximab
- Perform PET 6-8 wks after chemo and 8-12 wks after RT

ORIGINAL CONTRIBUTION

Changes in the Use and Costs of Diagnostic Imaging Among Medicare Beneficiaries With Cancer, 1999-2006

- Study of national claims data in Medicare beneficiaries between 1997 and 2006.
- NHL are among the most imaged and expensive to treat cancers in the US (63 411 $ in the first 2 yrs in 2006 – 6% is imaging alone)
- The annual increase in total costs for NHL care has been 4.6%
  - The annual increase in imaging costs for NHL is nearly twice as high at 8.8%.
  - The use of CT scans for NHL has remained relatively stable during the study period
  - The use of FDG-PET scans increased by 39% annually.

PET scan in lymphoma: Current recommendations

Table 7. Recommendations for PET (PET/CT) Scans in Lymphoma Clinical Trials

Histology	Pretreatment	Midtreatment	Response Assessment	Post-Therapy Surveillance
DLBCL	Yes*	Clinical trial	Yes	No
HL	Yes*	Clinical trial	Yes	No
Follicular NHL	Not	Clinical trial	Not	No
MCL	Not	Clinical trial	Not	No
Other aggressive NHLs	Not	Clinical trial	Not‡	No
Other indolent NHLs	Not	Clinical trial	Not‡	No