18F-FDG PET-CT IMAGING IN MELANOMA

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AZ Groeninge and KULeuven

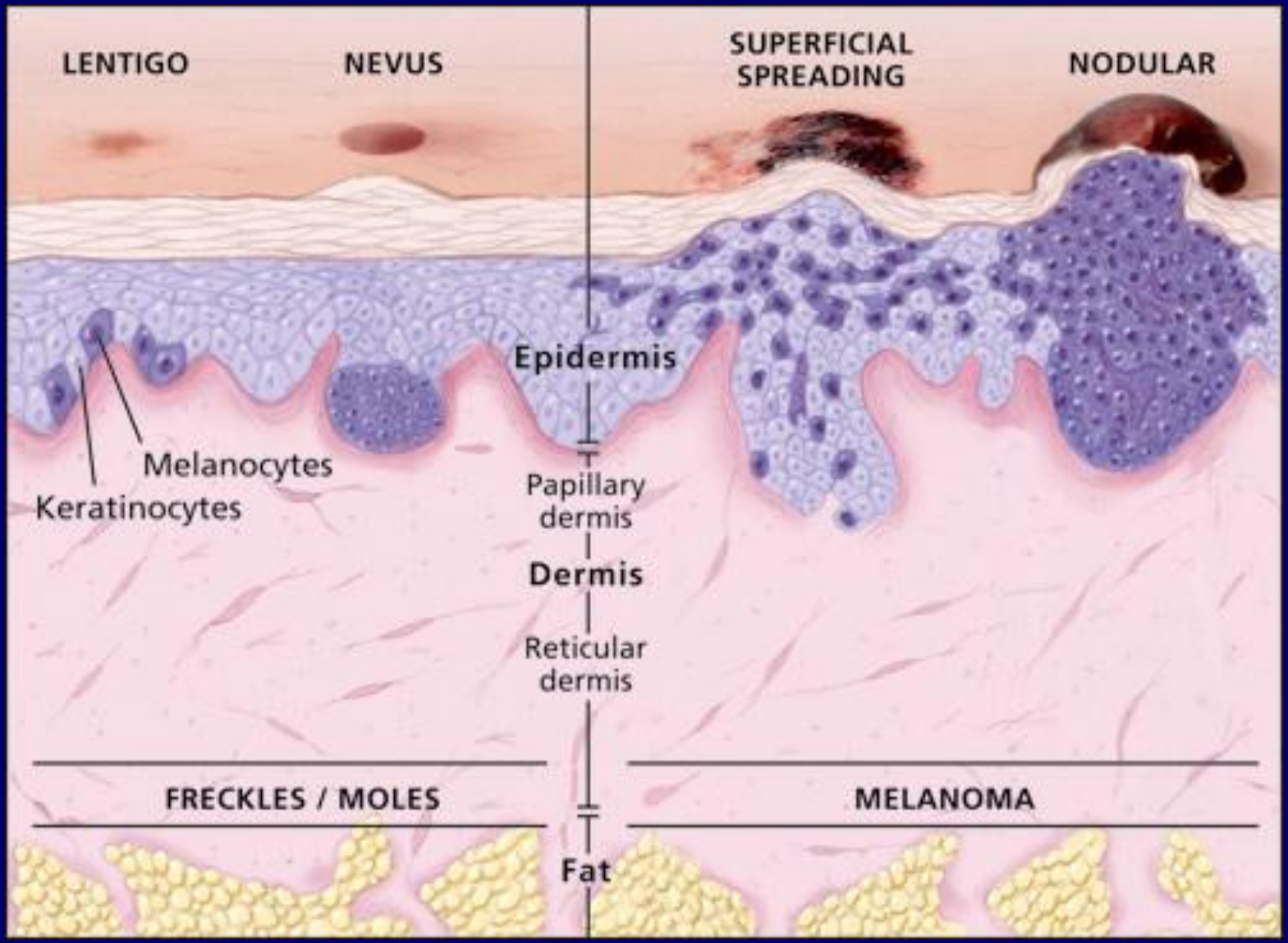
Belgium

- INTRODUCTION
  - Incidence
  - Diagnosis
  - Staging
  - Treatment

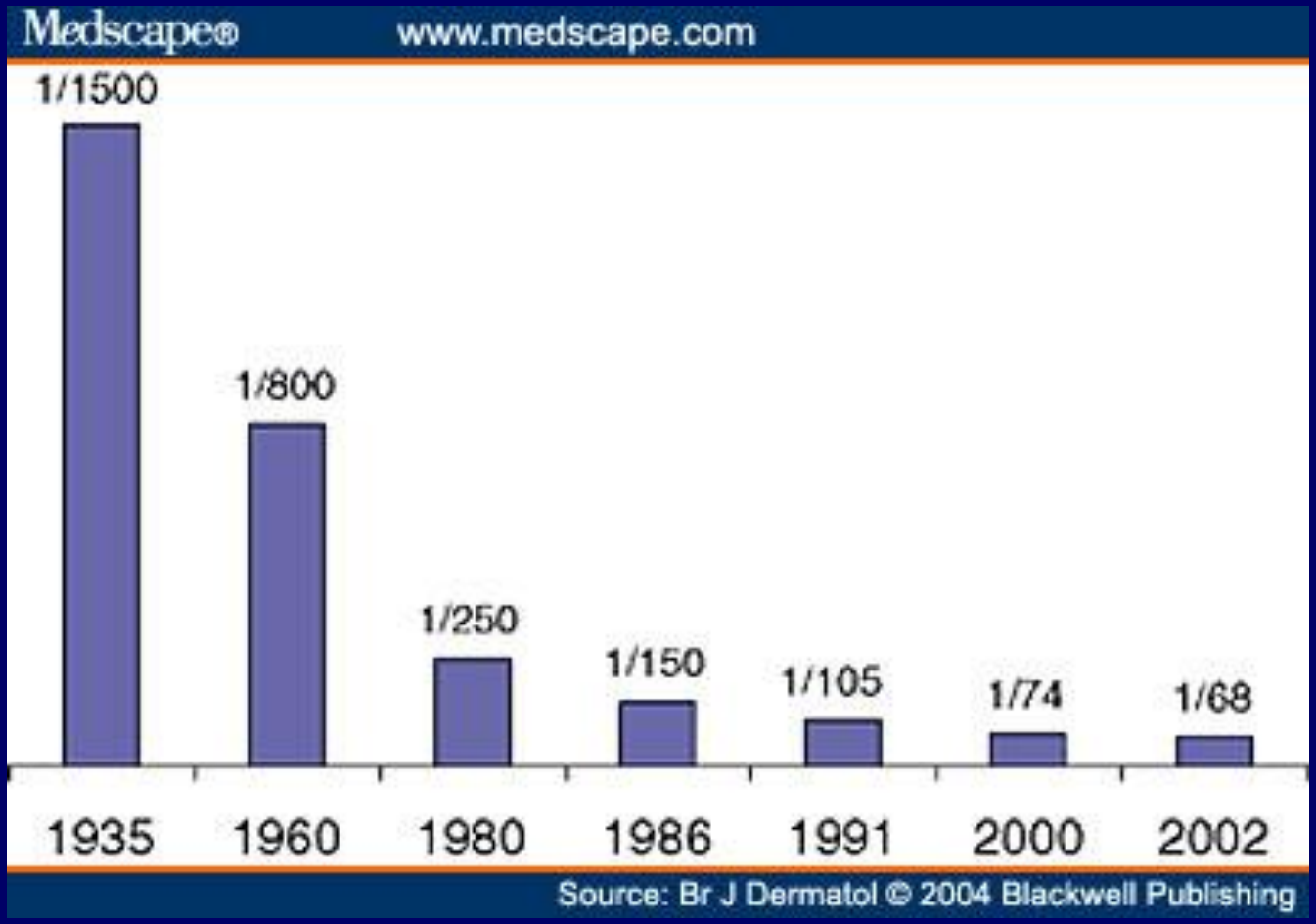
- FDG PET(-CT) IMAGING IN MELANOMA
  - Staging
  - Prognosis and response assessment

MELANOMA

- Malignant
- Most agressive skin tumour
- Originates from pigment cells in basal layer of the epidermis


LENTIGO
NEVUS
SUPERFICIAL SPREADING
NODULAR
Epidermis
Melanocytes
Keratinocytes
Papillary dermis
Dermis
Reticular dermis
FRECKLES / MOLES
MELANOMA
Fat

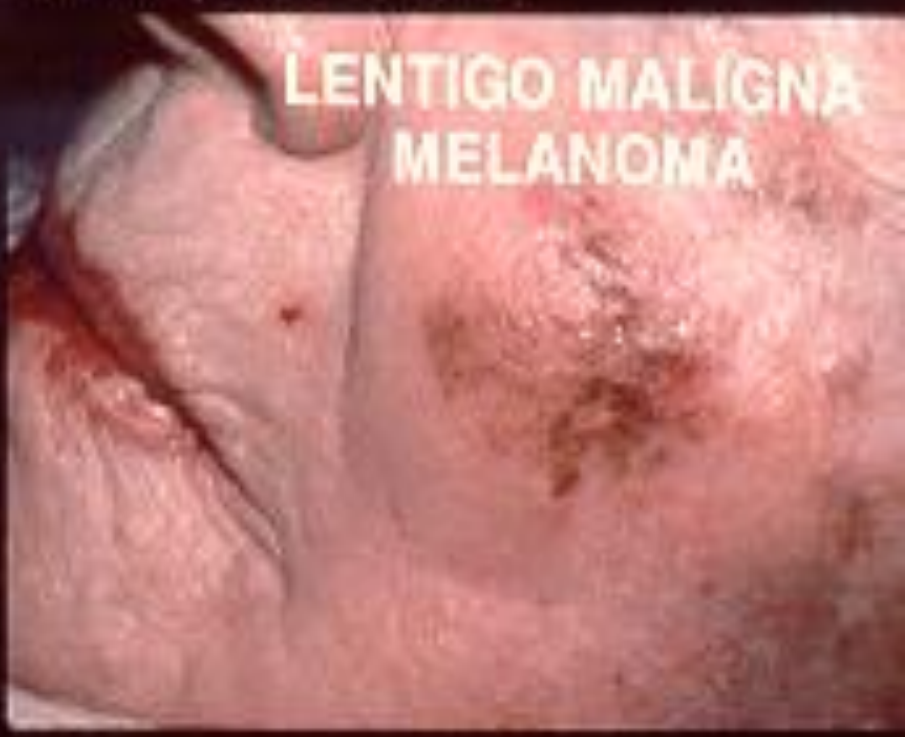
Life time risk incidence MM in USA

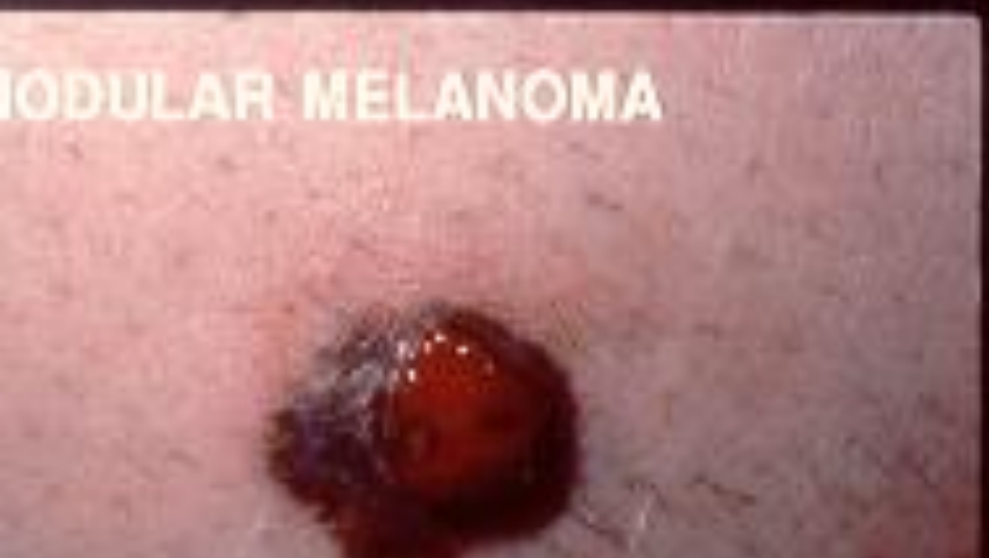


Predisposing Factors

- Sun exposure: UVA, UVB
- Familial atypical mole melanoma syndrome
- Xeroderma Pigmentosa

MALIGNANT MELANOMA





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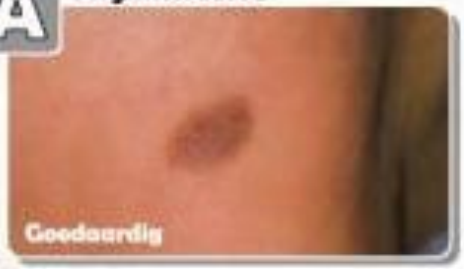
Diagnosis

- History
  - Family History
  - Sun exposure
  - Bleeding, pain
- Physical
  - ABCDE

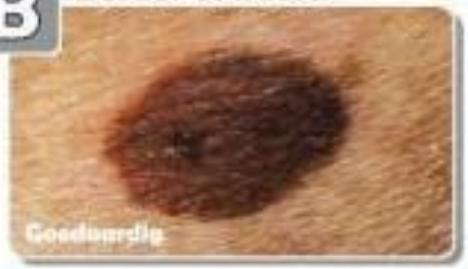
A Asymmetrie



Gewone pigmentvlekken zijn symmetrisch: wanneer je een lijn door het midden van de vlek trekt lijkt de ene helft goed op de andere.

Melanomen zijn meestal asymmetrisch: je bekomt geen gelijke helften.

B Border of boord

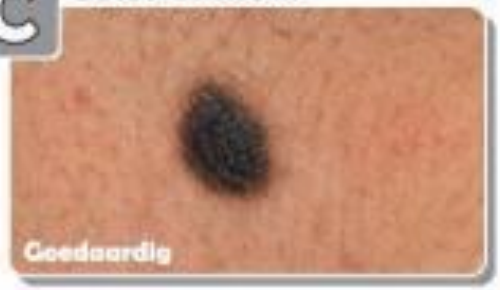


Gewone pigmentvlekken zijn glad, rond of hebben een regelmatige vorm.

Melanomen hebben vaak onregelmatige randen met inkepingen.

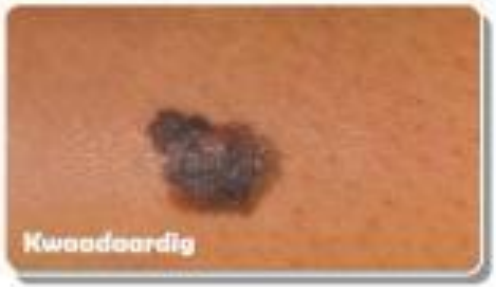
http://www.euromelanoma.org/belgium/folder-abcde

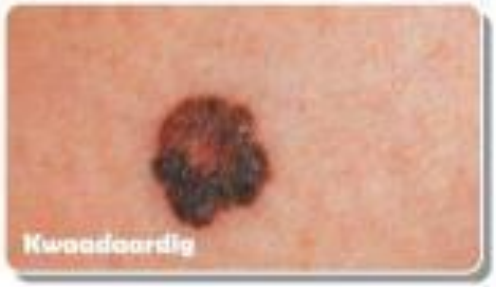
C Color of kleur



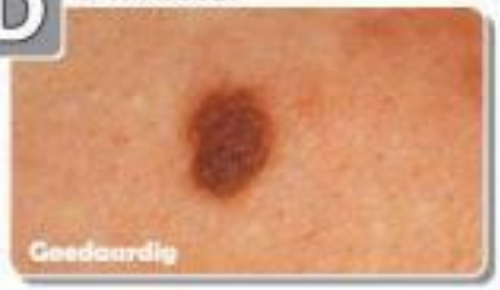
Gewone pigmentvlekken hebben meestal 1 egale kleur.

Kleurschakeringen met verschillende tinten bruin en zelfs zwart, roze, rood en wit zijn vaak een eerste teken van Melanoom.



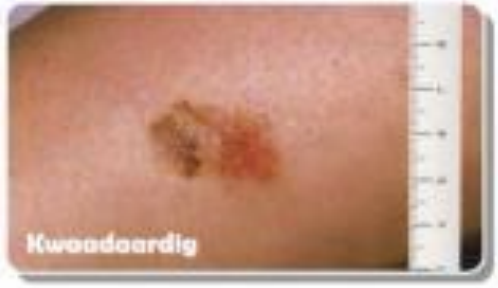


D Diameter



Gewone pigmentvlekken zijn meestal kleiner dan 6 mm in diameter.

Melanoom is meestal groter en neemt toe in diameter en dus in oppervlakte (6 mm = de oppervlakte van het gommetje van een potlood).



E Evolutie

Een pigmentvlek die verandert in de loop van de tijd moet nagekeken worden, zeker als dit gepaard gaat met één van bovenstaande kenmerken.

Hoe meer ABCDE-kenmerken in een vlek voorkomen, hoe verdachter die is.

http://www.euromelanoma.org/belgium/folder-abcde

Biopsy

- Histopathological confirmation remains the golden standard
  - H&E
  - S-100B:

    The protein is present in high concentration in cells of the central nervous system and in melanocytic skin lesions. It is also found in tumours like schwannoma, glioma and malignant melanoma
  - HMB-45: monoclonal antibody

    This antibody reacts with a neuraminidase sensitive oligosaccharide side chain of a glycoconjugate present in immature melanosomes. It reacts with junctional and blue nevus cells. Non-melanocytic cells are negative.

Patients' prognosis

- Defined by
  - Tumour depth
  - Potential ulceration
  - Distant metastases: poor survival 4-6 months

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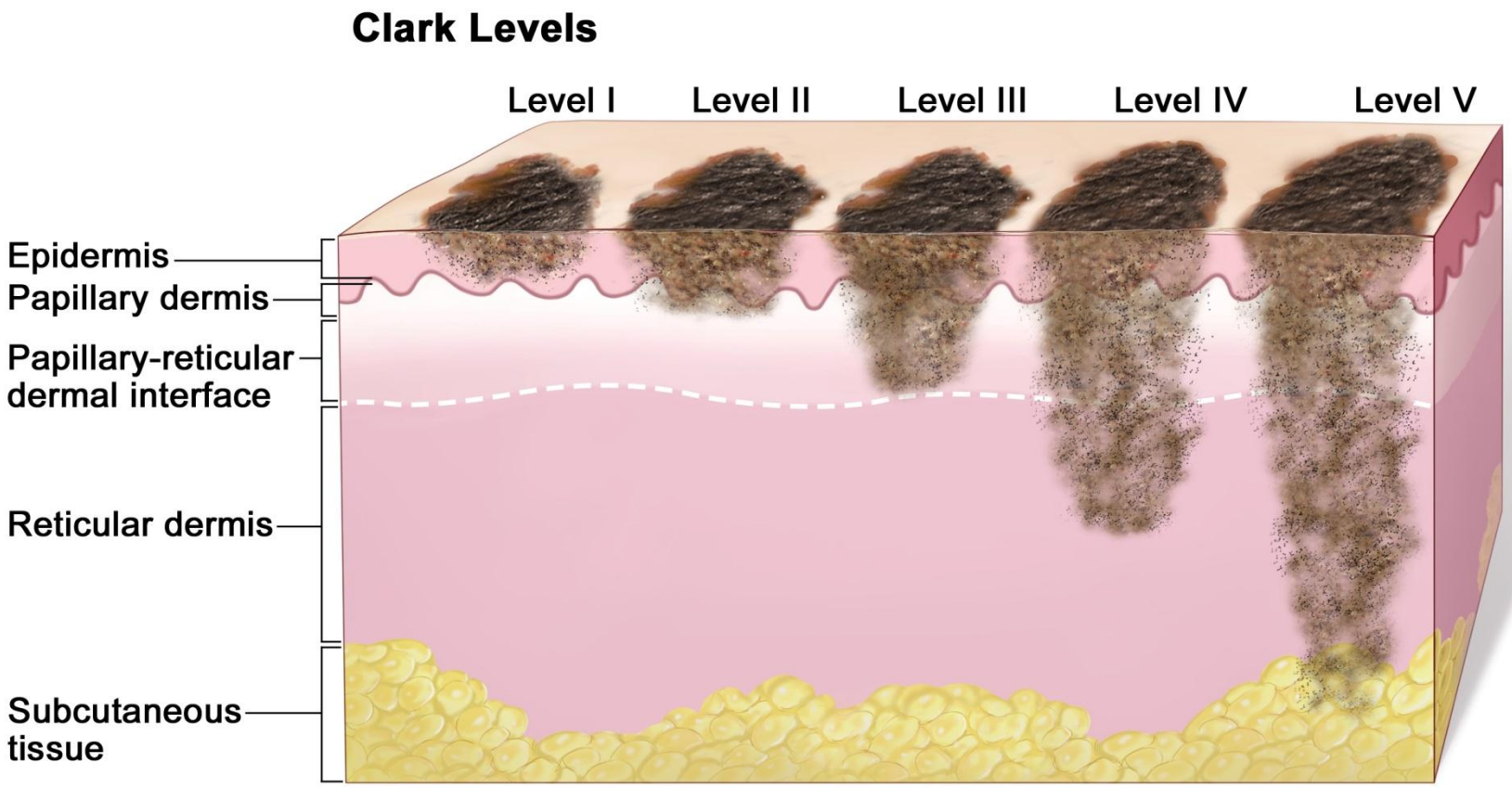
- FDG PET(-CT) IMAGING IN MELANOMA
  - Staging
  - Prognosis and response assessment

Clark Levels



Melanoma TNM classification 2009

Return to article

Table 1. Melanoma TNM Classification

T classification	Thickness	Ulceration Status
T1	≤ 1.0 mm	a: without ulceration and level II/III
		b: with ulceration or level IV/V
T2	1.01-2.0 mm	a: without ulceration
		b: with ulceration
T3	2.01-4.0 mm	a: without ulceration
		b: with ulceration
T4	> 4.0 mm	a: without ulceration
		b: with ulceration
N classification	**No. of Metastatic Nodes**	**Nodal Metastatic Mass**
N1	1 node	a: micrometastasis*
		b: macrometastasis†
N2	2-3 nodes	a: micrometastasis*
		b: macrometastasis†
		c: in transit met(s)/satellite(s) without metastatic nodes
N3	4 or more metastatic nodes, or matted nodes, or in transit met(s)/satellite(s) with metastatic node(s)	
M classification	**Site**	**Serum Lactate Dehydrogenase**
M1a	Distant skin, subcutaneous, or nodal mets	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

*Micrometastases are diagnosed after sentinel or elective lymphadenectomy.

†Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.

Final Version of 2009 AJCC Melanoma Staging and Classification
J. Clin. Oncol., December 20, 2009; 27(36): 6199 - 6206

AJCC 2002 stage groupings for cutaneous melanoma

AJCC 2002 stage groupings for cutaneous melanoma

Stage	Clinical stage grouping*			Pathologic stage grouping•		
0	Tis	N0	M0	pTis	N0	M0
IA	T1a	N0	M0	pT1a	N0	M0
IB	T1b	N0	M0	pT1b	N0	M0
	T2a	N0	M0	pT2a	N0	M0
IIA	T2b	N0	M0	pT2b	N0	M0
	T3a	N0	M0	pT3a	N0	M0
IIB	T3b	N0	M0	pT3b	N0	M0
	T4a	N0	M0	pT4a	N0	M0
IIC	T4b	N0	M0	pT4b	NO	M0
IIIΔ	Any T	N1-3	M0			
IIIA				pT1-4a	N1a	M0
				pT1-4a	N2a	M0
IIIB				pT1-4b	N1a	M0
				pT1-4b	N2a	M0
				pT1-4a	N1b	M0
				pT1-4a	N2b	M0
				pT1-4a/b	N2c	M0
IIIC				pT1-4b	N1b	M0
				pT1-4b	N2b	M0
				Any T	N3	M0
IV	Any T	Any N	Any M1	Any T	Any N	Any M1

* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.
• Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not need pathological evaluation of their lymph nodes.
Δ There are no Stage III subgroups for clinical staging.

Malignant Melanoma:
Relative Survival According to AJCC Stage

Stage	TNM Classification	5 Year Survival Rate (%)
IA	T1a N0 M0	>95
IB	T1b N0 M0	80-95
	T2a N0 M0	
IIA	T2b N0 M0	70-80
	T3a N0 M0	
IIB	T3b N0 M0	50-70
	T4a N0 M0	
IIC	T4b N0 M0	30-50
IIIA	T1-4a N1a M0	60-70
	T1-4a N2a M0	50-60

Malignant Melanoma:
Relative Survival According to AJCC Stage

Stage	TNM Classification	5 Year Survival Rate (%)
IIIB	T1-4a N1b M0	40-50
	T1-4a N2b M0	20-40
	T1-4a/b N2c M0	30-50
	T1-4b N1a/N2a M0	30-45
IIIC	T1-4b N2a M0	20-30
	T1-4b N2b M0	10-30
	Any T N3 M0	10-30
IV	Any T any N M1	5-10
	Any T any N M2	<5
	Any T any N M3	<5

Swetter, Susan M., MD. “Malignant Melanoma. emedicine.medscape.com/article/1100753-print

- INTRODUCTION
  - Incidence
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  - Treatment
- FDG PET(-CT) IMAGING IN MELANOMA
  - Staging
  - Response assessment
  - Prognosis

Treatment

- Excision
- SN procedure with or without lymphadenectomy
- (Intransit) metastases resection
- Adjuvant therapy
  - Chemotherapy: systemic or locoregional
  - Radiotherapy

Role of nuclear medicine in MM

- Sentinel node procedure
- FDG-PET and combined modality PET/CT

CLINICAL AJCC STAGE I/ II: STAGING

Histology regional LN

⇓

Most important prognosticator

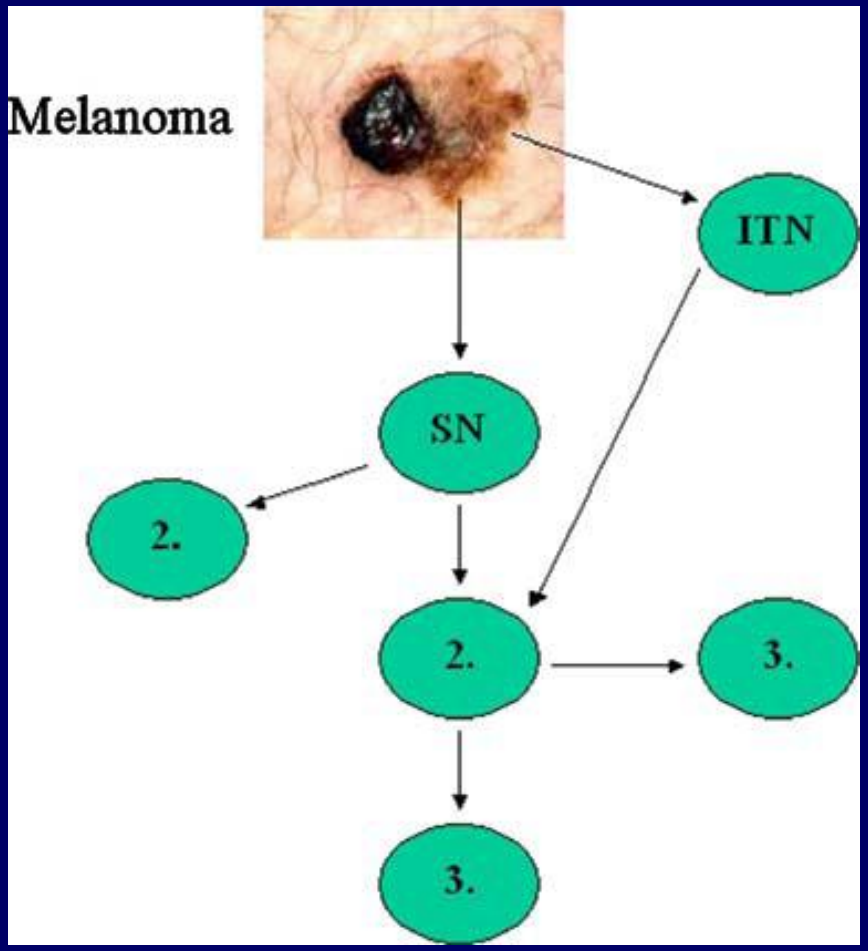
⇓

If +, survival benefit high dose adjuvant interferon α-2b

⇓

Lymph Node mapping/Sentinel Node

Sentinel node principle



SN : sentinel node

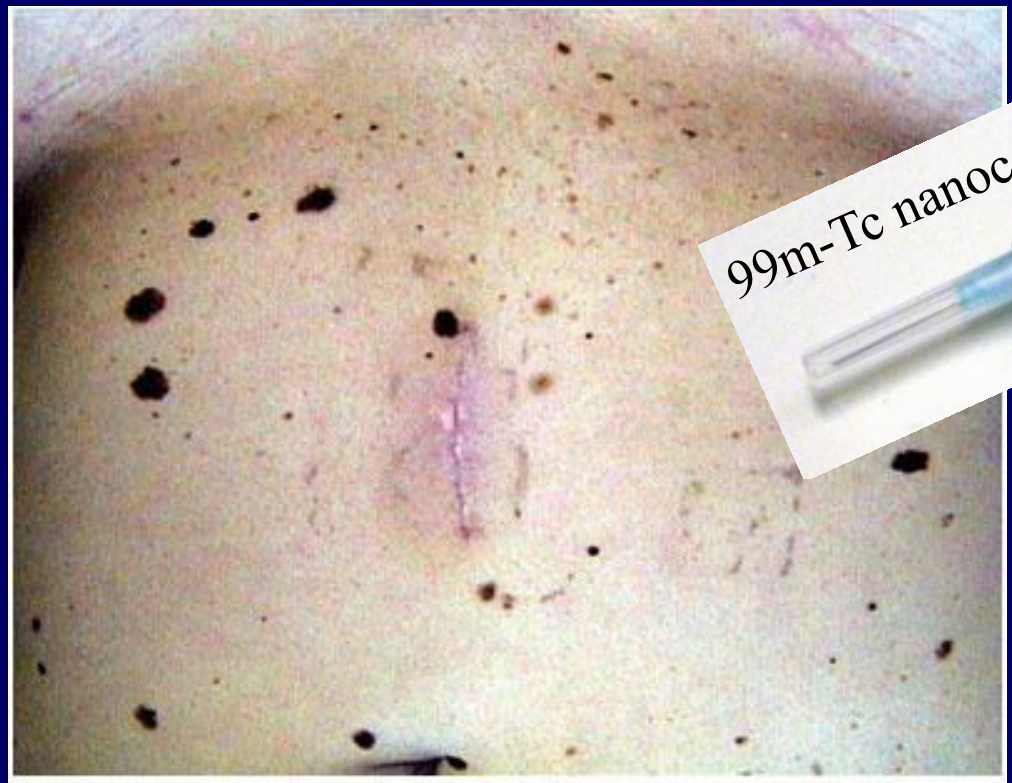
ITN : interval node

2. : second echelon

Interval nodes
The so-called interval or in-transit nodes are lymph nodes lying along the course of a lymphatic collecting vessel, often in subcutaneous fat [9], between the primary tumour and the draining lymph node basin. Such nodes are on a di drainage pathway from the tumour and should be consider to be SNs. They are clinically as important as SNs in recognized lymph node basins. They are reported to be present in between 3 and 10% of the patients [9–12]. Inter nodes should be removed along with the SNs in standard node basins, since they contain metastatic disease almost a often and may represent the only metastatic nodes

Eur J Nucl Med Mol Imaging (2009) 36 : 1713-1742
EANM-EORTC general recommendations for sentinel node diagnostics in melanoma

SLN procedure after resection MM



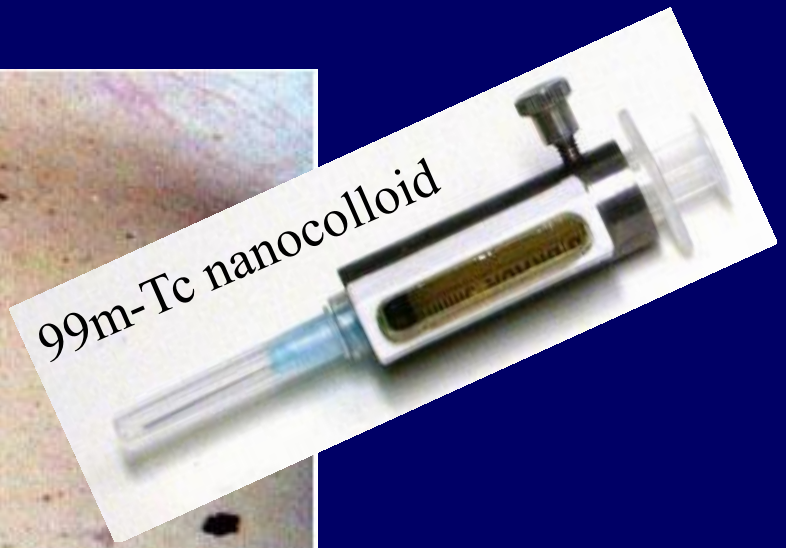
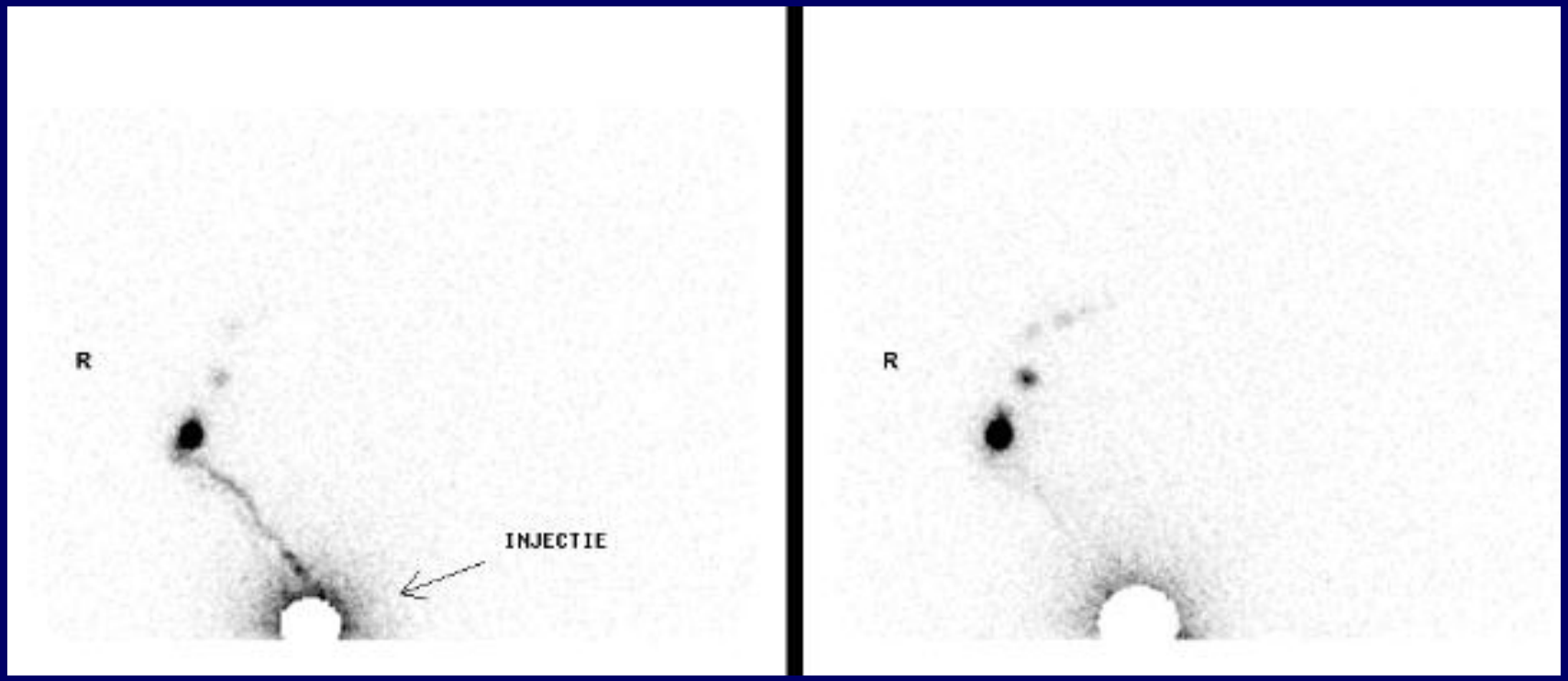


Figure 1: Anterior abdominal wall with a 3 cm long linear scar, resultant from previous exeresis of an extensive superficial melanoma with Breslow 1 mm and Clark level III. Note pigmented lesion on upper left portion of the scar, later diagnosed as *in situ* melanoma

Lymphoscintigraphy



- INTRODUCTION
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- FDG PET(-CT) IMAGING IN MELANOMA
  - Staging (primary and recurrence)
  - Prognosis and response assessment

CLINICAL AJCC STAGE I/ II :
FDG-PET (-CT)in primary staging

	Nb	***Stage***	***Sens***	***Spec***
Wagner et al. *J Clin Oncol 1999*	70	I/II	9 %	93 %
Wagner et al. *Cancer 2005*	144	I/II	21 %	97 %
Singh et al. *Mel Res 2008*	*52*	I/II	14 %	95 %

CLINICAL AJCC STAGE III/IV :
FDG-PET (-CT) in primary staging

	Nb.	*Stage*		*Sens*	*Spec*	*Accuracy*
Strobel et al. *Radiology 2007*	124	III/IV	PET/CT	98%	94%	96%
Pfannenberg et al. *Eur J Cancer 2007*	64	III/IV	PET/CT			86.7%

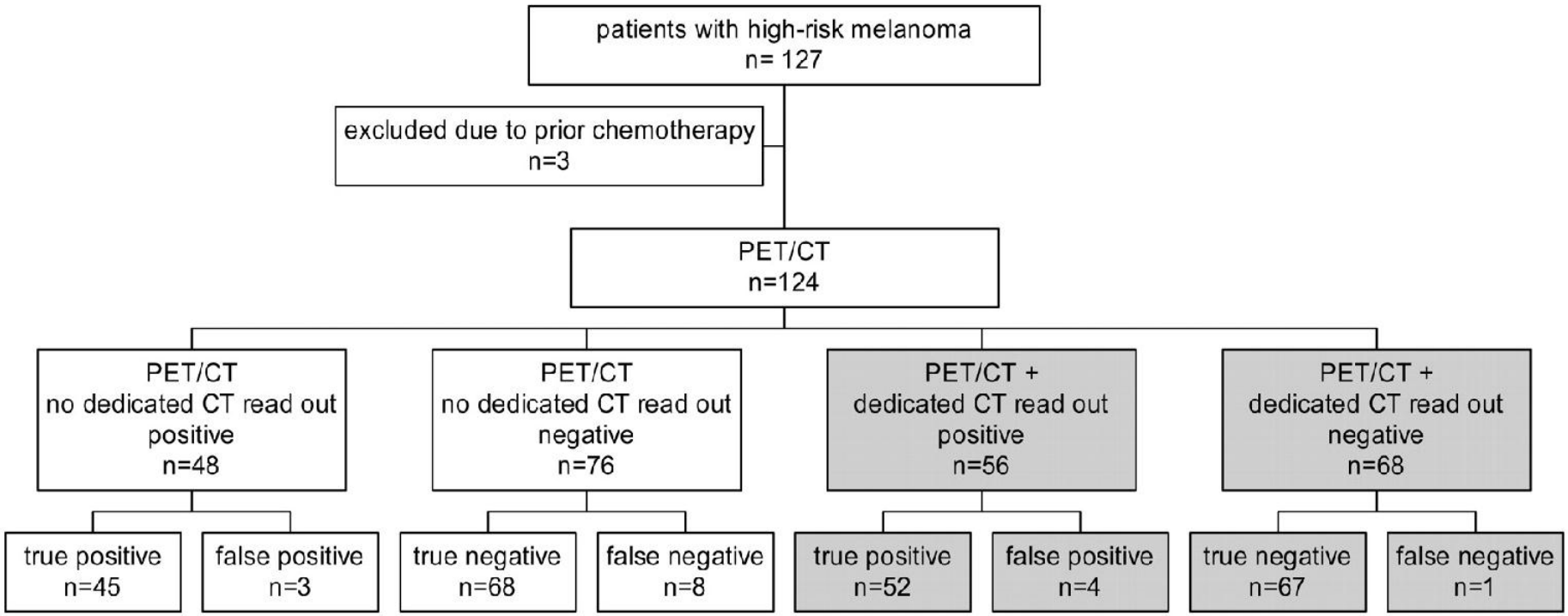
High-risk Melanoma: accuracy of FDG-PET/CT with added CT morphologic information for detection of metastases

- Prospectively, n=124
- In 53/124: metastases were found
  - 46/53 had increased FDG uptake
  - 7/53 had no or faint FDG uptake
    - In coregistration with CT: interpreted as metastases, mostly lung lesions

	Sensi	Speci	Accuracy
PET	85%	96%	91%
PET/CT	98%	94%	96%

Strobel et al, EJNMI 2007

High-risk melanoma: accuracy of FDG PET/CT with added CT morphologic information for detection of metastases



Strobel, Radiology, August 2007, 244: 566-574

Parameter	PET/CT	PET/CT plus Dedicated CT Interpretation
Sensitivity	85 (45/53)	98 (52/53)
Specificity	96 (68/71)	94 (67/71)
Positive predictive value	94 (45/48)	93 (52/56)
Negative predictive value	89 (68/76)	99 (67/68)
Accuracy	91 (113/124)	96 (119/124)

Strobel, Radiology, August 2007, 244: 566-574

Prospective comparison of 18F-FDG PET/CT and whole body magnetic resonance imaging in staging of advanced MM

- Overall accuracy PET/CT 86.7% ⟷ overall accuracy wb MRI 78.8%
- PET/CT more accurate
  - in N staging
  - Detecting skin M+
  - Subcutaneous M+
- MRI more sensitive in
  - Liver M+
  - Bone M+
  - Brain M+
- MRI less sensitive, but more specific in lung M+
- WB imaging changes treatment in 64% of patients
- WB staging in advanced MM: most accurate combining wb PET-CT and organ specific wb MRI including brain, liver and bone marrow protocol

Pfannenberg et al, Eur J Cancer 2007 Feb;43 (3): 557-64

Recurrence and mixed groups

	Nb
• Fuster et al, JNM 2004	112
• Reinhardt et al. *J Clin Oncol 2006*	250
• Mottaghy et al. *EJNMI 2007*	102

Is 18F-FDG PET more accurate than standard diagnostic procedures in the detection of suspected recurrent melanoma?

- n = 112
- Cinical suspicion of recurrent disease
- Stage I and II: 65% locoregional recurrence
- Stage III and IV: 72% distant recurrence

	Patient based sensitivity	Patient based specificity	Overall accuracy
PET	74%	86%	81%
CT	58%	45%	52%

Fuster et al, JNM 2004; 45:1323-1327

Is 18F-FDG PET more accurate than standard diagnostic procedures in the detection of suspected recurrent melanoma?

- PET is better than standard diagnostic clinical procedures in detecting locoregional disease and distant metastases at all sites except the lung.

- The use of PET as a routine clinical tool can lead to substantial change in the clinical management of suspected recurrent melanoma: 36%

Fuster et al, JNM 2004; 45:1323-1327

Diagnostic performance of whole-body dual modality 18F-FDG PET/CT imaging for N- and M- staging of malignant melanoma: experience with 250 consecutive patients

- N=250, retrospective, stage I-IV and different time points in course of disease
- Treatment change to PET/CT findings 48.4%

	Overall accuracy	Accuracy N staging	Accuracy M staging
PET	92.8%	92%	93%
CT	78.8%	86%	84%
PET/CT	97.2%	98%	98%

Reinhardt, March 2006, JCO, volume 24, number 7

Table 1. Patient and Tumor Characteristics

				No. of Patients											
				Histology				Tumor Depth (mm)				AJCC Stage			
	No. of Patients	Female/Male (No. of patients)	Age (years)	NM	SSM	ALM	LMM	≤ 1.0	1.01-2.0	2.01-4.0	> 4.0	I	II	III	IV
Primary staging	75	30/45	54 ± 18	35	25	6	1	8	22	16	21	7	26	37	5
Therapy control	42	17/25	58 ± 16	17	12	6	1	6	4	12	14	2	6	19	15
Recurrence staging	65	25/40	64 ± 14	27	26	6	2	11	13	17	20	10	17	31	7
Follow-up	68	33/35	57 ± 14	34	18	9	2	4	29	21	9	3	39	21	5

NOTE. AJCC stage is initial pathology staging. Patients with occult melanoma (N = 23) were not included in histology and tumor depth. Patients with occult melanoma and lymph node metastases were considered as N-positive.
Abbreviations: AJCC, American Joint Committee on Cancer; NM, nodular melanoma; SSM, superficial spreading melanoma; ALM, acral lentiginous melanoma; LMM, lentigo maligna melanoma.

Table 9. Detection of Visceral and Nonvisceral Metastases by CT, FDG-PET, and FDG-PET/CT*

	CT		FDG-PET		PET/CT		
	No.	%	No.	%	No.	%	Total No.
Nonvisceral	279	74.0	353	93.6	368	97.6	377
Visceral	188	64.2	242	82.6	293	100	293
Total	467	69.7	595	88.8	661	98.7	670

NOTE. This comparison included all 670 metastases detected according to the standard of reference.
Abbreviations: CT, computed tomography; FDG, [^{18}F]-fluorodeoxyglucose; PET, positron emission tomography.
*Nonvisceral, CT versus PET and CT versus PET/CT: $P \leq .00001$; PET versus PET/CT, $P \leq .005$; visceral and total, $P \leq .00001$ for all comparisons.

Reinhardt, March 2006, JCO, volume 24, number 7

Diagnostic performance of whole-body dual modality 18F-FDG PET/CT imaging for N- and M- staging of malignant melanoma: experience with 250 consecutive patients

- PET/CT detected more visceral and nonvisceral metastases compared to PET alone or CT alone

- PET/CT has a high diagnostic performance for N- and M-staging of melanoma patients
  - whole body imaging
  - Detection or exclusion of distant metastases

Direct comparison of 18F-FDG PET/CT with PET alone and with side-by-side PET and CT in patients with MM

- Retrospective, 127 scans in 102 pts, stages between Ia and IIIb
- Heterogenous population:
  - > 1 mm tumour depth: 57 high risk, 25 low risk
  - 49 primary staging, 78 restaging

	Sens	Spec	PPV	NPV
PET alone	86%	94%	96%	80%
Side-by-side PET-CT	89%	94%	96%	83%
PET-CT	91%	94%	96%	87%

Mottaghy et al, EJNMI 2007, Sep; 34(9): 1355-64

- Early stage MM: PET/CT did not lead to change in treatment. Ultrasound is superior.
- PET/CT should be included in stage III and IV.
- PET/CT offers better lesions localisation and characterisation.

Mottaghy et al, EJNMI 2007, Sep; 34(9): 1355-64

Meta-analyses in staging malignant melanoma

Meta-analyses

			Sens	***Spec***
Mijnhout et al.	*Cancer 2001*	11 studies	79%	86%
Krug et al.	*Radiology 2008*	28 studies (2905 pt)	83%	85%

⇓

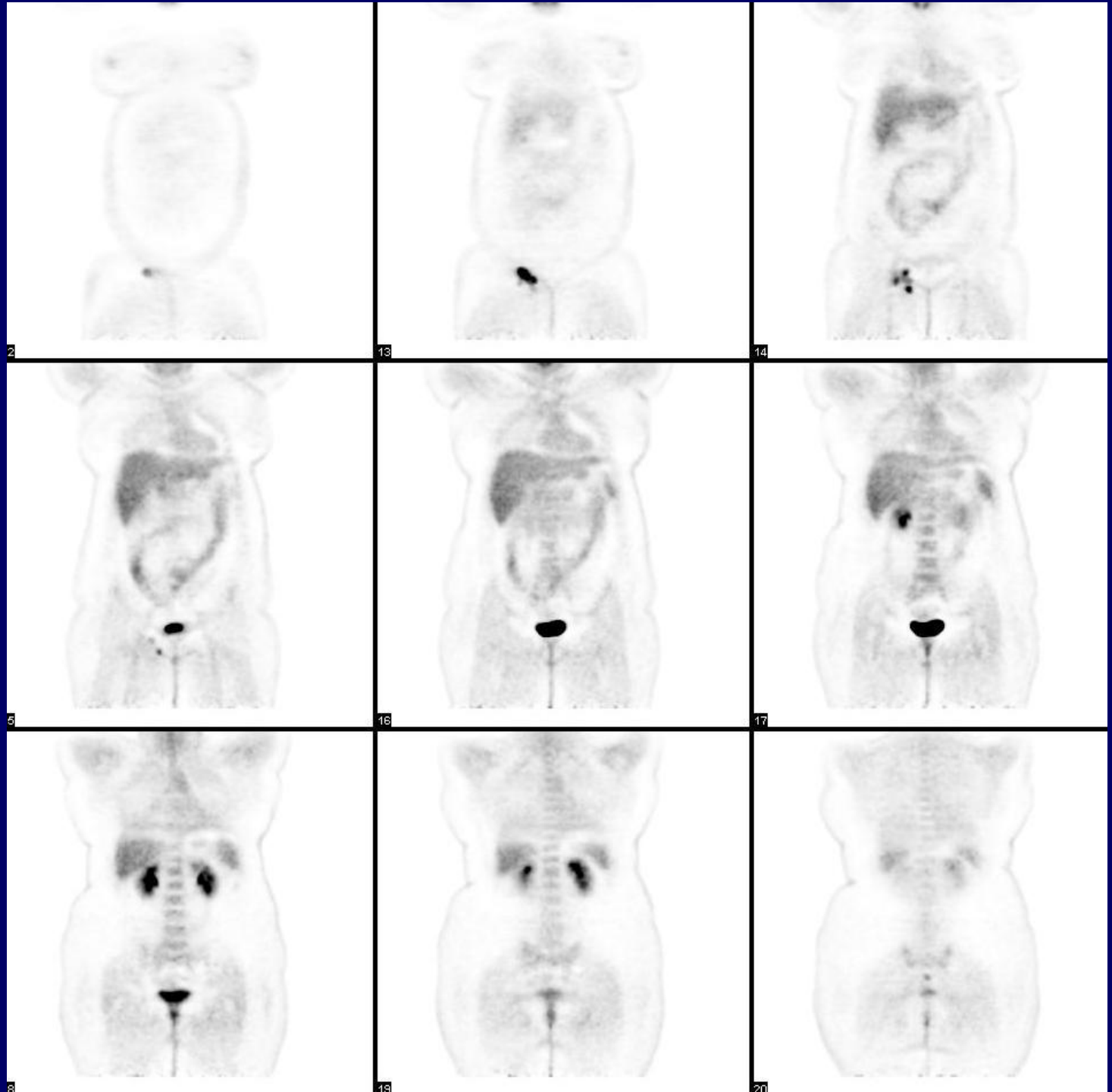
- stage I/II: PET is inferior to SLNB
- stage III/IV: PET could replace conventional imaging in staging except for brain (MRI) and lung (CT)
- management change in 15%-64% of pts
- PET/CT more precise than PET alone
- lower limit of PET resolution is 80 mm^3
- malignant melanoma is typically FDG avid

Conclusions staging MM

- FDG-PET can not replace SN procedure for detection of micrometastasis in stage I-II
- FDG-PET could replace conventional imaging in stage III and IV MM
  - Except brain: MRI
  - Lung: CT
- FDG-PET can alter treatment in stage III and IV MM
- Hybrid PET/CT imaging provides better localisation and charaterisation of lesions

PBR, female, 37 y

- History of melanoma in the right lower limb (stage IIB at primary diagnosis)
- Presenting with painless swelling of the right groin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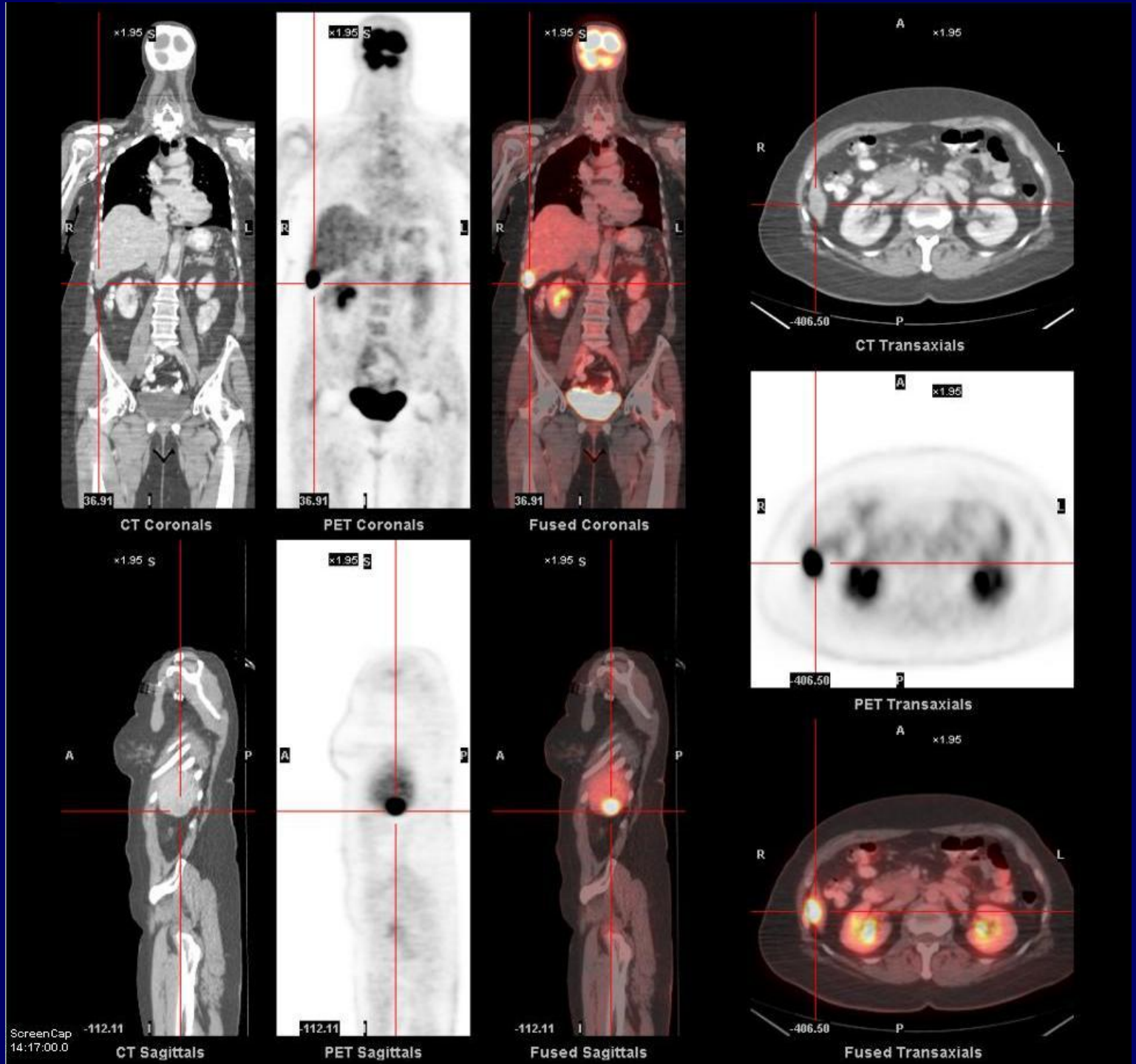
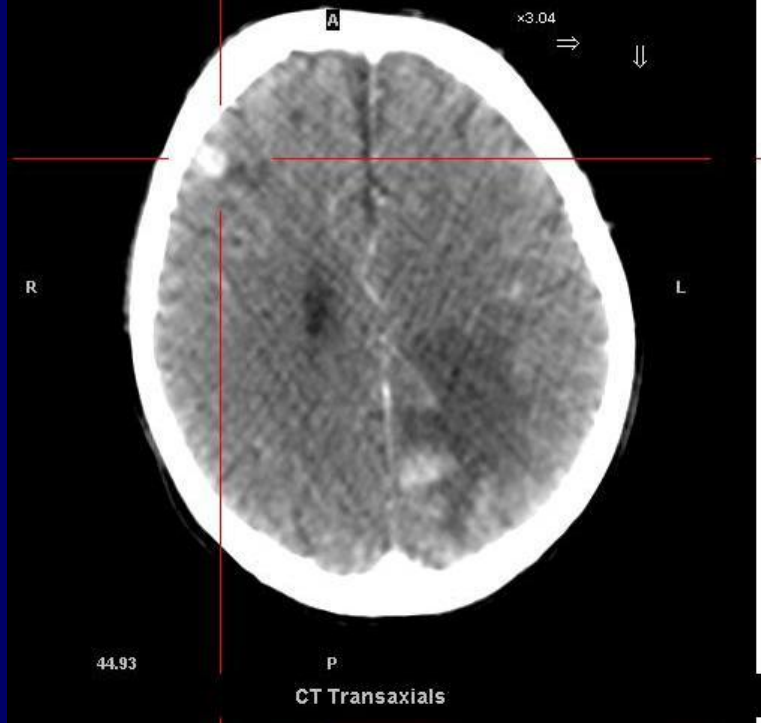

CT Coronals
PET Coronals
Fused Coronals
CT Transaxials
PET Transaxials
CT Sagittals
PET Sagittals
Fused Sagittals
Fused Transaxials
ScreenCap
14:17:00.0

VRO, male, 36 y

-Jan 2006: resection malignant melanoma right scapula, stage IIA, no PET scan performed

-Re-excision with negative sentinel node

- oktober 2007: epileptic insult



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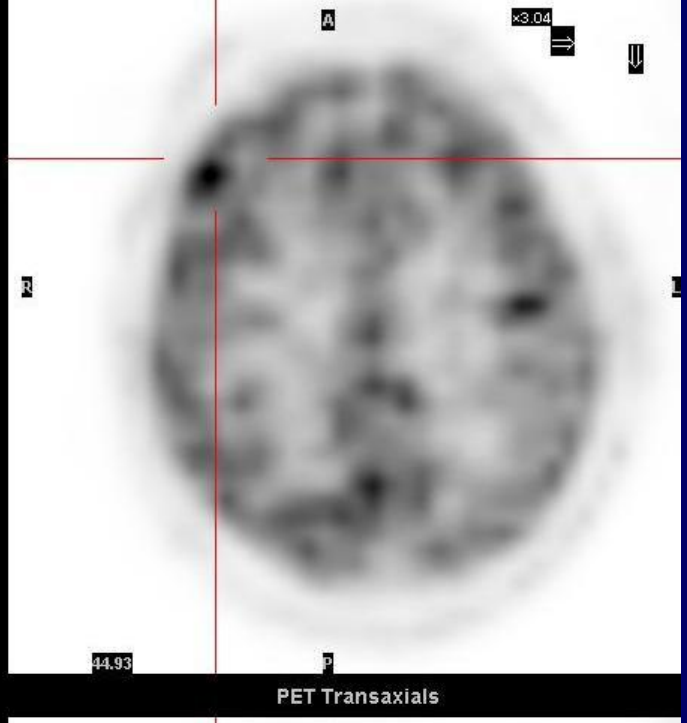

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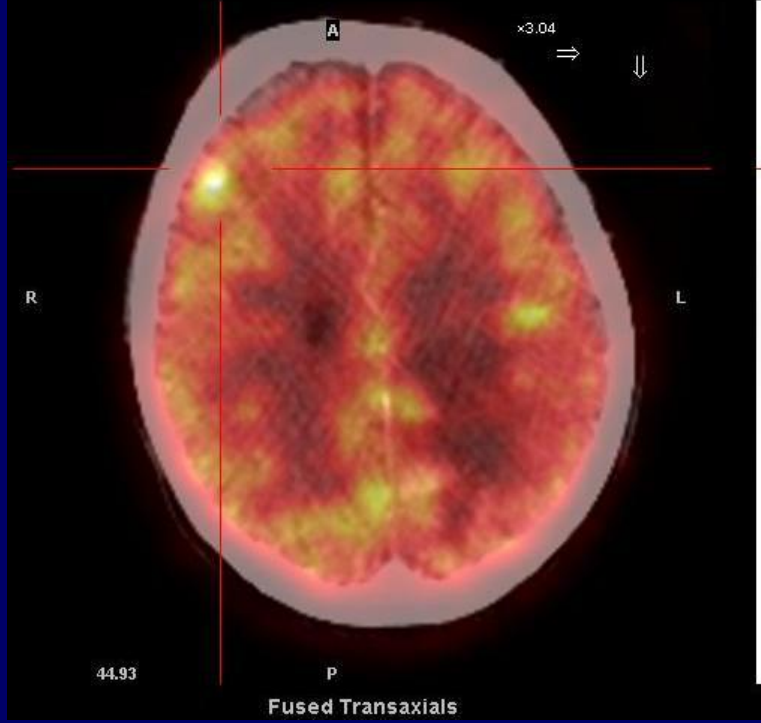

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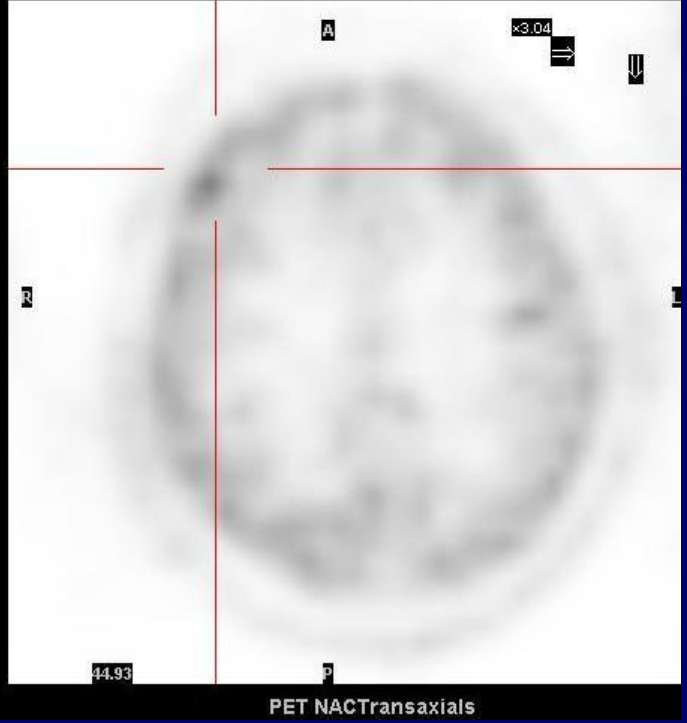
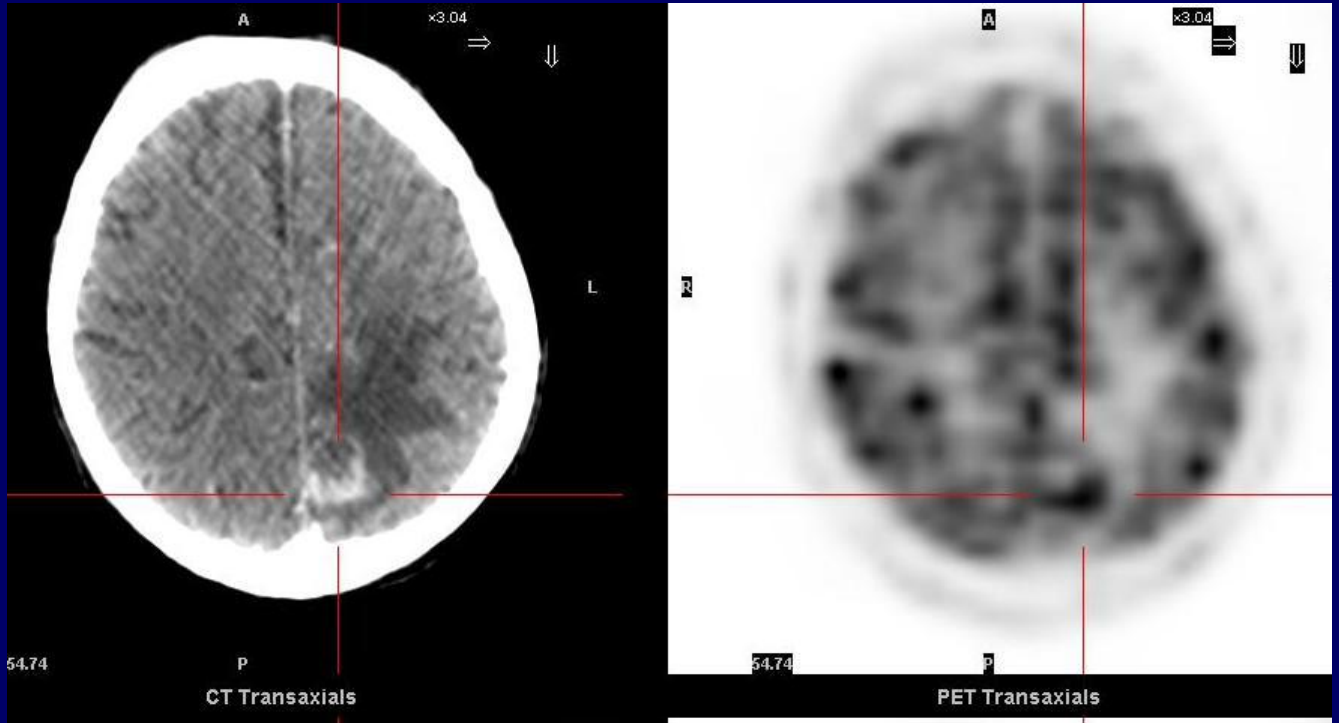


PET NACTransaxials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CT Transaxials

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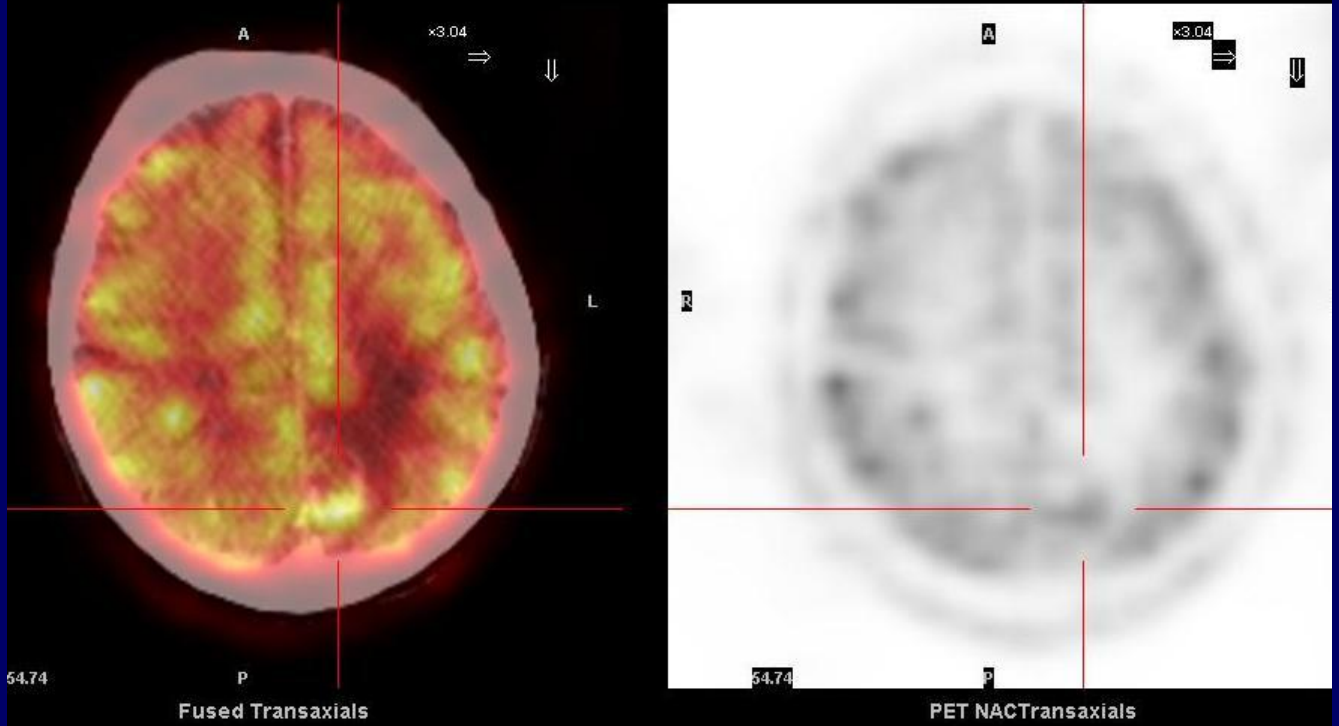
PET Transaxials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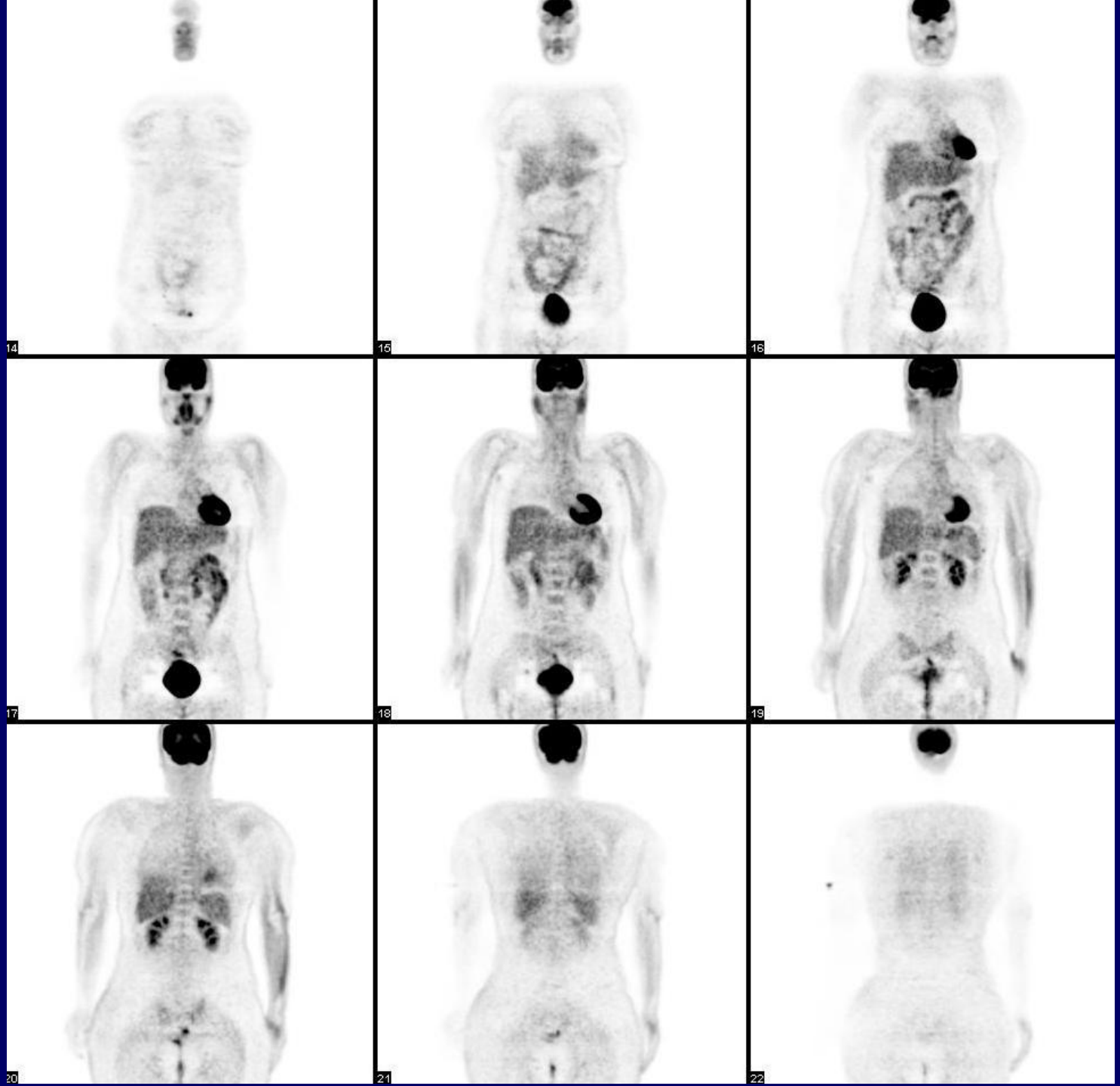
PET NACTransaxials

JKA, female, 22 y

One year follow-up after resection
of stage IIIA melanoma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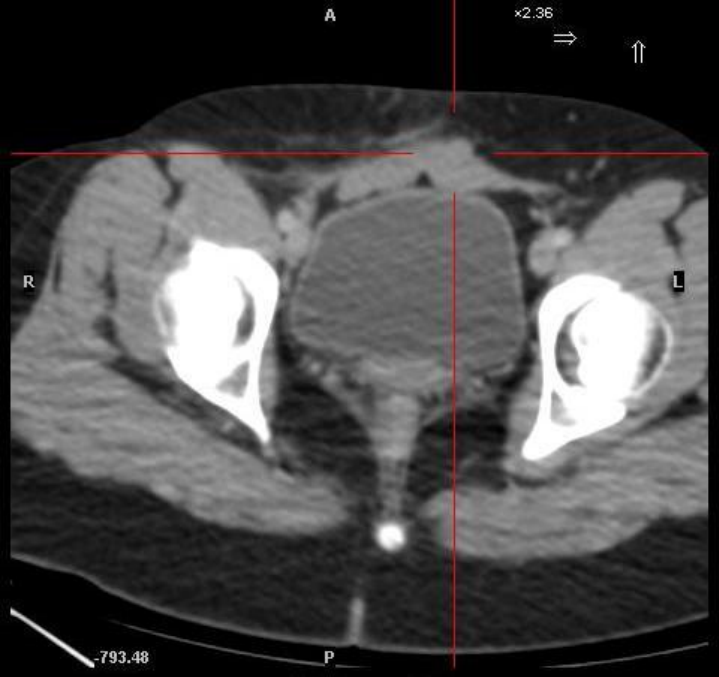

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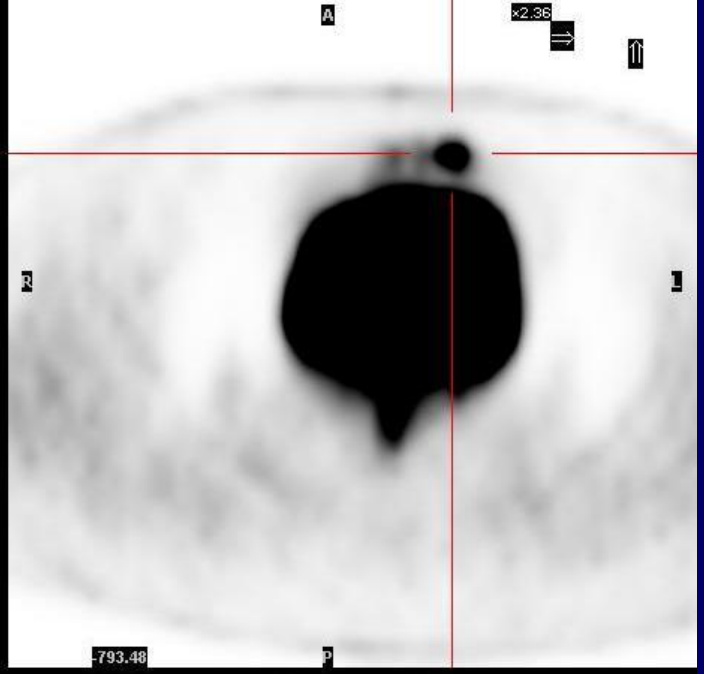

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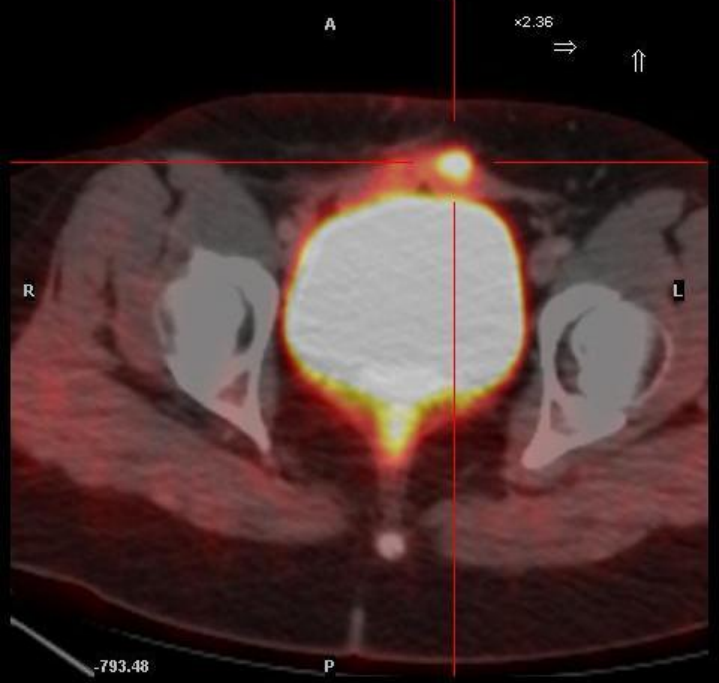

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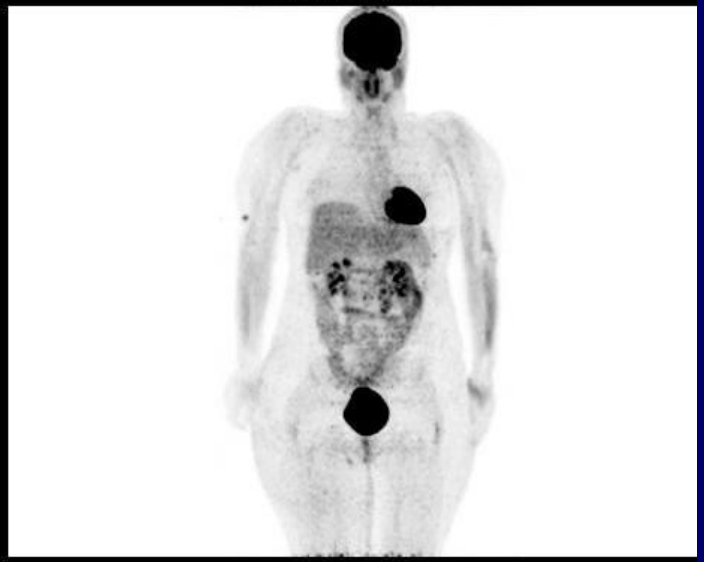
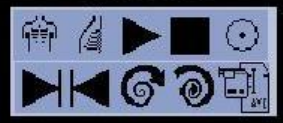
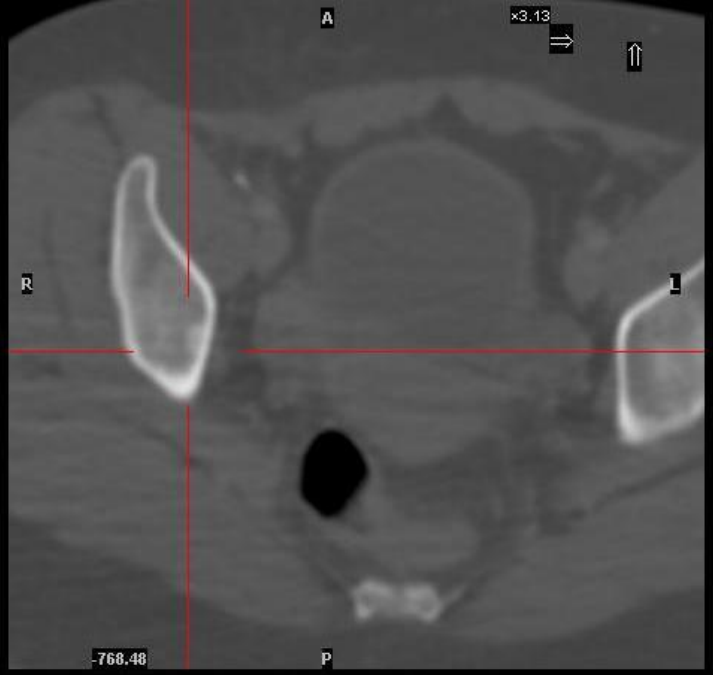




MIP Navigate



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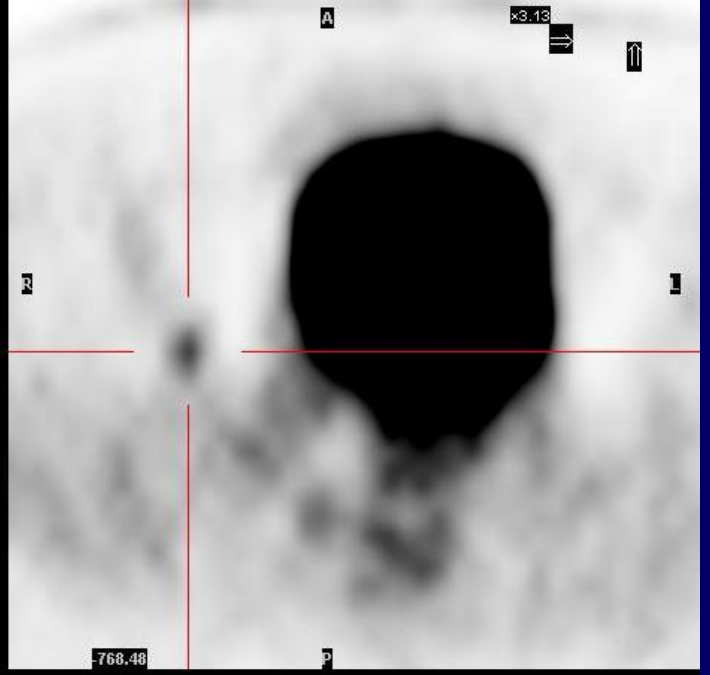

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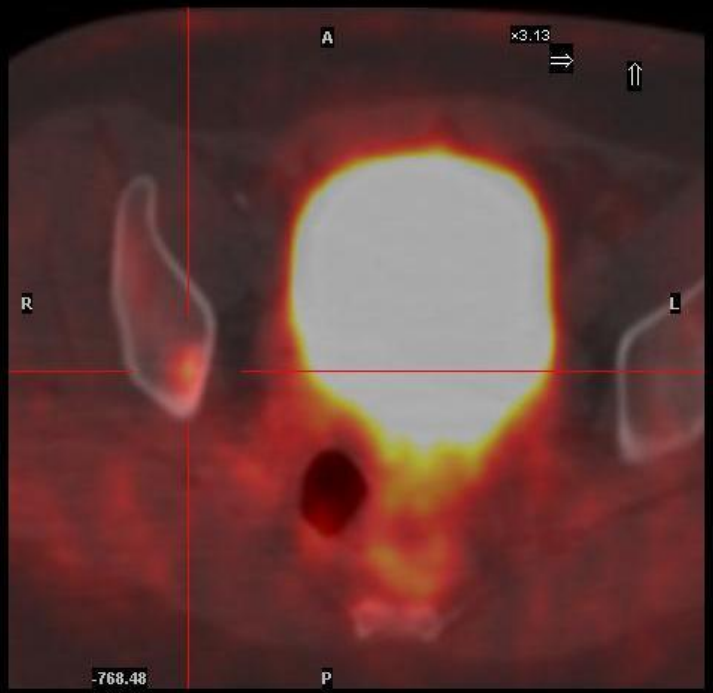

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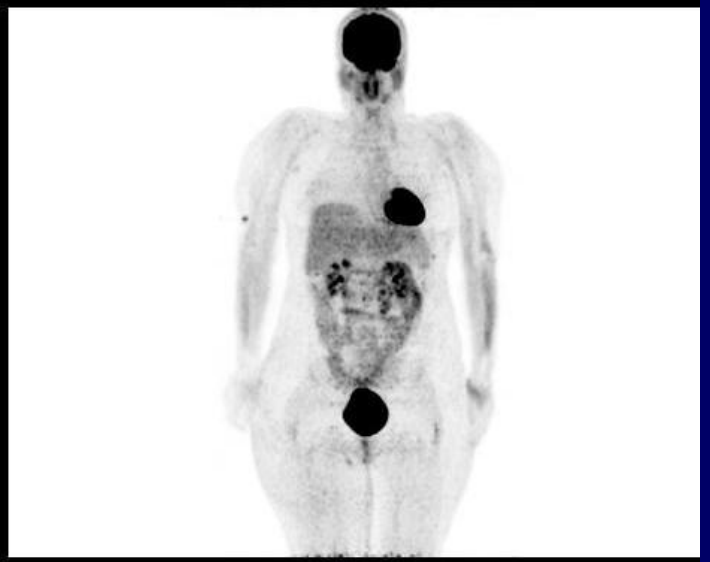

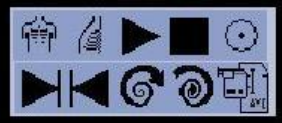

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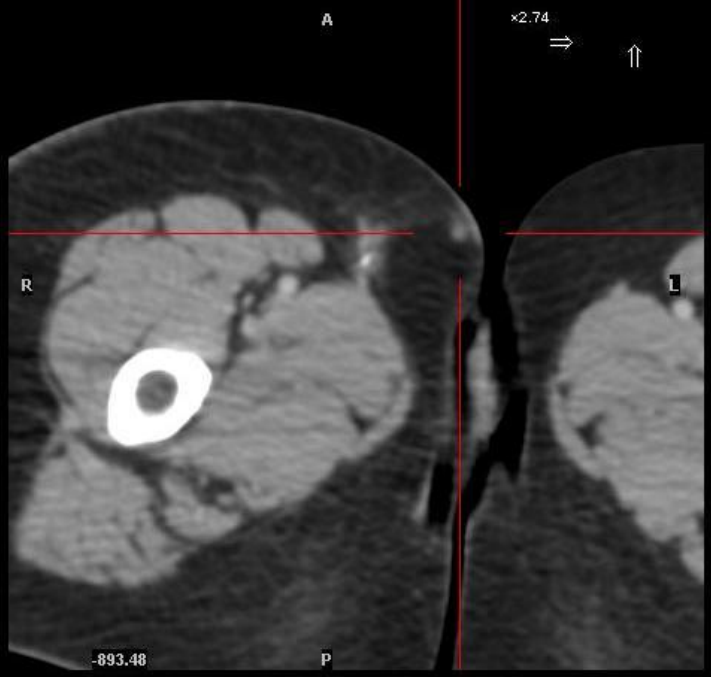

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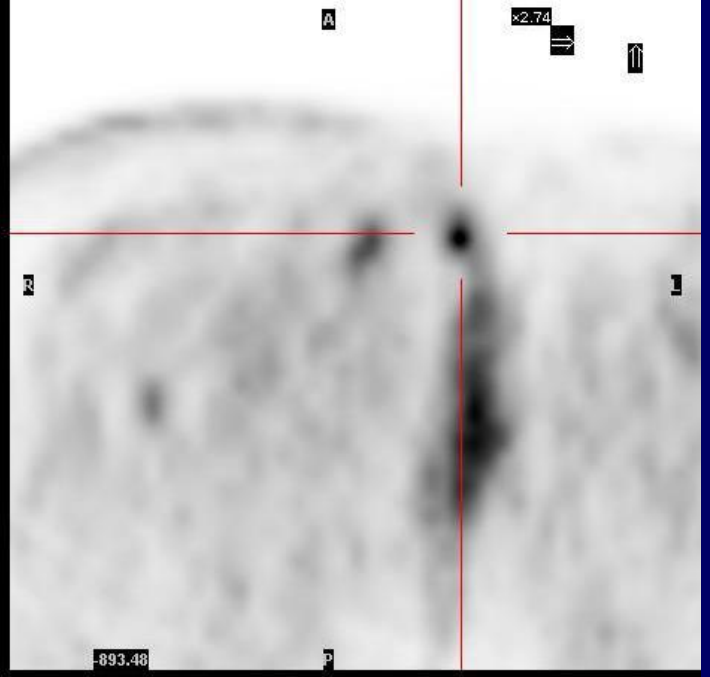

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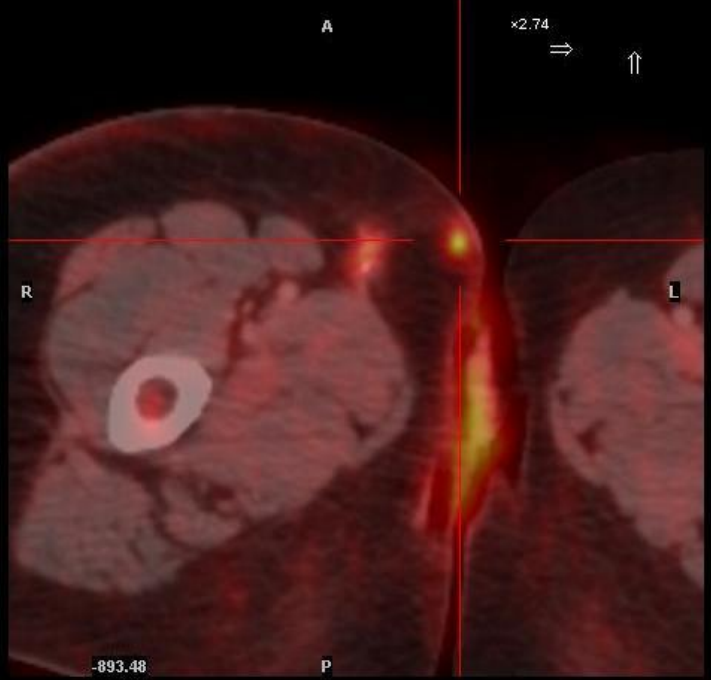

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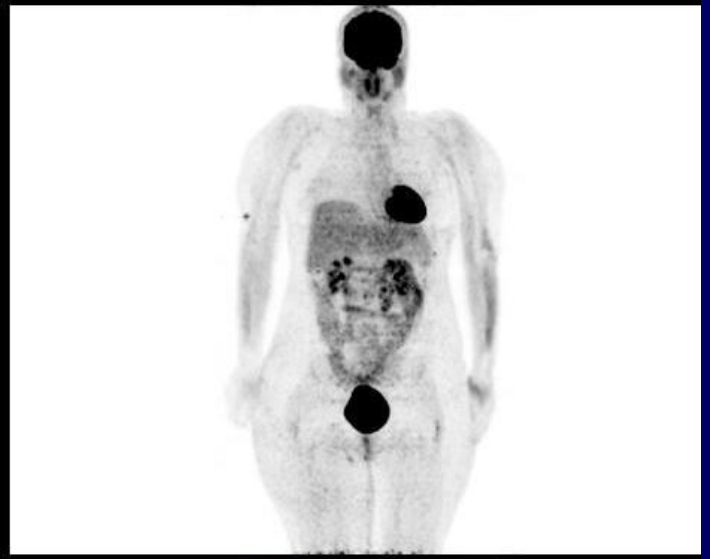

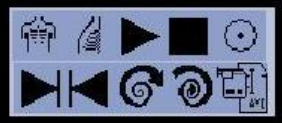

MIP Navigate

- INTRODUCTION
  - Incidence
  - Diagnosis
  - Staging
  - Treatment

- FDG PET(-CT) IMAGING IN MELANOMA
  - Staging

  - Prognosis and response assessment

PET-CT in prognosis and response evaluation

- Bastiaannet et al, Ann Surg Oncol 2006 Jul;13(7): 919-26
- Hofman et al, Nucl Med Commun 2007
- Strobel, EJNMI 2008

Level of FDG uptake predicts risk for recurrence in melanoma patients presenting with lymph node metastases

- N = 38 pts, retrospective
- No statistical difference in survival with low or high SUVmean
- DFS prolonged with low SUV mean

Bastiaannet et al, Ann Surg Oncol 2006 Jul;13(7): 919-26

Level of FDG uptake predicts risk for recurrence in melanoma patients presenting with lymph node metastases

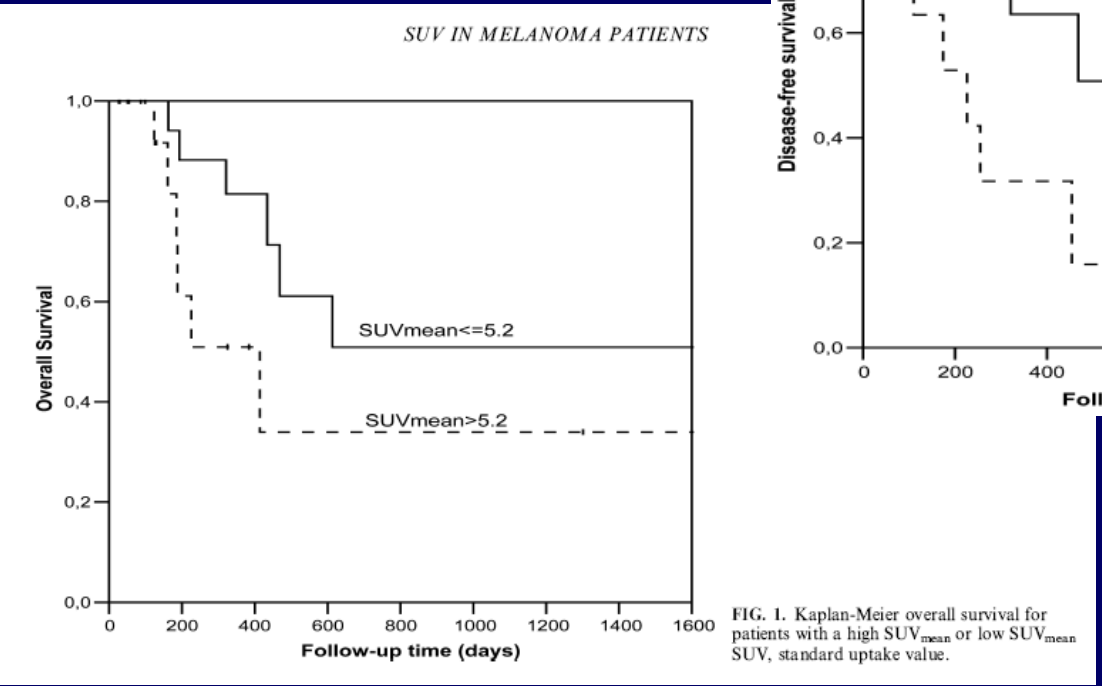

FIG. 1. Kaplan-Meier overall survival for patients with a high SUV_{mean} or low SUV_{mean} SUV, standard uptake value.

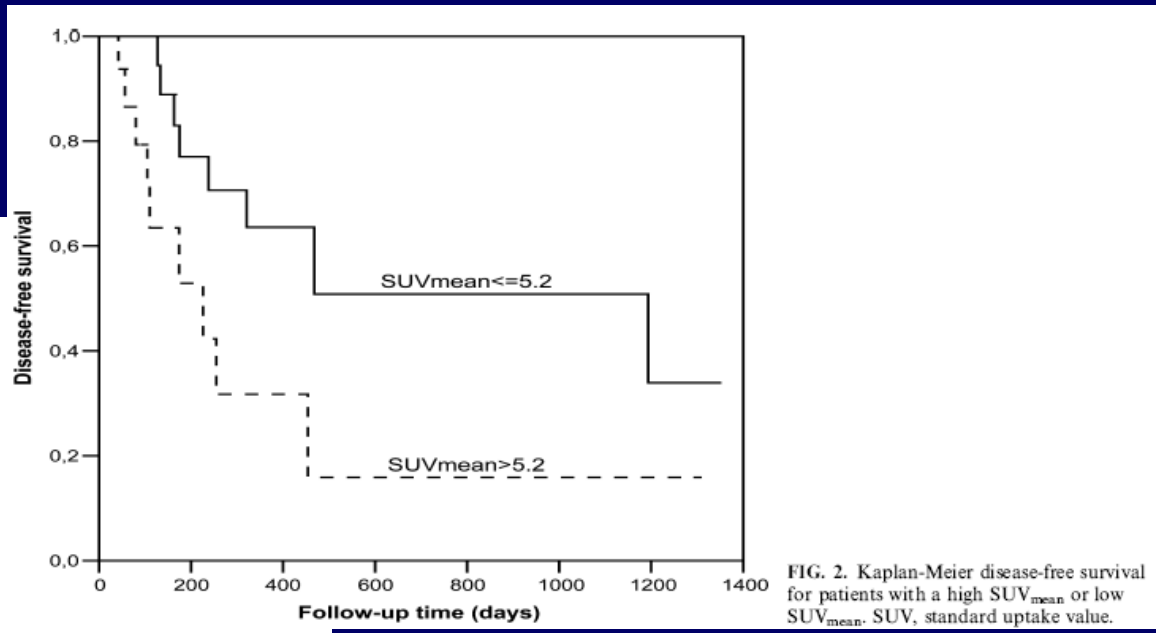

FIG. 2. Kaplan-Meier disease-free survival for patients with a high SUV_{mean} or low SUV_{mean}. SUV, standard uptake value.

Bastiaannet et al, Ann Surg Oncol 2006 Jul;13(7): 919-26

Assessing response to chemotherapy in metastatic melanoma with FDG-PET: early experience

- 7 patients
- Baseline PET and after 2-3 cycles of chemotherapy
- All metastases had intense FDG uptake at baseline
- CMR longest mean survival

	N° out of 7	Mean survival in days
CMR	1	679
PMR	2	206
PMD	4	129

Hofman, Nucl Med commun 2007 Dec; 28 (12): 902-6

Chemotherapy response assessment in stage IV melanoma patients-comparison of 18F-FDG-PET/CT, CT, brain NMR and tumormarker S-100B

- Stage IV melanoma:
  - incurable
  - poor 5y survival of 6%
  - brain M+ in 18% to 46% of pts
- Need for tools to evaluate early succes or failure of chemotherapy
- N = 25 pts, proven distant M+
- Different chemotherapy

Strobel, EJNMI (2008) 35: 1786-1795

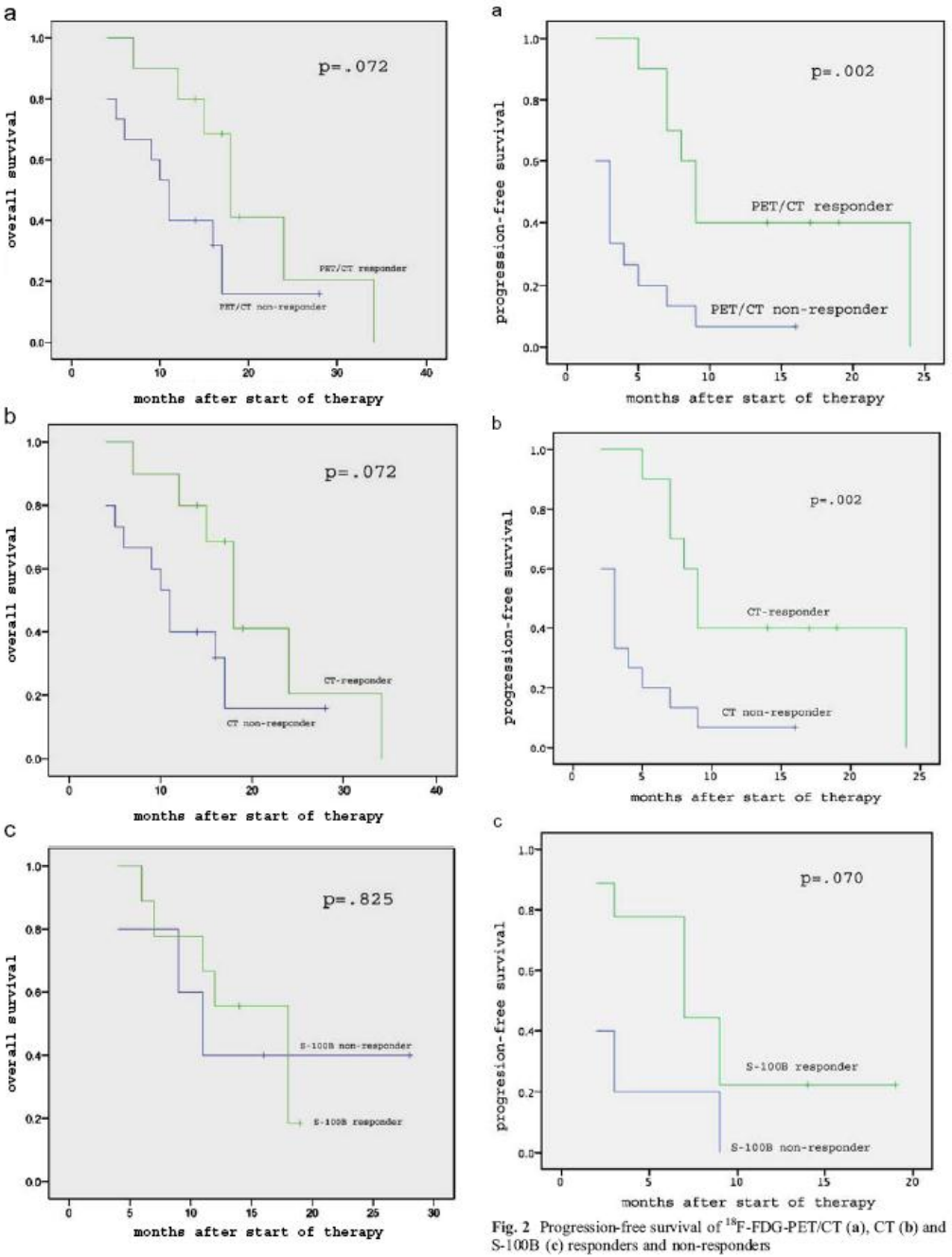

Fig. 2 Progression-free survival of ^{18}F-FDG-PET/CT (a), CT (b) and S-100B (c) responders and non-responders

Strobel, EJNMI (2008) 35: 1786-1795

Chemotherapy response assessment in stage IV melanoma patients-comparison of 18F-FDG-PET/CT, CT, brain NMR and tumormarker S-100B

- PET-CT and CT alone show complete agreement in responders vs non-responders
- 36% pts failed to show elevated S-100B values despite proven distant metastases

Strobel, EJNMI (2008) 35: 1786-1795

CONCLUSIONS

In melanoma patients, FDG PET is useful:

- For primary staging of advanced clinical stage melanoma and in tumor recurrence
- Hybrid PET-CT offers the best sensitivity and specificity
- Response assessment and prognosis: further studies are needed

In melanoma patients, FDG PET is not useful:

- For staging of clinical stage AJCC I/≤IIb