Clinical applications of newer radionuclide therapies

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- Radio-iodine was first used in the treatment of metastasized thyroid carcinoma in 1943.
- Its success in terms of tumour response, quality of life improvement and survival was considered a ‘miracle’, as in those days metastatic cancer was generally fatal.
- Inspired by this, many efforts have been made to apply radioisotope therapy to other tumours.

- Targeted radionuclide therapy involves the use of radiolabeled tumor-seeking molecules to deliver a cytotoxic dose of radiation to tumor cells.

- One of the most important difference between targeted radionuclide therapy and external beam irradiation is the finite range of ionizing particles emitted.

- Radionuclides that decay by the following three general categories of decay have been studied for therapeutic potential :

    1. Beta-particle emitters
    2. Alpha-particle emitters
    3. Auger electron

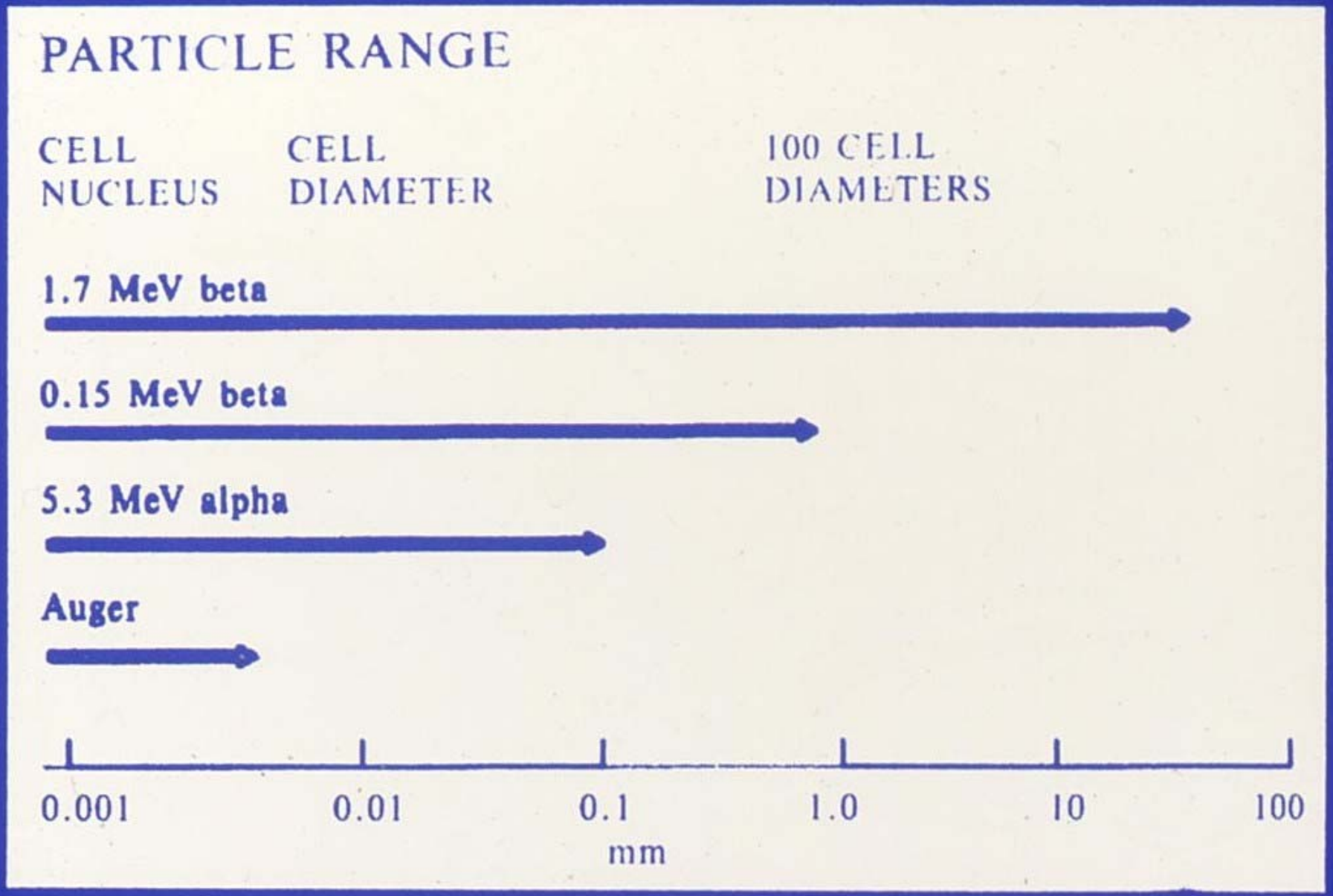


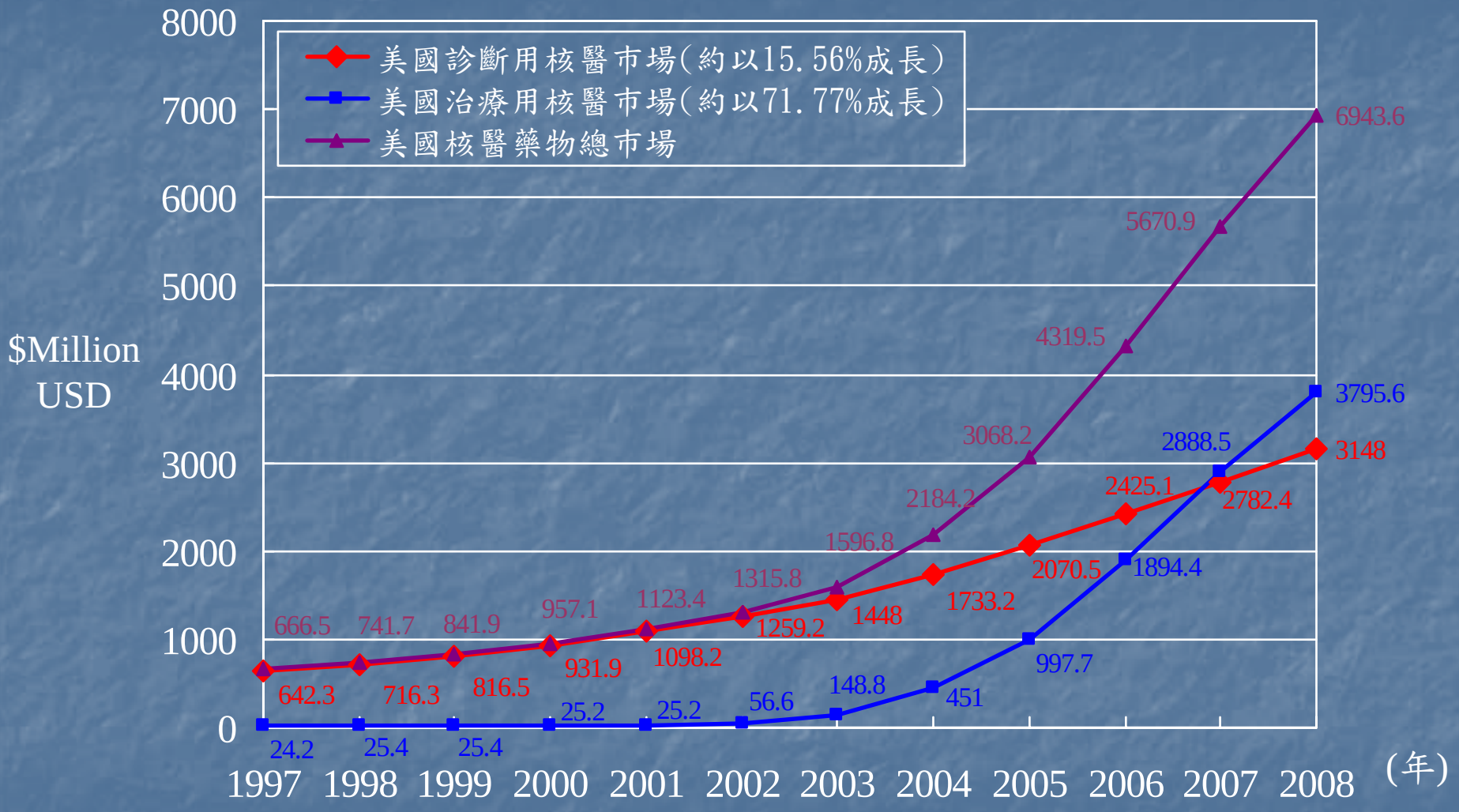
Fig. 1. Typical range or particulate emissions vs cell diameter

Advantages of Targeted Radionuclide Therapy

- Tumor specific, with sparing of healthy tissue (low toxicity).
- No limit to the absorbed dose (no limit to the number of treatment).
- Radiation can be delivered to subclinical tumors and metastases that are too small to be imaged and thereby treated by surgical excision and external beam therapy.

產業評析

一、美國核醫藥物市場



資料獲自美國Bio-Tech Systems, Inc. July 2003

美國治療用核醫藥物銷售金額統計分析

2002 年

癌症分類	治療人次(年)	銷售金額(US,百萬)	主要核醫藥物	2008 年銷售排名(US,百萬)
淋巴癌	1,500	31.0	Y-90-Zevalin（April 2002，FDA 通過）I-131-Ritaxan; Y-90-Epratuzomab; In-111,Lu-177-OctreoTher	1.新試劑：1167.0 2.治療用同位素：402.0 3.Ho-166,Y-90-CEA-Cide：397.5 4.Y-90-Zevalin,I-131-Ritaxan：315.0 5.I–131-Cotara TNT：240.0 6.New Lymphoma Agents：180.0 7.I-131-Bexxar：161.5 8.Ho-166-NeoRxSTR Myeloma：135.0 9.Y-90-Epratuzomab：112.5 10.Ho-166-NeoRxSTR-Bone Cancer：112.5 11.ProstaCide：112.5 12.NeoTide：97.5 13.Y-90/Lymphoma：97.2 14.MelanomaCide：67.5 15.OctreoTher：63.0 16.MyelomaCide：60.0 17.AFP-Cide：60.0 18.Metastron：15.6 19.Qudramet：15.3
骨疼痛	8,700	25.6	Sy-89-$SrCl_2$(Metastron) Sm-153-EDTMP(Quadramet)	
合　計	10,200	56.6		
2008 年				
淋巴癌	50,000	881.1	Y-90-Zevalin; I-131-Ritaxan; I-131-Bexxar; I-131-Anti-CD30;Anti-CD22; Y-90-Epratuzomab; In-111-Lu-177-OctreoTher; 其他新試劑	
直腸癌	20,000	408.9	Ho-166,Y-90-CEA-Cide; I-131-CotaraTNT	
肺癌	16,500	287.1	Re-188-NeoTide; Ho-166,Re-188,Y-90-CEA-Cide; 其他新試劑	
骨癌	13,000	226.2	Ho-166-NeoRx(DOTMP);其他新試劑	
骨髓癌	13,000	226.2	Ho-166-NeoRx(DOTMP); Ho-166-MyelomaCide	
內分泌腫瘤	7,500	130.5	In-111,Lu-177,Y-90-OctreoTher; 其他新試劑	
多囿體瘤癌	20,500	356.7	Re-188,Ho-166-CEA-Cide; I-131-CotaraTNT(Tumor Necrosis Therapy);其他新試劑	
腦癌	10,000	174.0	I-131-CotaraTNT;其他新試劑	
肝癌	12,000	208.8	131,Y-90-AFP-Cide; Pt-195m-AFP-Cide;其他新試劑	
胰臟癌	16,500	287.1	NeoRx-Pretarget; Y-90-CEA-Cide; 其他新試劑	
前列腺癌	17,500	304.5	ProstaCide; 其他新試劑	
黑色素癌	7,500	130.5	MelanomaCide; 其他新試劑	
骨疼痛	10,500	31.0	Sr-89-$SrCl_2$(Metastron) Sm-153-EDTMP(Qudramet)	
其他癌病	10,000	174.0	其他新試劑	
合　計	228,000	3826.5	—	

備註：1.其他新試劑係指不同放射性同位素標幟胜肽或單株抗體。

2.美國 FDA 已通過 13 種單株抗體治療藥物；並有超過 100 種單株抗體尚在臨床試驗或開發中。

The European Association of Nuclear Medicine has issued guidelines on so-called ‘established’ therapies (www.eanm.org), i.e.

1. Hyperthyroidism
2. Thyroid carcinoma
3. Refractory synovitis
4. Bone metastases
5. MIBG therapy
6. ^{32}P therapy
7. Lipiodol therapy

Newer therapies include:

1. Radio-peptide therapy
2. Radio-immunotherapy of lymphoma
3. Microsphere therapy for liver cancer

Radiopeptide therapy

Radiolabelled meta-iodobenzylguanidine (MIBG)

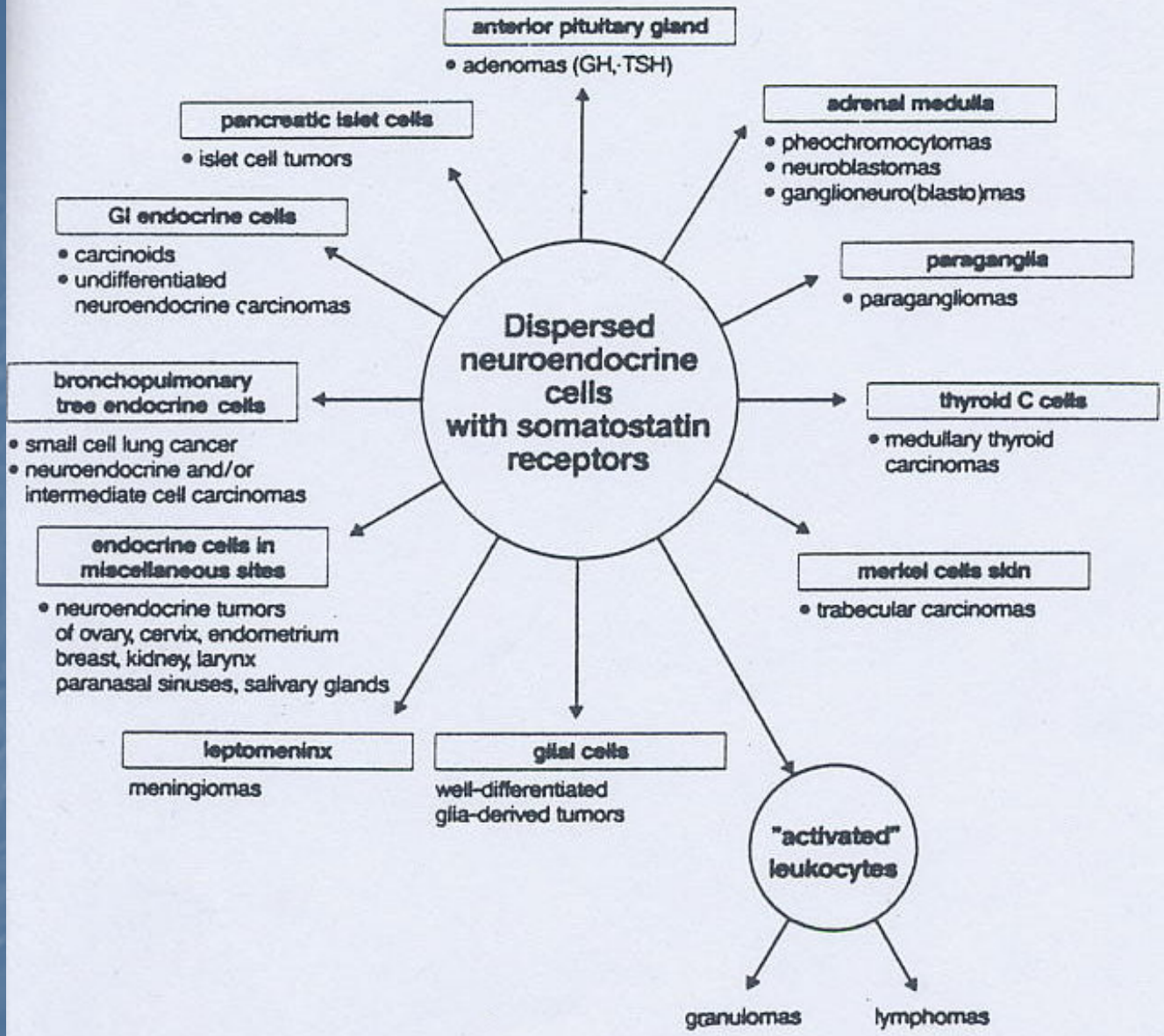
- A norepinephrine analog and false neurotransmitter .
- Peptides specific to hormone receptors
  (mainly the somatostatin hormone analogue octreotide).
- Highly sensitive and specific for the detection of primary
  and secondary neuroendocrine tumours.
- This has led to their use as radiotherapeutic agents in neuro-endocrine tumours (NET).

Neuro-ectodermic NET

- As the sensitivity of radiolabelled MIBG scanning is higher than octreotide as a result of higher observed tumoural uptake in these type of neurogenic tumours, the radiation dose delivered through ^{131}I-MIBG is also higher.
- This makes use of radiolabelled octreotide therapy in neuroblastoma and pheochromocytoma less feasible than ^{131}I-MIBG therapy.

Gastro-entero-pancreatic (GEP) NET

- The neuro-endocrine tumours of endodermic origin, also called gastro-entero-pancreatic tumours, are a heterogeneous group characterized by generally good prognosis, but important disparities of the evolutionary potential.
- In the aggressive forms, the therapeutic strategies are limited.
- Human somatostatin receptors (hSSTR 1–5), which mediate the antiproliferative effects of somatostatin are present in normal tissues and in several tumours.
- The systemic radionuclide therapy using radiolabelled peptides (essentially somatostatin analogues), which can act at the same time on the primary tumour and its metastases, constitutes a tempting therapeutic alternative currently in evolution.



Dispersed neuroendocrine cells with somatostatin receptors. [Derived from Ref. 267.]

Table 2 – Peptides affinities

Peptides	SST1	SST2	SST3	SST4	SST5
Somatostatin[28]	5	3	8	6	4
Octreotide	>10000	2	200	>1000	20
DTPA-octreotide	>10000	10	400	>1000	300
In-DTPA-octreotide	>10000	20	200	>1000	250
DOTA-octreotide	>10000	15	30	>1000	60
DOTA-lanreotide	200	2	2	2	2
Y-DOTA-lanreotide	>10000	20	300	>1000	15
DTPA-Tyr^3-octreotate	>10000	4	>10000	>1000	>1000
In-DTPA-Tyr^3-octreotate	>1000	1	>1000	430	>1000
DOTA-Tyr^3-octreotide	>10000	15	900	>1000	400
Y-DOTA-Tyr^3-octreotide	>10000	10	400	>10000	115
DOTA-Tyr^3-octreotate	>10000	2	>1000	500	600
Lu-DOTA-Tyr^3-octreotate	>10000	2	>1000	500	200
Ga-DOTA-Tyr^3-octreotate	>10000	0.2	>1000	300	380

Kd in nM; modified from Ref. [13,14]

Summary and future perspectives

- The field of radionuclide therapy in NET is steadily increasing.
- Radiolabelled DOTATOC compares very well to traditional therapies.
- New radiopeptides will probably extend beyond the framework of the neuro-endocrine tumours.
- The efficacy of this type of treatment may also be further enhanced through the use of radiosensitizers, the upregulation of receptor expression on tumours, and increased organ protection.

Table 3 – The present and the future of peptide receptor-mediated radionuclide therapy

Somatostatin (SMS) receptors
Endodermic tumours
Neuro-ectodermic tumours
Other tumours: small-cell lung cancer (SCLC), medullary thyroid cancer, breast cancer, renal cancer, thyroid cancer, lymphoma
Brain tumour: medulloblastoma and glioma (*topical application*)

Cholecystokinin B/Gastrin (CCK-2) receptors
Medullary thyroid cancer, gastrointestinal stromal tumours (GIST), SCLC, GEP

Gastrin releasing peptide (Bombesin, GRP) receptors
Prostate cancer, breast cancer

Vasoactive intestinal peptide (VIP) receptors
GIST, other stromal tumours

Neurotensin (NT1) receptors
Exocrine pancreatic cancer, meningioma, Ewing sarcoma

Neuropeptide Y (NPY) receptors
Breast cancer (NPY-1), sex cord stromal ovarian tumour and adrenal tumour
(NPY-1 and NPY-2)

Glucagon-like peptide-1 receptors (GLP-1)
Insulinoma, gastrinoma

Corticotropin-releasing factor (CRF) receptors
Pituitary adrenoma, paraganglioma

α-Melanocyte stimulating hormone (α-MSH) receptors
Melanoma

Substance-P (SP) receptors
Glioma (*topical application*)

Integrin {α}v{β}3 receptors
Glioma (*topical application*)

Radionuclide therapy of haematological malignancies

- Radionuclide therapy for haematological malignancies goes back a long time in history.
- Treatment of leukaemia by ^{32}Phosphorus (^{32}P) was the first therapy modality with radioisotopes in 1930.
- Today ^{32}P is still used for polycythaemia vera and essential thrombocythaemia.

- This ‘old’ therapy has lately received the company of a new, more sophisticated therapy by radioisotope labelled antibodies i.e. radioimmunotherapy (RIT) for various haematological malignancies.
- High-dose RIT of myeloid leukaemia with b-emitting radionuclides is being investigated for intensifying anti-leukaemia therapy before stem cell transplantation.

RIT in B-cell lymphoma

- B-cell lymphomas are generally sensitive to treatment with chemotherapy and some are remarkably sensitive to radiotherapy.
- Chemotherapy, in combination with anti-CD20 antibody, rituximab, is considered by many a standard treatment for diffuse large B-cell lymphoma, as well as for follicular lymphoma.
- However, most patients with disseminated B-cell lymphoma are not cured.
- The need for improvements in the treatment of B-cell lymphoma and the radiosensitivity of the disease, provide the rationale for the study of systemic radiotherapy in this disease.

There are now two approved radiopharmaceuticals:

1. Zevalin (IDEC Pharmaceuticals, San Diego, CA and Schering AG, Berlin)
2. Bexxar (Glaxo SmithKline, Philadelphia, PA) for the treatment of B-cell lymphoma.

Two further radiopharmaceuticals have been evaluated in clinical trials:

1. Epratuzumab (Lymphocide, Immunomedics Inc., Morris Plains, USA), (an ^{90}Y labelled humanised antibody directed against the B linage restricted antigen CD22)
2. Lym-1 (Oncolym, Peregrine Pharmaceuticals Inc, Tustin, USA), (a murine antibody directed against an aberrant HLA-DR10 antigen Lym-1)

Summary and future perspectives

The success of RIT in lymphoma can be attributed to the combination of:

1. Radiosensitivity of the disease,
2. The targeting of highly expressed antigens by signalling antibodies
3. By antibodies that mediate other therapeutic effects in their own right.
4. In the myeloablative setting, data are even more impressing.
5. The role of RIT in other lymphomas and as a part of a combined treatment remains to be defined.

Loco-regional applications of radioisotopes for liver tumours

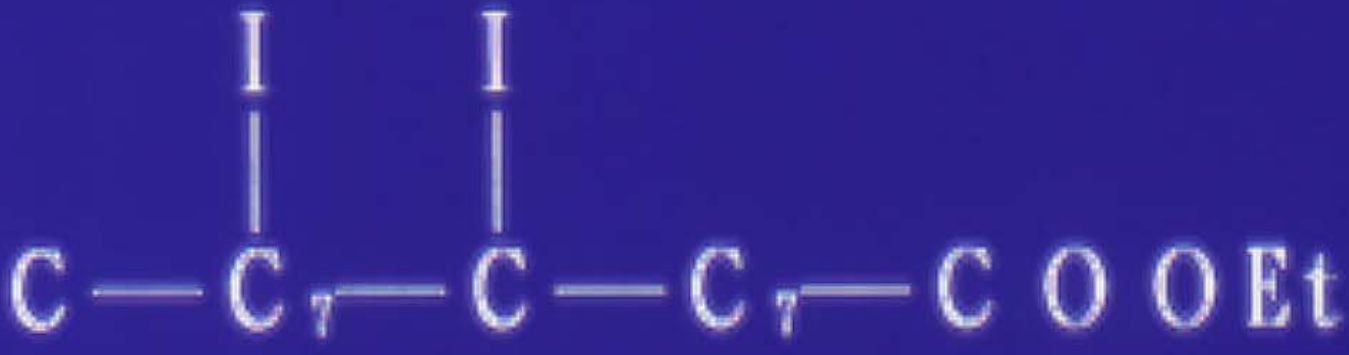
- Liver tumours are an important cause of morbidity and mortality in the world.
- Colorectal carcinoma (CRC), the most important cause of liver metastases, is the second most mortal cancer in Europe.
- Hepatoma is worldwide the most important cancer.
- Secondary liver failure is a natural course of disease in many of these patients.
- For both liver metastases and HCC, surgery (resection, liver transplantation) is central for curative treatment.
- However, only 10–25% of cases are operable and postoperative recurrences are frequent.

- In CRC, several lines of systemic chemotherapy are used, more recently in conjunction with new antibodies to EGFR and VEGF. With these modalities, response rates have increased from 15% to up to 35%.
- In HCC there is no standard effective systemic chemotherapy.
- For these reasons, loco(-regional) therapy modalities have increasingly been employed, although its use varies enormously according to available interest and expertise.

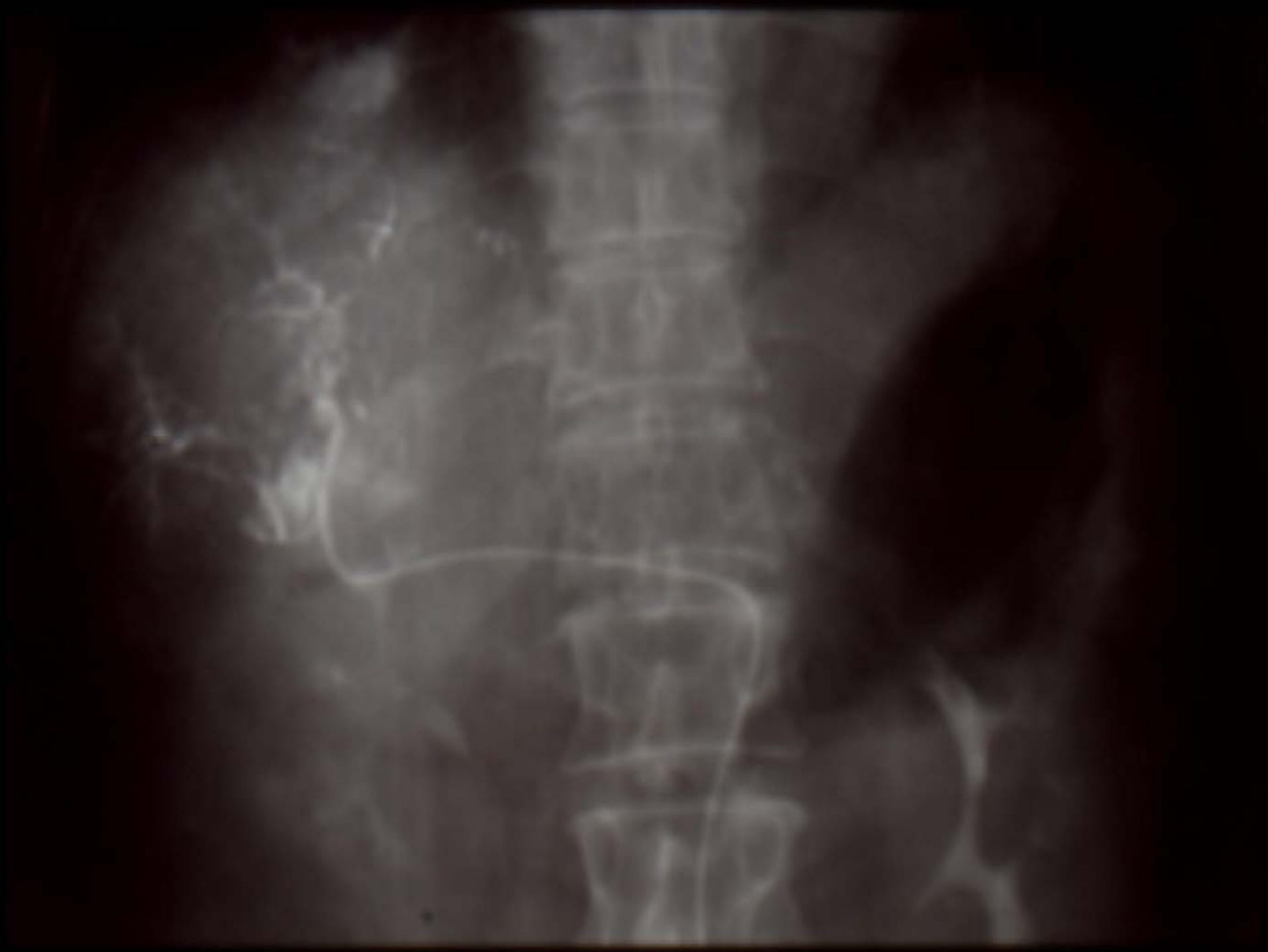
Trans-arterial radionuclide therapy of the liver

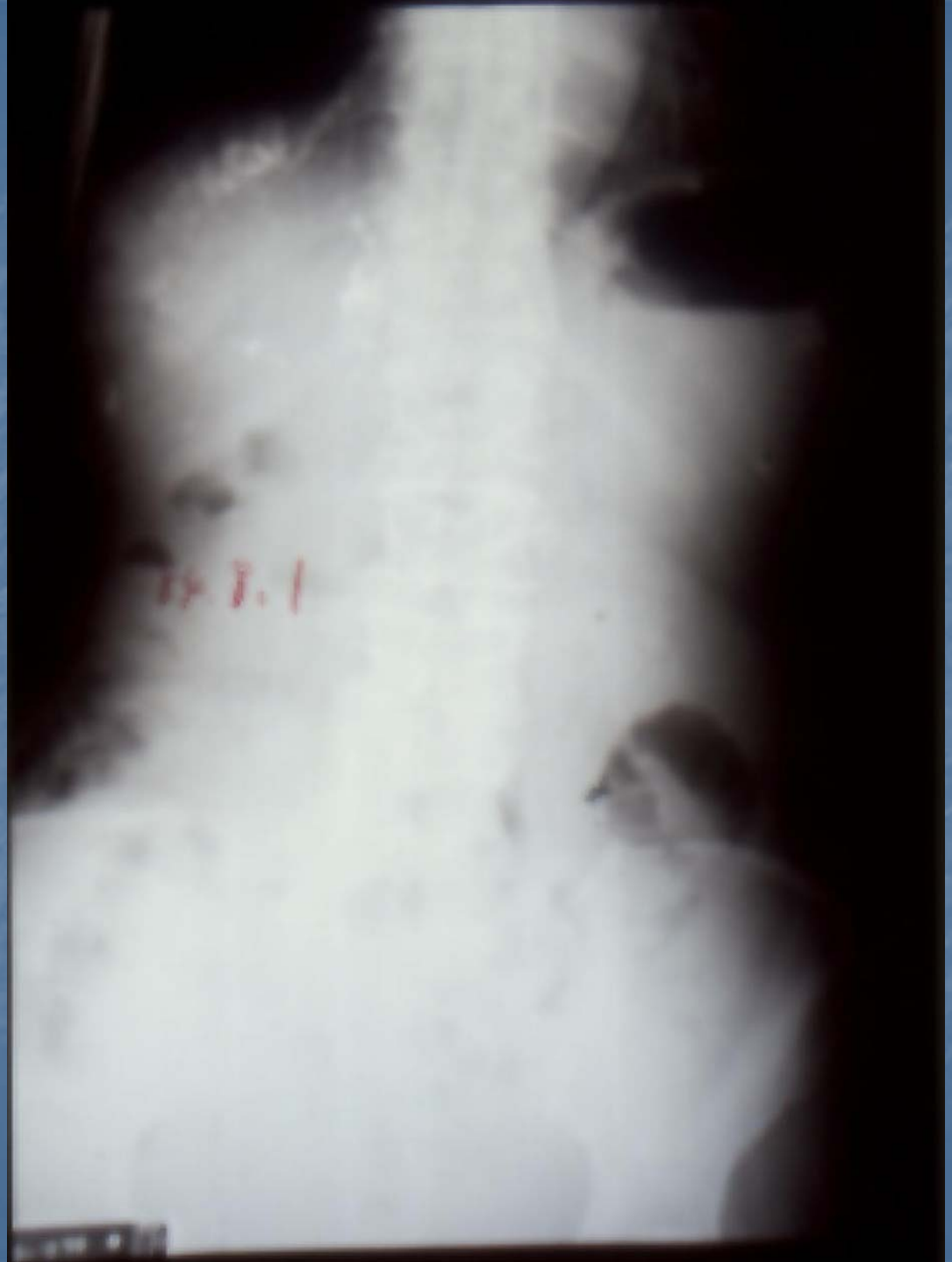
- Historically, radionuclide therapy for HCC and liver metastases dates back to the early seventies, when Phosphorus (P)-32 labelled with albumin colloids were first used.
- When injected into a hepatic artery, such particles preferentially lodge in the hypervasculature of liver tumours (small arterioles, capillary sinusoids) and internally irradiate the neighbouring tumour tissue.
- Today, two of these products are commercially available, i.e. resin microspheres (SIR-spheres, SIRtex) and glass spheres (Theraspheres, Nordion)

- Lipiodol is a fatty acid ester derivative of natural, iodine-rich seed oil previously used as CT contrast agent, commercially available labelled with ^{131}Iodine(I) (Lipiocis, Schering S.A.).



Lipiodol : $C_{17}H_{33}I_2COOC_2H_5$





Summary and future perspectives

- Lipiocis is a unique loco-regional treatment modality. Especially its adjuvant use to resection of HCC seems a particular easy and effective modality.
- In palliative HCC therapy it is equally effective as TACE, but at the cost of far lower complicating morbidity and mortality.
- SIRT is an adjunct, not a replacement for chemotherapy and has the potential for better local control and prognosis, without additional toxicity (New alinea).
- In both treatment modalities, patients may be downstaged to resection following treatment.

Conclusion

- Radionuclide therapy is a unique treatment modality lying between chemotherapy and external radiotherapy.
- The challenge for the next years is to select the most promising and appropriate targets for (pre-)clinical use, while at the same time optimally integrate its unique capabilities into the increasing number of other anti-cancer treatment strategies available.

治療用核醫藥物研發成功的要素

1. 主管機關的全力支持
2. 研究團隊的全力以赴
3. 管制單位的適度配合
4. 合作廠商的財務及技術支援


自強不息
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感謝

所有參與核醫治療藥物研發的工作夥伴


謝謝指教