^{131}I-MIBG Therapy

Dr Sandip Basu
Radiation Medicine Centre (BARC)
Tata Memorial Centre Annexe, Parel, Mumbai

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Looking at the Viability of ^{131}I-MIBG Therapy in the background of evolution of PRRT

Indications for I-131 MIBG therapy

- 1. Metastatic/Inoperable phaeochromocytoma
- 2. Metastatic/Inoperable paraganglioma
- 3. Stage III or IV neuroblastoma
- 4. Metastatic/Inoperable carcinoid tumour
- 5. Metastatic or recurrent medullary thyroid cancer

WHO Classification of GEP NET: the major areas of use of PRRT

WHO 2000 [2.24]	WHO 2010 [2.25, 2.26]
Well differentiated (neuro)endocrine tumour (WDET)	Neuroendocrine tumour G1
Well differentiated (neuro)endocrine carcinoma (WDEC)	Neuroendocrine tumour G2
Poorly differentiated (neuro)endocrine carcinoma (PDEC)	Neuroendocrine carcinoma G3 — Large cell — Small cell
Mixed exocrine–endocrine carcinoma	Mixed adeno-neuroendocrine carcinoma
Tumour-like lesions	Hyperplastic and pre-neoplastic lesions

Thoracic NET: WHO Classification

TABLE 2.4. WHO (2004) CLASSIFICATION OF NEUROENDOCRINE TUMOURS OF THE LUNG [2.29, 2.30]

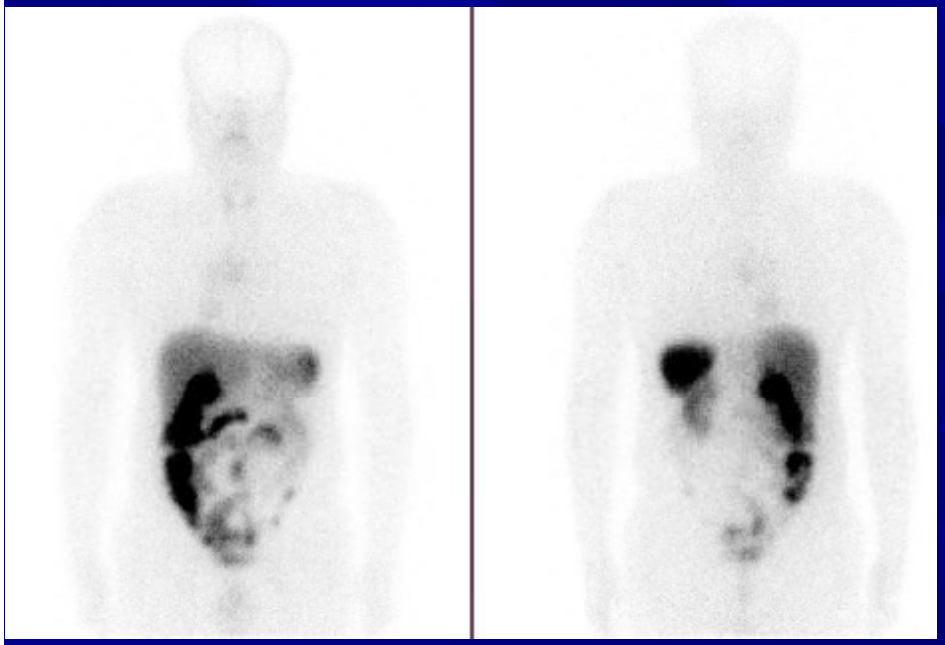
Type	Differentiation grade	Mitosis per 2 mm² (10 HPF)[a]	Other features
Typical carcinoid	Well differentiated	<2	No necrosis
Atypical carcinoid	Well differentiated	2–10	With/without necrosis
Large cell neuroendocrine carcinoma	Poorly differentiated	11; median: 20	With necrosis; large cells
Small cell neuroendocrine carcinoma	Poorly differentiated	11; median: 80	With necrosis; small cells

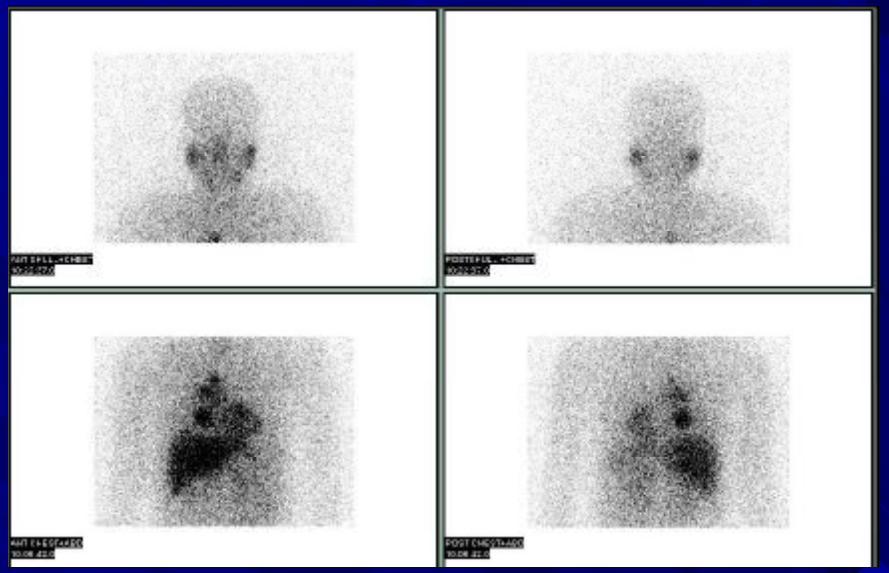

CAUTION

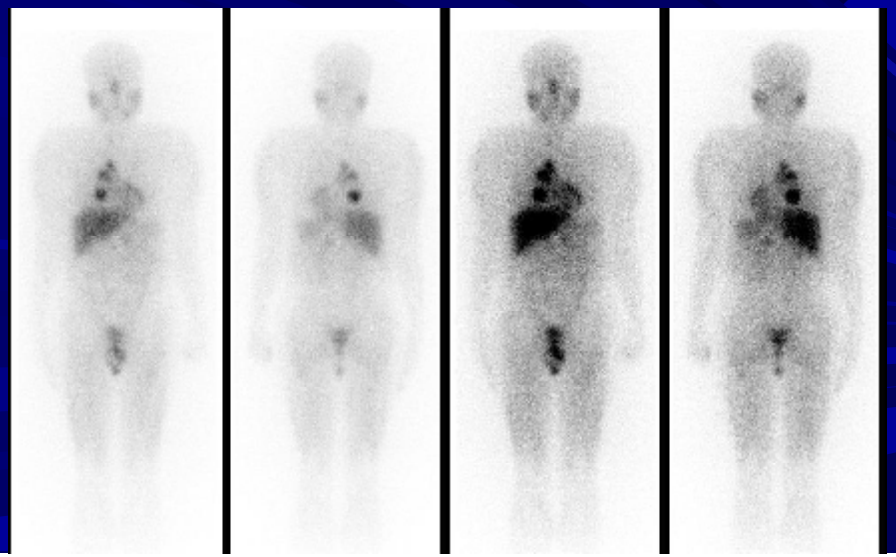
Foreseeing the Clinical use of ^{131}I-MIBG therapy in the era of PRRT

- Scan feature: Most important determinant
- Tumor Histology: NBL, Pheo, Paraganglioma
- Pediatric Age group: A very important determinant esp in v/o renal toxicity of PRRT
- Harder beta of I-131 compared to Lu-177
- Documented renal toxicity of PRRT & relatively long experience with 131I-MIBG

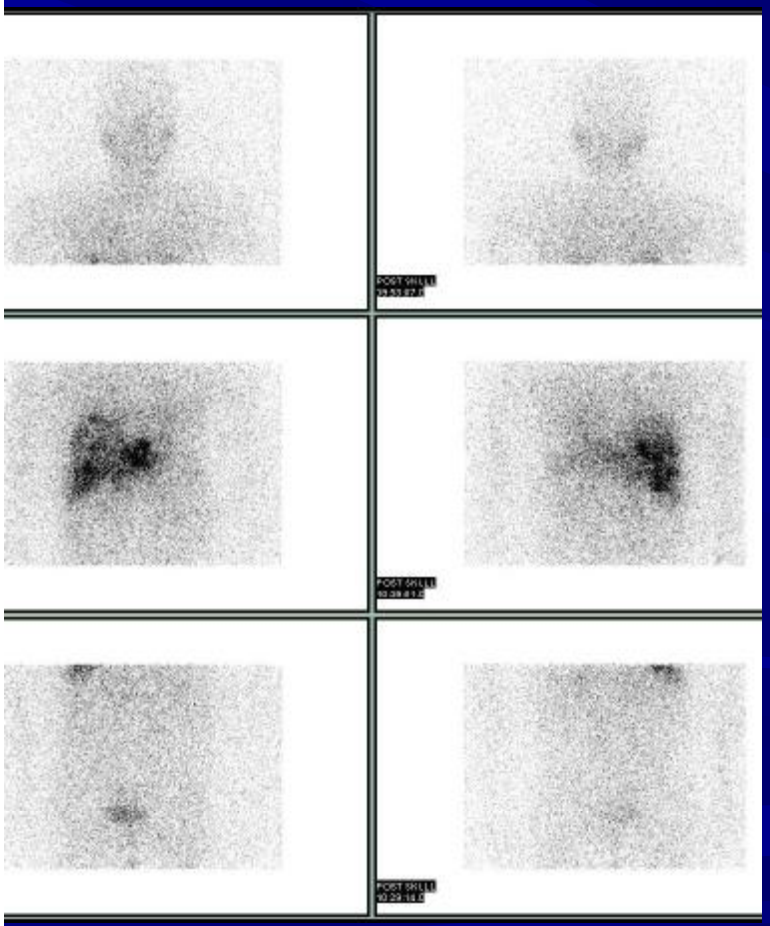
35 /M; Inoperable Lung Carcinoid (atypical). Hynic TOC scan showed SSTR positive lesions in right lung and right mediatinum. MIBG avid lesions in right lung and right mediastinum. More number of lesions were appreciable on the MIBG scan than the HYNIC-TOC scan. Also these lesions showed more affinity for MIBG rather than HYNIC TOC. Patient was subjected to treatment with 3 cycles of I-131 at an interval of 3 months with symptomatic relief as well as the subsequent MIBG scans showed decrease MIBG uptake in the lesions indicating good response.

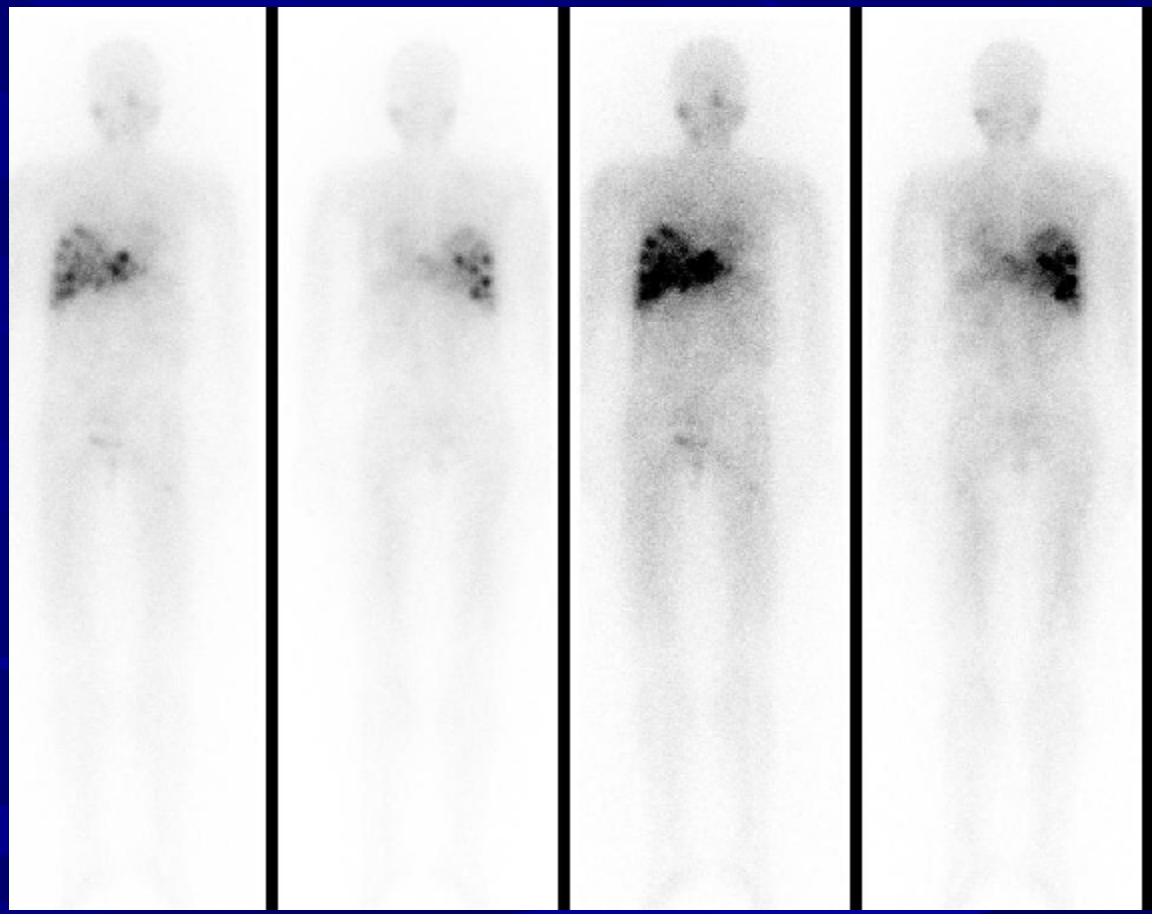




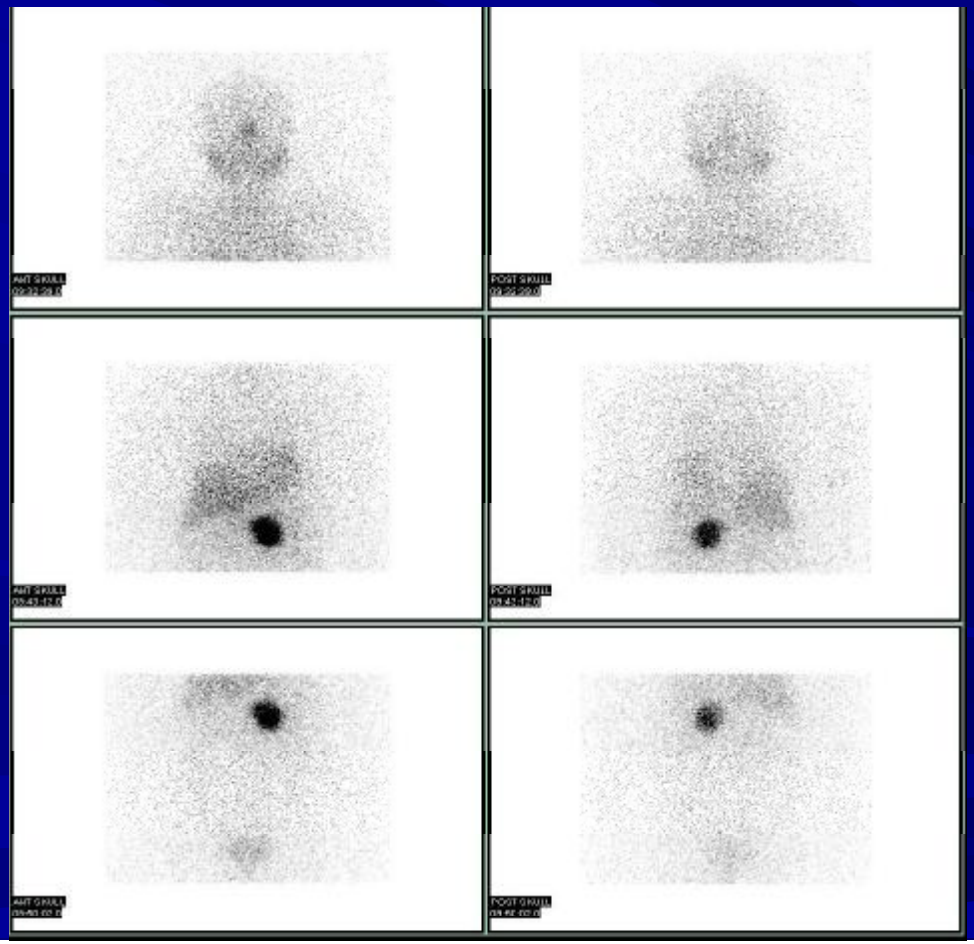


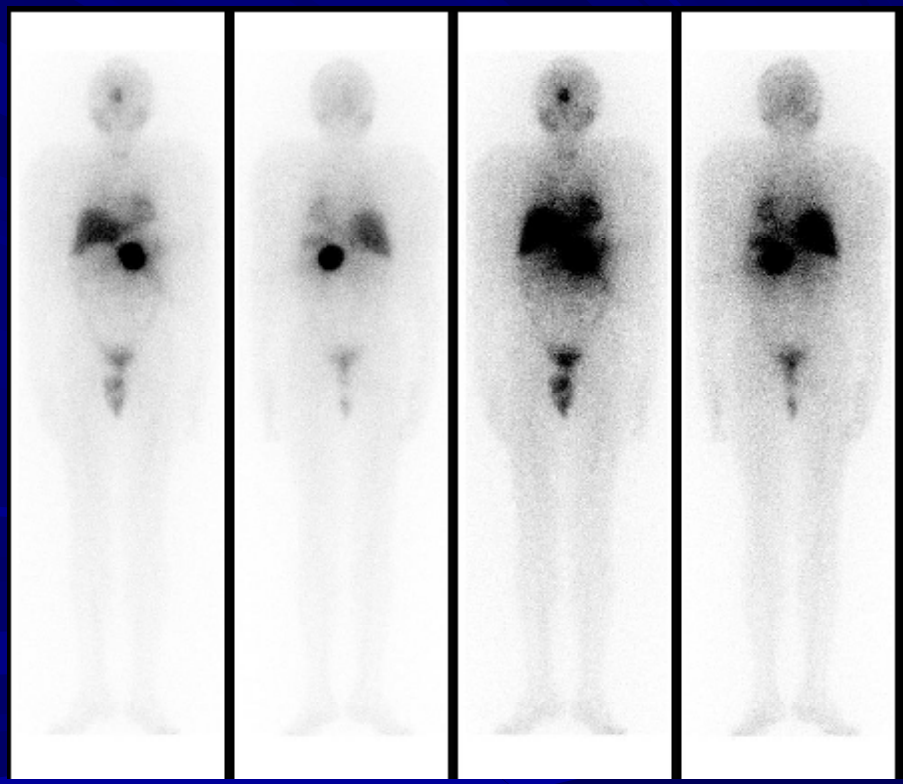
35/F, k/c/o MEN IIa; Post total thyroidectomy and left adrenalectomy; Calcitonin is substantially elevated. Presented with multiple metastatic lesions in both lobes of liver. HYNIC-TOC scan was normal. MIBG scan demonstrated avid tracer accumulation. Following treatment with 4 #, patient was asymptomatic though calcitonin was elevated (reduced from baseline), the USG (Abdomen) demonstrated calcification in the metastatic foci and regression of the left lobe lesion.

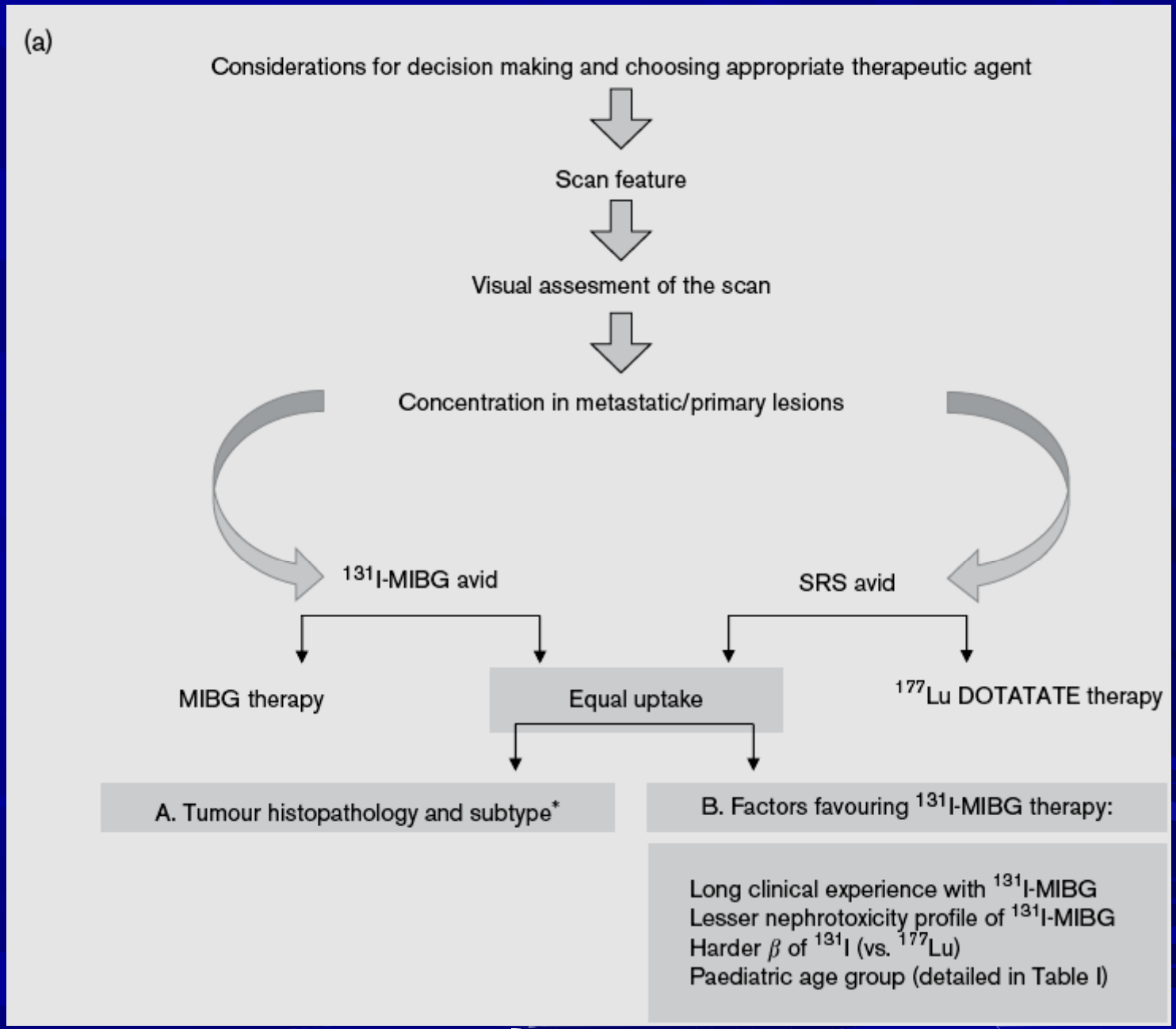




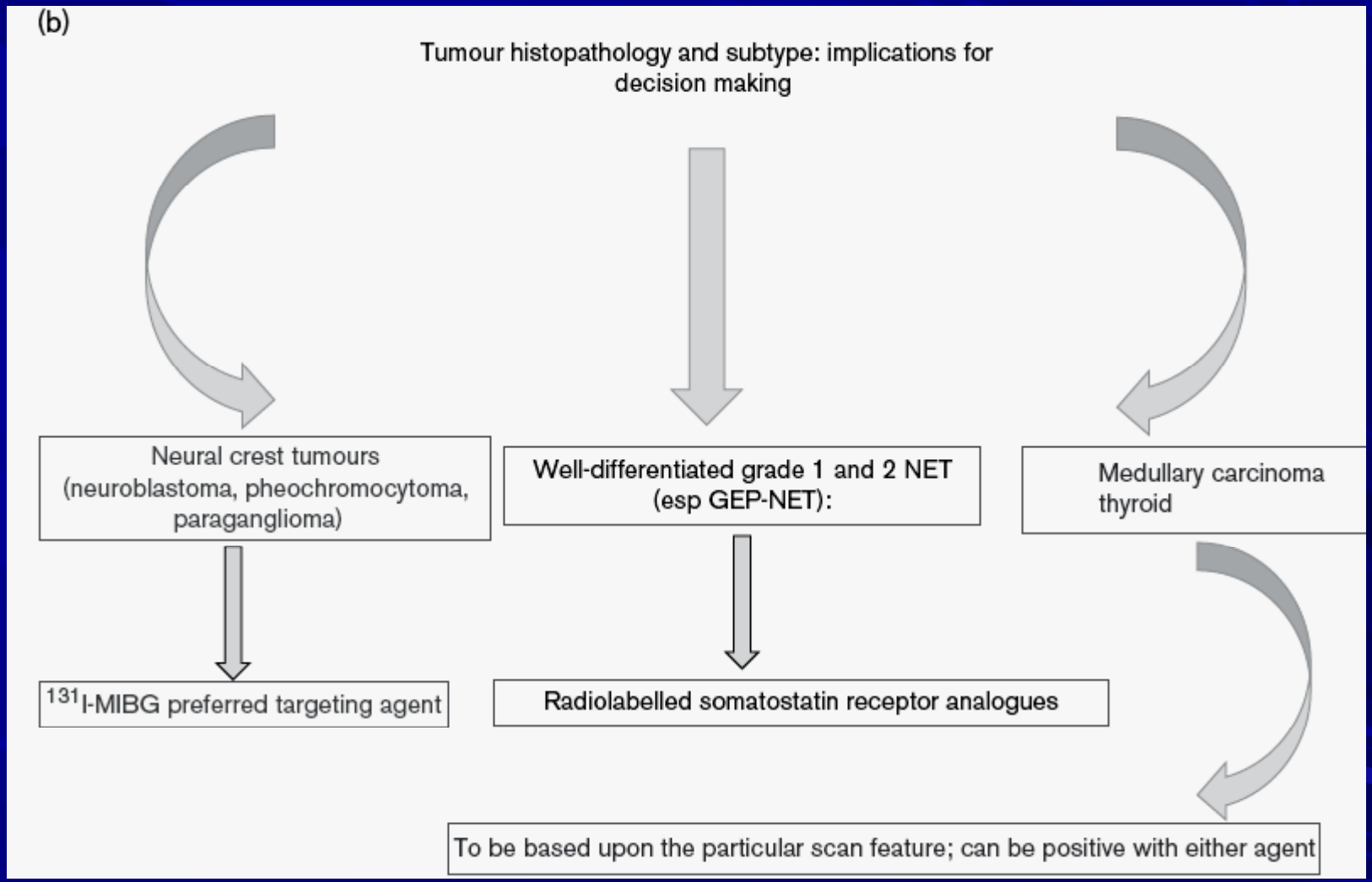
64/M; Inoperable Paraganglioma; Symptom: abdominal pain and fluctuating BP. Both HYNIC-TOC as well as MIBG scan showed positive lesions in the left suprarenal region with lesion showing high aviditiy for both the tracers. Patient was subjected to I-131 MIBG therapy owing to the higher beta max of I-131 than that of Lu-177 used in PRRT. Patient has shown symptomatic relief with a decrease in the tumour markers (Pre therapy VMA: 11.7/24 hrs and Posttherapy VMA: 6.4/24 hrs) indicating good response.







Basu, Abhyankar, Jatale. Nucl Med Commun 2015 Jan;36(1):1-7.



Nucl Med Commun 2015 Jan;36(1):1-7.

Pediatric Age group: the considerations favoring I-131 MIBG Therapy

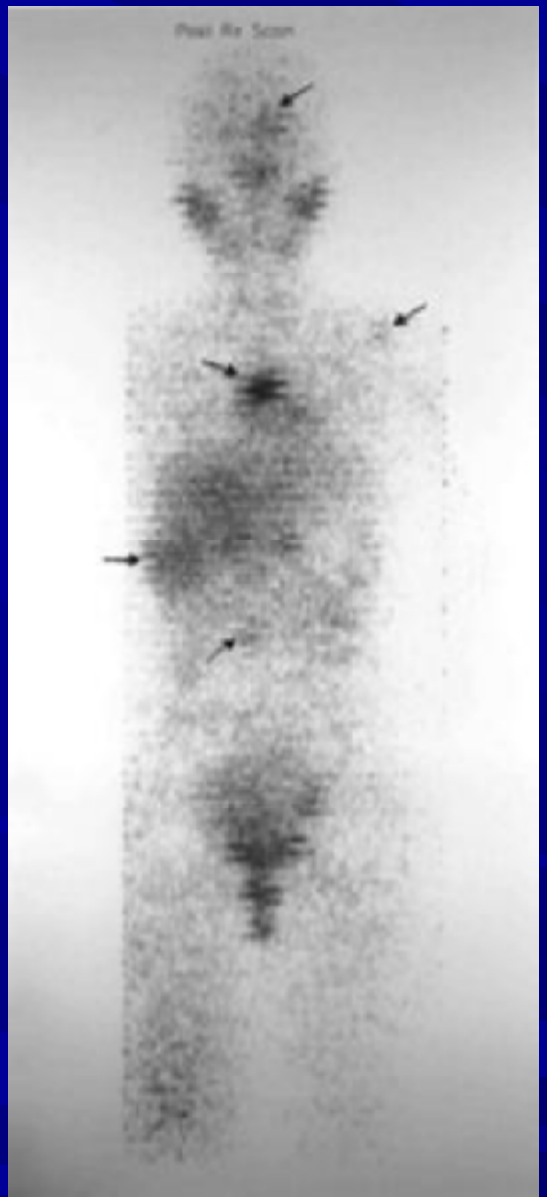
1. Documented Renal toxicity of PRRT assumes important consideration in pediatric age group for 2 specific reasons: (a) Intensive pretreatment (Neuroblastoma) with nephrotoxic chemotherapy viz. cisplatin and ifosfamide and (b) Relatively immature renal function especially in infants.

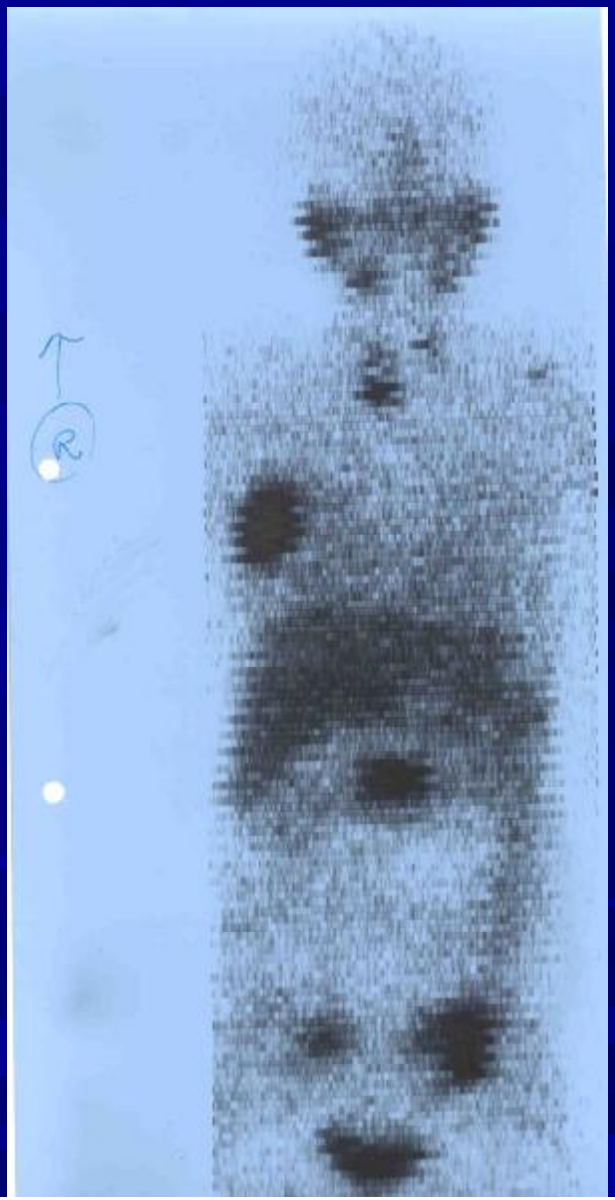
2. Amino acid infusion for renal protection during PRRT (and its consequential known adverse effect of emesis due to metabolic acidosis) is less validated till date in infant & paediatric age group, many of whom will be relatively sick

3. Vast majority are Neuroblastoma, which are predominantly ^{131}I MIBG avid.

Nucl Med Commun 2015 Jan;36(1):1-7.

[131I] Metaiodobenzylguanidine therapy in neural crest tumors: varying outcome in different histopathologies





Therapeutic Response Assessment

- Decrease in tumors volume
- Hormonal Response: Decline in catecholamine and metabolite levels
- Symptomatic Response: Decrease in Blood pressure

Stable disease and improved health-related quality of life (HRQoL) following fractionated low dose ^{131}I-metaiodobenzyl-guanidine (MIBG) therapy in metastatic paediatric paraganglioma: observation on false ''reverse'' discordance during pre-therapy work up and its implication for patient selection for high dose targeted therapy

The British Journal of Radiology, *79* (2006), e53–e58

Table 1. Summary of the quality of life data at multiple time points

Baseline performance	Lack of energy, trouble meeting needs of life, aches or pain, bothered about side effects of treatment, feeling ill, forced to spend time in bed, satisfaction with family communication about illness, sadness, satisfaction about coping with illness, losing hope, nervousness, anxiety about dying, anxiety about condition getting worse, able to work, able to enjoy work or life, sleep, content with the quality of life at that instant: all these had a reduced performance status prior to treatment
At the time of work up before 2nd therapy	All the components except pain showed an improvement by at least 2 grades. Pain was graded 3 at this time point
3 months following 3rd therapy	All except pain were graded either normal or one grade below normal. ''Pain'' was graded as 2 at this time point, which showed gradual improvement with time

Using three consecutive low doses of 131I-MIBG: Excellent symptomatic and hormonal responses were observed.

[131I] Metaiodobenzylguanidine therapy in neural crest tumors: varying outcome in different histopathologies

Table 10 Comparative data of treatment response in different subgroups

Response	Group A (stage III NBL)	Group B (stage IV NBL)	Group C (pheochomocytoma +paraganglioma)	Group D (metastases+carcinoid)	Total no. of patients
VGPR	–	1 (9%)	–	–	1 (3%)
PR	4 (57%)	3 (27%)	1 (8%)	–	8 (25%)
SD	2 (29%)	6 (55%)	11 (92%)	2 (100%)	21 (66%)
PD	1 (14%)	1 (9%)	–	–	2 (6%)
Subjective response	2 (30%)	4 (36%)	9 (75%)	2 (100%)	17 (63%)

PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

Both single high dose or multiple fractionated doses are equally effective in improving the quality of life in metastatic/recurrent pheochomocytoma/paraganglioma

Rachh et al. Nucl Med Commun 2011;32(12):1201-10

[131I] Metaiodobenzylguanidine therapy in Neuroblastoma: Report on efficacy

A median dose of 9.5 mCi/kg of 131I-MIBG was delivered in 32 courses to 20 patients. The objective response rate to the first therapy was 31%. (J Pediatr Hematol Oncol. 2003 Oct;25(10):769-73.

Most studies report a response rate of 30–40% with ^{131}I-MIBG in this population.

[131I] Metaiodobenzylguanidine therapy in neural crest tumors: varying outcome in different histopathologies

Table 5 Characteristics of group C

Case no.	Sex, age	Primary tumor site	Time from diagnosis to MIBG therapy (months)	Primary tumor conc. MIBG	Metastases	U. VMA	[^{131}I] MIBG therapy courses	Cumulative dose	Tumor response after MIBG therapy	Clinical course and outcome
1	M/57	Lt adrenal	8	No	Bone (m)	E	2	224	SD	Alive 15 months NF
2	F/19	Extra-adrenal between aorta and ivc	3	Yes	Bone (m)	E	3	370	SD	Alive 89 months SD
3	M/65	Pre- and para-aortic rgn	6	Yes	Mediastinum	E	1	204	SD	Death 14 months SD
4	M/55	RP ln	3	Yes	Bone (m)	E	1	244	SD	Alive 6 months NF
5	M/36	Left adrenal	14	Yes	Lung, ln, bone (m) liver	E	2	324	SD	Alive for 21 months SD
6	M/20	Left adrenal	3	Yes	–	E	5	513	SD	Alive for 20 months PD and NF
7	M/20	Right adrenal	2	No	Lung	E	2	422	PR	Alive for 15 months SD
8	F/16	Rt adrenal	16	Yes	Liver, lung, bone (m)	E	3	386	SD	Alive 19 months NF
9	M/51	B/l adrenal	2	Yes	–	E	4	273	SD	Alive 38 months NF
10	F/20	Right adrenal	48	Yes	Ln	E	4	354	SD	Alive 74 months NF
11	M/14	Right adrenal	4	Yes	Liver	E	1	199	SD	Alive 6 months SD
12	F/36	Bladder	6	Yes	Lung, liver, ln	E	2	313	SD	Alive 36 months SD

Bone(m), multiple sites of metastases; conc., concentration; MIBG, metaiodobenzylguanidine; NF, no follow-up; PD, progressive disease; PR, partial remission; SD, stable disease; U. VMA, urine vanillylmandelic acid.

Rachh et al. Nucl Med Commun 2011;32(12):1201-10

^{131}I-MIBG therapy in metastatic Phaeochromocytoma and Paraganglioma

- The median initial dose was 7.4 GBq (200 mCi; median cumulative dose was 22.2 GBq (600 mCi)
- Objective tumour response was achieved in 47% of the patients. Biochemical response rate was 67%, and symptomatic response was seen in 89% of the patients
- Haematologic complications were the most common side effects and were observed in 26% of the patients

Gedik GK et al. Eur J Nucl Med Mol Imaging. 2008 Apr;35(4):725-33

High-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma

- 50 patients with metastatic PHEO or PGL, age 10 - 64 years, were treated with 492-1,160 mCi (median, 12 mCi/kg). Cumulative dose administered ranged from 492 -3,191 mCi.

- The overall complete response (CR) plus partial response (PR) rate in 49 evaluable patients was 22%. 35% of patients achieved a CR or PR in at least one measure of response without progressive disease, and 8% of patients maintained stable disease for greater than 12 months. 35% of patients experienced progressive disease within 1 year after therapy.

Gonias et al. J Clin Oncol. 2009 Sep 1;27(25):4162-8.

High-dose [131I]metaiodobenzylguanidine therapy for patients with metastatic pheochromocytoma and paraganglioma

- Toxicities included grades 3 to 4 neutropenia (87%) and thrombocytopenia (83%).

- Grades 3 to 4 nonhematologic toxicity included acute respiratory distress syndrome (n = 2), bronchiolitis obliterans organizing pneumonia (n = 2), pulmonary embolism (n = 1), fever with neutropenia (n = 7), acute hypertension (n = 10), infection (n = 2), myelodysplastic syndrome (n = 2), and hypogonadism (n = 4).

MIBG therapy: Available data on efficacy

- There are basically two treatment strategies: one or two high-dose treatments or multiple low-dose treatments.
- Symptomatic relief in the vast majority of patients treated, both following high-dose treatment and low-dose maintenance treatment.
- Biochemical responses can be observed in about half of the patients, whereas radiographic responses are described in roughly one third of the patients.

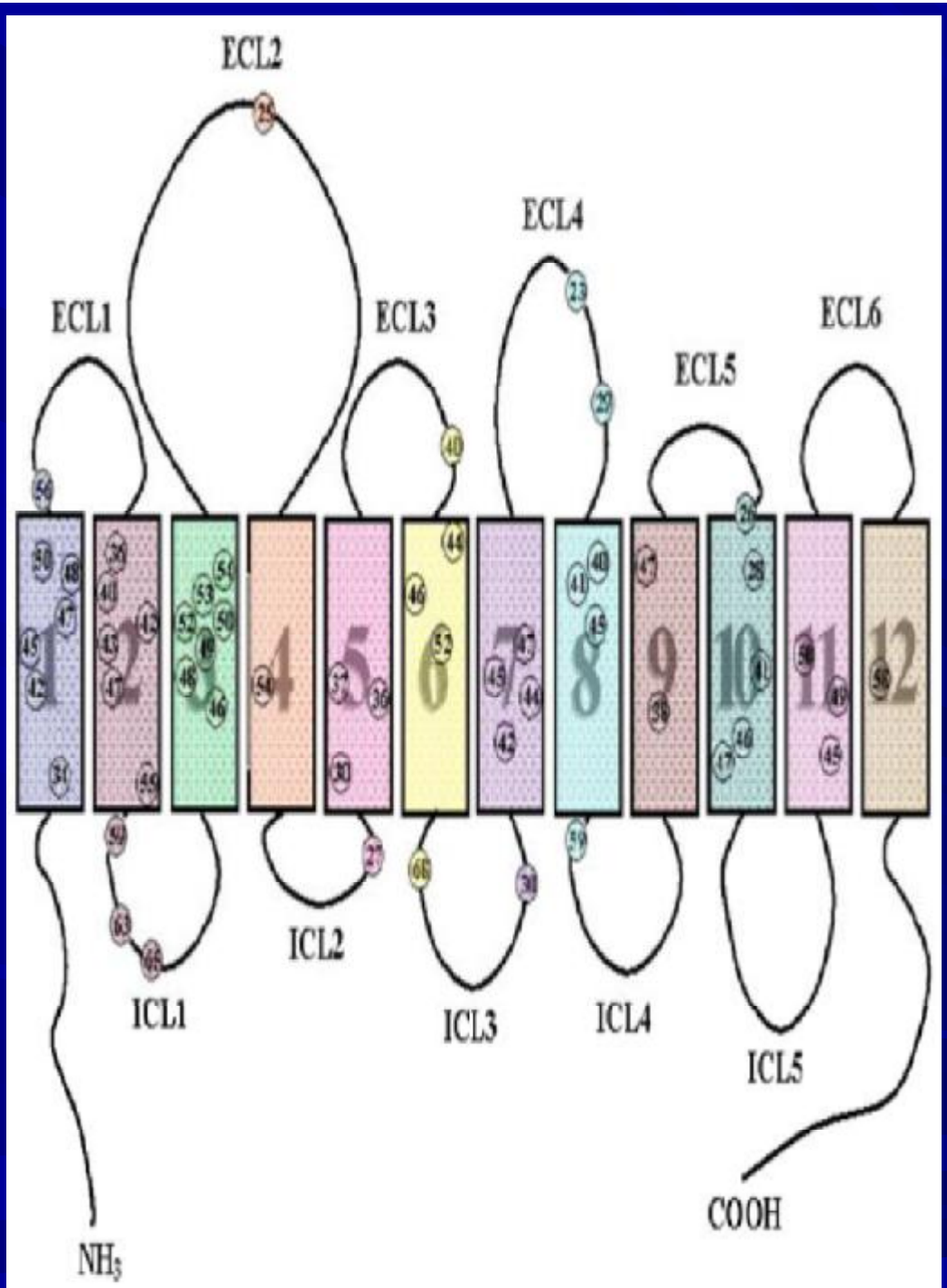
Dose Reduction

- Low white blood cell and platelet counts.
- Massive bone marrow invasion and/or
- Impaired renal function

Risk of Myelosuppression

- Temporary myelosupression: 4–6 weeks post-therapy (an isolated thrombocytopenia)

1. Common in children with neuroblastoma after chemotherapy (60%), quite remote in adults.
2. In patients who have bone marrow involvement at the time of ^{131}I-mIBG therapy
3. In patients with delayed renal ^{131}I-mIBG clearance



The noradrenaline transporter molecule (NET)

617 amino acids protein with twelve transmembrane domains, encoded by the SLC6A2 gene

- Active uptake, which is specific, high-affinity, saturable, adenosine triphosphatase–dependent, only occurs in cells that synthesize NET

- Passive diffusion, which is nonspecific, low-level, energy independent, and unsaturable, and takes place in all cells)

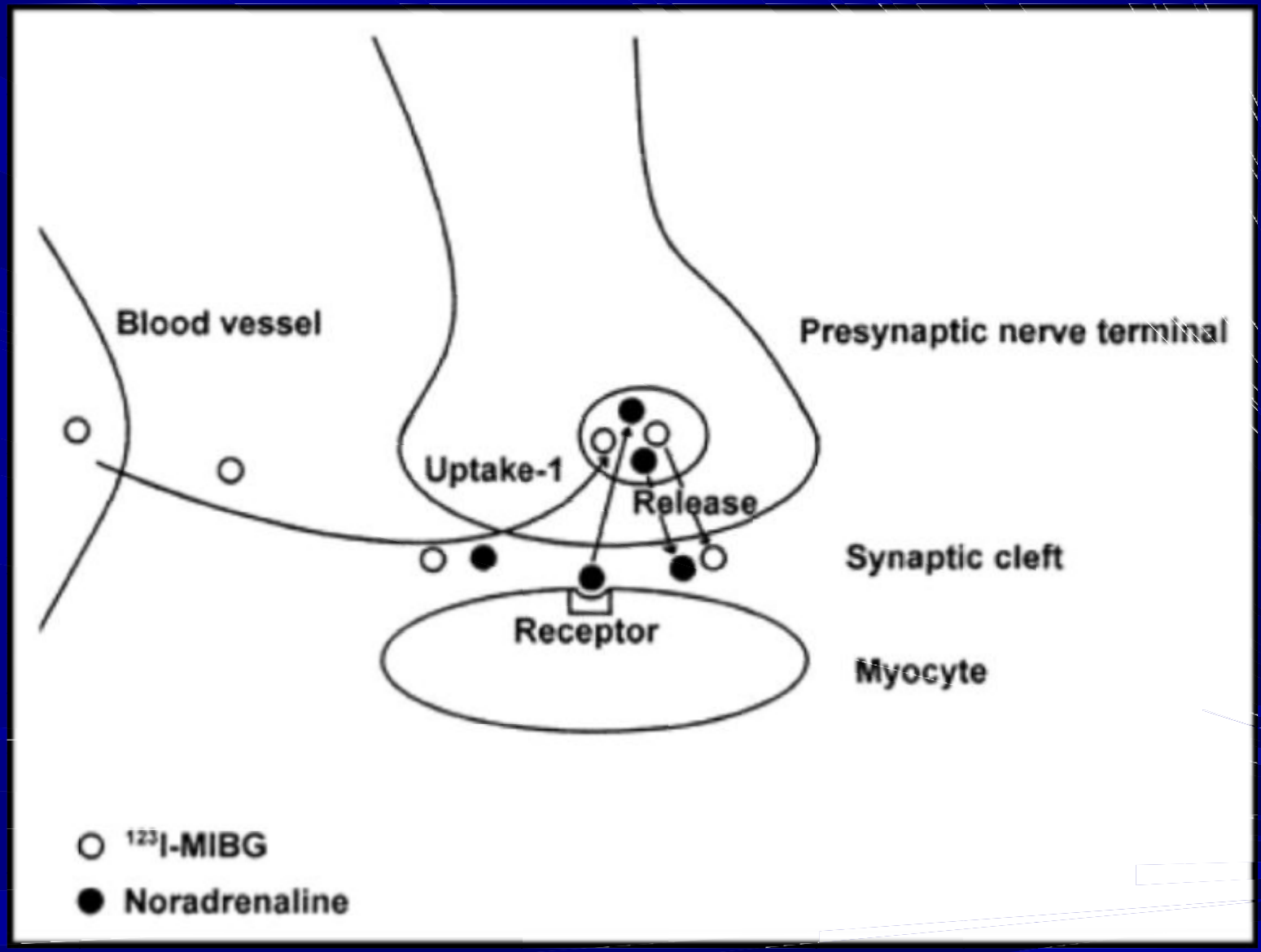
- The specific uptake process is about 50 times more efficient than passive uptake

^{131}I MIBG: Mechanism of Localization

- Taken into cells by either the energy-dependent type I amine uptake mechanism (specific, high affinity, saturable, 50 times more efficient) or by passive diffusion.

- The transfer of mIBG from intracellular cytoplasm into catecholamine storage vesicles (neurosecretory vesicles) is mediated by an ATPase-dependent proton pump.

In neuroblastoma, neurosecretory granules are thought to play a minor role and a fast re-uptake after passive outward diffusion is suggested


Blood vessel
Presynaptic nerve terminal
Uptake-1
Release
Synaptic cleft
Receptor
Myocyte
123I-MIBG
Noradrenaline

Drugs interfering MIBG uptake

Drugs known to interfere	Drugs expected to interfere
Labetalol (1,2)	Adrenergic blocking agents (2) e.g. Bretylium, Guanethidine
Reserpine (2,3)	Sympathomimetics (2) e.g. Amphetamine, Dopamine, Isoprenaline, Terbutaline
Calcium-channel blockers (4) e.g. Nifedipine, Verapamil	Phenothiazines (1), e.g. Chlorpromazine, Promethazine
Tricyclic antidepressants (1) e.g. Amitriptyline, Imipramine	Butyrophenones (1) e.g. Droperidol, Haloperidol
Sympathomimetics (2) e.g. Ephedrine	Thioxanthines (1) e.g. Maprotiline, Trazolone
Cocaine (1)	

Presumed mechanism:

(1) = uptake-1 inhibition

(2) = depletion of granules
(3) = transport inhibition
(4) = uncertain

Many drugs interfere with uptake of MIBG, particularly tricyclic antidepressants, sympathomimetics (e.g., pseudoephedrine), and certain antihypertensives (labetalol, reserpine).

Thyroid Blockade

Compound	Adults	Children (15–50 kg)	Children (5–15 kg)	Children (<5 kg)
Capsules	mg/daily			
Potassium iodate	170	80	40	20
Potassium iodide (KI)	130	65	32	16
Lugol solution 1%	1 drop/kg per day with a maximum of 40 (20 drops twice daily)			
Capsules	mg/daily			
Potassium perchlorate	400	300	200	100

Lugol's 5% solution

It consists of 5% iodine and 10% potassium iodide (KI) in distilled water with a total iodine content of 130 mg/mL.

EANM guidelines. MIBG therapy

Iodine-131-metaiodobenzylguanidine Therapy In Neuroblastoma: Issues

- As first line treatment before chemotherapy in Stage III/IV disease:

  Advantages: **Reserve chemotherapy for the adjuvant setting and delay the development of chemoresistance**

- Iodine-131-metaiodobenzylguanidine as initial *pre-operative induction treatment* in stage 4 neuroblastoma patients over 1 year of age.

1. The objective response rate at this point was 66%.
2. After pre-operative therapy and surgery, the overall response rate was 73%.

Kraker et al. Eur J Cancer. 2008 Mar;44(4):551-6.

Issues requiring further clarification

- Optimal administered activity per treatment cycle
- Total number of treatments and treatment interval by tumour type
- Role of 131 I-mIBG in neuroblastoma:

1. In first line treatment
2. In multimodality treatment (e.g. combined with topotecan and/or bone marrow ablative therapy with stem cells rescue)


Thank You