

Lung carcinoma

Signs

- Finger clubbing
- Nicotine staining
- Cervical sympathetic (Horner's syndrome)=
partial ptosis/ miosis (pupil constriction)/
enophthalmos/ anhydrosis
- Wasting of hand

Lung carcinoma

Differential diagnosis

- Benign tumors-papilloma/ carcinoid/ leiomyoma
- Metastasis
- Primary malignant-mesothelioma/ soft tissue sarcoma
- Chronic lung abscess
- Radiographic artifact-nipple shadow

Lung carcinoma

Investigation

- CXR
- Sputum cytology
- Bronchoscopy
- CT
- MRI
- Bone scan
- Indirect laryngoscopy
- Lung function test

TNM STAGING OF LUNG CANCER

Supraclavicular Scalene(ipsi-/contralateral)	Mediastinal (contralateral) (ipsilateral)	Subcarinal (contralateral) (ipsilateral)	Hilar (contralateral) (ipsilateral)	Peribronchial (ipsilateral)	LYMPH NODE (N)
+	+	+	+	+	N3
-	-	+	+	-	N2
-	-	-	-	+	N1
-	-	-	-	-	N0

Stage IV
M1 (any T, any N)

Stage III B

Stage III A

Stage II A Stage II B

Stage I A Stage I B Stage II B

MO

Stage 0
(Tis, N0, M0)

METASTASES (M)
M0 : Abscent
M1 : Present
Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1

Tis : Carcinoma *in situ*

Staging is not relevant for Occult Carcinoma(Tx, N0,M0)

* Including direct extension to intrapulmonary nodes
** Including superior sulcus tumor

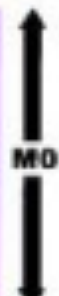
(& : and) (/ : or) (& / : and /or)

T1	T2	T3	T4	PRIMARY TUMOR (T)
a&b&c	any of a,b,c,d	(a&c)/b/d	(a&c)/d	Criteria
≤ 3 cm	> 3 cm	any	any	a. Size
No invasion proximal to the lobar bronchus	Main bronchus (≥ 2 cm distal to the carina)	Main bronchus (< 2 cm distal to the carina)	-	b. Endo-bronchial location
surrounded by lung or visceral pleura	Visceral pleura	Chest wall **/ diaphragm/ mediastinal pleura/ parietal pericardium	Mediastinum/ trachea/heart/ great vessels/ esophagus/ vertebral body/ carina	c. Local Invasion
-	Atelectasis/ obstructive pneumonitis that extends to the hilar region but doesn't involve the entire lung	Atelectasis/ obstructive pneumonitis of the entire lung	Malignant pleural/peri-cardial effusion or satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung	d. Other

Supraclavicular	Scalene(ipsi-contralateral)		Mediastinal		Subcarinal	Hilar		Peribronchial (ipsilateral)	LYMPH NODE (N)
	(contralateral)	(ipsilateral)	(contralateral)	(ipsilateral)		(contralateral)	(ipsilateral)		
+	+	+	+			+			N3
-	-	-	+	+		-			N2
-	-	-	-	-		-	+	+	N1
-	-	-	-	-		-	-	-	N0

TUMOR STAGING SYSTEM

Stage IV
M1 (any T, any N)

Stage III B			
Stage III A			
Stage II A	Stage II B		
Stage I A	Stage I B	Stage II B	

T1	T2	T3	T4	PRIMARY TUMOR (T)
a&b&c	any of a,b,c,d	(a&c)/b/d	(a&c)/d	Criteria
≤ 3 cm	> 3 cm	any	any	a. Size
No invasion proximal to the lobar bronchus	Main bronchus (≥ 2 cm distal to the carina)	Main bronchus (< 2 cm distal to the carina)	-	b. Endo-bronchial location
surrounded by lung or visceral pleura	Visceral pleura	Chest wall **/ diaphragm/ mediastinal pleura/ parietal pericardium	Mediastinum/ trachea/heart/ great vessels/ esophagus/ vertebral body/ carina	c. Local Invasion
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Treatment of lung cancer is related to tumor stage: Stage I and II are operated

METASTASES (M)

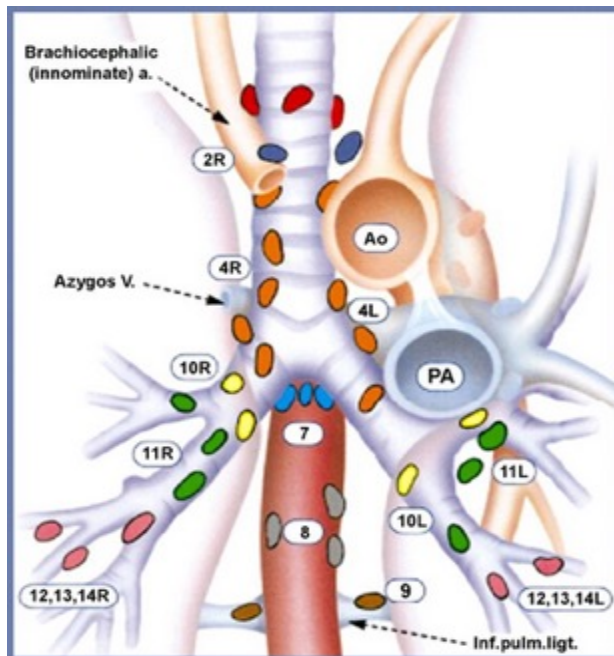
M0 : Absent

M1 : Present

Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1

Stage III (i.e. mediastinal lymph node involvement) is treated by combined therapy and is most difficult to detect!

Stage IV is only palliative.



Superior Mediastinal Nodes

- 1 Highest Mediastinal
- 2 Upper Paratracheal
- 3 Pre-vascular and Retrotracheal
- 4 Lower Paratracheal (including Azygos Nodes)

N₂=single digit, ipsilateral

N₃=single digit, contralateral or supraclavicular

Aortic Nodes

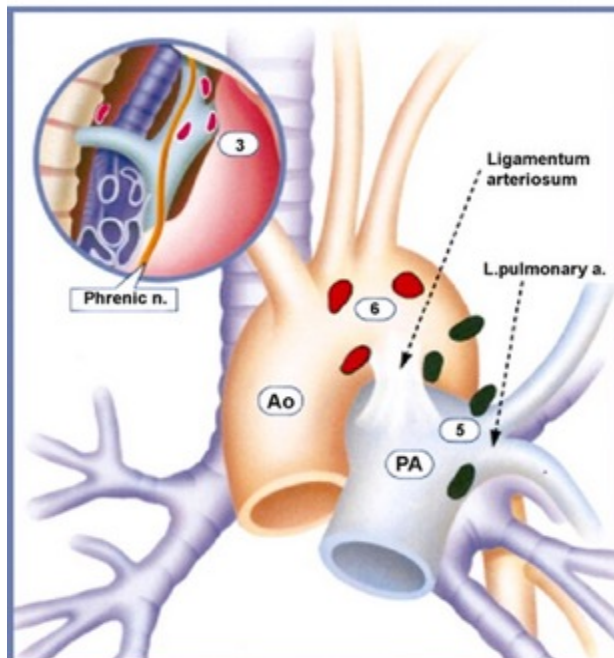
- 5 Subaortic (A-P window)
- 6 Para-aortic (ascending aorta or phrenic)

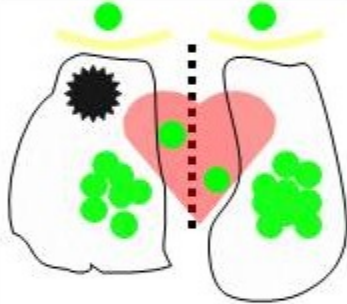
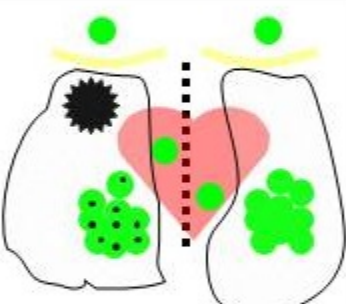
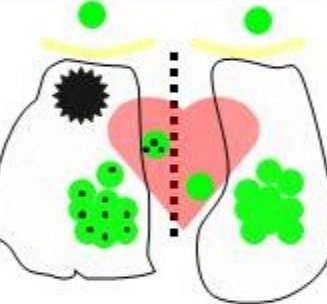
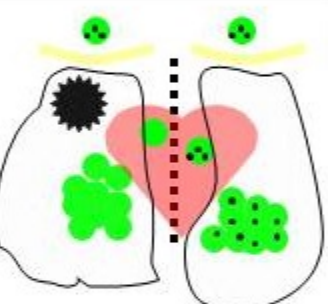
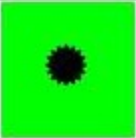
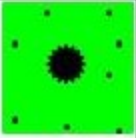
Inferior Mediastinal Nodes

- 7 Subcarinal
- 8 Paraesophageal (below carina)
- 9 Pulmonary Ligament

N₁ Nodes

- 10 Hilar
- 11 Interlobar
- 12 Lobar
- 13 Segmental
- 14 Subsegmental



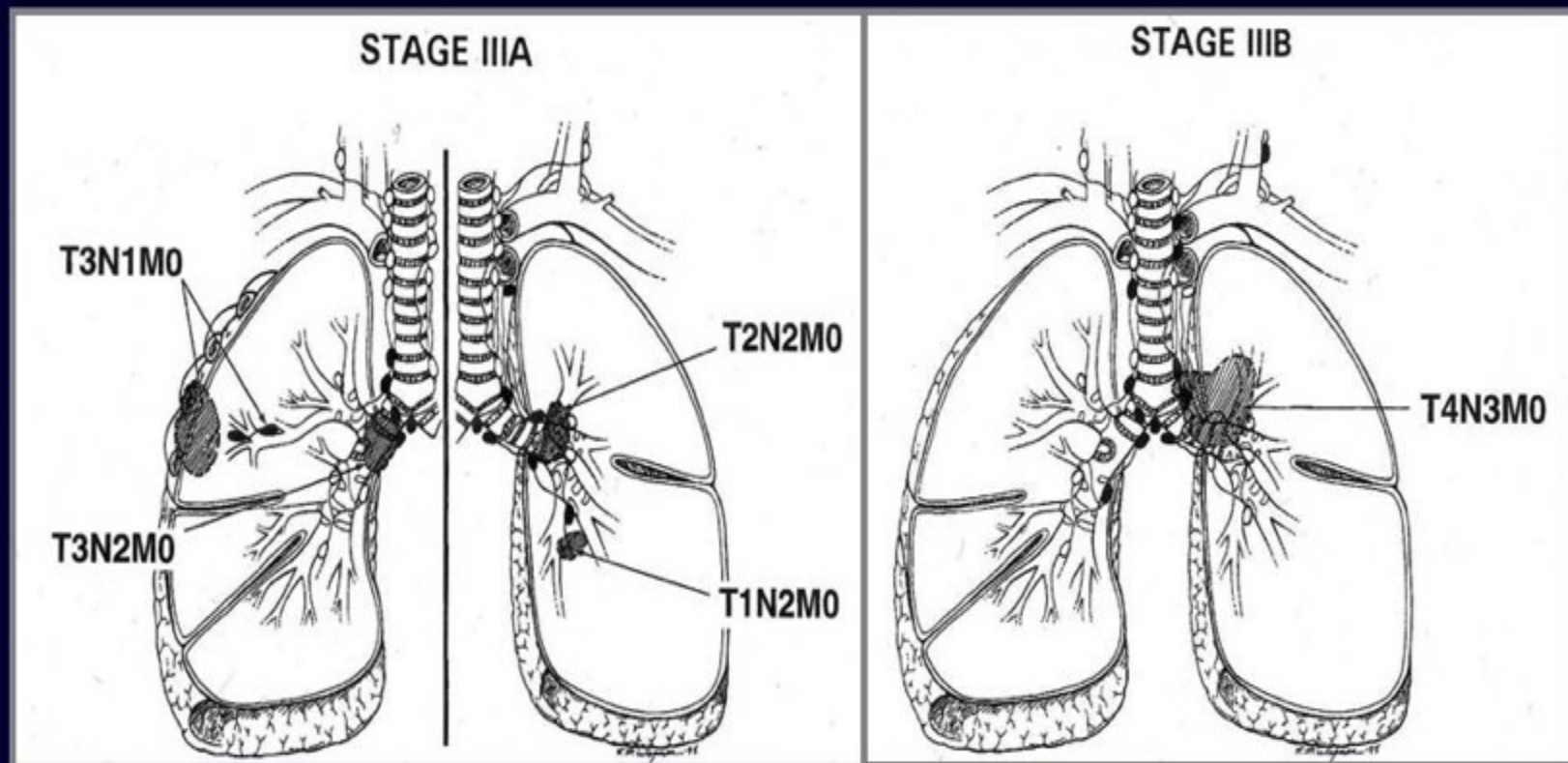
Tumor size	T1 < 3 cm 	T2 3-7 cm  (T2a 3-5 cm; T2b 5-7 cm) Atelectasis (part of lung) Invasion: Visceral pleura, main bronchus ≥ 2 cm from carina	T3 > 7 cm  Atelectasis (whole lung) Invasion: Phrenic nerve, diaphragm, chest wall mediastinal pleura, main bronchus < 2 cm from carina, parietal pericard	T4  Invasion mediastinal organs/ vertebral bodies/ carina /tumor nodules in different ipsilateral lobe
Lymph node	 N0 No lymph nodes involvement	 N1 Ipsilateral bronchopulmonary/ hilar	 N2 Ipsilateral mediastinal/ subcarinal	 N3 Contralateral hilar/ contralateral mediastinal/ supraclavicular
Metastasis	M0  No metastasis	M1  Bilateral lesions Distant metastasis malignant pleural effusion	<div>© TheBestOncologist.com</div> <div>2010</div>	

Staging lung carcinoma based on TNM classification scheme

Stage	TNM
Ia	T1 N0 M0
Ib	T2 N0 M0
IIa	T1 N1 M0
IIb	T2 N1 M0
	T3 N0 M0
IIIa	T3 N1 M0
	T1-3 N2 M0
IIIb	T4 N0-2 M0
	T1-4 N3 M0
IV	Any T Any N M1

Based on AJCC staging system 1997

Stage III Non-Small Cell Lung Cancer



Ipsilateral mediastinal nodes (N2)
T3 tumors with N1 or N2 nodes

Contralateral (N3)
T4 (Heart, great vessels, esophagus, vertebral body, carinal tumor, malignant pleural effusion)

F-18-FDG PET in Lung Cancer

	SPN	Nodal staging	Distant metastases
Sensitivity	96%	88%	94%
Specificity	80%	92%	97%

False negatives

- Bronchioalveolar carcinoma (low metabolic activity)
- Slow growing adenocarcinoma
- Bronchial carcinoid (low metabolic activity & low mitotic activity)

False positives

- Pulmonary tuberculosis
- Histoplasmosis
- Sarcoidosis
- Wegener's granulomatosis
- Other fungal of granulomatosis

Lung Cancer

Histologic Classification (WHO)

Small cell lung cancer (SCLC) : 20 %

Non-small cell lung cancer (NSCLC): 80 %

- **Adenocarcinoma: 30 %**
 - **(Including alveolar cell carcinoma)**
- **squamous cell carcinoma : 30 %**
- **large cell carcinoma : 10 %**
- **Carcinoid: 1 %**
- **bronchoglandular carcinoma: 0.5 %**

in 5 -10% discordant findings of experts

Indications for F-18-FDG PET in Lung Cancer

- Solitary pulmonary nodule
- Ln- staging of known lung cancer
- Staging for distant metastases of known cancer
- Therapy monitoring
- PET/CT – Radiotherapy planning
- Detection of recurrence

FDG PET Literature Summary in Oncology

**JNM 2001; 42:1S-93S
(419 articles: 1993-2000)**

- Average FDG PET accuracy**

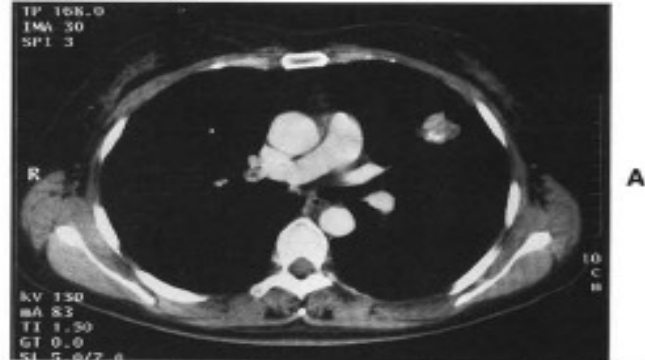
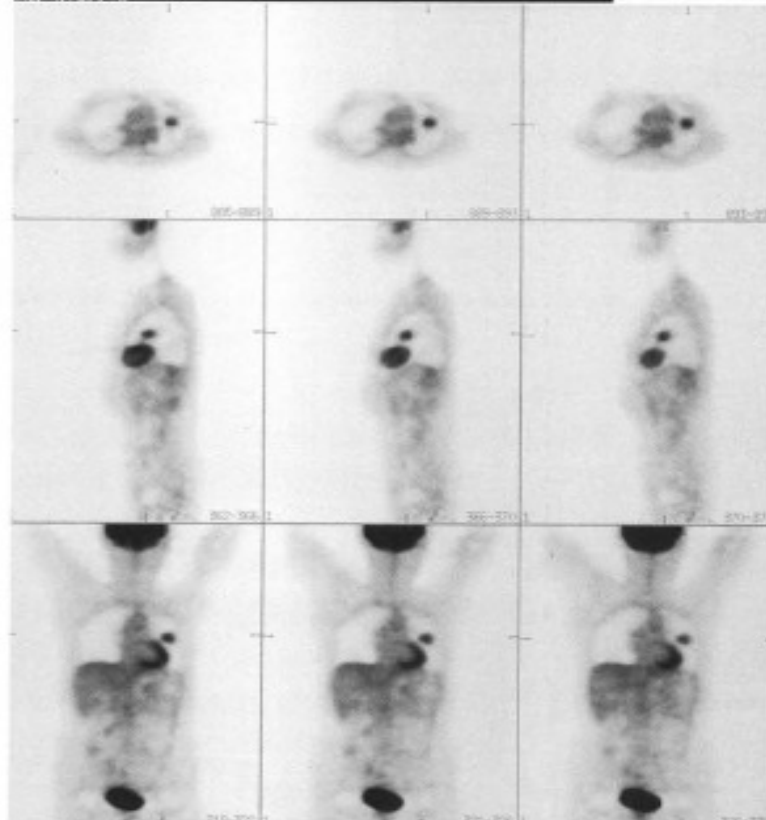
Sensitivity: 84% (84-87%) n=18402

Specificity: 88% (88-93%) n=14264

Accuracy : 87% (87-90%) n= 9994

Average management change

30% n=5062

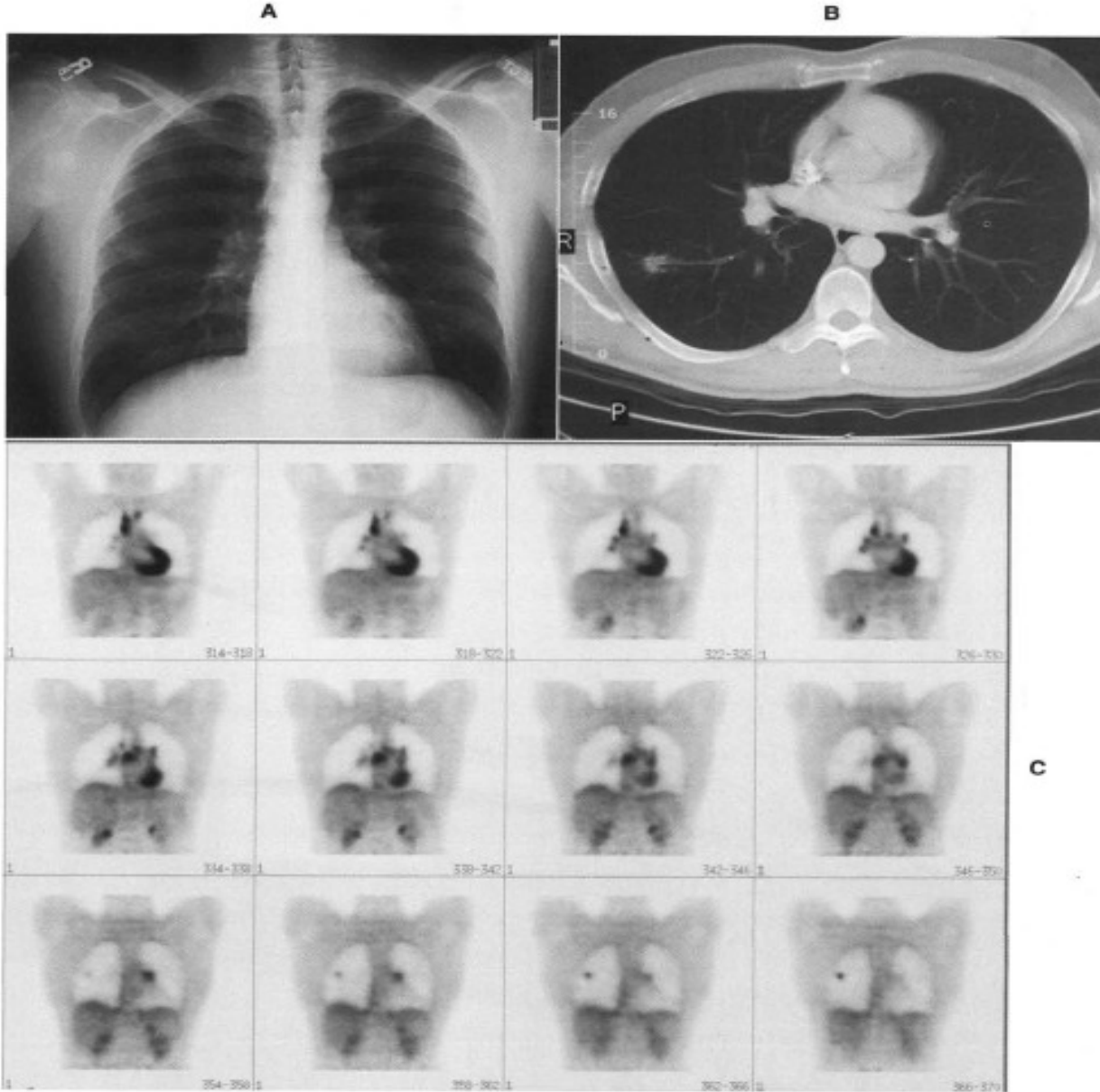


A 67-year-old man has a 2.5-cm left upper lobe lung lesion detected on chest radiographs and confirmed with CT (*A*). ^{18}F fluorodeoxyglucose positron emission tomography (FDG-PET) scan is shown (*B*).

1. What percentage of all newly discovered pulmonary nodules are malignant?
2. What percentage of single pulmonary nodules are indeterminate in etiology after chest radiography and CT examination? What percentage ultimately are benign?
3. What is the likelihood of lung cancer in this case?
4. What are causes for false-negative/false-positive ^{18}F FDG-PET studies?

Single pulmonary nodule

1. Only 20% to 30% are malignant. Higher for smoker 50%.
2. CXR/CT criteria, 30% - 40% are indeterminate, 50% are benign.
3. High.
4. False negative: lesion $< 1\text{cm}$, bronchoalveolar carcinoma and carcinoid tumors. False positive: benign tumor, inflammatory, infection (TB).



A 33-year-old male smoker has a poorly defined right mid-lung density on chest x-ray (*A*, *marked*). CT reported a 1.5-cm lesion with infiltrative margins in the superior segment of the RLL (*B*) but no other abnormality.

1. Describe the ^{18}F FDG-PET scan findings (*C*). Sequential coronal slices are shown.
2. How has this PET scan affected the patient's preoperative staging?
3. What is the overall accuracy of CT and MR for preoperative staging of lung cancer?
4. What is the overall accuracy of ^{18}F FDG-PET for preoperative lung cancer staging?

Lung carcinoma staging

1. Focal increased uptake corresponding to the nodule on CT. Abnormal uptake is seen in the right and left paratracheal regions, the right and left hilum and mediastinum.
2. FDG PET has preoperatively upstaged the patient, who is no longer a surgical candidate.
3. 65%
4. 85%

Breast carcinoma

Epidemiology

- UK = 45000 cases
- 325 arising in men
- 12000 death per annum
- Peak age incidence 50-70 years

Breast carcinoma

Etiology

- Family history
- Menstruation > 12 or stop >55 years
- On HRT
- Women with no children
- Women have had children late > 30 years
- Overweight
- Alcohol

Breast carcinoma

Classification

- Ductal carcinoma in situ
- Lobular carcinoma in situ
- Inflammatory breast carcinoma
- Paget's disease of the breast
- Basal cancers
- Male breast cancer

Breast carcinoma

Differential diagnosis

- Fibroadenoma
- Breast abscess
- Fat necrosis
- Galactocoele

Breast carcinoma

Investigations

- Mammography
- FNA
- Ultrasound
- MRI
- Excision biopsy

Tumor size T	Tumor size < 2 cm  T1	Tumor size 2-5 cm  T2	Tumor size > 5 cm  T3	Tumor extends to skin or chest wall  T4
Lymph Nodes N	N0 No lymph node metastasis	N1 Metastasis to ipsilateral, movable, axillary LNs	N2 Metastasis to ipsilateral fixed axillary, or IM LNs	N3 Metastasis to infraclavicular/supraclavicular LN, or to axillary and IM LNs
Metastasis M	M0 No distant metastasis	M1 Distant metastasis	احسن اونکولوجیست www.TheBestOncologist.com © The Best Oncologist™ LN= Lymph Nodes; IM= Internal Mammary	

Table 1: Breast Cancer T, N, and M Categories

Primary Tumor (T):

TX: Primary tumor cannot be assessed

T0: No evidence of primary tumor

Tis: Carcinoma in situ (DCIS, LCIS, or Paget's disease of the nipple with no tumor mass)

T1: Tumor is ≤ 2 cm

T2: Tumor is >2 cm but <5 cm

T3: Tumor is >5 cm

T4: Tumor of any size growing into the chest wall or skin

Lymph Node Status (N):

NX: Nearby lymph nodes cannot be assessed

N0: Cancer has not spread to nearby lymph nodes

N1: Cancer has spread to 1 to 3 axillary lymph nodes, and/or tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (ipsilateral mobile axillary nodes)

N2: Cancer has spread to 4 to 9 axillary lymph nodes under the arm, or cancer has enlarged the internal mammary lymph nodes (ipsilateral fixed axillary nodes)

N3: One of the following applies:

- Cancer has spread to 10 or more axillary lymph nodes
- Cancer has spread to the lymph nodes under the clavicle
- Cancer has spread to the lymph nodes above the clavicle
- Cancer involves axillary lymph nodes and has enlarged the internal mammary lymph nodes
- Cancer involves 4 or more axillary lymph nodes, and tiny amounts of cancer are found in internal mammary lymph nodes on sentinel lymph node biopsy (ipsilateral internal mammary nodes metastasis)

Metastases (M):

MX: Presence of distant metastases cannot be assessed

M0: No distant spread

M1: Spread to distant organs is present

DCIS: ductal carcinoma in situ; LCIS: lobular carcinoma in situ.

Source: References 6, 12, 21.

GIST

- Mesenchymal neoplasm
- 70% arise from stomach
- 25% arise from small intestine
- Express growth factor receptor with tyrosine kinase activity (c-kit) – detect by CD117
- Highly malignant
- Resistant to conventional treatment

Staging TNM (Gastrointestinal)

- Tis – carcinoma in situ
- T0 – no evidence of primary
- TX – primary cannot be assessed
- T1 – involving lamina propria/submucosa
- T2 – involving muscularis propria/subserosa
- T3 – penetrates serosa
- T4 – involving adjacent structures
- N0 – 1 – 6 nodes involved
- N2 – 7 -15 nodes involved
- N3 - > 15 nodes
- M0 – no distant metastasis
- M1 – distant metastasis

Colon carcinoma

Epidemiology

- UK = 36000 cases, 22000 men and 16000 women
- 3rd commonest
- 16000 deaths per annum
- Occur 50 years of age

Colon carcinoma

Etiology

- Diet – high meat/fat/calorie/alcohol
- First degree
- Polyps
- Chronic Crohn's colitis

Colon carcinoma

Symptoms

- Change in bowel habit
- Blood per rectum
- Mucus per rectum
- Tenesmus
- Obstructive symptoms
- Iron deficiency anemia

Colon carcinoma

Investigations

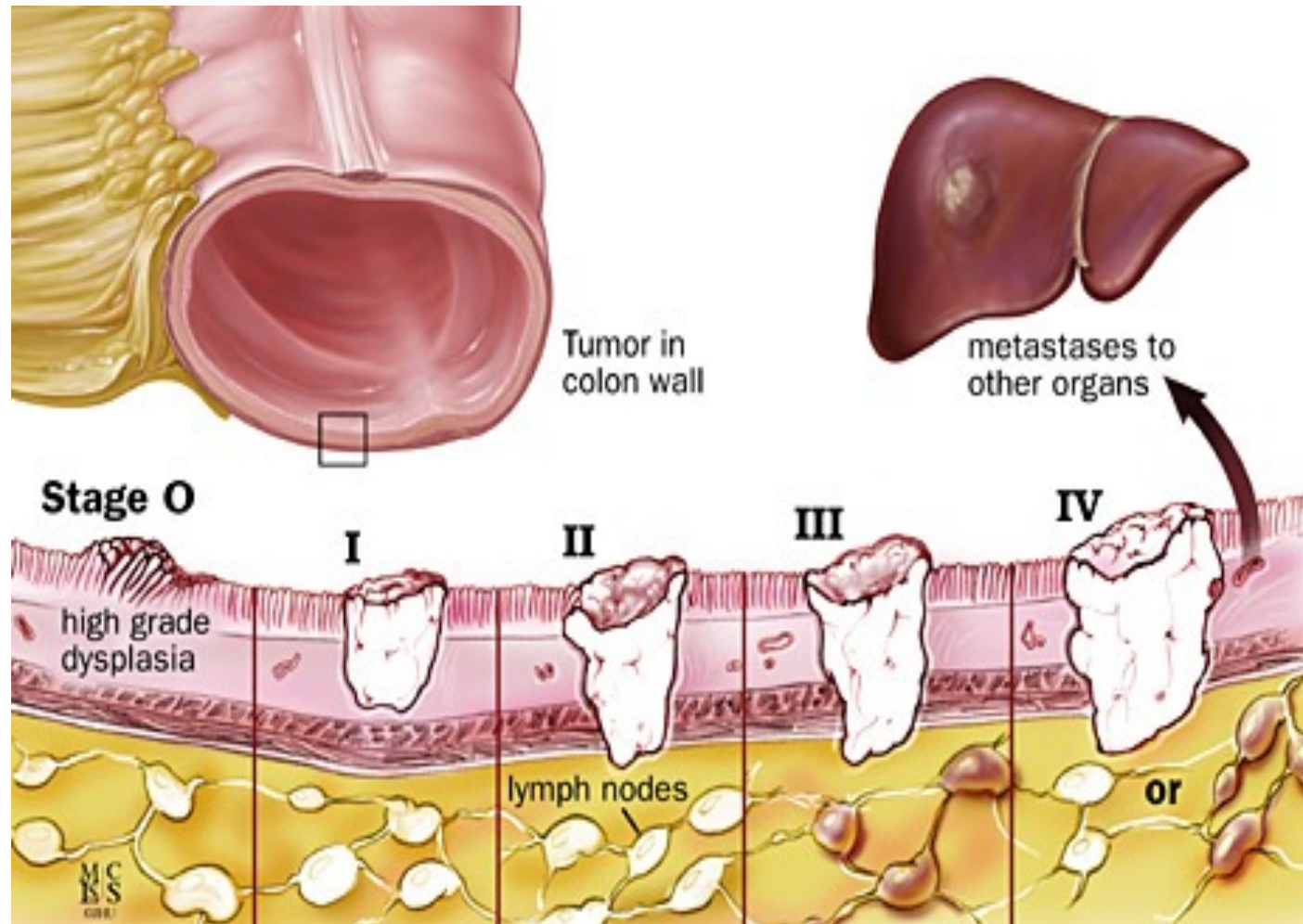
- Digital PR examination
- Double contrast barium enema
- Colonoscopy
- CT
- MRI

Colon carcinoma

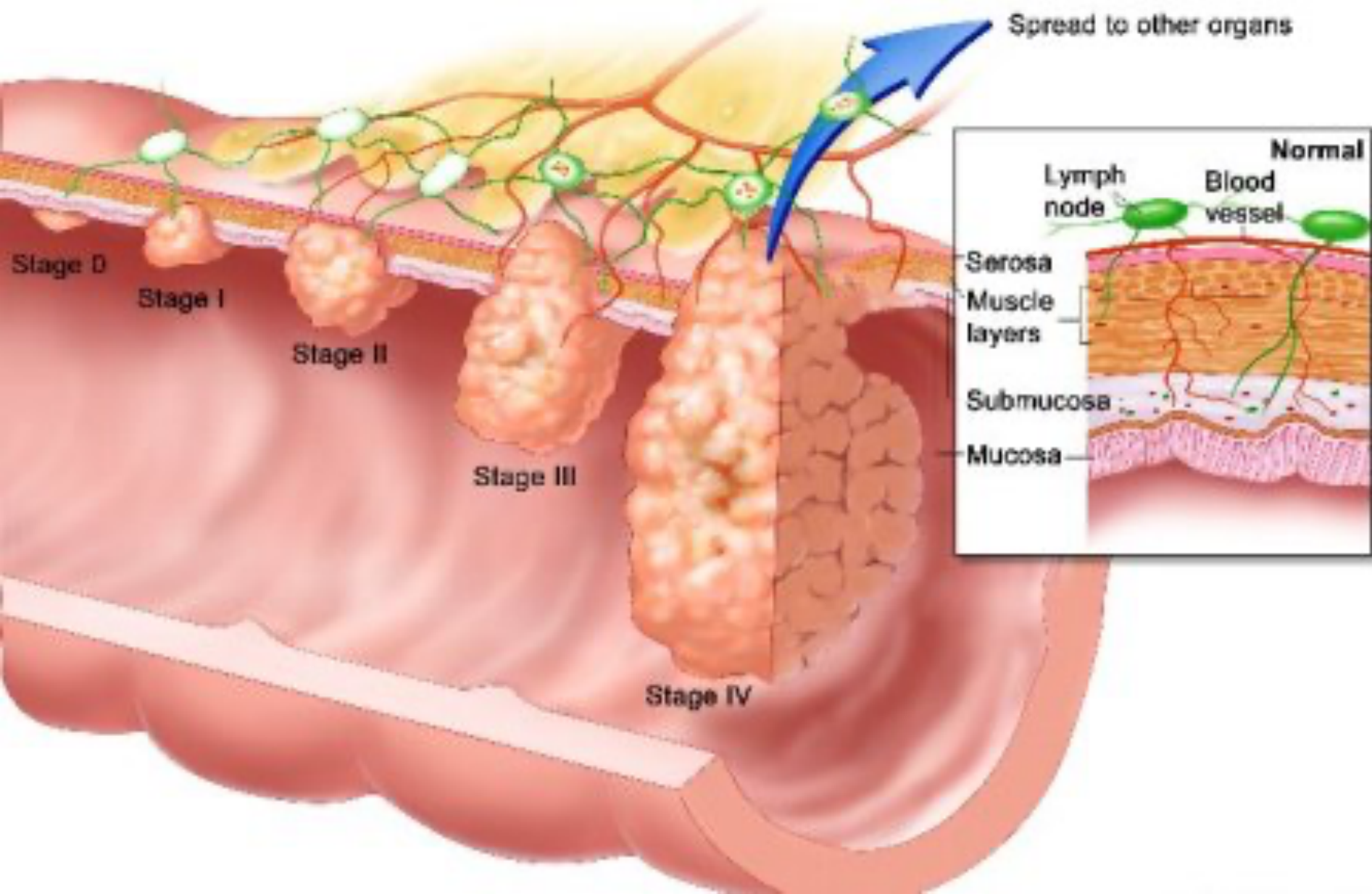
DUKES Staging

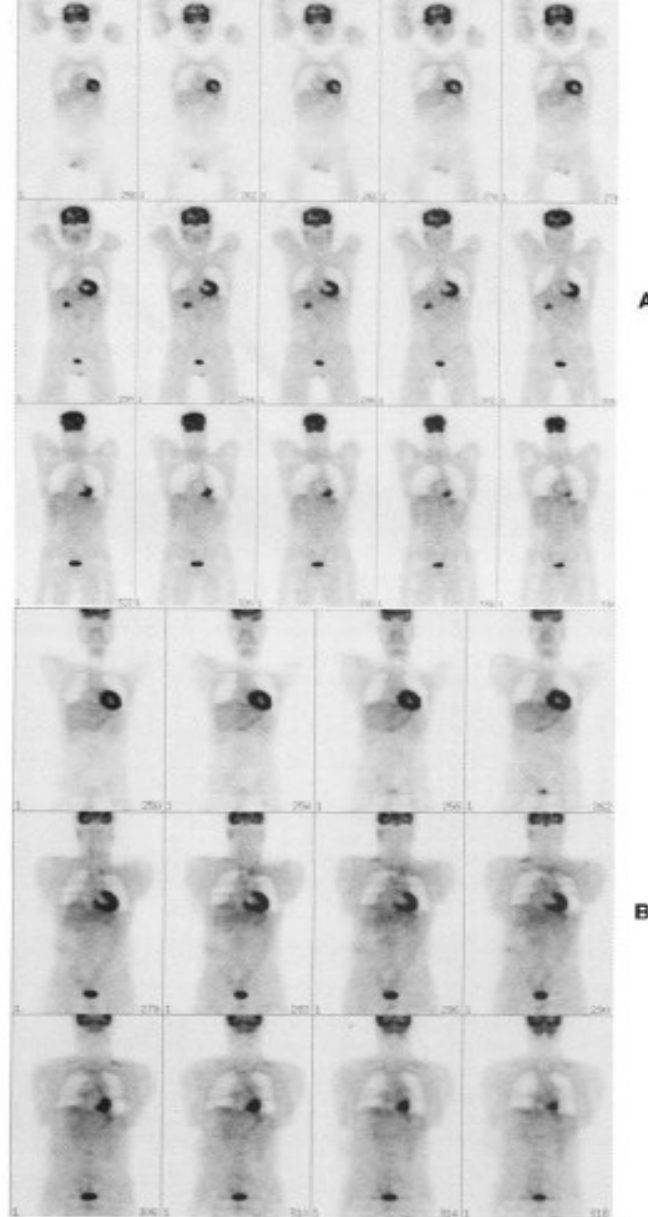
- Dukes' A/ stage A – invasion into but not through bowel wall
- Dukes' B/ stage B – involving bowel wall but not lymph nodes
- Dukes' C/ stage C – involvement of nodes
- Dukes' D/ stage D - metastasis

TNM colorectal carcinoma



TNM colorectal carcinoma





A

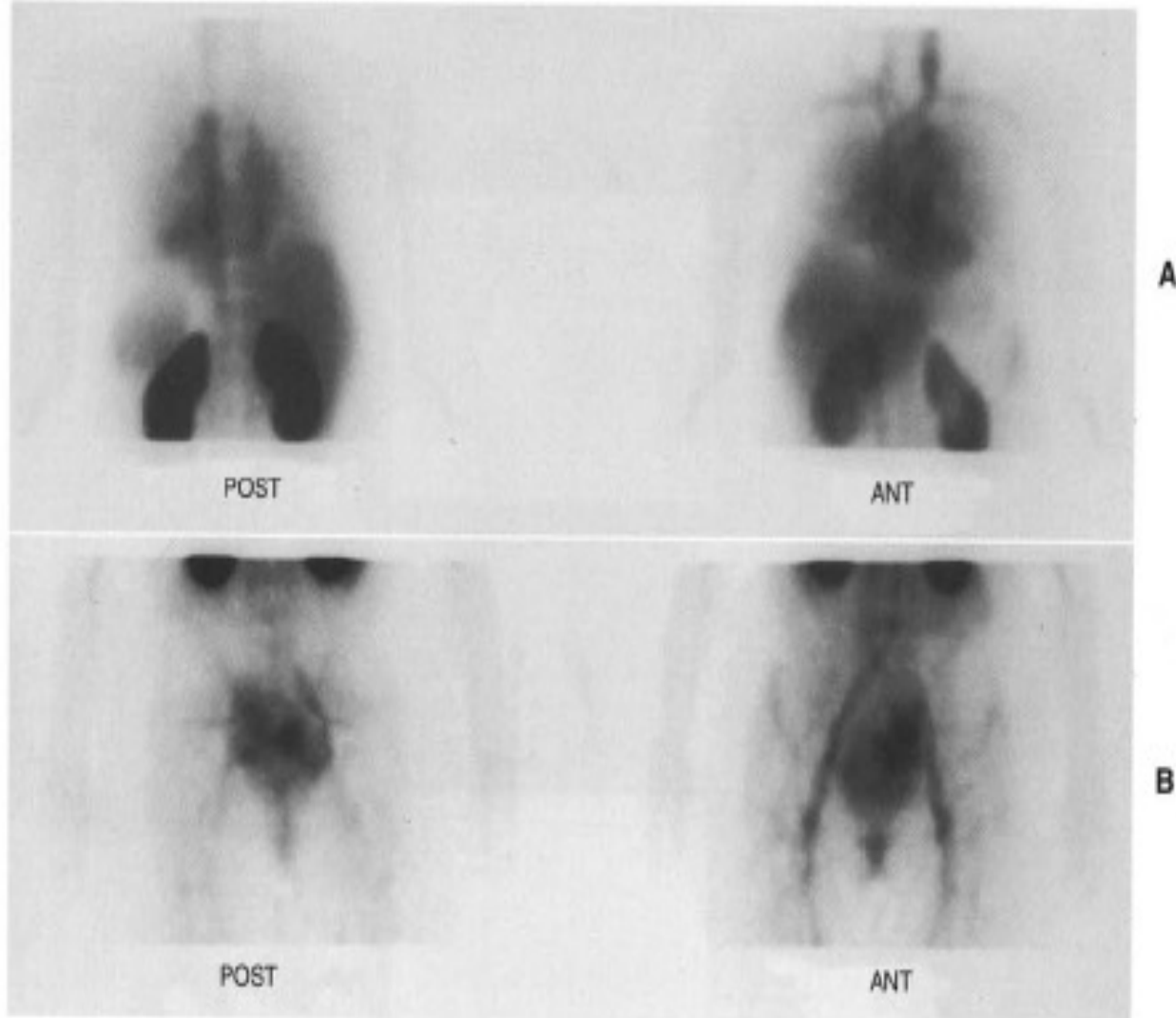
B

A 69-year-old man has a history of colorectal carcinoma and surgical resection. The carcinoembryonic antigen (CEA) level is increasing and the CT scan shows a new 2.3-cm lesion in the right lobe of the liver.

1. FDG-PET scan (A) was then obtained. What are the findings?
2. Why was the FDG-PET scan ordered?
3. What are clinical indications for FDG-PET in colorectal carcinoma?
4. FDG-PET scan (B) was performed 6 months after resection of the liver lesion. Describe the findings.

Colorectal carcinoma

1. Increased uptake consistent with tumor in the liver corresponding to CT mass. No other liver lesions or metastases are seen elsewhere.
2. Surgical resection is planned. The preoperative FDG PET scan is used to determine the presence of any other metastases in the liver or elsewhere.
3. a. increased serum CEA with normal conventional imaging. b. equivocal lesion with conventional imaging. c. preoperative staging before curative resection.
4. Negative scan. No evidence of tumor.



A 56-year-old woman, with a history of colorectal carcinoma, underwent resection 1 year ago and now has a rising serum carcinoembryonic antigen (CEA) level. A ^{99m}Tc CEA planar study is shown.

1. Describe the scintigraphic findings and give your interpretation.
2. What is the relative accuracy of this study compared with CT?
3. List clinical indications for a ^{99m}Tc CEA study.
4. What other radiopharmaceuticals have been used to localize colorectal carcinoma?

Colorectal carcinoma

1. Large abnormal region of increased uptake in the pelvis consistent with recurrent tumor. A large tumor is present in the left pelvis adjacent to the bladder in addition to multiple small sites of tumor uptake.
2. Tc-99m CEA is superior to CT in extrahepatic abdomen and pelvis but equal to CT in detecting tumor in the liver.
3. Rising serum CEA level with negative CT findings. Potentially resectable recurrent disease, usually in the liver, done to exclude other metastases that would preclude surgery.
4. In-111 Oncoscint and FDG PET

Prostate carcinoma

Epidemiology

- UK = 35000 cases = 12% cancer cases and 10000 deaths per annum
- Age over 70 years
- 2nd most common after lung carcinoma

Prostate carcinoma

Symptoms

- Prostatic outflow obstructive symptoms: poor stream/ frequency/ terminal dribble/ nocturia
- Erectile dysfunction
- Haematospermia
- Bone pain
- Hypercalcemia

Prostate carcinoma

Investigations

- PSA = normal 4 ng/ml
- Blood test = hypercalcaemia
- Biopsy
- IVU
- CT scan
- Bone scan
- MRI

TABLE 1: 2002 TNM staging system of prostate cancer

Localized disease

T1a	Tumor incidental histologic finding in $\leq 5\%$ of resected tissue; not palpable
T1b	Tumor incidental histologic finding in $> 5\%$ of resected tissue
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA level)
T2a	Tumor involves one-half of one lobe or less
T2b	Tumor involves more than one-half of one lobe but not both lobes
T2c	Tumor involves both lobes

Local extension

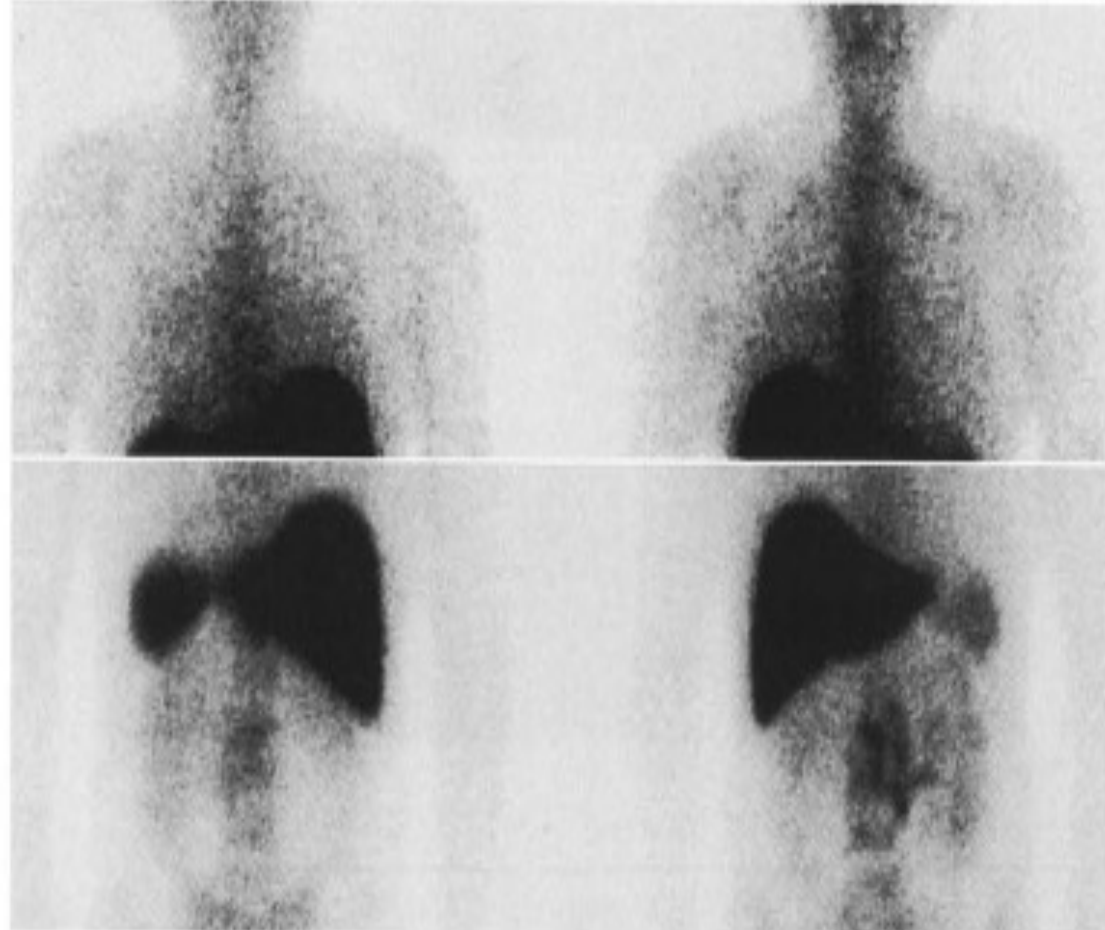
T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Bladder invasion, fixed to pelvic side wall, or invasion of adjacent structures

Metastatic disease

N1	Positive regional lymph nodes
M1	Distant metastasis

PSA = prostate-specific antigen

Adapted from Greene FL, Page DL, Fleming ID, et al (eds): AJCC Cancer Staging Manual, 6th ed. New York, Springer-Verlag, 2002.



A 64-year-old man had prostatectomy for prostate cancer 3 years ago. Now the serum prostate-specific antigen (PSA) level is increasing. Bone scan and CT findings are negative. ¹¹¹In ProstaScint scan is shown.

1. What is the mechanism of uptake?
2. Compare the accuracy of CT and MRI with ¹¹¹In ProstaScint for detecting prostate cancer metastases after prostatectomy.
3. What are the abnormal imaging findings on this study? Give your interpretation.
4. How does the ProstaScint study affect the patient's therapy plan?

Prostate carcinoma

1. In-111 labeled monoclonal antibody directed against the prostate specific membrane antigen, a glycoprotein expressed by normal and prostate cancer cells.
2. CT and MRI sensitivity ranges from 5% - 20%. Accuracy of In-111 ProstaScint is 70%.
3. Paraaortic upper abdominal uptake consistent with tumor adenopathy. Focal uptake in the left upper chest consistent with tumor.
4. Recurrent tumor limited to the prostate bed or metastatic pelvic nodes require radiation ports. Extrapelvic metastases require systemic therapy.

Cervical carcinoma

Epidemiology

- UK = 2700 cases, 900 deaths per annum
- Age 40 – 50 years
- 24000 carcinoma in situ (CIN III)

Cervical carcinoma

Etiology

- HPV
- Intercourse at early age
- Lower socioeconomic group
- Oral contraceptive
- Miscarriage
- Smoking

Cervical carcinoma

Symptoms

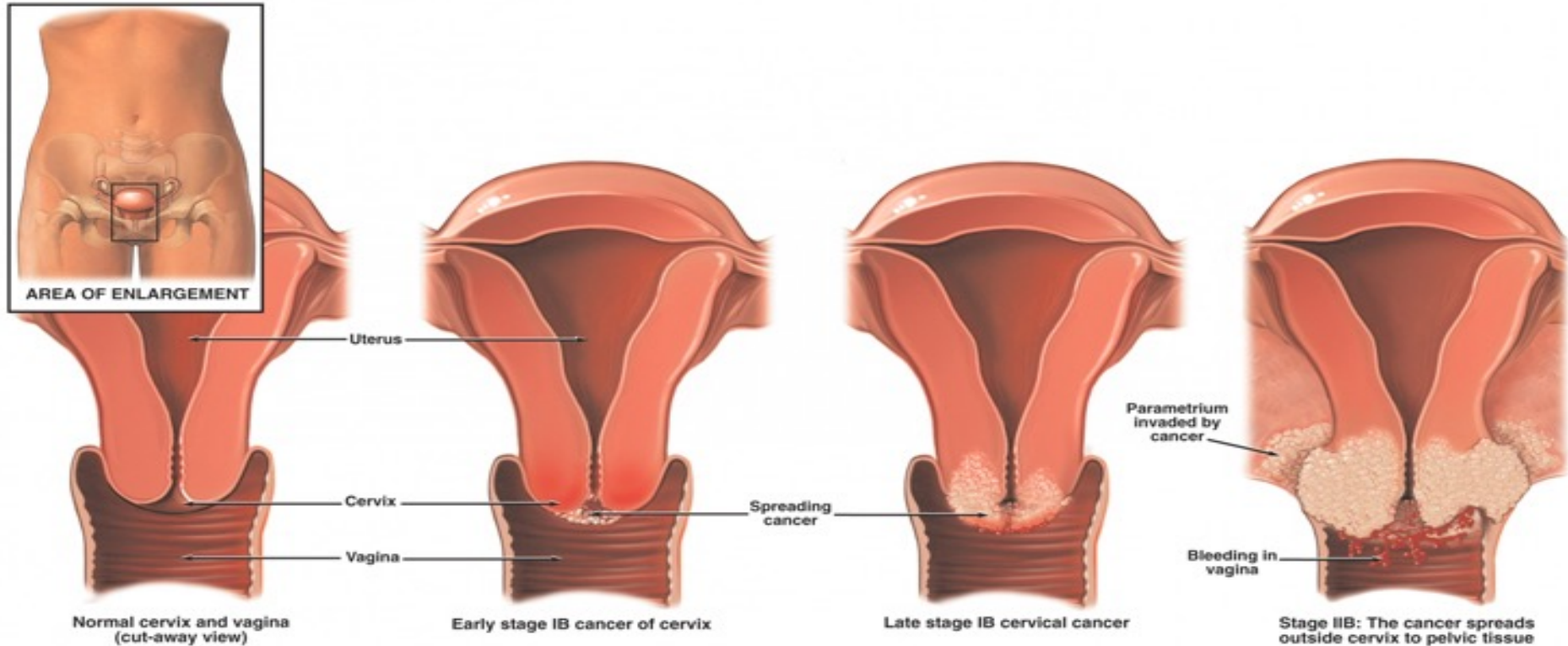
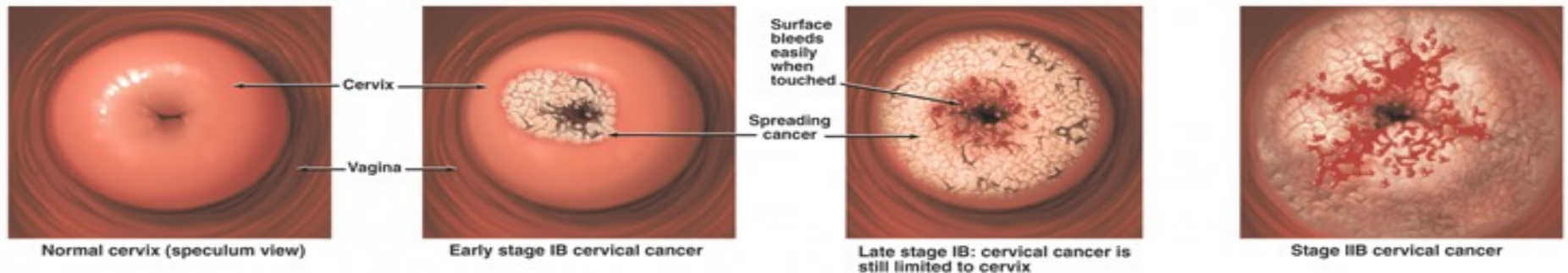
- Vaginal bleeding
- Vaginal discharge
- Hematuria
- Low back pain
- Renal failure due to bilateral ureteral obstruction

Cervical carcinoma

Investigations

- Cervical cytology
- Biopsy
- CT scan
- MRI

Cervical carcinoma



Cervical carcinoma

Stage I – Cancer confined to cervix

Stage IA – Microinvasive disease

Stage IA1 – Stromal invasion less than 3 mm

Stage IA2 – Stromal invasion 3–5 mm, not in excess of 7 mm in horizontal spread

Stage IB – Lesions greater than 7 mm in horizontal spread

Stage II – Involvement beyond cervix, including vagina except for the lowest third, or infiltration of parametrium but not extending to pelvic sidewall

Stage IIA – Involvement of upper two-thirds of vagina, without lateral extension into parametrium

Stage IIB – Lateral extension into parametrial tissue but not extending to pelvic sidewall

Stage III – Involvement of lowest third of the vagina or pelvic sidewall or causes hydronephrosis

Stage IIIA – Involvement of lowest third of vagina

Stage IIIB – Involvement of pelvic sidewall or hydronephrosis

Stage IV – Cancer extends beyond reproductive tract

Stage IVA – Involvement of bladder or rectal mucosa

Stage IVB – Distant metastasis or disease outside true pelvis

Ovarian carcinoma

Epidemiology

- UK = 6600 cases
- 2.3 % of all cancer cases
- 4400 cases deaths per annum

Ovarian carcinoma

Pathology

Common appearance

- Pseudomucinous cyst
- Serous cyst

Microscopic appearance

- Epithelial adenocarcinoma
- Germ cell tumors

Ovarian carcinoma

Investigation

- Serum CA 125
- CXR
- Ultrasound
- CT scan

Ovarian carcinoma staging

- IA: growth limited to one ovary
- IB: growth limited to both ovaries
- IC: IA or IB with capsule involvement, tumor rupture, positive washings/ascites
- IIA: extension or metastasis to uterus and/or fallopian tubes
- IIB: extension to other pelvic tissues
- IIC: IIA or IIB with capsule involvement, tumor rupture, positive washings/ascites
- IIIA: microscopic abdominal peritoneal implants
- IIIB: abdominal peritoneal implants ≤ 2 cm
- IIIC: abdominal peritoneal implants > 2 cm, positive retroperitoneal or inguinal lymph nodes
- IV: distant metastasis (cytologic positive pleural effusion and parenchymal liver metastasis)

Hodgkin's Lymphoma

Epidemiology

- UK = 1500 cases, 850 men and 650 women with 350 deaths per annum
- Two peak incidence in young 20 – 30 years and over 70 year

Hodgkin's Lymphoma

Etiology

- Epstein Barr virus

Hodgkin's Lymphoma

Symptoms

- B symptoms:
 1. Fever $> 38^{\circ}\text{C}$
 2. Weight loss $> 10\%$
 3. Night sweat

Hodgkin's Lymphoma

Sign

- Enlarge nodes at neck
- Hepatosplenomegaly
- Abdominal mass
- Inguinal nodes

Hodgkin's Lymphoma

Differential diagnosis

- Infection: pyogenic/ TB or viral
- Leukemia
- carcinoma

Hodgkin's Lymphoma

Investigations

- Blood count
- ESR
- Serum LDH
- Alkaline phosphatase
- Marrow
- CXR
- CT/ MRI
- PET scan
- Biopsy

Non Hodgkin's lymphoma

Epidemiology

- UK = 10000 cases, 5300 for men and 4800 for women with 4500 deaths per annum
- Occurs equally in men and women
- More 50 years of age

Non Hodgkin's lymphoma

Epidemiology

- UK = 10000 cases, 5300 for men and 4800 for women with 4500 deaths per annum
- Occurs equally in men and women
- More 50 years of age

Non Hodgkin's lymphoma

Etiology

- Infective agents : EBV/ helicobacter/ human T cell lymphotropic virus/ HIV
- Altered immune status
- Irradiation

Non Hodgkin's Lymphoma

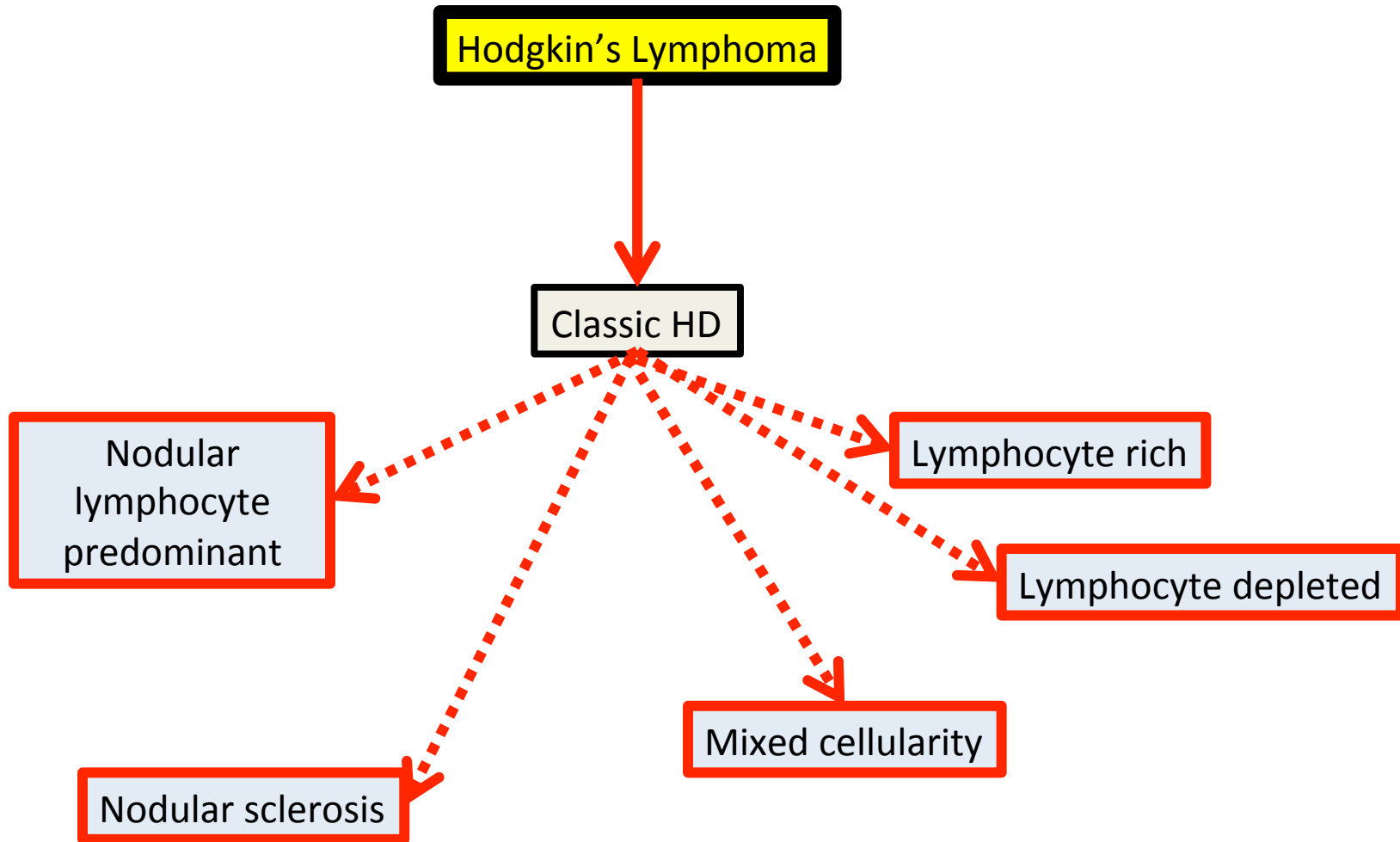
Sign

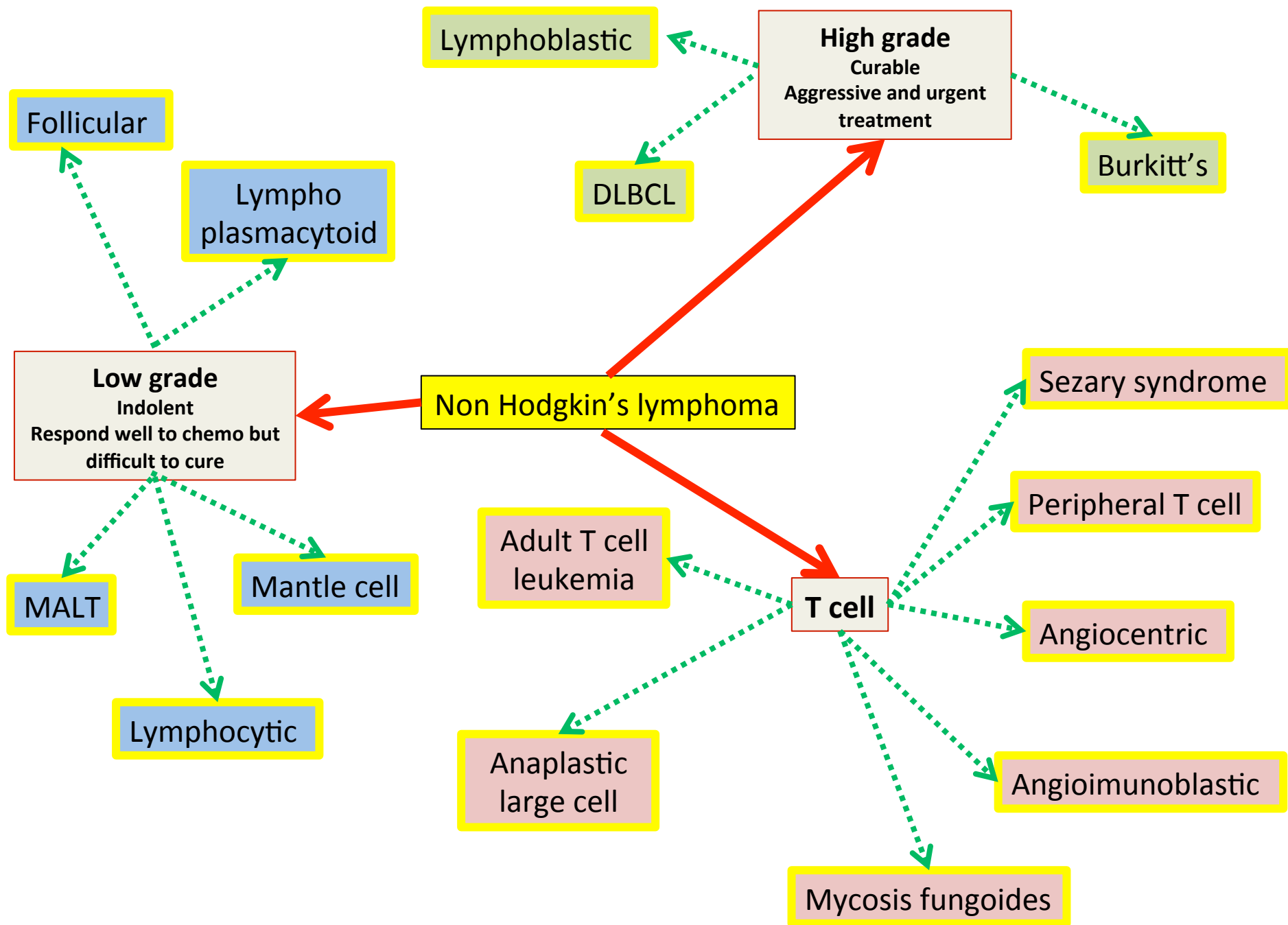
- Enlarge nodes at neck
- Hepatosplenomegaly
- Abdominal mass
- Inguinal nodes

Non Hodgkin's Lymphoma

Investigations

- Blood count
- ESR
- Serum LDH
- Alkaline phosphatase
- CSF - DLBCL
- Marrow
- CXR
- CT/ MRI
- PET scan
- Biopsy





Ann Arbor staging classification for Hodgkin and non-Hodgkin lymphomas

Stage I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (IE)*
Stage II	Involvement of two or more lymph node regions or lymphatic structures on the same side of the diaphragm alone (II) or with involvement of limited, contiguous extralymphatic organ or tissue (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III) which may include the spleen (IIIS) or limited, contiguous extralymphatic organ or site (IIIE) or both (IIIES)
Stage IV	Diffuse or disseminated foci of involvement of one or more extralymphatic organs or tissues, with or without associated lymphatic involvement

All cases are subclassified to indicate the absence (A) or presence (B) of the **systemic ("B") symptoms** of significant unexplained fever, night sweats, or unexplained weight loss exceeding 10 percent of body weight during the six months prior to diagnosis.

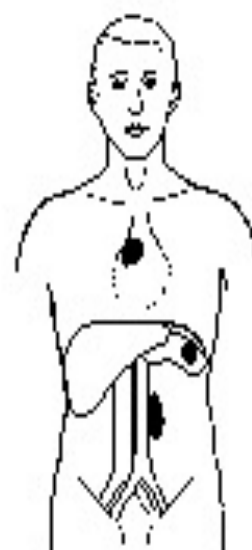
"Ann Arbor" Staging Classification



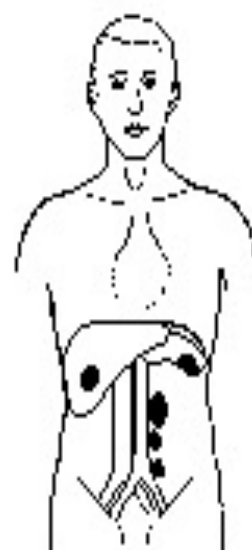
Stage I



Stage II



Stage III



Stage IV

single lymph node region
or single extralymphatic
site (Ie)

two or more sites, same side
of diaphragm or $\bar{c}$ contiguous
extralymphatic site (IIe)

both sides of diaphragm or $\bar{c}$
spleen (III_s) or contiguous
extralymphatic site (III_e)

diffuse involvement
of extralymphatic
sites $\pm$ nodal disease

Stage subdivision: A-asymptomatic B-unexplained weight loss >10% in 6m and/or fever and/or night sweats

Extralymphatic = tissue other than lymph nodes, thymus, spleen, Waldeyer's ring, appendix & Peyer's patches

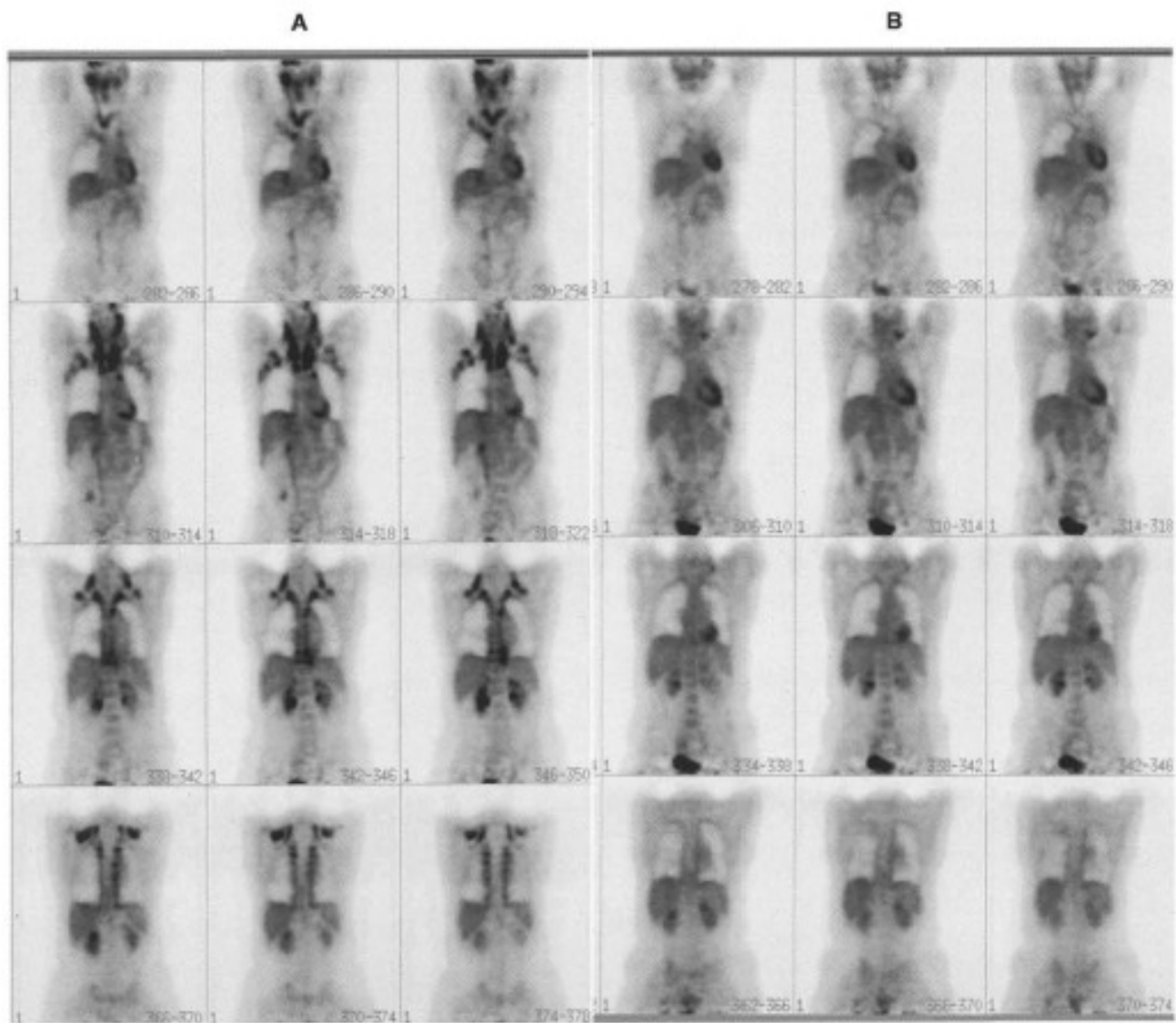
FDG-(18F) uptake in lymphomas (n>5)

TYPE (WHO classification)	proportion of FDG + cases	% of NHL
Hodgkin's lymphoma	98%	-
Large B cell lymphoma	100%	30%
Mantle cell lymphoma	100%	6%
Follicular lymphoma	98%	22%
Plasma cell myeloma / plasmocytoma ⁺	85%	> 5%
Marginal zone B cell lymphoma (MALT)	67%	8%
Small lymphocytic lymphoma*	58%	7%
Peripheral T cell lymphoma	40%	7%

Elstrom et al. *Blood*. 2003 ; 101 : 3875-3876, except

*Jérusalem et al, *Ann Oncol*. 2001 ; 12 (6) : 825-830

+ Bredella et al. *AJR* 2005 ; 184 : 1199-1204

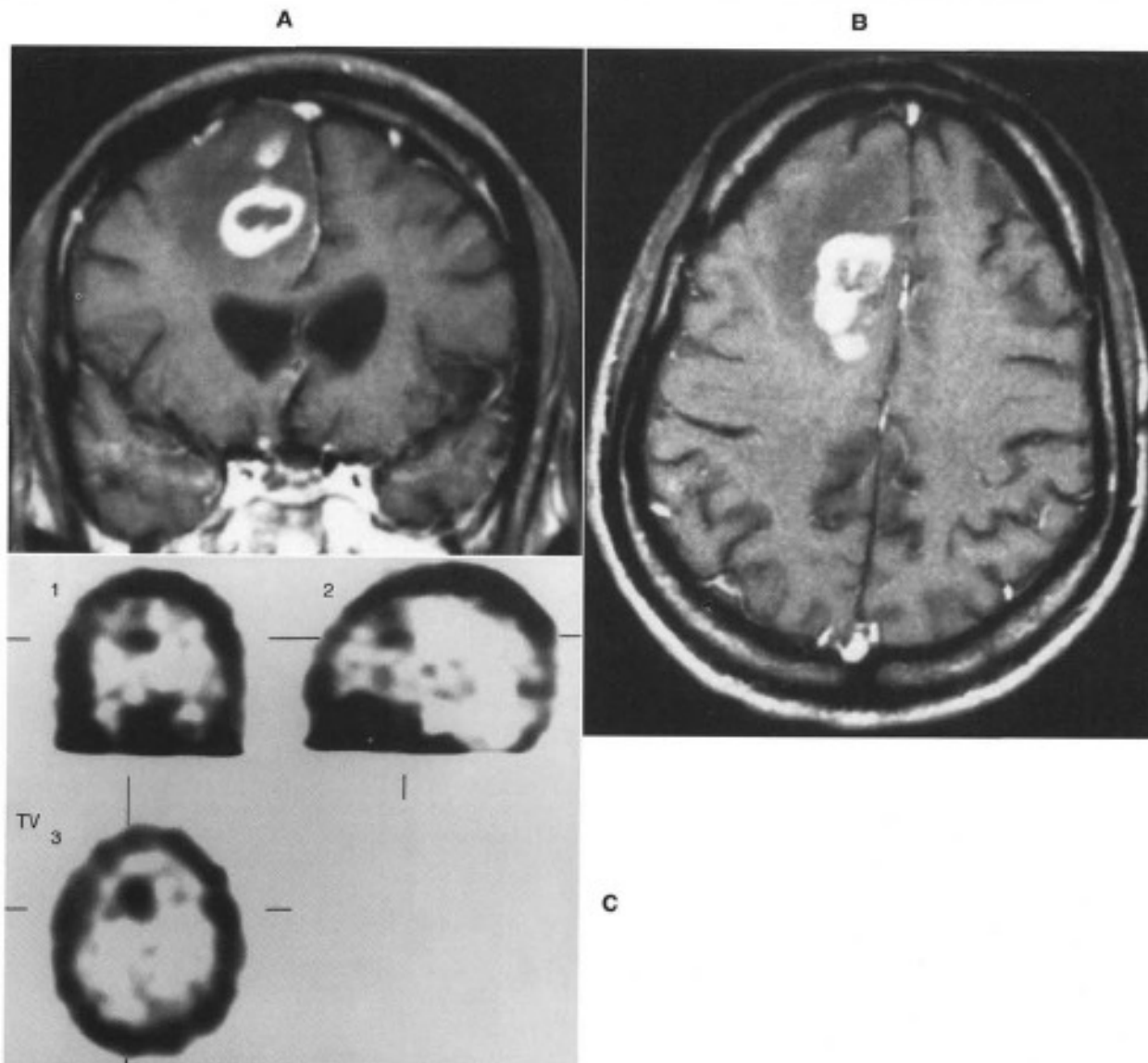


A 34-year-old woman with recently diagnosed Hodgkin's disease presenting as a left neck mass. Two ^{18}F FDG-PET scans were performed 3 days apart.

1. What is the mechanism of uptake of this radiopharmaceutical?
2. Describe the findings of the first study (A) and the second study (B) and explain how the study could have changed so dramatically in only 3 days.
3. What is the half-life of ^{18}F ? ^{15}O , ^{15}N , ^{11}C ?
4. What is the radiation dose to the target organ? What other organs have high uptake?

Hodgkin's disease

1. FDG is glucose analog. Increased FDG uptake occurs with increased glucose metabolism. Is taken up intracellularly and phosphorylated similar to glucose, however, unlike glucose, it can not be metabolized further and is intracellularly trapped.
2. a. intense multifocal uptake bilaterally in the neck, upper chest and parasternal regions. b. uptake limited to the left neck. Study a. abnormalities are caused by muscle tension. Diazepam 5 mg was taken just before study b.
3. 110 minutes. 2. 10 and 20 minutes. It is important to remember that the half life of positron are very short.
4. 3.2 rads/ 5 mCi to urinary bladder. Brain and heart.

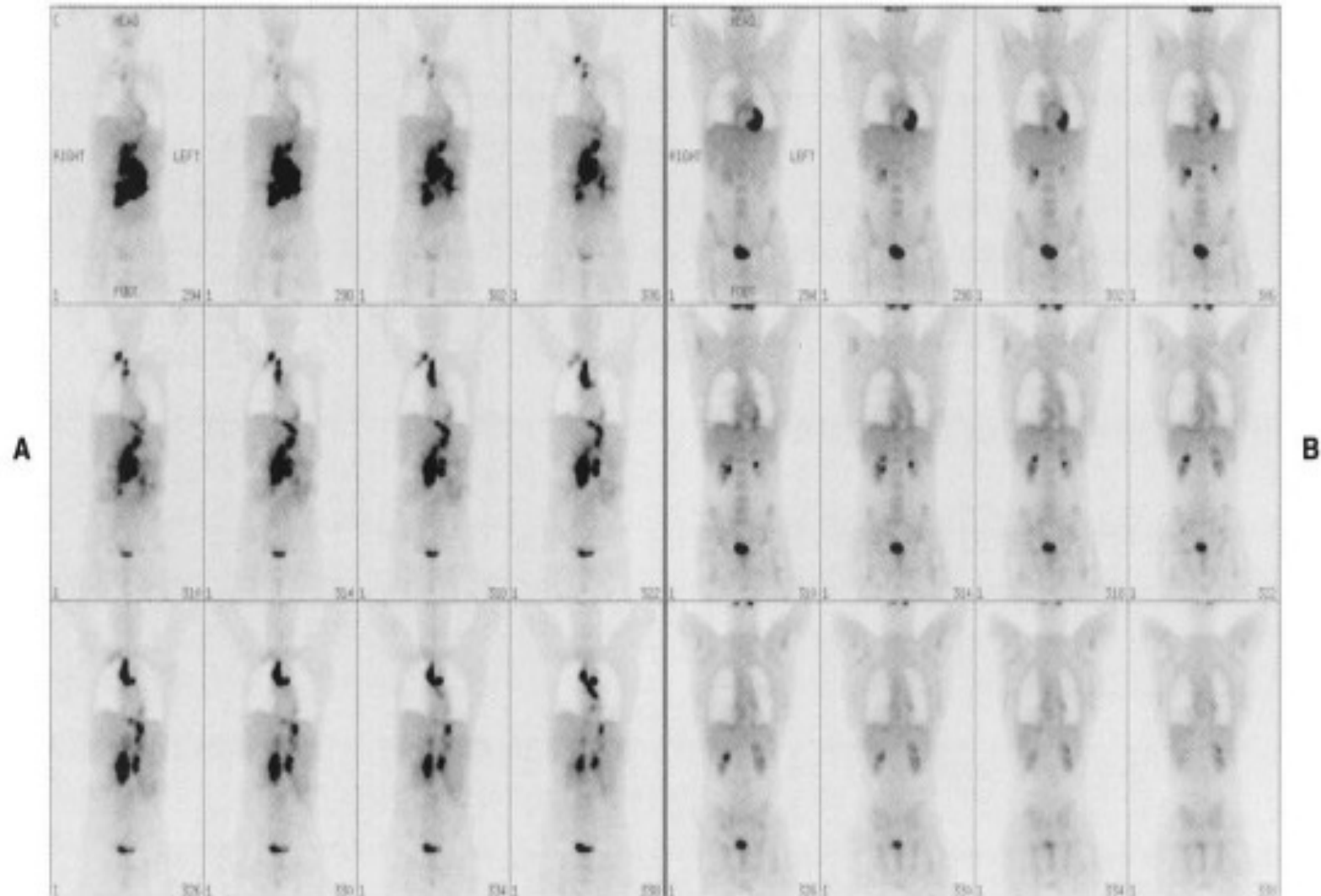


A 35-year-old-man with AIDS has a new intracranial abnormality on MRI (*A* and *B*) of uncertain origin. A SPECT study (C1, coronal; C2, sagittal; C3, transverse) was ordered to assist in the differential diagnosis.

1. What is the radiopharmaceutical?
2. What is the differential diagnosis before the SPECT study?
3. What is the likely diagnosis after the radionuclide study?
4. What is the accuracy of the radionuclide method?

Intracranial lymphoma

1. Tl-201 was used. Tc-99m sestamibi also can be used, however it is taken up by choroid plexus and could pose diagnostic problems in some cases.
2. Tumor, particularly lymphoma, versus infection, usually toxoplasmosis or infection e.g.. CMV or herpes simplex.
3. Malignant lymphoma.
4. 90% sensitivity and false negative < 10%.

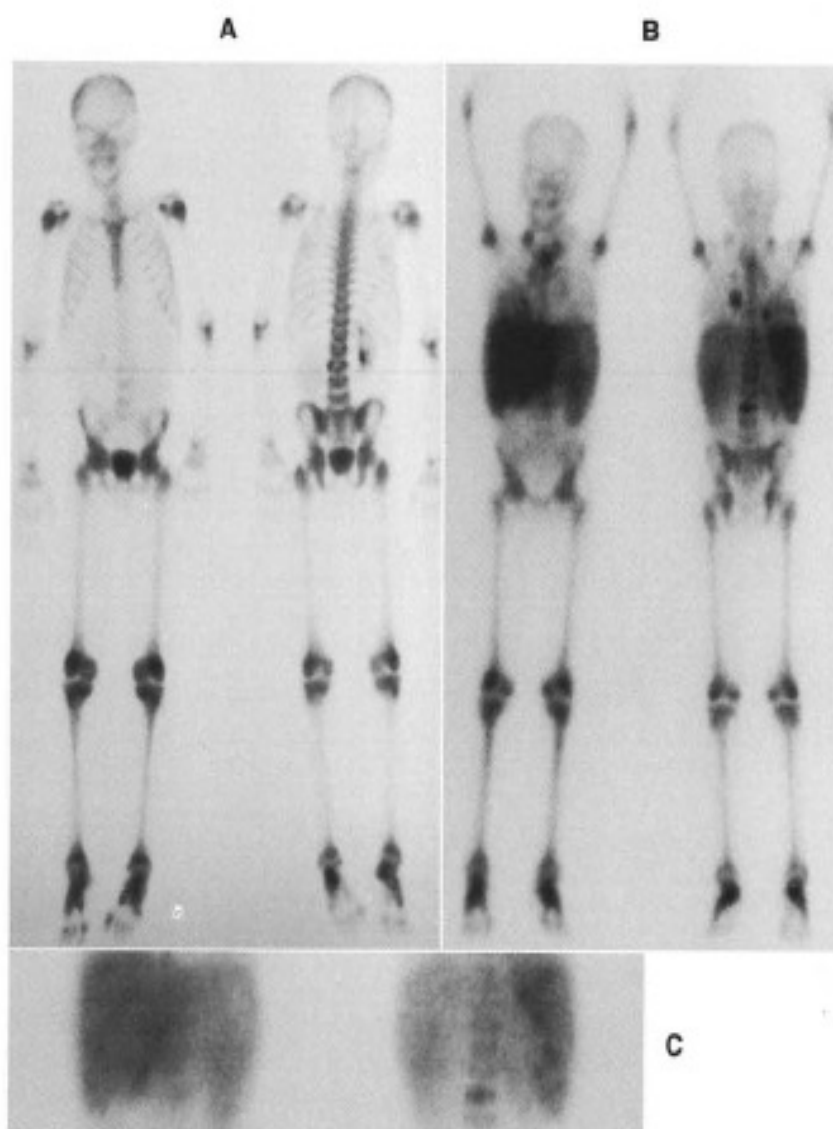


A patient with malignant B-cell lymphoma. Initial FDG-PET study (A) shows tumor above and below the diaphragm. Postchemotherapy CT shows a residual abdominal mass. Posttherapy FDG-PET (B).

1. Is remission complete or partial based on the CT and subsequent PET study?
2. What are the limitations of CT for staging and restaging of disease in patients with lymphoma?
3. List imaging limitations of ^{67}Ga .
4. What are the advantages of ^{18}F FDG-PET compared with ^{67}Ga ?

Lymphoma

1. CT scan is indeterminate, but FDG PET demonstrates a complete response.
2. CT assessment of tumor response is based on a decrease in the size of the mass or complete resolution. Post therapy residual masses are common and CT cannot differentiate residual tumor from post therapy fibrosis and necrosis.
3. Multiple high energy photopeak: 185, 300, 394 resulting in poor image resolution, need delayed images from 2 to 3 days.
4. Study completed 2 hours after injection. FDG PET target to background ratio higher and image quality superior to Ga-67.

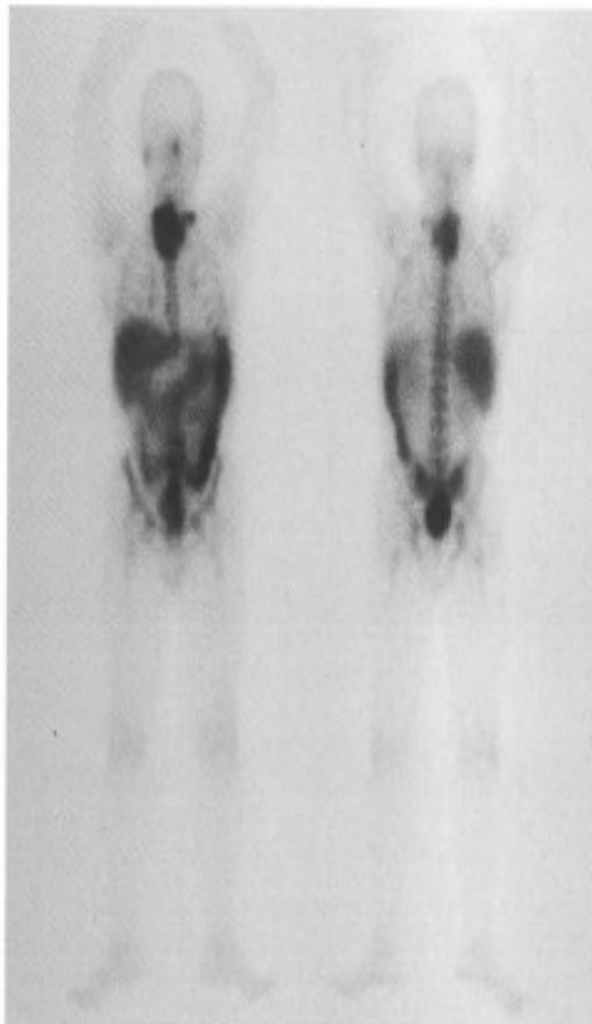
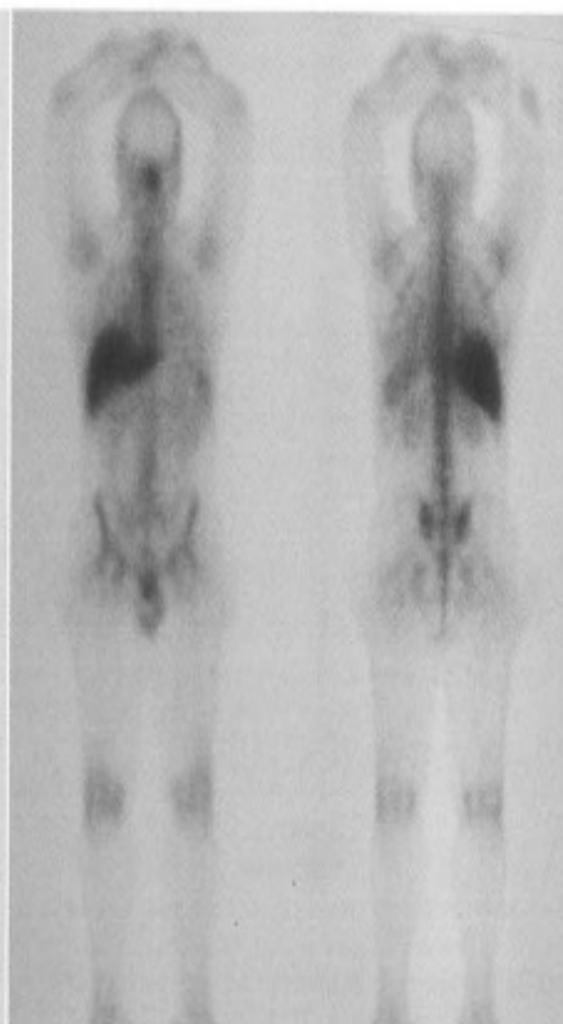


A 9-year-old patient had back pain and fever for 4 weeks. Bone (A), gallium-67 whole-body (B) and abdominal spot views (C) are shown.

1. Describe the scintigraphic findings on the bone and gallium scans.
2. When both tests are ordered at the same time, which should be performed first?
3. Provide the differential diagnosis and the most likely diagnosis.
4. Based on the available information, characterize the stage of disease.

Hodgkin's disease

1. The bone scan shows mild increased uptake at L3. The Ga-67 scan shows abnormal uptake in the L3 vertebral body, bilateral neck, mediastinum, right paratracheal regions, posterior thorax, right lung base and liver.
2. Bone scan.
3. Hodgkin's disease, TB or atypical mycobacteria; Hodgkin's disease likely.
4. Stage IV.

A**B**

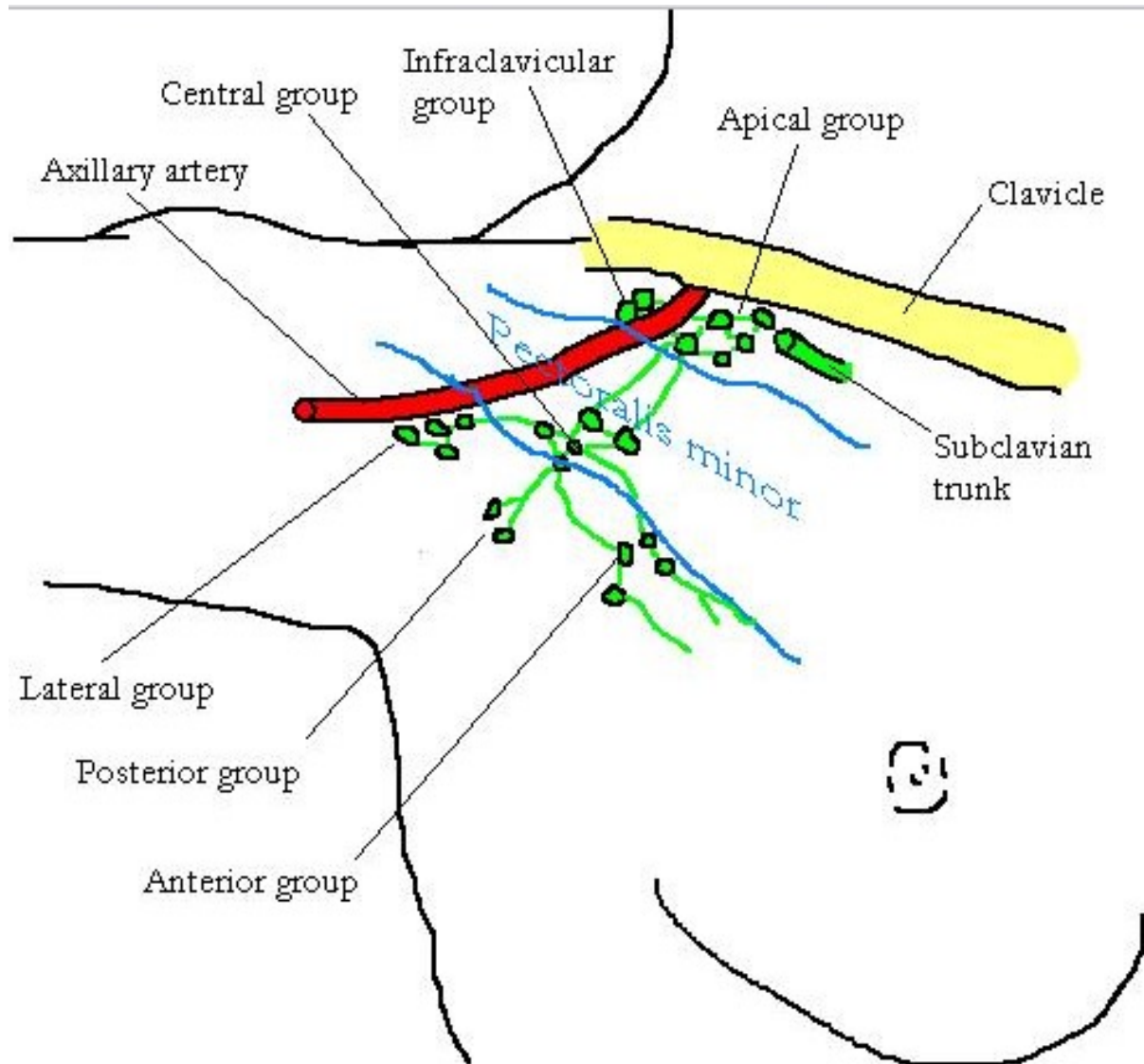
A 32-year-old man has non-Hodgkin's lymphoma. *A* shows the ^{67}Ga study at initial staging, and *B* was performed after a full course of chemotherapy. CT showed a residual chest mass after chemotherapy.

1. What is the adult dose of ^{67}Ga for tumor evaluation? When is imaging performed?
2. Compare the accuracy of ^{67}Ga and CT for initial staging and evaluating response to therapy.
3. Describe the findings of the two studies and interpret them.
4. How can the problem of bowel activity be minimized on ^{67}Ga scans?

Non Hodgkin's lymphoma

1. Adult dose is 10 mCi. Imaging performed 48 to 72 hours after injection.
2. CT provides better sensitivity for initial staging. Ga-67 is superior to CT after therapy and residual masses after therapy.
3. a, large mass in the anterior mediastinum extends to supraclavicular regions. b. complete response to therapy. The residual chest mass on CT caused by necrosis and fibrosis, not tumor.
4. Laxative may be given, and imaging may be delayed as needed at 4 to 7 days after injection.

Axillary LNs



Sentinel node

- Is the **first lymph node bed** which a tumor cell would come if it penetrated into lymphatic fluid.
- If axillary sentinel node is tumor free < 3% chance of any tumor metastasis
- Radiopharmaceutical= Tc-99m SC injected subdermally/ periareolar/ intradermal or peritumoral

Indication:

women who have a biopsy-proven carcinoma of the breast in whom definitive surgery and axillary node clearance is planned and on whom there are no palpable axillary lymph nodes.

- Contraindication:
 - High tumour grade (T3, T4, tumour >4cm)
 - Palpable lymph node: lymphatic flow to metastatic LN may be obstructed and may not be identified.
 - Multifocal or multicenter cancers: procedure may not reflect all possible sentinel LN.
 - poor health status
 - known dissemination
-
- Relative contraindication:
 - Disrupted lymphatic pathways due to previous surgical excisional biopsy or surgical procedures in axilla
 - Neoadjuvant chemotherapy: up to 33% false negative due to lymphatic changes, fibrosis or patchy killing of metastatic foci.
 -
- Precaution:
 - Pregnancy is not contraindication (but only for blue dye) as the dose to fetus is negligible.
 - lactating: suspend for 24hr

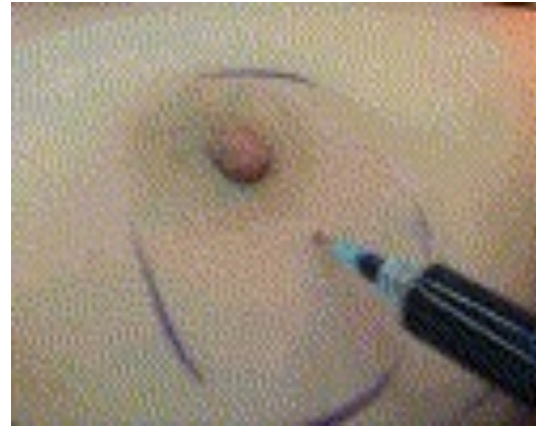
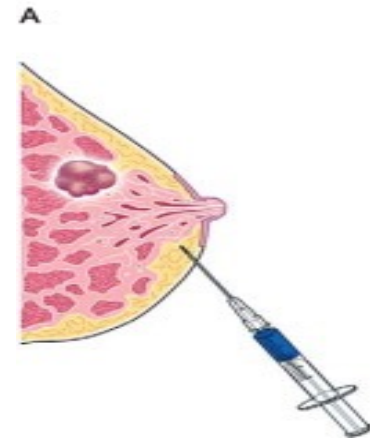
Axillary node dissection is more effective at lowering the risk of local recurrence than axillary node sampling, which in turn is more effective than no axillary surgery. No evidence was identified on the effectiveness of excision of the supra-clavicular and internal mammary chain nodes compared with no excision.⁶¹

The New Zealand guidelines concluded that SLNB was an appropriate method of staging the axilla as there was no difference in axillary recurrence or overall survival. There was limited or no trial data available on the effectiveness of SLNB vs axillary lymph node dissection in the following subgroups:

- Women with tumours > 3cm
- Women with multicentric/multifocal tumours
- Women with clinically positive nodes
- Pregnant or breastfeeding women
- Women with known allergies to radioisotopes or blue dye
- Women with previously treated breast cancer or axillary surgery on the affected side

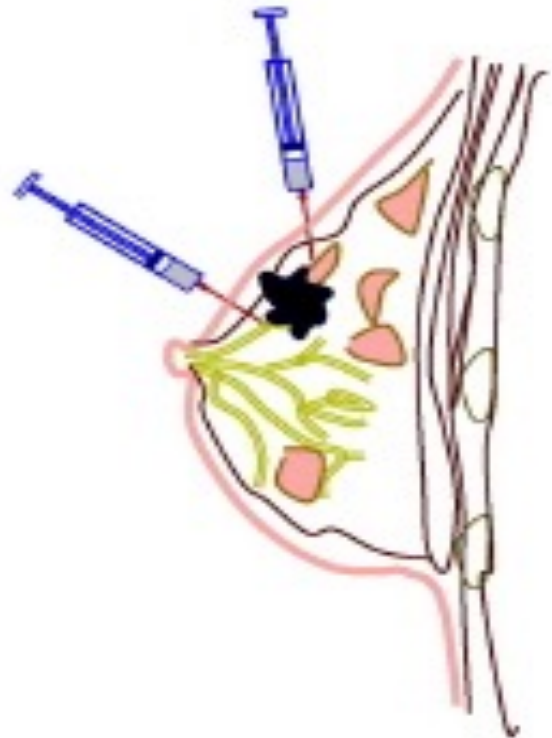
Periareolar injection (particularly upper quadrant tumour)

- Rationale:
 - rich subareolar lymphatic plexus of Sappey.
 - common centrifugal lymphatic pathway.
- Advantage: for less experience, non-palpable primary, faster tracer migration than subdermal
- Disadvantage: shine through activity, may miss parasternal



Peritumoral 4 to 8 injections (0.5 – 1.0mCi in total of 3 to 7ml) within 1cm surround the tumour or biopsy site

- Preferred in predominantly medial and central localization, where parasternal spread is suspected.
- (ultrasound guidance in deep seated lesion)



False positive

- second-tier nodes, in particular if dynamic imaging is not performed
- lymphangioma or lymphatic lakes (focal dilatations of lymphatic collecting vessels) mistaken for a SN. (these lakes are usually not visible on delayed images. A true SN remains hot on delayed scans)
- Skip lesion
- skin folds and other tissues containing radioactivity, but no node. (use of SPECT-CT)

Malaysia GCP on Breast ca Mx 2010

RECOMMENDATION

Sentinel node biopsy should not be carried out in women with clinically involved nodes. The safety and efficacy of sentinel node biopsy for breast cancer > 3cm or multifocal disease has yet to be demonstrated in randomised controlled trials. As such, it is not recommended for these groups. **(Grade A)**

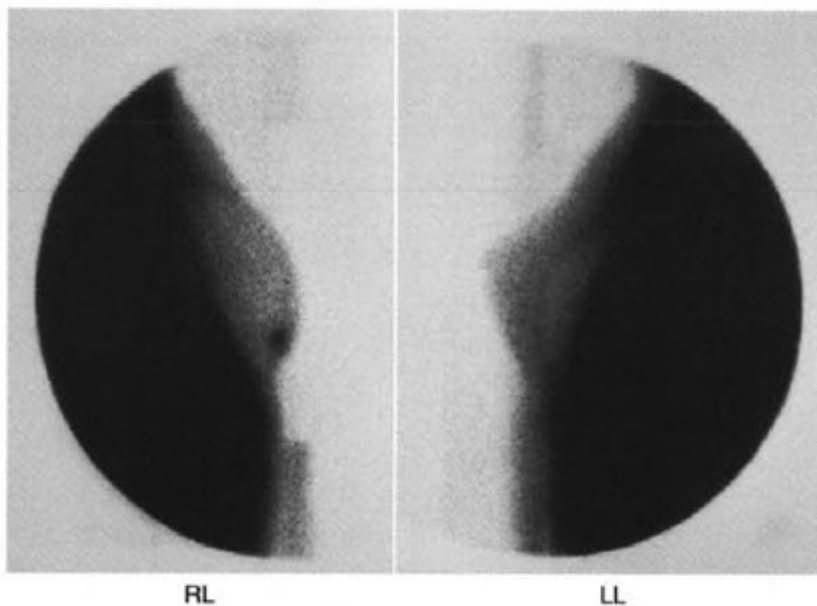
Sentinel lymph node biopsy may be offered to the following :

- Unifocal tumour of $\leq 3\text{cm}$
- Clinically non-palpable axillary nodes **(Grade B)**

Sentinel lymph node biopsy should only be performed by surgeons who are trained and experienced in the technique. **(Grade A)**

Dual technique with isotope and blue dye in performing the sentinel lymph node biopsy is preferred. **(Grade A)**

- The ASBS guidelines:
 - Surgeons anticipating the use of SNB as their sole means of staging the axilla should first perform 30 validation cases with accurate identification of SL 85% of the time and false-negative $\leq 5\%$.

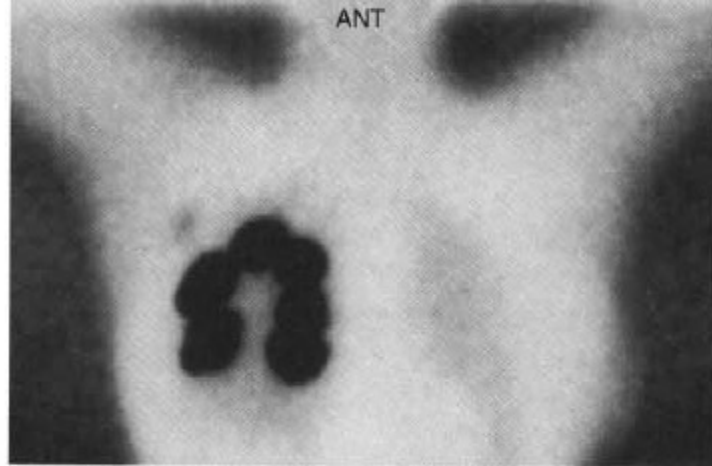
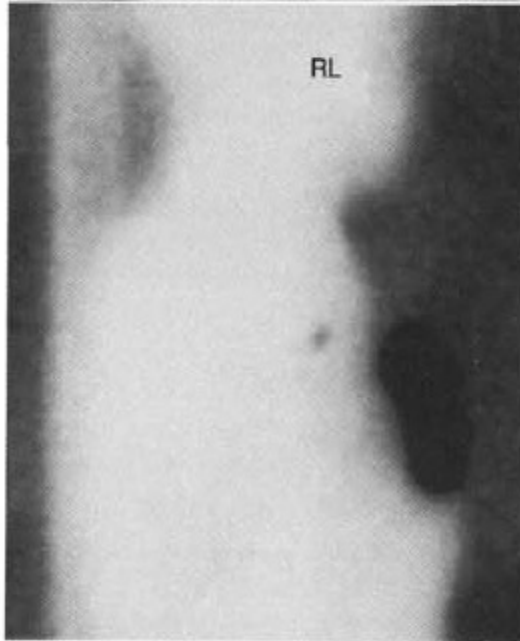


Scintimammography in two different patients; *A*, a mammographically detected right breast mass; *B*, a palpable mass adjacent to a right breast prosthesis.

1. What is the radiopharmaceutical? What is its mechanism of uptake?
2. Describe the imaging findings and give an interpretation.
3. What is the accuracy of conventional mammography and scintimammography for breast cancer?
4. What are causes of false-negative and false-positive findings on scintimammography?

Scintimammography

1. Tc-99m sestamibi lipophilicity allows it to enter the cell where it is concentrated in the mitochondrial region related to charge.
2. Patient A has prominent focal uptake in a right breast mass. Patient B has definite focal uptake at the periphery of the breast prosthesis.
3. Accuracy of conventional mammography: sensitivity, 70% to 95%; positive predictive value for cancer, 20% - 30%. Scintimammography trial: sensitivity/specificity, 75%/83%
4. Most false negative findings are in lesions less than 1 cm. False positive findings occur in fibroadenomas and benign and malignant tumors other than breast cancer



A 49-year-old woman was referred for breast lymphoscintigraphy after recent biopsy of a right breast mass and the diagnosis of breast cancer.

1. What is the implication of axillary node involvement in breast cancer?
2. What is a sentinel node?
3. What is the purpose of sentinel node biopsy?
4. What is the radiopharmaceutical used, and how is the study performed?

Scintimammography

1. The 5 year survival rate for breast cancer decreases with axillary node involvement. Adjuvant chemotherapy is indicated.
2. A sentinel node biopsy drained by the lymphatics in a nodal basin.
3. If the sentinel node biopsy is tumor negative, no axillary dissection is needed. If positive, axillary dissection is performed.
4. Tc-99m sulfur colloid is often used. It is injected around the lesion or biopsy site. Imaging usually is performed. At surgery a gamma probe is used to help locate the sentinel node.

Head and neck carcinoma

- PET sensitivity for recurrence is 76-96%
- Negative predictive value > 90%

Thyroid carcinoma

- PET sensitivity for poorly differentiated carcinoma > 90%
- Benefits for: **anaplastic** and **Hurtle cell variant** of follicular

Medullary thyroid carcinoma

- Arises from parafollicular cells
- Does not accumulate I-131
- PET sensitivity 78% and specificity 79%
- Can evaluate with :
 1. Somatostatin
 2. DMSA pentavalent
 3. Thallium 201
 4. Tc-99m sestaMIBI

Esophageal carcinoma

- PET sensitivity 95%
- LNs involvement sensitivity >70%
- LNs involvement specificity >90%
- Distant metastasis accuracy 83%

Colorectal carcinoma

- Primary sensitivity >90% : CT 60%
- LNs involvement sensitivity 85 – 99%
- LNs involvement specificity 71 – 87%
- Alter management 29 – 36%

Melanoma

- PET sensitivity > 90% and specificity 87%
- PET alter treatment 20 – 26%

- A feto protein for hepatocellular carcinoma
- Ca 19-9 for pancreatic carcinoma
- PET less sensitive for hepatocellular carcinoma

Breast carcinoma

- PET sensitivity 88% and specificity 79%
- > 2-5 cm PET sensitivity 92%
- < 2 cm PET sensitivity 68%
- LNs involvement sensitivity 79-100% and specificity 66-100%
- False negative:
 1. Well differentiated
 2. Slow growing : lobular/tubular/DCIS

Ovarian carcinoma

- PET sensitivity for staging and restaging (50-90%)
- PET specificity 60-80%
- PET alters management 15% cases

**PET false – ve in
ovarian carcinoma**

Mucinous
cystadenocarcinoma

Well differentiated
cystadenocarcinoma

Disseminated peritoneal
carcinomatosis

Borderline tumors

Stage I tumors confined to
the ovary

Testicular carcinoma

- PET sensitivity 84%
- PET negative predictive value is 94%

Neuroendocrine tumor

Peptide-Based Probes for Cancer Imaging

- Specific targeting of tumors through selective molecules, a promising strategy in oncology (diagnostic or for therapeutic)
- Regulatory peptides represent such a class of molecules developed for specific cancer targeting
- a peptide is any combination of amino acids linked together with peptide bonds

- Regulatory peptides physiologically play a modulatory role in the human body - brain; gastrointestinal tract; and endocrine, vascular, or lymphoid systems
- mediate their functions through high-affinity, specific, usually G-protein–coupled receptors
- **physiologic** peptide **receptors** - relatively **low density** in physiologic organs
- massively **overexpressed in** numerous **cancers**

Advantages of peptides

- small size → implying good tissue diffusion
- target accessibility
- no antigenicity
- easy synthesis
- adequate radiolabeling

TABLE 1
Peptide Receptors, Corresponding Cancer Indications, and Peptide Probes

Peptide	Receptor	Cancer Indication	Peptide probe	Reference
Somatostatin	sst ₂	Neuroendocrine tumors*	DTPA-octreotide	3 (review)
			DOTA-TOC	
			DOTA-TATE	
			Hynic-TATE, HYNIC-TOC	
			N ₄ -TATE	
			¹⁸ F-carbohydrated-TATE	4
	sst ₂ /sst ₃ /sst ₅	Neuroendocrine tumors*	DOTA-NOG/DOTA-BOC	5
	sst ₁ /sst ₂ /sst ₃ /sst ₄ /sst ₅	Neuroendocrine tumors	DOTA-pan-somatostatin (KE-88)	6
	sst ₂	Neuroendocrine tumors	DOTA-sst ₂ -antag (antagonist)	8
	sst ₃	Neuroendocrine tumors	DOTA-ODN-8-sst ₃ (antagonist)	8
CCK, gastrin	CCK ₂	Medullary thyroid cancer*	DTPA-minigastrin	10 (review)
			DTPA-CCK ₈ (nonsulfated)	
			Demogastrin	
			DOTA-minigastrin 11 and 9	14
Bombesin	GRP-R	Prostate cancer*; breast cancer*	RP 527	12
			AMBA	15
			DOTA/DTPA-panbombesin	16
			Demobesin 1 (antagonist)	17
GLP-1	GLP-1 R	Insulinomas*	[Lys ⁴⁰ (Ahx-DTPA)NH ₂]-exendin-4	13
			[Lys ⁴⁰ (Ahx-DOTA)NH ₂]-exendin-4	
NPY	Y ₁	Breast cancer; sarcomas	[Lys(DOTA) ⁴ ,Phe ⁷ ,Pro ³⁴]NPY	20
RGD peptides	α _v β ₃ -integrin	Various*	Various	21 (review)

*Proof of principle in vivo in patients available.

TATE = [Tyr³,Thr⁸]octreotide.

Somatostatin

- Octreotide (synthetic derivative)
- Growth Hormone Inhibiting Peptide
- Produce in GI system
 - Stomach, intestine, delta cell pancreas
- Inhibits release of multiple peptides: gastrin, CCK, glucagon, growth hormone, insulin, secretin, vasoactive intestinal peptide, TSH, and pancreatic polypeptide
- Alters splanchnic blood flow

Somatostatin Receptor Imaging

- What are somatostatin receptors
- Types - SSt1 → SSt5
- Basis of SR imaging
 - stable somatostatin analog linked to a chelator that can bind radioactive metals (^{111}In , $^{99\text{m}}\text{Tc}$, ^{68}Ga)
 - Selectively bind to these somatostatin receptors and will actively be taken up by the cells through a process called receptor-ligand internalization → accumulation of radioactivity in the tumor

Somatostatin Receptor Positive Tumours

High expression of receptors

- Gastro-entero-pancreatic tumours (GEP)
 - (e.g.: carcinoids, gastrinoma, insulinoma, glucagonoma, VIPoma, etc.), functioning and non functioning
- Sympatho-adrenal system tumours
 - (phaeochromocytoma, paraganglioma, neuroblastoma and ganglioneuroma)
- Medullary thyroid carcinoma
- Pituitary adenoma
- Merkel cell carcinoma
- Small cell lung cancer

Low expression of receptors

- Breast carcinoma
- Melanoma
- Lymphomas
- Prostate carcinoma
- Non-small cell lung cancer
- Sarcomas
- Renal cell carcinoma
- Differentiated thyroid carcinoma
- Astrocytoma
- Meningioma

Somatostatin receptor expression in GEP-NET

Main features

Characteristics

Receptor incidence	80-100% (Most pancreatic and gut NET) 50-70% (Insulinomas)
Receptor density	predominantly high
Receptor distribution	predominantly homogeneous
Receptor expression	differentiated tumor > undifferentiated tumor
Receptor subtype	SSt2 » SSt1 = SSt5 > SSt3 » SSt4
Receptor localization	usually membrane bound (sst2)

Incidence of SST-R

Results of *in vitro* Studies

in vitro receptor status

- Gastrinoma, Glucagonoma
- Insulinoma
- Paraganglioma
- Medullary Thyroid Carcinoma
- Carcinoid
- Small Cell Lung Cancer
- Pheochromocytoma

100 %

72 %

92 %

38 %

88 %

57 %

73 %

Somatostatin analogues (1)

OctreoScan[®]

- Introduced 1992: large number of clinical studies
- effective in diagnosis and staging of tumors expressing
- SST-R 2
- expensive

Indications for ^{68}Ga DOTA conjugate peptide imaging

- primary indication is the imaging of NETs
- in non-NET imaging – if treatment with radiolabeled therapeutic SST analogues is considered

Indications for ^{68}Ga DOTA conjugate peptide imaging in NETs

- localise primary tumours and detect sites of metastatic disease (staging)
- follow-up of patients with known disease to detect residual, recurrent or progressive disease (restaging)
- determine SST receptor status (patients with SST receptor-positive tumors are more likely to respond to Octreotide therapy)
- select patients with metastatic disease for SST receptor radionuclide therapy (with ^{177}Lu or ^{90}Y -DOTA-peptides)
- monitor the response to therapy (surgery, radiotherapy chemotherapy or SST receptor radionuclide therapy)

NEUROENDOCRINE TUMOURS (NETs)

- start in neuroendocrine cells of the embryological gut
- occur most commonly in the digestive system
- rare (5.25/100 000/year)
- all ages; highest incidence from the fifth decade upwards
- (behaviour) may be
 - non-cancerous (benign) or cancerous (malignant).
 - functioning (hormone-secreting) or non-functioning (non-hormone secreting).
- Examples:
 - Carcinoid – GI, bronchial
 - GEPs - Gastroenteropancreatic tumours - which include:
 - Insulinomas; gastrinomas; glucagonomas; VIPomas; somatostatinoma

Pathology of Neuroendocrine Tumours

Markers for neuroendocrine tissue: -

- neuron specific enolase
- chromogranin A
- synaptophysin

Markers for mitotic activity:

- Ki-67(MIB1): proliferation rate
- < 5 % staining -> *slow growing / indolent*

Classification of neuroendocrine GEP tumours (GEP-NETs) by site of origin and by hormonal activity

Intestinal neuroendocrine tumours (carcinoids, about two-thirds of GEP-NETs)

- with carcinoid syndrome (30% of carcinoids)
- without carcinoid syndrome (70% of carcinoids)

Pancreatic endocrine tumours (PETs) (about one-third of GEP-NETs)

- Non-functioning (45%–60% of PETs)
- Functioning (40%–55% of PETs)
 - Gastrinoma, excessive gastrin production, Zollinger–Ellison syndrome
 - Insulinoma, excessive insulin production, hypoglycaemia syndrome
 - Glucagonoma, excessive glucagon production, glucagonoma syndrome
 - VIPoma, excessive production of vasoactive intestinal peptide (VIP), watery diarrhoea, hypokalaemia–achlorhydria (WDHA) syndrome
 - PPoma, excessive pancreatic polypeptide (PP) production, (generally classified as non-functioning PETs)
 - Somatostatinoma, excessive somatostatin production
 - CRHoma, excessive corticotropin-releasing hormone (CRH) production
 - Calcitoninoma, excessive calcitonin production
 - GHRHoma, excessive growth hormone-releasing hormone (GHRH) production
 - Neurotensinoma, excessive neurotensin production
 - ACTHoma, excessive production of adrenocorticotrophic hormone (ACTH)
 - GRFoma, excessive production of growth hormone-releasing factor (GRF)
 - Parathyroid hormone-related peptide tumour

GEP-NET neoplasm: WHO classification

- WHO 1 Well differentiated endocrine tumour
 - WHO 2 Well differentiated endocrine carcinoma
 - WHO 3 Poorly differentiated endocrine carcinoma
- Mixed exocrine-endocrine tumours
- Tumour-like lesions

Clinical Presentation

- endocrine pancreatic tumours,
 - often present with metastatic disease,
 - insulin-producing tumours - benign in 85% of cases
- well-differentiated (neuro-)endocrine tumours of the small intestine (midgut carcinoids),
 - The largest group of GEP-NETs,
 - present with the carcinoid syndrome in 30%,
 - flushing, diarrhoea and endocardial fibrosis

Prognosis

- 5-year survival rate
 - endocrine pancreatic tumours (80% for all stages)
 - 60%–100% for localized disease
 - 40% for regional
 - 25% for metastatic
 - ‘classical’ midgut carcinoids,
 - 60% for all stages.
 - high-grade poorly differentiated neuroendocrine carcinomas
 - median survival of 10 months
- negative prognostic factors in GEP-NETs
 - pancreatic localization,
 - poor degree of differentiation
 - distant metastases

Diagnosis

Susp. of NET



Typical Symptoms
⇒ Diagnostic Pathways



Tests for
Hormone Production



Imaging
Procedures



Therapy

Diagnostic Methods:

- (Endo-) Sonography
- Endoscopy
- MRI (CT Scan)
- **Somatostatin Receptor PET/CT or Scintigraphy (SRS)**

Foregut

Midgut

Hindgut

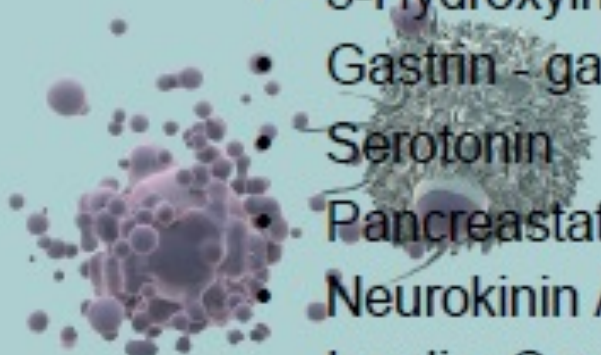
Diagnosis of neuroendocrine tumors

1. Markers for neuroendocrine tissue

- General markers have been used for screening purposes in patients without distinct clinical hormone-related syndromes
 - Chromogranin A (CGA)
 - Serum neuron-specific enolase
 - Synaptophysin

2. Specific markers for the diagnosis and the follow-up includes

- 5-Hydroxyindoleacetic acid (urinary metabolite of serotonin)
- Gastrin - gastrinoma
- Serotonin
- Pancreastatin
- Neurokinin A (substance K)
- Insulin, C-peptide, serum glucose levels - insulinoma



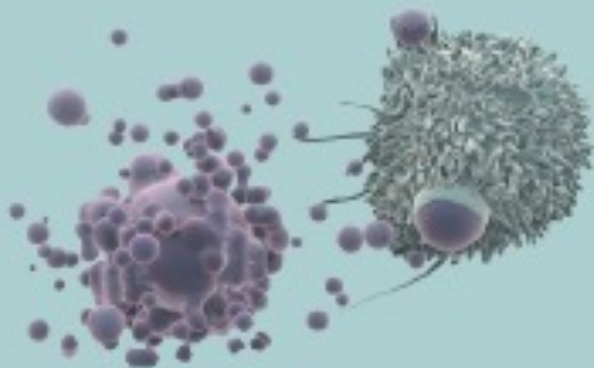
Diagnosis of Neuroendocrine Tumor

- Serial measurements of these markers are made every 3 to 6 months.
- The absolute value of CGA is not a determinate of tumor burden; nor can it rule out or confirm metastases.
- Changes in CGA level by 25% over the baseline are considered significant.
- There has been a concordance between the CGA levels and the findings on ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy. A CGA level in the reference range has been found to be highly predictive of normal scintigraphy results.



Diagnosis of Neuroendocrine Tumor

3. Markers for mitotic activity – Ki-67 proliferation index
4. Proposed of gene expression in GIT neuroendocrine carcinoma which could be useful diagnostic and/or therapeutic targets.



Diagnosis of NETs

Imaging modalities commonly used include :

- Conventional radiology - transabdominal USG, computerized tomography (CT) and magnetic resonance imaging (MRI), selective angiography with or without hormonal sampling
- Nuclear imaging - somatostatin receptor scintigraphy (SRS) with SPECT, bone scintigraphy
- Endoscopic ultrasonography and various intraoperative methods.

For localization of both primary and metastatic lesions, the primary imaging method used should be SRS (Octreoscan®) – ¹¹¹Indium labeled somatostatin analogs.

However, none of the techniques available have 100% sensitivity and multiple imaging modalities might be needed to detect small tumors.

Anatomical Imaging for Detection of Pancreatic NET

<u>Procedure</u>	<u>Sensitivity</u>
CT	20 - 40%
Sonography	20 - 40%
Angiography	20 - 70%
Endosonography	50 - 75%
MRI	50 - 75%
Intraoperative palpation	90%
Ga-68 SMS-R PET/CT *	> 90%

** unpublished data*

PET scanning

- ^{18}F FDG PET - only in poorly differentiated GEP-NET tumours
- ^{18}F DOPA or ^{68}Ga DOTA-octreotate – detects somatostatin receptors

Methodology

- Similar to FDG PET-CT protocol except
 - No special preparation required; serum glucose measurements not necessary
 - Radiopharmaceutical – ^{68}Ga DOTATATE (100 – 150MBq)
 - Time of imaging – 45 minutes post-injection



Image showing the physiological distribution of ^{68}Ga -DOTA-D-Phe1,Tyr3)-octreotate.

- 1 - pituitary gland;
- 2 - submandibular salivary gland;
- 3 - thyroid uptake;
- 4 - adrenal;
- 5 - liver;
- 6 - spleen;
- 7 - bone marrow of the iliac crest.

Possibly the tonsils should be pointed out as well.

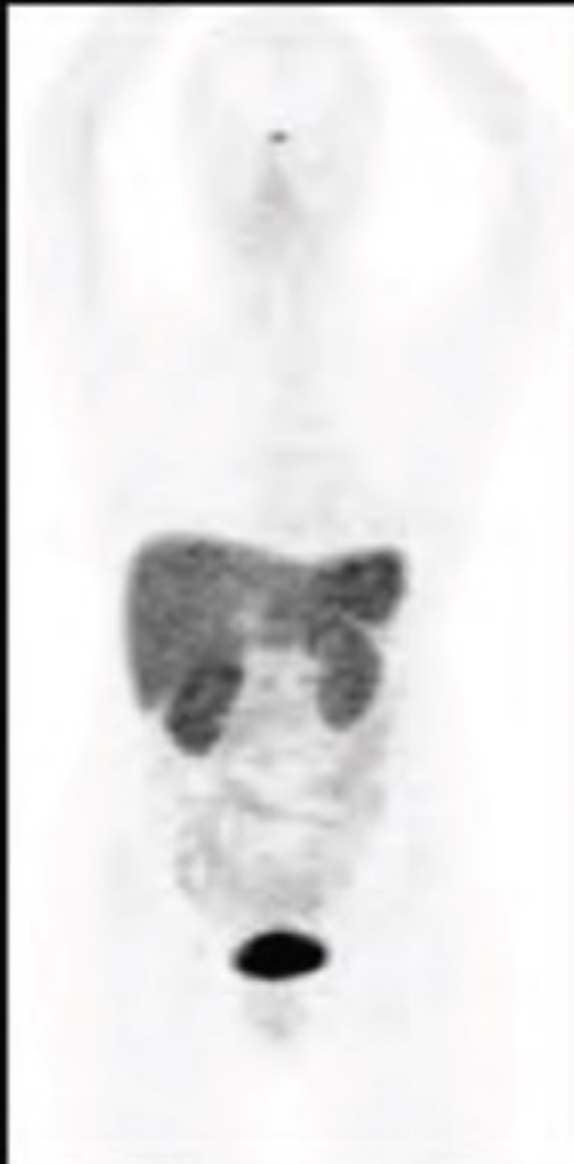
Table 1 Maximum and mean SUVs recorded in the different organs

Organ	SUV _{mean} (average)	SUV _{mean} (range)	SUV _{max} (average)	SUV _{max} (range)
Pituitary gland	5.1	2.1-8.5	7.6	3.5-11.1
Parotid gland	3.5	1.4-6.5	4.2	1.7-7.3
Submandibular	3.0	1.6-4.2	3.6	1.9-5.3
Palatine tonsil	1.8	0.7-3.6	2.3	0.8-3.8
Thyroid	3.0	1.2-8.7	3.9	1.4-7.7
Lymph nodes	1.1	0.3-4.2	1.1	0.5-2.2
Breast	0.3	0.1-0.4	0.3	0.1-0.4
Thymus	0.8	0.4-1.3	1.0	0.4-1.5
Lungs	0.7	0.2-1.3	1.3	0.6-2.3
Blood pool	0.7	0.2-1.1	0.9	0.2-1.6
Bone marrow	0.7	0.2-2.2	1.5	0.4-2.7
Liver	7.2	3.6-10.2	8.2	4.7-11.3
Spleen	24.9	17-32.2	27.9	22-35
Pancreas	4.2	3.0-7.6	4.8	3.1-8.1
Stomach	6.0	2.1-11.4	7.3	2.5-13.8
Small bowel	4.4	2.7-7.8	5.2	3.7-8.6
Large bowel	3.5	1.5-8.2	4.0	2.1-8.6
Adrenals	9.7	3.6-16.5	12.5	7.3-19.5
Kidneys	11.1	5.7-14	13.6	11.2-16.1
Prostate	3.7	2.6-4.5	4.4	3.5-5.2

SUV, standardized uptake value.

Normal Scan

- Pituitary gland
- Salivary glands
- Thyroid gland
- Liver
- Spleen
- Kidneys
- Adrenals
- Pancreas –
uncinate
- Bladder
- Stomach wall
- Bowel



⁶⁸Ga DOTA-NOC receptor PET/CT: SUV of normal organs

SUV normal tissue (n = 40 patients)	Mean	Range
Liver (n.s.)	5.6	3.7-7.5
Spleen with and without sandostatin (p < 0.05)	17.8	4.7-38.0
	8.8	4.7-10.2
	24.2	19.3-38.0
Lung (n.s.)	1.0	0.5-1.8
Thyroid (n.s.)	2.5	1.4 - 3-5
Pituitary gland (n.s.)	3.1	1.1-5-6
Kidneys (n.s.)	14.1	7.9-22-8
Background (n.s.)	1.00	0.7-1.2

^{68}Ga DOTA-NOC receptor PET/CT: SUV of primary tumors and metastases

SUV primary tumors (n = 40 patients)	Mean	Range
Primary tumours	19.2	8.2-38.0
Liver mets	20.9	3.3 -105
Lymph node mets	9.5	4.2-22.3
Bone mets	13.6	3.0-20.4
Brain mets	12.3	4.6-17.2
Lung mets	2.3	1.6-5.6
Abdominal mets	14.8	5.8 - 34.1

Indications

- Diagnosis
- Staging
 - Primary staging - before PRRT, receptor status, detection of primary tumors in CUP syndrome
- Treatment response
- Follow up
 - in patients with rising **tumor markers (chromogranin, serotonin, calcitonin, glucagon)** for detection of recurrence
- Restaging

Advantages PET/CT

- Provides functional (PET) and anatomical (CT) information with highest accuracy of image fusion
- Short acquisition times
- CT-based attenuation correction
- Quantitative (SUV) PET data

Comparison between In-111 OctreoScan SPECT/CT and ^{68}Ga -DOTATOC-PET/CT

- 36 patients
- 100 % of findings in OctreoScan were visible in the ^{68}Ga -DOTA-TOC PET/CT study
- In 24/36 (67 %) of the patients, additional metastases were detected in the ^{68}Ga -DOTA-TOC PET/CT study
- In all cases, more precise localization with PET/CT
- 95% of the " ^{68}Ga -DOTA-TOC lesions" were visible already 10 min. p.i.

• *Bihl et al. (Stuttgart/Germany), DGN Congress
Basel 2005*

^{68}Ga DOTA-NOC PET/CT: Imaging Results

- SUV in liver metastases was as high as 105 whereas SUVs in normal tissue were in the range of 0.4 (lung) to 31.5 (spleen). In all patients, weakly SMS expressing normal organs (pituitary gland, adrenals, thyroid) were clearly visible.
- Brilliant PET/CT images of all known tumor lesions and in addition small lymph node and bone metastases (< 5 mm) were easily visualized as early as 10 min p.i.
- Significantly more (~20%) lesions were detected as compared to scintigraphy / SPECT using Tc-99-EDDA-HYNIC-TOC (or In-111-OctreoScan SPECT) and results of CT and MRI were clearly surpassed (e.g. for detection of small lymph node, liver or bone metastases).
- Sandostatin given s.c. 6 hours before imaging reduced the specific uptake by a factor of 4

Conclusions: ^{68}Ga Receptor PET/CT

The Bad Berka Experience

- Receptor PET/CT using the Ga-68-labeled somatostatin analogue DOTA-NOC enables the molecular imaging of neuroendocrine tumors and their metastases with very high diagnostic accuracy (largest series of patients studied worldwide: 523 studies in 50 weeks).
- Advantages:
 - Semiquantitative, reproducible data (SUV) which can be used for selecting patients for PRRT and evaluation of therapy response
 - fast protocol (60-90 min.), patient friendly, low radiation burden
 - flexibility, daily use, lower (!) cost than Octreotide scintigraphy
- a new gold standard for *in vivo* SMS receptor imaging
- Comparative studies with Y-86-DOTA-NOC will allow to determine tumor and kidney dosimetry prior to subsequent PRRT using Y-90 or Lu-177-labeled somatostatin analogues.

Pheochromocytoma and Paraganglioma

Pheochromocytoma - rare catecholamine-secreting NETs arising from chromaffin cells of the adrenal medulla

- 0.5% of patients with hypertension
- 4 to 6.5% in patients with adrenal incidentaloma
- Behavior
 - Most catecholamine secreting tumors > 2 cm
 - Reside in one of the adrenal glands
 - 10-20% are multiple, extra-adrenal or malignant

Paragangliomas - chromaffin cell tumors arising in the sympathetic and parasympathetic paraganglia



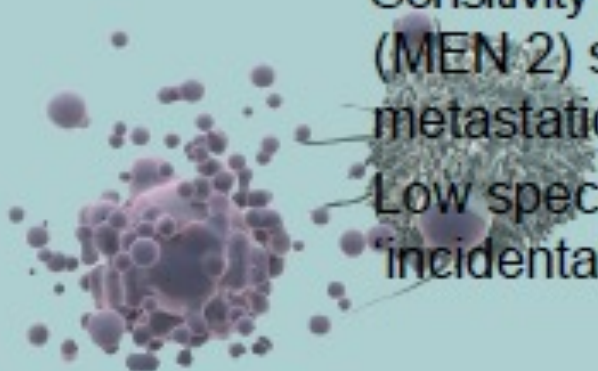
Pheochromocytoma and Paraganglioma

- The presence of a pheochromocytoma or functioning paraganglioma are usually suggested by the clinical symptoms or family history of a patient with familial disease.
- Confirmed diagnosis - by measurements of urinary and plasma catecholamines and their metabolites.
- Localization of tumor after biochemical diagnosis - Imaging studies with CT and MRI

High sensitivity in sporadic tumors (98-100% sensitivity)

Sensitivity decreases in Multiple endocrine neoplasia type 2 (MEN 2) syndrome, extra-adrenal, recurrent or metastatic lesions.

Low specificity - high prevalence of adrenal 'incidentalomas'



Pheochromocytoma and Paraganglioma

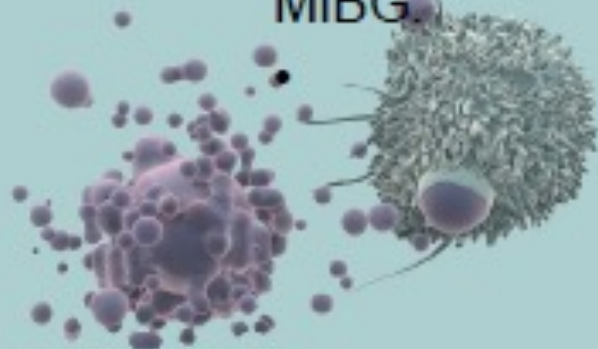
PET

- FDG - Sensitivity approximately 70% for solitary benign or malignant pheochromocytoma

Alternative modality when MIBG scintigraphy fails to image the tumor

- ^{11}C -HED - Visualization of both primary and metastatic deposits (90% sensitivity) within minutes of tracer administration

Spatial resolution and a tumor-to-background ratio $> ^{123}\text{I}$ -MIBG



Pheochromocytoma and Paraganglioma

- ^{18}F -DOPA

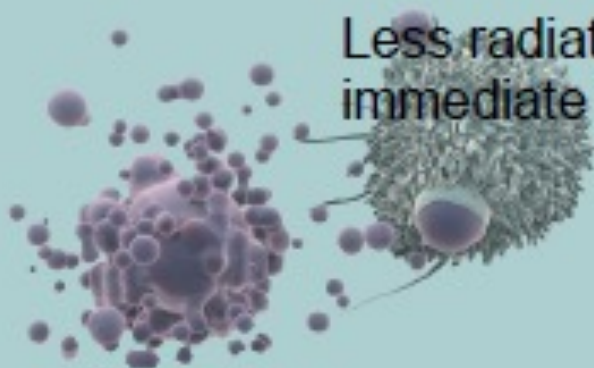
Excellent imaging

Diagnostic sensitivity is superior to FDG and ^{68}Ga -DOTA-peptides

Very small lesions are detected and well localized by PET/CT

Easy interpretation : Lack of visible ^{18}F -DOPA uptake in normal adrenals

Less radiation exposure, no need of thyroid blockade, immediate imaging after injection.



Neuroblastoma

- Arises from precursors of the sympathetic nervous system
- Most common extracranial, highly malignant, solid tumor of childhood.
- Strong propensity to metastasize to cortical bone, bone marrow, lymph nodes and liver.
- Assessment of extension of the disease

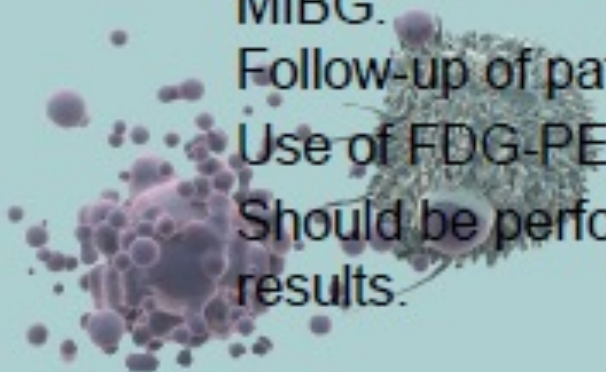
CT (or MRI), bone scintigraphy, MIBG scintigraphy, bone marrow biopsies and urine catecholamine metabolites

FDG-PET - can depict lesions and also those that fail to accumulate MIBG.

Follow-up of patients at high risk of progressive disease

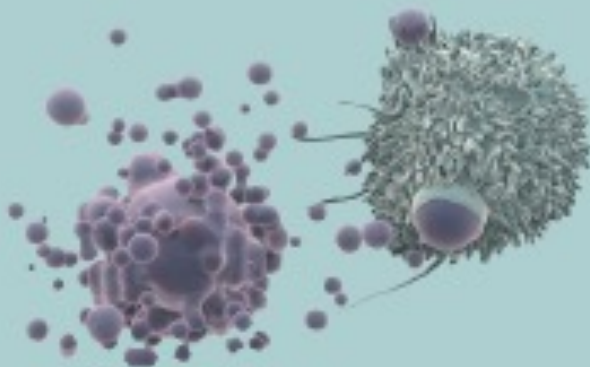
Use of FDG-PET combined with a bone marrow examination

Should be performed only if MIBG scintigraphy gives negative results.



Neuroblastoma

Shulkin et al compared the role of ^{123}I -MIBG and ^{11}C -hydroxyephedrine PET and demonstrated that ^{11}C -HED-PET has high sensitivity for detecting neuroblastoma.

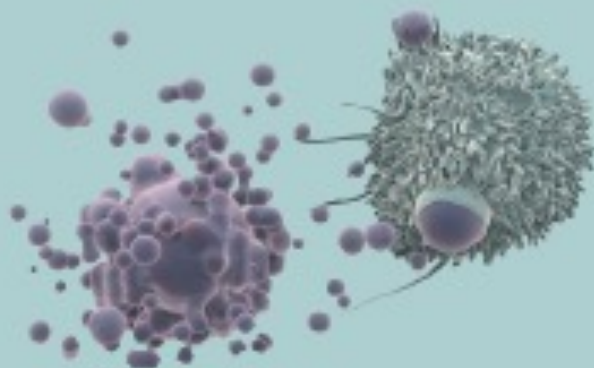


Medullary Thyroid Carcinoma

- Originating in the parafollicular cells (C cells) of the thyroid
- Secrete calcitonin and carcinoembryonic antigen (CEA)
- 3 - 12% of thyroid cancers
- May occur in either sporadic (75-80% of cases) or inherited forms (20-25%).
- Often invasive and progressive with high potential of metastases.
- Radionuclide imaging has a minor role in the preoperative evaluation of MTC but essential in the postoperative follow-up.
- Patients with postoperative normal levels of calcitonin and CEA are considered surgically cured
- Despite aggressive surgery, about 50% of patients with MTC develop a recurrence -> usually difficult to localize, even with high resolution diagnostic imaging

Medullary Thyroid Carcinoma

- Hoegerle and colleagues reported good sensitivity for ^{18}F -DOPA-PET in medullar thyroid cancer (63%) with other imaging procedures (^{18}F -FDG- PET 44%, SRI 52%)
- Evaluating the receptor density before peptide receptor radionuclide therapy with ^{177}Lu or ^{90}Y labeled DOTA-TATE.



Radionuclide therapy

Hepatocellular ca

I-131 lipiodol

Rhenium 188 lipiodol

Yttrium 90 microsphere

Hyperthyroid / thyroid ca

I-131 NaI

Polycythemia vera

Phosphorus 32 phosphate

Bone metastasis

Phosphorus 32 phosphate

Rhenium 188 HEDP

Samarium 153 EDTMP

Strontium 89 chloride

Intra vascular therapy

Phosphorus 32 phosphate

Rhenium 188

Intra articular therapy

Phosphorus 32 phosphate

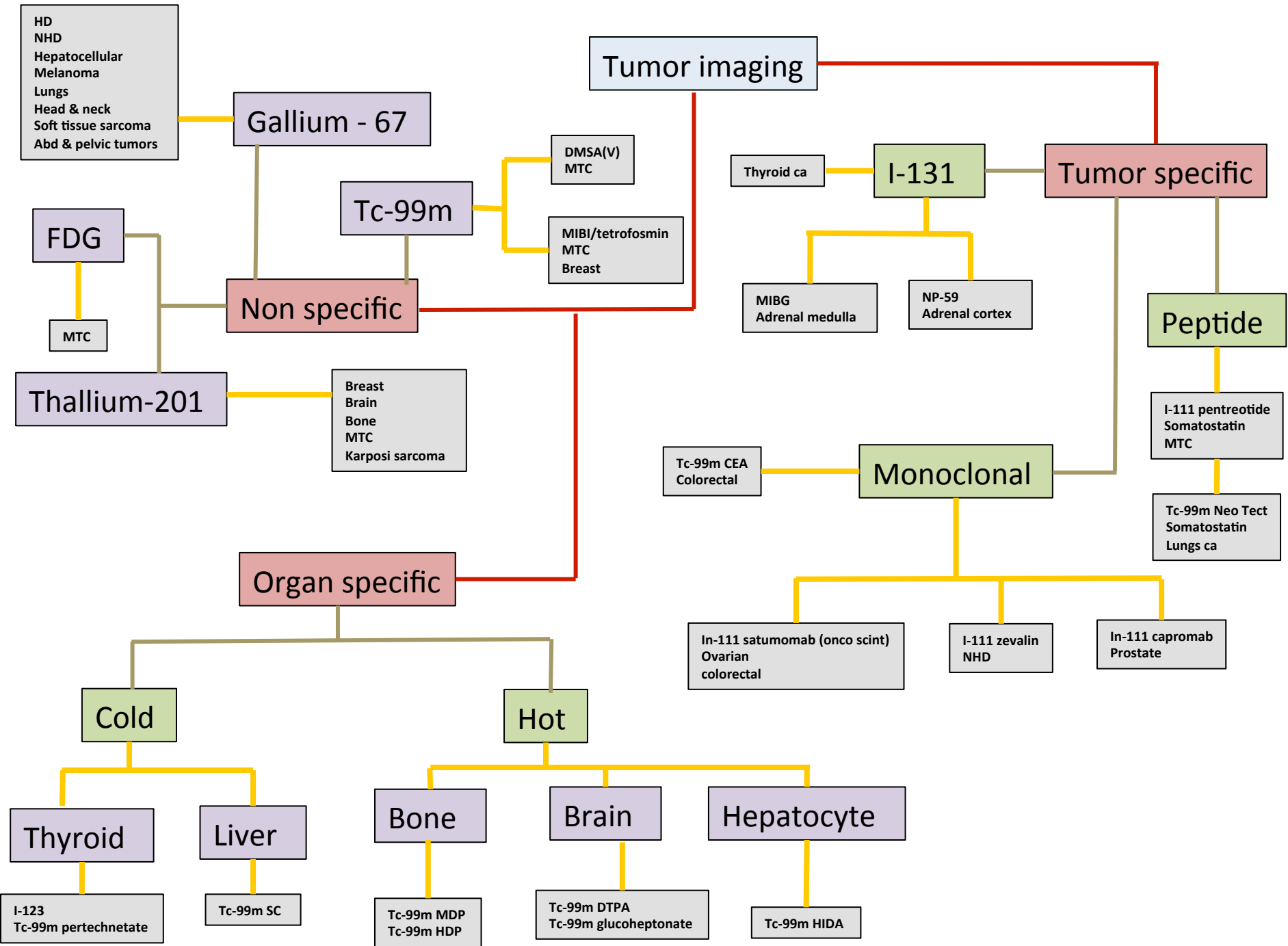
Yttrium 90 citrate

Intra cavity therapy

Phosphorus 32 phosphate colloid

Non Hodgkin's Lymphoma

I-131 anti CD 20 antibody



What is the mechanism of G-67 uptake
in tumors?

What is the mechanism of G-67 uptake in tumors?

- It's binds to serum iron transport molecules such as transferrin, which transport Ga-67 to the tumors.
- Ga-67 enters the extracellular fluid space via the tumor's leaky capillary endothelium.
- It's bound to the tumor cell surface by transferrin receptors and then transported into the cell, where it binds to proteins such as ferritin and lactoferrin, which are increased concentration in tumors.

Ga-67 uptake is normally seen in which of the following organs: salivary glands, lacrimal glands, thymus, spleen, breast and heart?

Ga-67 uptake is normally seen in which of the following organs: salivary glands, lacrimal glands, thymus, spleen, breast and heart?

- Normal uptake : salivary glands and lacrimal glands. Spleen has uptake but is low level. Breast uptake is variable and most prominent in post partum.
- Children after chemo : thymus
- Not normal : heart due to myocarditis and pericarditis.

Which malignant tumors useful for Ga-67 for diagnosis, staging and re staging?

Which malignant tumors useful for Ga-67 for diagnosis, staging and re staging?

- Hodgkin's disease
- Lymphoma
- Hepatoma
- Melanoma

Which of the following statement associated with Hodgkin's and non Hodgkin's lymphoma?

- A. Contagious spread of LN involvement in young patients.
- B. Multicentric disease with a highly variable clinical course and high incidence of extranodal tumor involvement.
- C. Mediastinal masses are common.
- D. Abdominal involvement of mesenteric and retroperitoneal nodes is common.
- E. High cure rate.
- F. Variable clinical course that can be indolent or rapid lethal

Which of the following statement associated with Hodgkin's and non Hodgkin's lymphoma?

HD

- Contagious spread of LN involvement in young patients.
- Mediastinal masses are common.
- High cure rate.

Non HD

- Multicentric disease with a highly variable clinical course and high incidence of extranodal tumor involvement.
- Abdominal involvement of mesenteric and retroperitoneal nodes is common.
- Variable clinical course that can be indolent or rapid lethal

Tc-99m sestamibi has been used for determination of malignancy of breast masses.

- A. Its accuracy is higher for palpable than for non palpable masses.
- B. Its sensitivity is poor for lesions less than 1 cm in size.
- C. Fibroadenomas are always negative.
- D. Useful for dense breast patients, previous surgery, radiation therapy and breast implants.

Tc-99m sestamibi has been used for determination of malignancy of breast masses

- TTFT

Regarding In-111 capromab pendetide (ProstaScint)

- A. Murine monoclonal antibody against a prostate specific membrane antigen express by more than 95% of prostate adenocarcinomas.
- B. Its main indication is for localization of soft tissue metastases after prostactomy in patients with a rising PSA and negative bone scan.
- C. Elevated human murine antibody (HAMA) titers are observed in 50% of patients.
- D. SPECT is mandatory for the pelvis.

Regarding In-111 capromab pendetide (ProstaScint)

- TTFT

Regarding In-111 Octreoscan

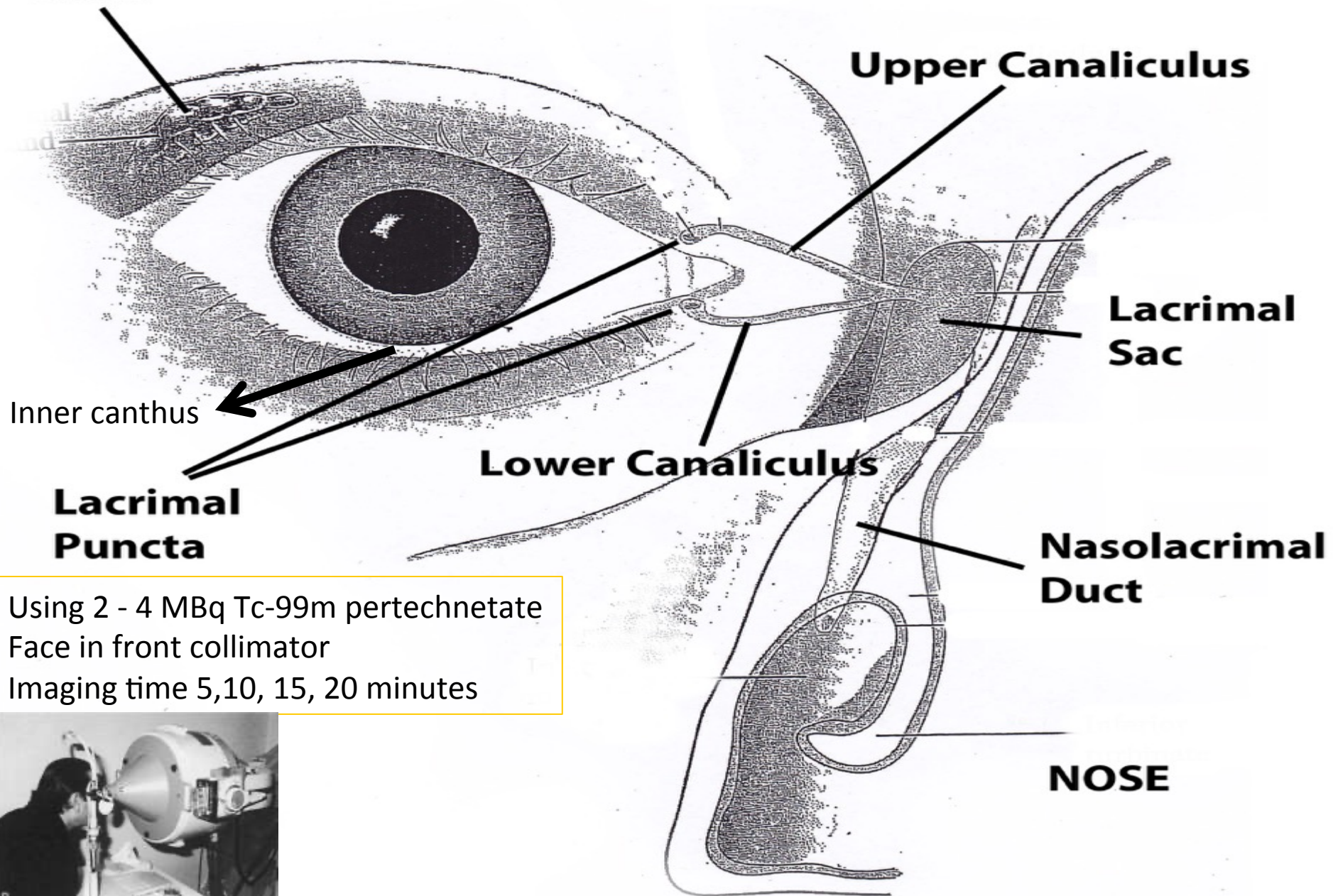
- A. It is somatostatin receptor imaging agent.
- B. The sensitivity for all NET is very high.
- C. Highest uptake is seen in the spleen and kidneys.
- D. Only NET have somatostatin receptors.

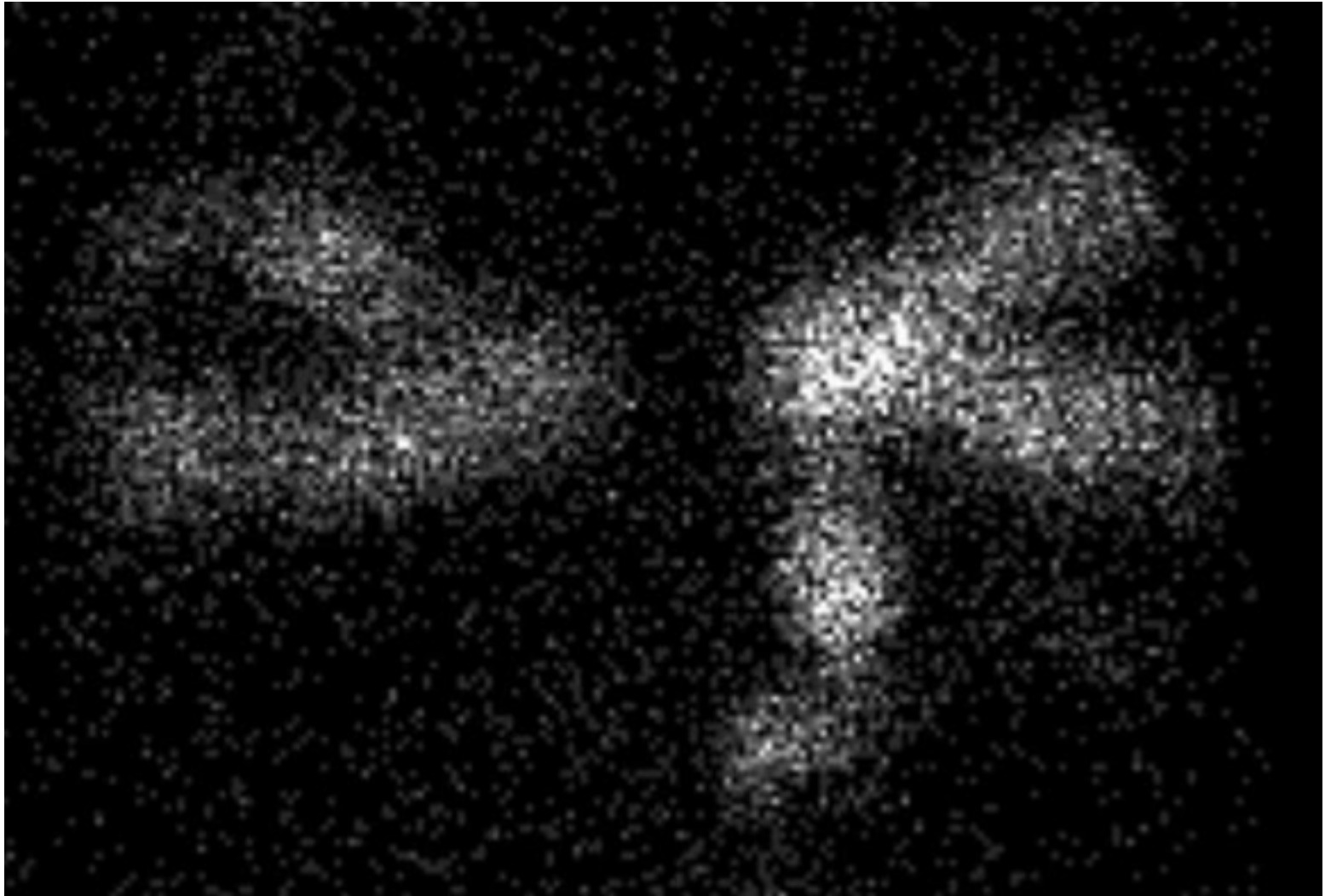
Regarding In-111 OctreoScan

- TFTF

**Lacrimal
Gland**

Lacrimal drainage study





Dacryoscintigram : Normal drainage on the left eye with obstruction on the right eye at the level of common canaliculus

Radiosynovectomy

Radiosynovectomy

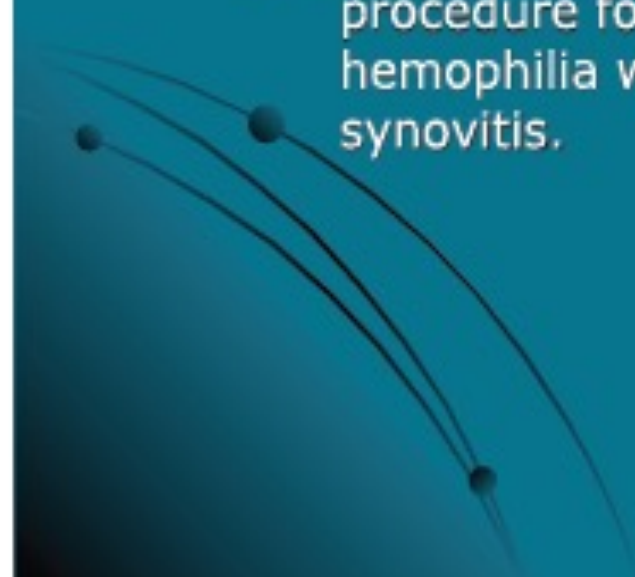
Also called as radiosynoviorthesis

- The ablation of synovial tissue
 - By way of injected radiopharmaceuticals
- 

History

- Radiosynovectomy (RSV) is a local form of radiotherapy that was first used by Fellingner et al. in 1952
- Radionuclides were used therapeutically for the relief of bone pain associated with metastatic cancer and the management of rheumatoid arthritis (RA).
- Applied for treatment of resistant synovitis of individual joints after failure of long-term systemic pharmacotherapy and intra-articular steroid injections.
- Relieves pain and inflammation from RA

Radiosynovectomy

- Now it is accepted as an alternative to surgical synovectomy in cases of RA or other inflammatory arthropathies
 - In recent years, it has become a life-altering procedure for patients with moderate to severe hemophilia who suffer from chronic, debilitating synovitis.
- 

Haemophilia

- A hereditary sex-linked disease due to defective gene of the X chromosome
- Resulting in an insufficient production of the VIII coagulation factor in type A haemophilia (85% of cases) or the IX factor in type B haemophilia.
- 3 forms of this disease:

Type	Deficient	Hemorrhagic episodes in joints & muscles
Severe	Factor levels < 1%,	spontaneously
Moderate	Factor levels between 1 and 5%,	following minor trauma
Mild	Factor level >5%.	only after major trauma or surgery

Haemophilia

- 25% of pts w haemophilia are candidates for RSV in developed country
 - World Federation of Haemophilia – approximately 350-400,000 patients
 - 1:10,000 in the paediatric population.
- 

Haemophilia

- Intra-articular haemorrhage is the most common musculoskeletal manifestation of haemophilia.
 - The knee is most commonly affected (30%) followed by elbow (25%), ankle (15%), hip (5%) and other joints (<2.5%).
 - Joint lesions usually evolve from hemarthrosis to chronic synovitis
- 

Hemorrhage



**Synovial
Inflammation**

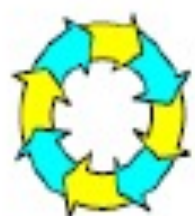


**Synovial
Impingement**

**Recurrent
Hemarthroses**



**Synovial
Hypertrophy**



**Direct Synovial Invasion
Enzymatic Degradation**



**End Stage
Arthropathy**

Acute Haemarthrosis

- stiffness, tingling & pain
- swollen, reddish, tender & hot



Principle of treatment:

To ablate the bleeding as soon as possible.

- Replacement therapy
- Aspiration (under factor coverage)
- Analgesia
- Restorative physiotherapy

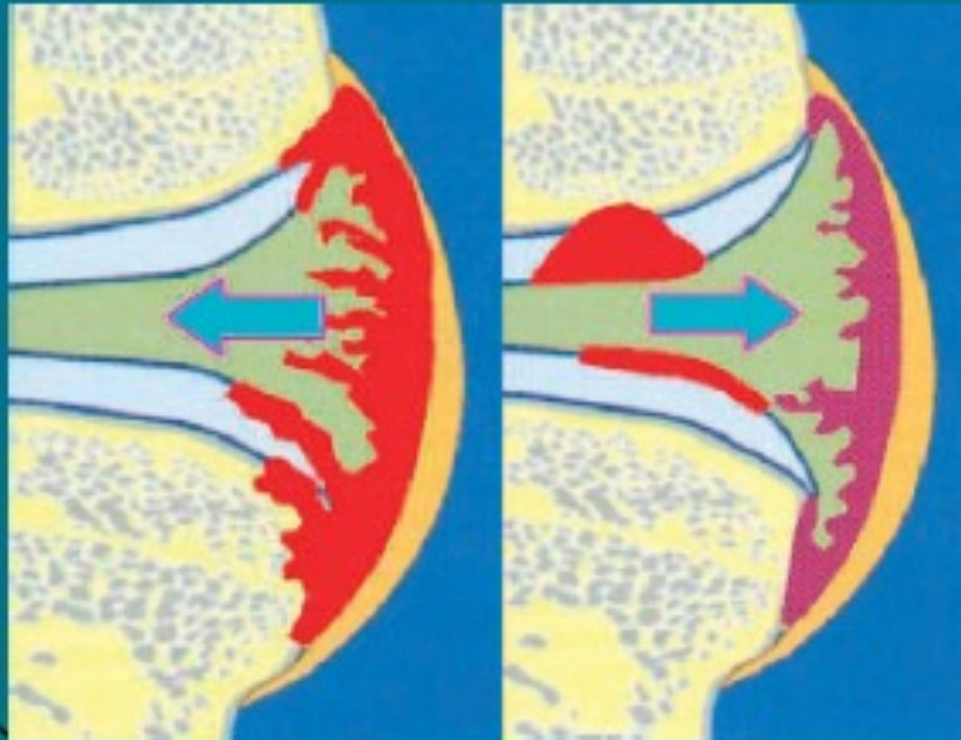
Chronic Haemarthrosis

Patients with severe haemophilia suffer from repeated hemarthrosis and early occurrence of haemophilic arthropathy.

Repeated joint bleeds leading to chronic synovitis.

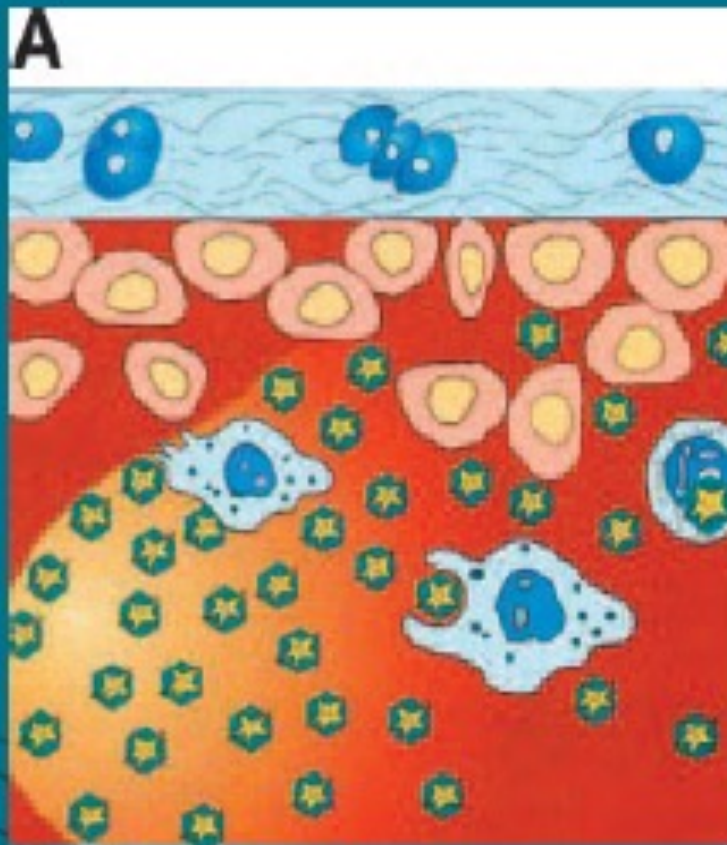


They affect an inflamed synovium, which is the connective tissue lining a joint cavity

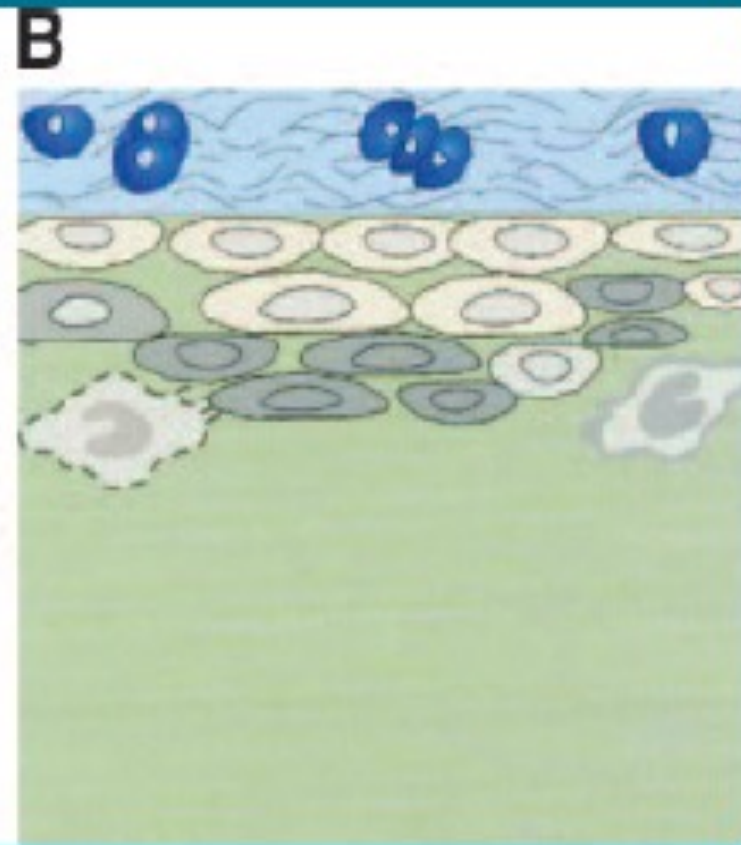


Synovitis in
arthritis

Activated
osteoarthritis



(A) Emitting colloidal particles (yellow stars) phagocytized by inflamed hypertrophic synovial lining with proliferating synoviocytes (pink). Top cartilage layer remains unaffected.



(B) Subsequent cell damage and sclerosis of synovial membrane.

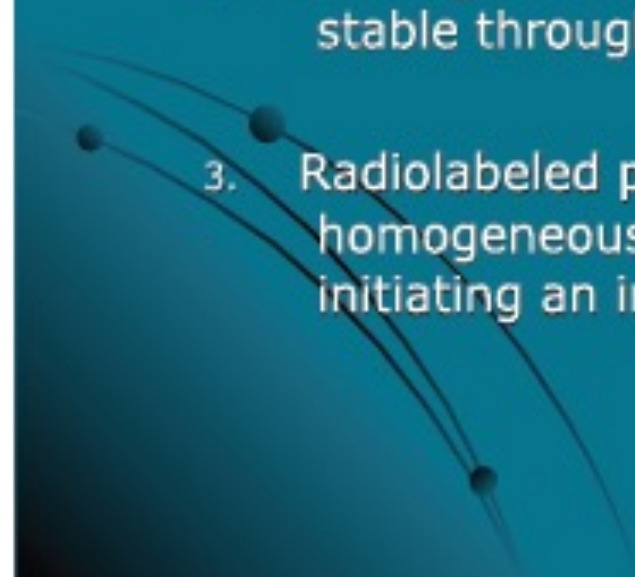
Radionuclides

- RSV is an intra-articular injection of a radionuclide in colloidal form.
- 3 radionuclides are in current use:

Radionuclides	Particles	Half life (d)	Average penetration of B emission (mm)	Joint
^{90}Y	Citrate/silicate	2.7	3.6	Knee
^{186}Re	Colloid/sulfide	3.7	1.1	Hip, shoulder, elbow, wrist, ankle, subtalar
^{169}Er	Citrate	9.4	0.3	MCP, MTP, proximal IP

Radionuclides

The ideal radiopharmaceutical for RSV :

1. It should be attached to a particle that is sufficiently small to be phagocytized but not so small that it might leak from the joint before being phagocytized,
 2. Binding between radionuclide and particle should be stable throughout the course of the RSV and
 3. Radiolabeled particles should be distributed homogeneously in the intraarticular space without initiating an inflammatory response.
- 

Procedure

Pre-procedure:

- Identification of patients – NBC and Orthopaedic team, HKL
- Clotting factor replacement is given 30 minutes before procedure
- Antiseptic preparation of injection site
- Local anaesthesia, 1% lignocaine injected
- Injection of radiopharmaceuticals followed by flushing with steroids

Post-procedure:

- Apply plaster cast and immobilize 48-72 h
- Another 2 doses of clotting factor replacement
- No vigorous activities within 2 weeks
- Follow-up in 2 weeks, 3 months and 6 months under NBC

Contraindications

- Absolute contraindications:
 - Pregnancy & breastfeeding
 - Ruptured Baker's cyst (knee)
 - Local skin infection
 - Massive hemarthrosis.
- Relative contraindications:
 - age less than 20 y*
 - evidence of significant cartilage loss
 - joint instability with bone destruction.

*Patients younger than 20 y, the benefit of the treatment has to be greater than the potential hazard of the radionuclide.

Side Effect

- A temporary increase in joint pain due to radiation-induced synovitis may be observed.
- Lymphedema or fever may occur in rare cases
- Serious late side effects such as radionecrosis are very rare.
- Induction of malignancy is a theoretic potential side effect but has never been observed.

Outcome

- Deutsch et al. reported good-to-excellent results for RSV in 60%–80% of patients with hemarthrosis.
- In recent data Siegel et al reported:
 - 78% showed improved range of motion
 - 80% had significantly decreased frequency of bleeding
 - 80% had improved quality of life activities ie bicycling, walking, carrying objects, and performing daily chores.

Radiosynovectomy in Rheumatology, Orthopedics, and Hemophilia:
Schneider et al, J Nucl Med 2005; 46:48S–54S

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