Important Clinical Applications of ^{188}Rhenium for Radionuclide Therapy

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Abstract: Although established clinical utility is of key importance in choosing agents for radionuclide therapy, other key factors include costs and GMP availability of sterile, pyrogen-free, regulatory approved radiopharmaceuticals. No-carrier-added (NCA) ^{188}Rhenium(^{188}Re, 16.9 hour half-life; 155 keV gamma emission) is available on demand as ^{188}Re-perrhenate from saline elution of a ^{188}Tungsten/^{188}Rhenium(^{188}W/^{188}Re) generator. The availability and superb radionuclidic and chemical properties make ^{188}Re an excellent candidate for radionuclide therapy. This radioisotope is readily attached to a variety of targeting agents and also emits high energy beta particles (E_{max} 2.12 MeV) for therapy. Over the last 30 years the effectiveness of ^{188}Re for a variety of therapeutic applications has been established in multiple clinical studies. This overview provides a brief summary of clinical applications with ^{188}Re-labeled agents as an introduction to the detailed clinical discussions in the following papers. Although ^{188}Re-labeled radiopharmaceuticals for routine clinical use and accompanying reimbursement are not yet commercially available, several agents have been evaluated in clinical studies. In addition, a large number of ^{188}Re radiopharmaceutical agents have been developed and evaluated in pre-clinical studies over the last three decades. This review focuses on providing examples of ^{188}Re-labeled radiopharmaceutical agents which have entered late stage clinical use and have demonstrated good efficacy. These key applications include palliative treatment of skeletal metastases, intra-arterial therapy of liver cancer and post PTCA intravascular inhibition of arterial restenosis. Also, ^{188}Re radiopharmaceuticals had been developed and initially assessed for synovectomy and for marrow suppression. More recently, a unique device-based technology has entered clinical use for therapy of non-melanoma skin cancer using a ^{188}Re topical cream. Finally, ^{188}Re-antibodies are being developed for the potential therapy of infectious disease and this unique new therapeutic strategy is expected to enter clinical trials in the near future.

Keywords: Bone pain palliation, Cancer therapy, Liver cancer, Skin cancer, ^{188}Rhenium, ^{188}Tungsten/^{188}Rhenium Generator.

INTRODUCTION

An earlier paper in this issue summarizes the development and use of the ^{188}W/^{188}Re radionuclide generator to provide no-carrier-added (NCA) ^{188}Re for attachment to various radiopharmaceuticals for targeted therapy. This contribution provides a brief overview of several key ^{188}Re radiopharmaceuticals currently in clinical use as well as agents for developing new ^{188}Re therapeutic applications. Although various therapeutic radioisotopes have been evaluated in the clinical arena, many others represent promising candidates for evaluation (Table **1**). ^{188}Re represents a key therapeutic radioisotope which is readily available NCA from the ^{188}W/^{188}Re generator for which continued research interest spanning more than thirty years has been expressed by the research and clinical communities. In the last several years interest by the radiopharmaceutical community has evolved and the GMP manufactured generators are now available which provide NCA ^{188}Re as an active pharmaceutical ingredient (API, Table **1**). The first reported patient studies with ^{188}Re were limited to very specialized applications involving evaluation of ^{188}Re distribution in the nervous system [1] and for irradiation of the choroid plexus and central nervous system [2]. Although ^{188}Re is of interest for therapeutic applications because of the benefit of high energy beta emission (2.12 MeV), some early studies had actually focused on evaluation of this radioisotope for possible diagnostic applications [3-4].

Despite extensive research and the development of new technology and targeting strategies, the literature has really only reflected the regulatory approval and introduction of a limited number of therapeutic radioisotopes/radiopharmaceuticals for routine clinical use (Table **1**). As described in an earlier paper in this issue of *IJNMR*, in addition to the goal of decreasing ^{188}Re unit dose costs by optimization of generator use, the assured routine availability of reactor-produced ^{188}W and ^{188}W/^{188}Re generators are two key issues which must be further addressed as well. Use of the ^{188}W/^{188}Re generator system is particularly well suited for use in more remote areas and in developing regions where the logistics and high costs of regular radioisotope importation are important issues.

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Realization of the benefits for clinical use of ^{188}Re in developing regions was promoted by Dr. A. J. Padhy in the *Nuclear Medicine and Diagnostic Imaging Section* of the *International Atomic Energy Agency* (*IAEA*), which had teamed with ORNL in the early 1990's and various research centers to explore this possibility. Multi-institutional clinical projects were established for support of two key clinical programs focused on the use of various ^{188}Re agents for the transarterial therapy of non-resectable liver cancer [5-7] and for post angioplasty treatment for inhibition of coronary restenosis using ^{188}Re-liquid-filled balloons [8]. The very successful *Thematic Program on Health Care project* (Asia and Pacific Region, RAS/6/028) entitled "Management of Liver Cancer Using Radionuclide Methods With Special Emphasis on Trans-Arterial Radio-Conjugate Therapy and Internal Dosimetry" [6], was initiated in 2000, and represented the first IAEA-sponsored doctoral program. At the same time, these IAEA efforts were effectively coordinated through various *Coordinated Research Project* (*CRP*) programs organized by the *IAEA Industrial Applications Section,* which supported basic science studies for evaluation of ^{188}W production, development of new ^{188}W/^{188}Re generator prototypes, and for the development and pre-clinical evaluation of a variety of ^{188}Re-labeled radiopharmaceutical agents. The two ^{188}Re applications which have moved further forward into the clinical arena include the use of ^{188}Re-labeled agents for treatment of inoperable hepatocellular carcinoma (HCC) and for palliation of metastatic bone pain with ^{188}Re-HEDP. The goal of this paper is to provide an overview of the use of ^{188}Re-labeled therapeutic agents for the treatment of several clinically relevant conditions for targeted therapy with beta irradiation. In addition to the therapeutic benefits of the ^{188}Re high energy 2.12 β^- emission, the accompanying 155 keV gamma photon emission allows important theranostic benefits, for determination of biodistribution and biokinetics to evaluate dosimetry and to potentially correlate biodistribution with therapeutic response. Since the published literature describing the development and use ^{188}Re-labeled agents is becoming quite extensive, only snapshots of these technologies are described in this paper. As described in more detail in the accompanying paper, ^{188}Re is generated by beta-decay of ^{188}W, and conveniently obtained by saline elution of the ^{188}W/^{188}Re generator system, prepared using reactor-produced ^{188}W obtained by the ^{186}W(2n,γ)^{188}W route. The generator system is usually installed in-house and represents a very convenient, cost effective and on demand source of ^{188}Re. The eluted sodium ^{188}Re-perrhenate is then available for radiopharmacy preparation of various ^{188}Re-labeled therapeutic agents using chemistry similar for the introduction of ^{99m}Tc into diagnostic agents. Generally, generator activity levels of 0.5-1 Ci are commercially available, and in some cases, as GMP manufactured sterile systems. Currently, GMP-manufactured non-sterile generators are available from Isotope Technologies, in Munich, Germany, and from the JSCSSC RF-IPPE Institute in Obninsk, the Russian Federation. A GMP-produced sterile generator system equipped with a disposable ^{188}Re post elution concentration module is available from IRE-Elit, in Fleurus, Belgium (Knapp, Table **1**).

1. KEY CURRENT CLINICAL APPLICATIONS WITH ^{188}RHENIUM-LABELED RADIOPHARMACEUTICALS

1.1. ^{188}Rhenium-Hydroxyethylidene Disphosphonate (HEDP)

^{188}Rhenium-HEDP is the key agent which has evolved into further clinical studies from an impressive series of agents and strategies which have been developed and evaluated for the use of ^{188}Re-labeled agents for the treatment of metastatic bone pain. The first clinical studies with ^{188}Re-HEDP were reported in 1998 by Maxon [9-10], where the biodistribution and radiation dosimetry characteristics determined in preliminary studies in patients with skeletal metastases following intravenous administration of a 30 mCi dose (1110 MBq0) provided benefits and toxicity similar to data reported previously for ^{186}Re-HEDP. These investigators noted the expected benefits of on-demand availability of ^{188}Re from the ^{188}W/^{188}Re generator and in-house preparation (Figure **1**) of ^{188}Re-HEDP for treatment on an outpatient basis which has now evolved to a "kit"-based preparation. The ready availability of NCA ^{188}Re on demand from the ^{188}W/^{188}Re generator is an important technical and operational convenience which catalyzed the evaluation of several other agents for bone pain palliation based on ^{188}Re. Although ^{188}Re-labeled hydroxyethylidene diphosphonate (^{188}Re-HEDP) is the only ^{188}Re-labeled agent for bone pain palliation which has evolved for broader clinical use, other examples of ^{188}Re-labeled bisphosphonate ligands have been prepared and evaluated in pre-clinical studies. Examples of these ^{188}Re-phosphonate analogues which have been reported for potential metastatic bone palliation include dipicolymine alendronate [11], ethylenediamine-N,N,N′,N′- tetrakis (methylene phosphonic acid) [12] and 2-sulfonato-1,1-ethylidine bisphosphonic acid (SEDP) [13]. Evidently these ^{188}Re-

Table 1: Key Examples of Beta-Emitting Radioisotopes of Current Interest for Radiotherapy

Radioisotope Production Availability	Principal Emissions keV		Approved for Routine Clinical Use	Comment *
Reactor produced, available from batch production/processing				
Radioisotope Half-Life	Gammas keV (%)	β^- E_{max} MeV % Intensity		
^{169}Erbium .4 d	Very low Energy/int.	0.351	Yes	Clinical use limited to RS of small joints
^{166}Holmium 1.1117 d	80.6, 6.2 %	1.850, 50%	No	Many early stage clinical trials have been described. Also available from the ^{166}Dy(n,γ)^{166}Ho generator (below)
^{131}Iodine- 8.02 d	364, 81%	0.606, 89%	Yes	Widely used, thyroid cancer ablation, antibodies, etc.
^{177}Lutetium 6.68 d	497, 78 %	2.080,11%	Yes	$^{177}LuCl_3$ now available as "LuMark®" from AAA for Lutathera (DOTATATE) EndolucinBeta® from ITM, precursor for DOTATAE ^{177}Lu-617 targeted to PSMA, FDA approved for RadioMedix clinical trials
^{186} Rhenium 3.72 d	137, 8.6%	1.069, 80%	No	Re-186-HEDP withdrawn
^{188}Rhenium- 16.9 h	155, 15%	2.120, 71%	No	Although usually available from the generator (See below) can also be produced from ^{187}Re(n,γ)^{188}Re route
^{153}Samarium 2.0 d	103, 28%	0.808, 17%	Yes	^{153}Sm-EDTMP commercially available as an approved agent and widely used for bone pain palliation
Generator or accelerator produced				
^{166}Holmium	80.6, 6.2 %	1.850, 50%	No	RG, from ^{166}Dy decay
^{188}Rhenium 16.9 h	155, 15%	2.120, 71%	No	RG, from ^{188}W decay Multiple clinical trials in progress, Inter alia
^{90}Yttrium- 64.1 h	No γ's	2.280, 99.9%	Yes	RG, from ^{90}Sr decay Peptide/antibody therapy

*RS = radiation synovectomy; R = reactor; A = accelerator; RG = radionuclide generator; AAA = Advanced Accelerator Applications; ITM = Isotope Technologies Munich; PSMA = prostate specific antigen.

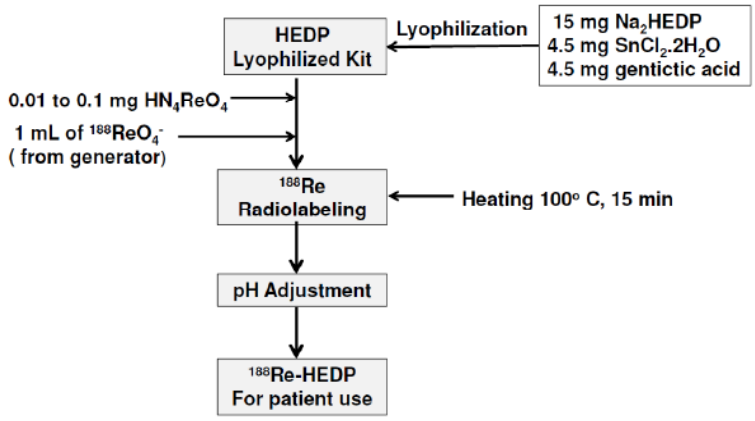

Figure 1: Schematic summarizing the preparation of ^{188}Re-HEDP.

phosphonate-based agents have not progressed to clinical studies.

Although other ^{188}Re phosphonate analogues have been evaluated but have evidently not yet progressed

to evaluation in the clinical arena, the ^{188}Re-dimercaptomethylsuccinic acid (^{188}Re-DMSA) non-phosphonate-based ^{188}Re-labeled agent (Figure **2**) [14-20] had also been developed and evaluated for treatment of metastatic bone pain. This agent was developed for potential therapy of various tumors as a "matched pair" to ^{99m}TcDMSA, which had demonstrated uptake in medullary carcinomas of head and neck, and medullary tumors [16]. This ^{188}Re-DMSA agent is unique since different stereoisomers are formed during radiolabeling with ^{188}Re. A very nice subsequent study isolated the multiple/three ^{188}Re-DMSA isomers prepared by stannous ion reduction by high performance liquid chromatography [19]. Evaluation of each of the isomers in animals studies, showed no differences in localization. This was a potential important benefit which meant that isomer separation would not have been required to optimize dosing and for potential further clinical evaluation of this agent for bone pain palliation. Systematic evaluation of the isomeric mixture of ^{188}Re components was followed by early phase safety and therapeutic studies in patients [14, 18]. In addition to the several papers which had described the synthesis, evaluation of the isomers, and pre-clinical evaluation of the, ^{188}Re-DMSA agent showed excellent localization in skeletal metastases, as may have been suspected from the localization of metastasis from breast carcinoma using ^{99m}Tc-DMSA. Subsequent clinical studies demonstrated high specific uptake ^{188}Re-DMSA in skeletal metastases, indicating possible use for therapy of skeletal metastases from prostatic carcinoma [18] and possibly from other primary carcinomas. However, because of high renal uptake the ^{188}Re(V)-DMSA agent has not been further evaluated for therapeutic efficacy in clinical studies.

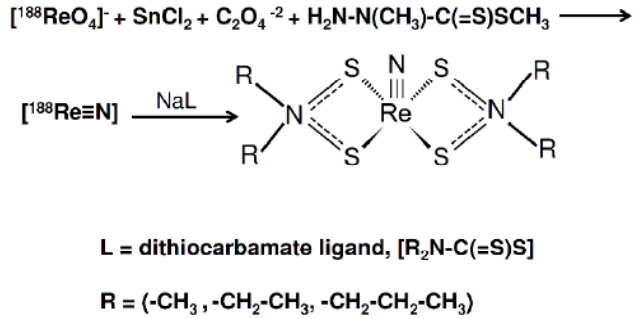

Figure 2: Structure of ^{188}Re-dimercaptomethylsuccinic acid (DMSA).

Subsequent studies focused on an evaluation if pH levels affected renal uptake. With the "matched pair" ^{99m}Tc(V)-DMSA analogue, for instance, increased pH values reduce renal uptake [20]. In order to assess the importance of the reducing agent for the Re(V)→Re(VII) reduction step, other investigators showed that ^{188}Re(V)-DMSA prepared by reduction with sodium meta-bisulfite demonstrated less renal uptake in animal studies [21-22] and that such complexes mixtures consisted of different isomer ratios. Interestingly, the complex prepared by the usual stannous reduction exhibited more prolonged skeletal retention. Although vascular clearance was the same for both preparations, kidney retention was greater for ^{188}Re(V)-DMSA prepared using stannous anion reduction. This may explain the differences observed in the relative biodistribution results between the ^{188}Re(V)-DMSA products prepared by the two different reducing agents. So in spite of some very careful and promising developmental studies, apparently despite the promising results of Blower and others, the clinical use of ^{188}Re-DMSA has not progressed further.

The ^{188}Re-HEDP agent moved forward in several clinical studies for bone pain palliation because of its efficacy, ease of preparation and low toxicity. Data from several very promising studies have been reported using ^{188}Re-HEDP [23-28] This agent shows good clinical efficacy and demonstrates pain palliation results similar to data described for phosphonate analogues radiolabeled with other beta-emitting radionuclides (^{153}Sm and ^{186}Re) and ^{89}Sr chloride [28] in patients presenting with metastatic bone disease form metastases from prostate, breast and lung cancer. As an example, 61 patients presenting with skeletal pain from bone metastases from cancer of the bladder, breast, kidney, lung, and prostate, were treated with doses of 31-188 mCi [23]. Good efficacy and overall pain relief of 80% with no evidence of hematopoietic or severe side effects were observed after one year. A response rate of 76% was reported from another study in which 27 patients with hormone refractory prostate cancer were treated with^{188}Re-HEDP [24]. Similar efficacy has also been observed treating patients with metastatic bone from lung cancer [25] and several other clinical studies with ^{188}Re-HEDP. A larger controlled study conducted in Bonn, Germany, focused on repetitive treatment, where a single dose or repeated doses of ^{188}Re-HEDP were administered to 64 patients. In addition, to slightly better pain relief, more importantly, repeated dosing with ^{188}Re-HEDP resulted and in an apparent therapeutic effect [24].

More recently, these authors in Bonn had retrospectively evaluated and compared the data from this study using single and multiple administrations of (^{188}Re-HEDP) on palliation and survival of prostate

cancer patients presenting with more than 5 skeletal metastases [29]. The ^{188}Re-HEDP was prepared using NCA ^{188}Re obtained from an in-house generator following dilution with carrier perrhenate. Although the use of high specific activity radiopharmaceuticals is a usual goal, it is important to note that the use of ^{188}Re-HEDP is a unique example where the Re specific activity must be decreased in order to provide sufficient mass for targeted uptake by an unknown mechanism. The data available for the 60 patients included PSA levels and Gleason scores, which were similar for the 3 groups, which consisted of Group A (n = 19) in which patients had received a single injection, Group B (n = 19) patients who had 2 injections and Group C (n = 22) in which patients had received 3 or more successive injections. When significant pain palliation was observed, it was independent of administration frequency. The mean 95% confidence interval survival data calculated from initiation of treatment were 4.50 ± 0.81 months for Group A (2.92-6.08), 9.98 ± 2.21 months (5.65-14.31) for group B, and 15.66 ± 3.23 (9.33-22.0) for group C. Values for pain palliation were 89.5% (Group A), 94.7% (Group B) and 90.9% (Group C). The number of lost life-years was significantly lower in Group C than the other two groups, although the 3 groups did not differ in Gleason score. An important observation was the 4.50 to 15.66 month improvement in post-treatment overall survival for multiple-injections in comparison with a single injection of ^{188}Re-HEDP. These studies in Bonn and similar studies by Liepe *et al.* with ^{188}Re-HEDP in Kassel, Germany, and also elsewhere, had clearly demonstrated that in house use of the ^{188}W/^{188}Re generator is feasible and allows on demand and cost-effective access to the excellent ^{188}Re-HEDP agent for bone pain palliation.

These combined clinical date have thus clearly demonstrated that efficacy using ^{188}Re-HEDP [28] is similar to other bone pain palliation agents radiolabeled with ^{186}Re and ^{153}Sm. There is also great interest in the possibility of enhanced synergistic effects by administration of chemotherapeutic agents and targeted radiopharmaceuticals radiolabeled with beta-emitting radiopharmaceuticals. Some studies have suggested synergy by evaluation of the combined efficacy of chemotherapy and radiation damage from ^{188}Re-HEDP. In a Phase I study, ^{188}Re-HEDP (1 mCi/kg) was intravenously administered after a 14 day increasing (<2,500 mg/m^2 total) oral dosage of capacitabine (Xeloda®) to prostate cancer patients (3 patients/in two cohort) with bone metastasis refractory to hormone therapy [30]. The results demonstrated that capacitabine has no apparent effect on ^{188}Re-HEDP biodistribution and excretion. Although unacceptable toxicity was observed in this initial MTD study, evidently, a Phase II study has been proposed to continue evaluation of the efficacy and potential synergistic effects of these two therapeutic strategies. More recently, similar combined effects of ^{188}Re-HEDP and taxanes have been reported in human prostate carcinoma cells *in vitro* [31].

Although the earlier routine effective clinical use of ^{188}Re-HEDP spanned over several years in Germany (Bonn and Kassel) and elsewhere, use of this agent at these centers is evidently not currently in progress. However, recent renewed interest in the benefits of using ^{188}Re-HEDP for treatment of intractable skeletal pain form metastases are reflected in the efficacious reports of studies in progress at the Meander Medical Center in The Netherlands [32-36] and in Coimbatore, India [37]. At the Meander Center, in house routine GMP production of ^{188}Re-HEDP had been instituted [32-36] and over 200 patients have been treated with ^{188}Re HEDP at this institution (R. Lange, *personal communication*). In studies conducted at the Comprehensive Cancer Centre at the Kovai Medical Centre in Coimbatore, the clinical efficacy of ^{188}Re-HEDP is also being evaluated [37]. Of particular importance for radiopharmacy preparation, several “kit” preparations have also been described for the preparation of ^{188}Re-HEDP for patient administration [39-43].

1.2. ^{188}Rhenium Labeled Particles for Transarterial Therapy of Hepatocellular Carcinoma (HCC)

Because of the widespread occurrence of inoperable hepatocellular carcinoma (HCC), especially in developing countries, the availability of cost effective radioactive therapeutic agents often offers the only option for these patients. For this reason, many approaches and technologies are being evaluated and the trans-arterial administration of therapeutic radioisotopes for trapping in the micro vascular of the tumor feeding arteries is an important accessible option for patient treatment and management. Interest in this therapy area has seen the evolution of several ^{188}Re-labeled agents, because of attractive radionuclidic properties and on demand availability. Several ^{188}Re-labeled Lipiodol-based agents have thus been developed and evaluated for this important application (*i.e*. IAEA trial) [44-49]. The development of radiolabeling “kits” [50-53] and impressive clinical experiences with this agent [54-85] have been

described. Also, various ^{188}Re-labeled microsphere preparations have been described as administration vehicles [86-91], "kits" have been developed [90] and patient studies reported [92-95]. Lipiodol is an ethiodized plant oil containing iodine and combined with very lipophilic fatty acid ethyl esters has been traditionally used for many years as a myelographic contrast agent. For therapy, ^{131}I-Lipiodol was developed for hepatic arterial administration, shows prolonged hepatic retention, and is widely used for HCC therapy [96-97]. Incorporation of the therapeutic ^{131}I radioisotope by exchange of the nonradioactive iodine had offered an opportunity to irradiate the tumor in addition to interfering with blood flow. However, this agent is difficult to prepare, can be unstable and ^{131}I emits high energy photons so significant radiation dose may not localized just to the desired treatment site.

^{188}Rhenium was recognized several years ago as an attractive alternative candidate to the use of ^{131}I for HCC targeting therapy because of its inexpensive availability on-demand from the ^{188}W/^{188}Re generator and a variety of ^{188}Re-labeled Lipiodol analogues have been prepared and evaluated. Although the use of ^{188}Re-labeled microspheres had appeared to be an attractive strategy because of the ease of preparation and particle stability [86-90], most approaches have focused on the combination/suspension of a very lipophilic ^{188}Re-labeled complexes with Lipiodol. One early approach involved suspending the readily prepared ^{188}Re-sulphur colloid in Lipiodol [98], while other approaches used the ^{188}Re-ECD agent for Lipiodol suspension. However, none of these agents have progressed to more expanded clinical studies, and a more focused approach [99] involved the very lipophilic ^{188}Re-TDD agent (2,2,9,9-tetramethyl-4,7-diaza-1,10-decane dithiol) agent initially developed and used in the IAEA-supported trials and had been used in several clinical trials (Figure **3**). Afterwards, the more lipophilic ^{188}Re-4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol (^{188}Re-HDD) agent had evolved from these investigators and was introduced for clinical use at several institutions [100-105]. To assess efficacy, ^{188}Re-HDD has been compared to ^{131}I-lipodol in a comparative evaluation in patients suffering from inoperable HCC [100]. The importance of this study demonstrated that ^{188}Re-HDD/lipiodol resulted in a cytotoxic effect and a lower radiation exposure for an expected higher tumor-killing effect than ^{131}I-Lipiodol. Under the leadership of Dr. A. J. Padhy, the *International Atomic Energy Agency* (*IAEA*) then prepared a protocol and conducted a multi-country Phase I/II clinical trial with ^{188}Re-HDD-Lipiodol demonstrating three complete responses and 19 partial responses in 185 patients in eight countries [5-7].

Further studies in a *Coordinated Research Project* (*CRP*) organized and funded by the *International Atomic Energy A*gency (*IAEA*) included a single HCC patient evaluation using ^{188}Re-HDD-lipiodol to evaluate dosimetry [101-102] where the maximum safely tolerated patient activity was estimated to be approximately 225 mCi (8511 MBq). The lungs were the dose limiting organ and most importantly, two doses of ^{188}Re-HDD-lipiodol resulted in complete disappearance of a large volume tumor and the patient

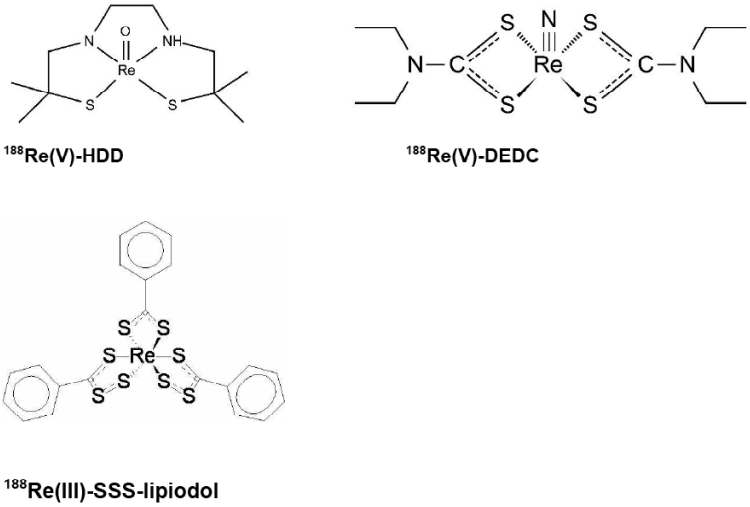

Figure 3: Chemical structures of ^{188}Re-labeled lipophilic agents for admixture with Lipiodol for transarterial administration for HCC therapy. ^{188}Re-(V)-HDD [^{188}Re-4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanethiol]. ^{188}Re-(V)-DEDC [^{188}Re-nitrido bis(diethylthiocarbamate)]. ^{188}Re-(III)-SSS-lipiodol [SSS = $(S_2CPh)(S_3CPh)_2$].

was disease free for 18 months. Subsequently, this group reported a large scale clinical trial involving 93 patients in India and Vietnam using ^{188}Re-HDD-lipiodol [103]. In Ghent, Belgium, studies confirmed that 28 patients receiving 35 treatments of ^{188}Re-HDD-lipiodol with activities ranging from 130-190 mCi tolerated the dose with no severe complications [104-105]. A significant reduction in AFP levels was measured in patients six weeks after treatment, and a response assessment showed partial response in 1, stable disease in 28, and disease progression in 2 treatments.

The use of ^{188}Re for the treatment of HCC is also in progress in Rennes, France, where preparation of a third agent - ^{188}Re(III)-SSS-lipiodol [SSS = $(S_2CPh)(S_3CPh)_2$] (Figure **3**)– has been developed [47-49]. Initial studies described the synthesis of this highly lipophilic agent and formation of the ^{188}Re(III)-SSS-lipiodol complex [59]. Studies in a porcine model [58] and a comparative evaluation of ^{188}Re-SSS-lipodol with ^{131}I-Lipiodol in rats bearing experimental hepatocellular carcinoma tumors demonstrated the expected more positive results from irradiation of the small rat tumors [59]. A summary of the Phase I open-label clinical trial at Rennes with ^{188}Re-SSS/Lipiodol is described in the US NIH directory (https://clinicaltrials.gov/ct2/show/NCT01126463). The combined evaluation of clinical studies with ^{188}Re-lipiodol agents have shown that this strategy is efficacious, although two issues which must be further improved, include increasing the ^{188}Re radiolabeling efficiency and *in vivo* stability of these agents to minimize liver leakage of activity and potential radiation exposure of non-target tissues.

Another approach for HCC therapy with ^{188}Re has described the preparation of the ^{188}Re-nitrido *bis* (diethylthiocarbamate) ("DEDC") agent as an alternative agent with increased radiolabeling yields [45]. The "kit" preparation of (DEDC) complex involves ^{188}Re(V) which is attached to nitrogen as a nitrile linkage (Figure **3**) [51-53]. Use of an automated synthesis module insures reproducible preparation of ^{188}ReN-DEDC-lipiodol and preparation of the Lipiodol mixture and reduces user radiation dose [106]. The ^{188}ReN-DEDC complex is highly lipophilic and is quantitatively extracted into lipiodol forming the administration mixture. With appropriate administration the ^{188}ReN-DEDC-lipiodol complex demonstrates good *in vivo* stability, shows selective tumor localization and results in impressive target/non-target tissue ratios [106, 107]. Initial clinical trials showed that ^{188}Re-DEDC could be a useful radiopharmaceutical for unresectable HCC therapy. As another example, preparation and pre-clinical evaluation have also been reported for ^{188}Re(N)(cys) (PNP), which is another example of a Re(V) nitrido complex, but clinical studies with this congener have evidently not yet been pursued [108].

Finally, the combined synergistic application of ^{188}Re-HEDP and other agents with chemotherapeutic agents may develop further. As an example, a recent Phase I safety study evaluated the combination of ^{188}Re-HEDP with capecitabine in patients with hormone refractory prostate cancer where 17 patients were treated with ^{188}Re-HEDP and different doses of capecitabine [30]. Preclinical studies have also evaluated the *In vitro* effects of both gemcitabine and 5-fluorouracil and ^{188}Re [106] and the spectacular supra additive effects of cytotoxic drugs and ^{188}Re in an *in vitro* model of HCC, demonstrating that the potential importance for further exploration of combined therapeutic approaches using ^{188}Re agents and targeted toxic agents may offer increased therapeutic effectiveness. More recently, combinational studies using soranfenib in a hepatoma cell line have shown positive results, [109, 110].

Continuation and expansion of the clinical use of such Lipiodol mixtures of these radiopharmaceuticals and potentially other ^{188}Re-labeled agents for the therapy of inoperable HCC is expected to continue, however, GMP commercial availability of such agents would be expected for wider use. The extensive earlier international clinical experience during the IAEA-supported international trial has recently served as the foundation for use of ^{188}Re-agents for current treatment of HCC in Coimbatore, India, and at several other centers.

2. EXAMPLES OF PIONEERING CLINIAL STUDIES WHERE ^{188}RHENIUM LABELED AGENTS PLAYED KEY ROLE FOR TECHNOLOGY DEVELOPMENT

2.1. Inhibition of Arterial Re-Stenosis Following PCTA

Percutaneous transluminal coronary angioplasty (PTCA) is a common treatment mode for patients suffering from artherosclerotic coronary artery disease where balloon inflation at the stenotic site restores flow (Figure **4**). However, because of the wound healing biological response to vessel damage, the resulting smooth muscle cell proliferation often results in the occurrence of restenosis in as high as 30–50% of the patients post angioplasty. For this reason there has been extensive, aggressive research to develop technologies which would effectively reverse the

incidence of coronary restenosis after PTCA. One important and successful strategy had been the use of radioisotopes emitting ionizing radiation to inhibit smooth muscle proliferation for this new "intravascular radionuclide therapy (IVRT)" method. A key example has been the use of ^{188}Re-liquid filled balloons for restenosis therapy which had been rapidly embraced in the 1990's by the interventional community. Single site clinical trials were initially conducted at the Cedars Sinai Medical Center in Los Angeles (Dr. Neil Eigler, *et al.)* [110-112] and at the Columbia University/ Presbyterian Hospital in New York City (Dr. Judah Weinberger, *et al*.) [113-121]. Subsequent initiation of clinical trials with this approach quickly followed in several countries (including Australia, Germany, Korea, Taiwan, etc.). A dedicated journal (*Cardiovascular Radiation Medicine*) was also introduced by Elsevier, which was published during the 1999-2004 period, but which had ceased publication when this technology was subsequently usurped by the use of drug eluting stents. The IAEA-supported trial also had high hopes, but because of the limited infrastructure available at many sites, introduction of this technology for the use of ^{188}Re-liquid filled balloons did not flourish and move forward as expected.

During this intense period of developed and evaluation, several companies were also established which were dedicated to the use of beta emitting radioisotopes for this unique application and launched effective technologies (^{192}Ir, Novoste; ^{188}Re, Vascular Therapies, etc.). It is impressive that such a large number of peer-reviewed papers had been published during this short time period in high level journals on this unique application use of ^{188}Re-intravascular therapy techniques.

The common occurrence of smooth muscle hyperplasia leading to arterial restenosis following balloon angioplasty is an unavoidable and well established complication associated with interventional procedures resulting from vascular hyperplasia in response to vessel wall damage (Figure **5**). Until relatively recently, the use of intravascularly placed beta-emitting radioisotope sources was in fact the only successful therapeutic approach to overcome this issue until the introduction of drug-eluting stents [122-123]. Evaluation of various radioisotopes and delivery approaches had rapidly progressed to clinical trials and included the use after-loader placed ^{192}Iridium- (^{192}Ir) wires and ribbons advanced through in-dwelling catheters, ^{32}Phosphorus (^{32}P) coated balloons and the use of ^{188}Re (^{188}Re) liquid-filled balloons, involving manual filling of a balloon with subsequent filling with ^{188}Re solution placed following angioplasty [110-121]. Use of the liquid-filled balloon offered a special bonus for the most effective approach for uniform vessel wall irradiation. Because of the rapid fall off of beta particle energy with radial distance, the use of solid sources was challenged by the difficulty of luminal centering. The difficulty in accurate luminal centering of the radioactive source would result in unavoidable consequence of non-uniform vessel wall irradiation, since reduced irradiation dose delivery (*i.e*. solid

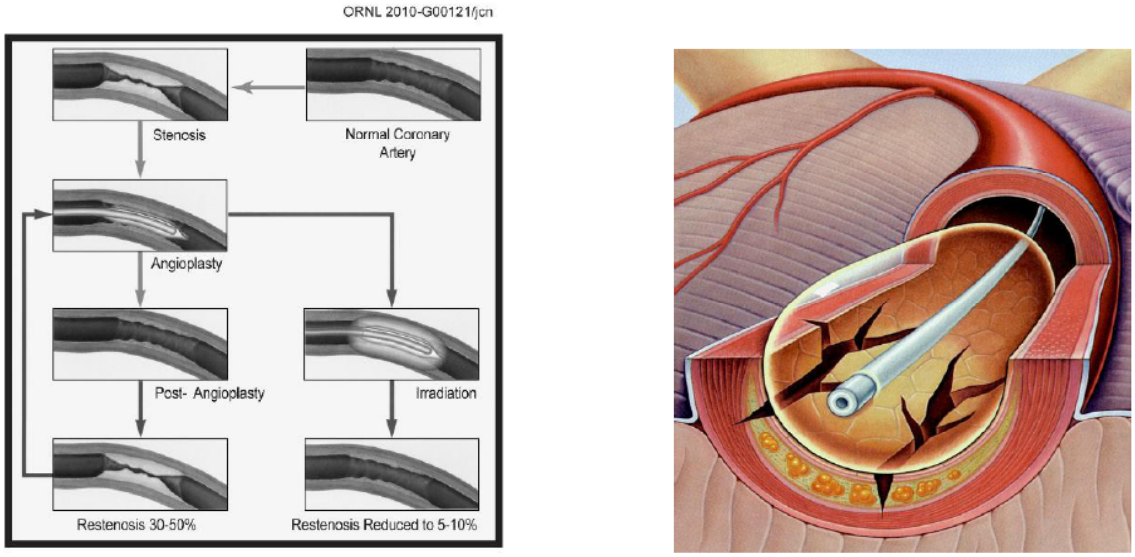

Figure 4: Left. Cartoon illustrating of the smooth muscle cell hyperplastic wound healing response to vessel damage from coronary balloon angioplasty and the use of post PTC irradiation for inhibition of restenosis. **Right**. Illustration of damage to intima from high pressure balloon inflation (With permission of the Editor, Science and Medicine, Vol. 3(3), 1996).

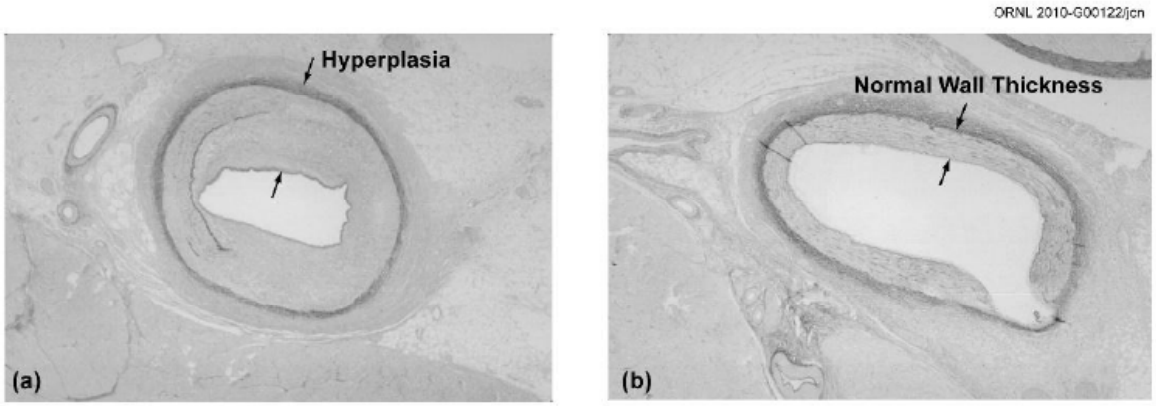

Figure 5: A swine coronary model illustrating balloon overstretch damage to a control vessel (**a**) compared with the effectiveness of post-vessel damage irradiation with a ^{188}Re-MAG3 liquid filled balloon (**b**).

source more distant than from contralateral wall) would stimulate smooth muscle cell hyperplasia. The advantages and eloquence for using the ^{188}Re liquid filled balloon thus included a *de facto* uniform contact with and thus uniform irradiation of the target wall region. Figure **5** illustrates the effectiveness of this strategy for inhibition of smooth muscle hyperplasia after balloon inflation in a porcine model. The obvious benefits of using the ^{188}Re-liquid filled balloon strategy thus generated wide-spread interest, and a large number of patients were subsequently treated with this therapy at centers in the Australia, Germany, Korea, Taiwan, and other countries, at self-funded single centers and in conjunction with the *International Atomic Energy Agency* (*IAEA*) established a *Coordinated Research Project* (*CRP*) in countries promoted and funded by Dr. A. Padhy, using generators available from ORNL.

The use of ^{188}Re-perrhenate for balloon inflation was first proposed for liquid balloon-filled inflation [124-135] and was then successfully introduced for clinical use [110-121]. Since possible unexpected balloon rupture would result in vascular release of ^{188}Re-perhenate and potential high thyroid and radiation exposure, animal studies evaluated thyroid pre-blocking and also post rupture displacement of perrhenate. These studies demonstrated that prophylactic pre-blocking with iodide (Lugol's) [136] and post thyroid displacement of ^{188}Re-perrhenate with perchlorate [137] effectively protected the thyroid from radiation exposure and one clinical case did report balloon leakage of ^{188}Re [138]. Preparation and initial clinical evaluation ^{188}Re-complexes that demonstrate high renal clearance as well as several hydrophilic complexes is another reported approach [139-147]. For the use of radioactive liquid filled balloons such as ^{188}Re, a close association was required between the interventionalist and nuclear medicine or radiation oncology physician administering the radioactive source for the successful use of this technology. Of particular importance is an accurate estimate of the dose prescription, which is accomplished with real time use in the catheterization suite of specially developed software using the balloon dimensions and lesion characteristics [148].

Several clinical studies had used various ^{188}Re-labeled species for post angiographic treatment of arterial segments which initially, which included ^{188}Re sodium perrhenate ($^{188}ReO_4^{-2}$) obtained by direct physiological saline elution of the ^{188}W/^{188}Re generator [111-121]. Use of ^{188}Re-perrhenate represented the most direct and simple route to obtain ^{188}Re, since perrhenate is exclusively and rapidly excreted *via* the urinary bladder in the very unlikely possibility of balloon rupture/leakage. Leakage of ^{188}Re from a perrhenate-filled balloon study was reported in one clinical case [138] but dosimetric analysis indicated no unacceptable radiation dose had been received. Several studies substantiated that thyroid localization of perrhenate could be blocked and displaced by treatment with Lugol's (NaI, sodium iodide) solution or with perchlorate [136-137]. Investigators also evaluated the preparation and clinical use of the $^{188}Re\text{-}MAG_3$ complex [140-146] and ^{188}Re-labeled DTPA (diethylene triaminepentaacetic acid) agents [147, 149-150], and preparation of the ethylene dicysteine complex (EC) [150], as an added precaution, since the rapid urinary bladder excretion of both of these agents is well established in the unlikely event of balloon rupture (< 1 in 10,000)].

Several studies had shown the positive results from using this technology. As one example, post angiographic analyses of 113 patients who had received 22.5 Gy [151-152] in a group of 225 patients using ^{188}Re liquid-filled balloons demonstrated that the target vessel revascularization rate was significantly lower in patients who had received radiation in comparison with data from 112 patients in the control group [154]. Although the data from such a small number of patients did not permit an accurate analysis, in another study a six-year clinical follow-up study after treatment with ^{188}Re filled balloon showed that the restenosis was lower in the case of ^{188}Re patients as compared to the controls [153, 155]. Unfortunately, IVRT with ^{188}Re-liquid filled balloons or use of other radioisotopes never developed to the promise that it offered due to the introduction and preferred use of drug coated stents. The results of typical trials resulted in significantly reduced incidence of restenotic segments compared to controls. Also, impressive angiographic data were still maintained in studies evaluated 2→6 years post treatment [149, 153-158]. In spite of the impressive results from this multiple studies, use of this technology for coronary vessels was rapidly abandoned with the introduction of drug-eluting stents.

More recently, however, this technology had been further developed and successfully extended for the treatment of restenosis of the peripheral arteries [159-161], using a device and technology developed by Flowmedical®, in Garching, Germany. ITM Munich had received full CE-certification and approvals for the rhenium-PTA and PTCA in September 2008 (http://www.itm.ag/content/view/49/92/). Despite several published studies with promising results, it is unclear if clinical use of this technology for the peripheral arteries is continuing. In addition, preliminary studies have also reported the use of ^{188}Re-liquid filled balloons for the successful treatment of refractory benign airway strictures [162] and keloids [163]. Apparently these studies have not further proceeded, but the positive results further illustrate the usefulness for inhibition of re-closure from smooth muscle hyperplasia can be avoided by radiation therapy in areas accessible by catheters for balloon inflation. Impressive results from several other IVRT studies have also been reported [163-184], before use of this technology using the ^{188}Re liquid-filled balloons was transcended by use of drug-eluting stents for restenosis therapy of both the coronary and peripheral arteries.

In fact, the effectiveness of the drug eluting stent and ^{188}Re-IVRT technologies are evidently very similar for the inhibition of arterial restenosis after PTCA. However, use of non-radioactive technologies which can be conducted in routinely available facilities of course has many practical advantages over techniques which require the availability, use and disposal of radioactive materials. The use of radioactive sources also requires special precautions, training and often the complementary involvement of staff with board certification in nuclear medicine or radiation oncology. Although an effective and productive symbiotic relationship between interventional and nuclear medicine/radiation oncology physicians at a number of institutions, this technology had unfortunately never really been embraced by the nuclear medicine community, and been essentially abandoned with the introduction of drug-eluting stents. However, use of these radioisotopic strategies for restenosis therapy represents an important chapter in understanding the effects of post PTCA occlusion and paved the way for the introduction of more recent technologies.

2.2. Radionuclide-Based Synovectomy with ^{188}Rhenium Labeled Agents

The use of radiopharmaceuticals containing beta-emitting radioisotopes for synovial irradiation *via* intra-articulation for treatment of rheumatoid arthritis is a well-established nuclear medicine procedure which is widely practiced worldwide. It is interesting, however, that the US FDA has always questioned the possibility of radionuclide leakage and irradiation of non-target tissues as the key factor why they would not be expected to approve such a technology for clinical use in the US, although the first studies had been described in the U.S. Many different radioisotopes have been evaluated in animal and clinical studies and commercially approved radioisotopes and preparations used for this therapy include ^{169}erbium-(^{169}Er) (Table **1**, for small joints), ^{186} Rhenium-(^{186}Re, for medium size joints) and ^{90}yttrium (^{90}Y, for large joints). Because of attractive radioisotopic and chemical properties, and generator availability, several radiopharmaceutical preparations continuing ^{188}Re have also been prepared, evaluated in animals and studied in humans [185-196]. The use ^{188}Re has been very attractive and used in a variety of studies, since the high energy β^- particles are especially useful for treating larger joints such as the knee. Inert vehicles for intra-articulation which have suitable biological properties for application in radiosynovectomy as seen in animal experiments to which beta-emitting radioisotopes have been attached

hydroxyapatite particles [191-192], microspheres [193-194] and rhenium colloids [195]. The results of a number of clinical studies have been reported [186-190] using ^{188}Re-labeled agents for this application but presumably because of the broad availability of approved agents for the same application, use of the ^{188}Re agents had not progressed to routine use.

2.3. ^{188}Rhenium Labeled Antibodies for Marrow Suppression

Rhenium-88-labeled antibodies have also been widely studied, although these agents have not entered routine clinical use [196]. One application using ^{188}Re peptide/antibodies which that been explored on a clinical basis in some detail is the impressive results of bone marrow ablation with a ^{188}Re "directly" labeled NCA 95 antibody *anti*-CD20 (*anti* NCA95) [197-203] which was evaluated as an adjuvant for conditioning of leukemia therapy. In spite of excellent myeloablative results the further use of this agent, however, has evidently not continued because of the unfortunate persistently high renal radiation doses. Because of the cost-effective routine availability of the ^{188}W/^{188}Re generator and facile preparation of directly ^{188}Re-labeled anti CD20, this approach may still have promise if methods become available that could significantly increase renal clearance.

3. EXCITING NEW THERAPEUTIC STRATEGIES USING ^{188}RHENIUM LABELED AGENTS

3.1. Rhenium-188 Treatment of Non-Melanoma Skin Cancer

A new device-based ^{188}Re brachytherapy technology could provide enormous benefit to patients presenting with head and neck BCC or SCC and precludes the post treatment disfigurement often encountered from surgery or from use of other more options. Beta-emitting radioisotopes have also been evaluated for tropical treatment (brachytherapy) of basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), the more common generally non-malignant non-melanoma forms of skin cancer. Such external applications of ^{188}Re are conducted as a device rather than an administered radiopharmaceutical, representing regulatory approval along a different path. One important parameter is the soft tissue penetration of beta penetration, and these values for several beta-emitting radioisotopes of interest for this application are illustrated in Figure **6**, in comparison to some other beta-, alpha- and Auger-emitting therapeutic radioisotopes of current interest. ^{188}Rhenium is well suited for this application since radiation should reach an average tissue depth of about 3 mm. Application of beta-emitting radioisotope impregnated materials to basal cell and squamous cell carcinomas, particularly of the face and neck, has practical appeal and benefits, for instance, in comparison to the time consuming and invasive "Mohs" surgical technique.

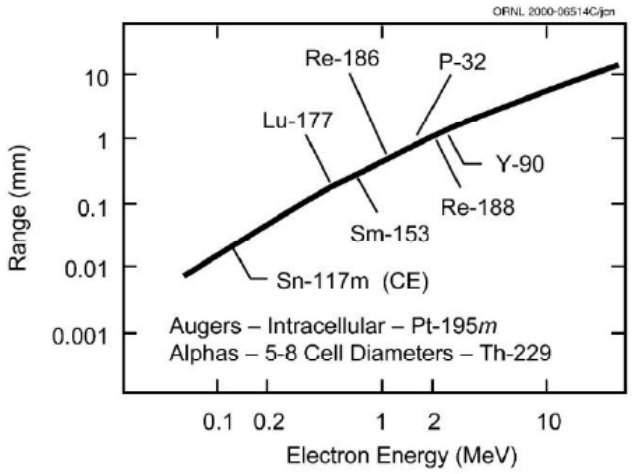

Figure 6: Comparison of estimated soft tissue penetration as a function of particle end-point energy of examples of beta-emitting radioisotopes.

The very common occurrence of BCC and SCC skin cancers has thus catalyzed the evaluation of a large variety of treatment approaches which would be effective but which would preclude disfigurement, especially for cancers of the head and neck. While the Mohs surgical excision technique has been practiced for some time, the simple use of brachytherapy or external beam therapy using gamma rays X-rays or electrons for treatment of basal cell and squamous cell carcinomas, are attractive radiation therapy techniques which offer simplicity, the general avoidance of disfigurement and other technical advantages. While exceptional precision is required for the excision of melanoma lesions, dangerous metastases are generally not an issue for treatment of basal cell and squamous cell carcinomas, and the use of ionizing radiation is very effective. One approach is the use of radioactive patches, which is a simpler and non-invasive treatment method for those patients where traditionally therapeutic modalities would lead potential to scarring and disfigurement. Several beta-emitting radioisotopes have been evaluated for therapy of non-melanoma skin cancer (Table **2**), including ^{166}holmium (^{166}Ho), ^{32}Phosphorus (^{32}P), ^{188}rhenium (^{188}Re) and ^{90}yttrium- (^{90}Y), which are generally embedded in

Table 2: Representative Beta-emitting Radioisotopes Evaluated for Superficial Brachytherapy of BCC and SCC Skin Cancer

Radioisotope	Tissue Irradiation Parameters		
	Radioactive Emission E_{max} MeV	Half-Life	Average mm Soft Tissue Penetration
^{198}Gold	β_{max} 0.96	2.7 days	≈ 4.2 mm
^{166}Holmium	β_{max} 1.85	26.8 hours	≈ 0.8 mm
^{31}Iodine	β_{max} 0.606	8.02 days	≈ 4.2 mm
^{192}Iridium	γ_{max} 0.672 (i.e. no β's)	73.8 days	≈ 4.1 mm
^{32}Phosphorus	β_{max} 1.71	14.29 days	≈ 8 mm
^{188}Rhenium	β_{max} 2.12	16.9 days	≈ 9 mm
^{90}Yttrium	β_{max} 2.3	64.1 hours	≈10 mm

patches which are directly applied to the cancerous area. Because of attractive radionuclidic properties and availability from an on demand generators system, a number of studies have evaluated use of ^{188}Re patches in both preclinical, and more recently, clinical settings. In one study, treatment of superficial experimental melanoma tumors induced in a C57BL/6 mouse model with ^{188}Re bandage [204] tumor regression and delay of tumor growth was observed in all treated animals as a function of radiation dose. In another animal study, ^{188}Re-labeled paper was used and successful treatment of mouse skin cancer and mouse sarcoma was demonstrated [205].

Use of homogeneously ^{188}Re imbedded nitrocellulose paper [204] was an early pre-clinical study which evaluated use of ^{188}Re for topical treatment of superficial skin cancer, where ^{188}Re-tin colloid was filtered through nitrocellulose filter paper following stannous chloride reduction of ^{188}Re sodium perrhenate [204]. The nitrocellulose paper was then contacted to acetone-soaked gauze to dissolve the nitrocellulose and bind the ^{188}Re-tin colloid to the gauze pad, and subsequent studies established the stability and tight binding of the ^{188}Re-bound gauze preparation. Tumor growth in BALBc and ICR mice (5-7 mm diameter, 1-3 mm thick) formed after inoculation with RT101 mouse skin cancer and sarcoma 180 cell lines treated with ^{188}Re-labeled paper preparation sections was evaluated after delivery of an estimated 50 and 100 Gy doses. While 60-75% remission was observed after four weeks in animals with sarcomas, complete tumor remission was seen in animals with RT101 tumors after this time period. These early data demonstrated that further topical brachytherapy studies with ^{188}Re applicators may be a simple and effective technique for therapy of non-melanoma skin cancer.

Because of anatomical locations which may be difficult to adequately reconstruct following surgical removal of basal cell and squamous cell carcinomas of the face and neck, the clinical use of locally applied beta-emitting radioisotopes thus offered an innovative alternative simple and inexpensive strategy [205-210], and ^{188}Re impregnated patches and creams have demonstrated dramatic removal of such lesions without accompanying disfigurement. Wider use of this promising technique is expanding and the required technology and applicators are available (OncoBeta® GmbH, Garching, Germany). Dose prescription is based on the beta penetration at the skin surface and the time of treatment. Figure **7** illustrates the dose penetration curves which have been developed for use of the ^{188}Re cream [206]. The ^{188}Re cream is applied over the tumor surface for a specified time determined by the dose prescription.

This approach is based on use of a ^{188}Re-impregnated cream for topical application which had initially been commercially developed as the "ITM Rhenium-SCT™" (Skin Cancer Therapy) which was initially available from the ITG portfolio. Results of reported studies have demonstrated this to be an excellent approach for treatment of non-melanoma skin cancers and the results of several clinical studies have been published [206-209]. An important advantage of this strategy is that application of the cream automatically matches the skin conformity and does require pre-preparation of a radioactive applicator to match the anatomy of the therapy site. Instead, the

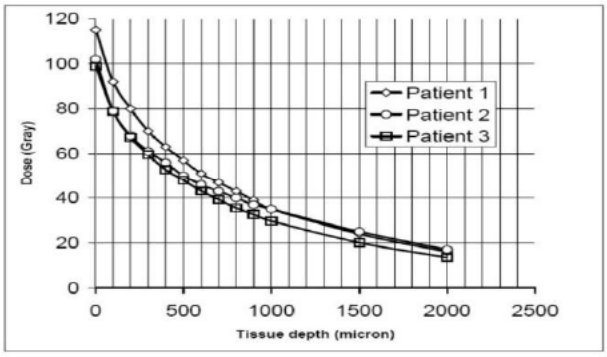

Figure 7: Examples of three human tissue dose adsorption curves used for ^{188}Re dose prescription using the ITG ^{188}Re-SCT™ applicator system (Courtesy of A. Sedda and C. Cipriani, Rome/Celano).

^{188}Re is embedded in a cream which is then applied to the treatment site, previously covered with surgical tape, with a special applicator. The Rhenium-SCT® is CE Labeled as a Medical Device and is now available from OncoBeta® GmbH who provide all the required hardware (treatment unit and applicator, Figures **8** and **9**), as well as disposables and accessories needed for the treatment. Radiation doses to patient and staff are low (0.05 – 0.1 mSv for the patient and in average 0.7 µSv per treatment for the operators) using the OncoBeta® system.

The results of studies reportedly conducted in over 1,000 patients in Italy have provided excellent results [Data provided by OncoBeta®] and have demonstrated good therapeutic efficacy of ^{188}Re for treatment of non-melanoma skin cancer. In addition to the on-demand availability of ^{188}Re from the ^{188}W/^{188}Re generator, which has a useful shelf-life of several months, the short 16.9 hour half-life and high dose rate from the 2.12 MeV beta emission are important properties which allow outpatient treatment for use of the ^{188}Re OncoBeta® technology. Before and after treatment example of the use of this technology for treatment of an ulcerated BCC of the scalp is illustrated in Figure **10**.

For the OncoBeta® "cream" preparation, ^{188}Re-sodium perrhenate is converted to a nano-colloid (200-800 microns) by use of a "kit" consisting of an HCl solution of thioacetamide and polyvinylpyrrolidone, which is then homogeneously combined with a synthetic acrylic resin material [206]. The treatment area is outlined visually and using dermoscopy epiluminescence to include a margin of typically 2-3 mm. Available literature from the OncoBeta company report that ^{188}Re treatment of over 700 patients with

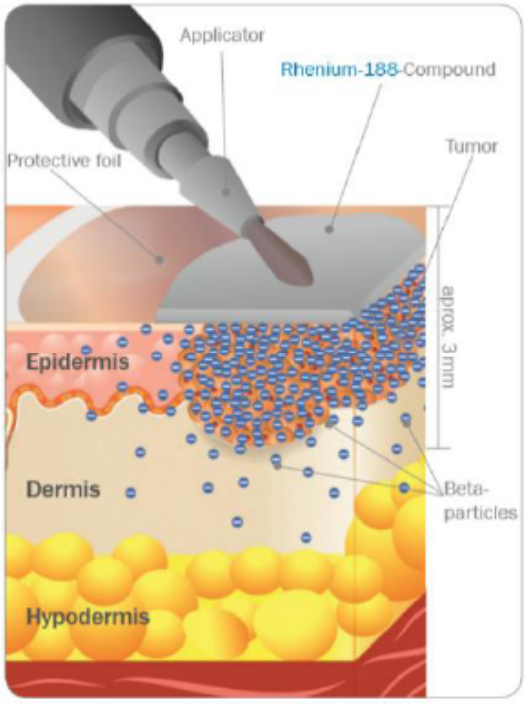

Figure 8: Cartoon illustrating use of the OncoBeta® applicator device for dispensing the ^{188}Re-labeled cream to the surface of a non-melanoma skin carcinoma and irradiation to a depth of about 3 mm with the 2.12 MeV beta particles emitted from ^{188}Re decay (Courtesy of Dr. Thomas Wendler, OncoBeta®, Garching, Germany).

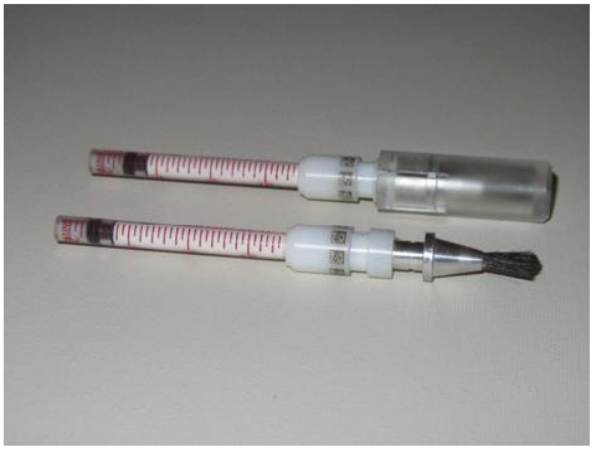

Figure 9: Dispensing tube for the OncoBeta® applicator device filled with the ^{188}Re-labeled cream which is fitted into the dispenser unit sown in Figure 7. The exposed brush shown in the lower photo is then used to dispense the ^{188}Re cream onto the tumor surface (Courtesy of Dr. Thomas Wendler, OncoBeta®, Garching, Germany).

BCC and SCC resulted in an overall 85% success rate. One recent published study enrolled 53 patients who presented with histologically confirmed basal cell (BCC) and squamous cell (SCC) carcinoma [205-208]. Almost all patients undergoing treatment have had

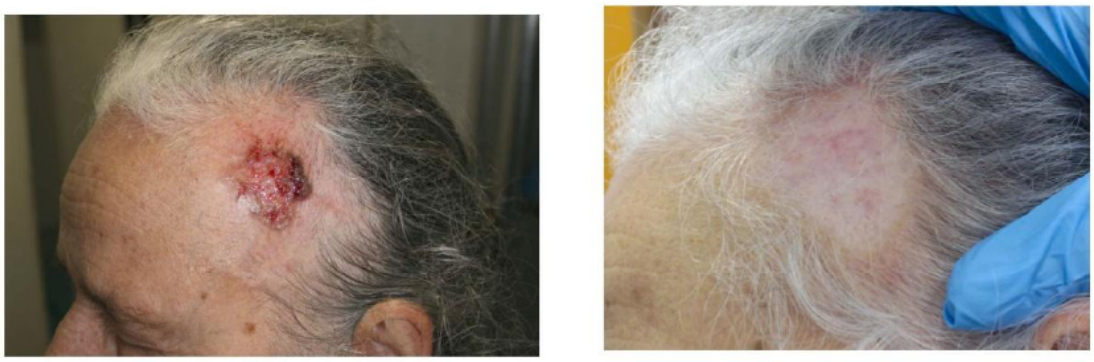

Figure 10: Example of an ulcerated scalp BCC before, and after 382 days following a single treatment with ^{188}Re (Courtesy of A. Sedda and C. Cipriani, Rome/Celano).

complete remission of the treated lesions. For the majority of the patients (89 %) the treatment is conducted during a single-session. In some cases, depending on the depth of the lesion and the dose prescription, several cream applications may be required. The OncoBeta® system appears easy to us, provides impressive non disfiguring results, has now progressed to broader clinical application, and it is hopeful that this device technology will continue to be enthusiastically accepted and employed by the dermatology/oncology communities. Treatment is usually completed within one hour in a single session, is painless requiring no anesthetic and has exhibited high response and low recurrence in treated patients. OncoBeta® GmbH is currently further developing, certifying and commercializing this ^{188}Re-based skin cancer treatment. The technology is evidently routinely used in Italy as a CE-certified medical device and hopefully evolving clinical studies with this technology in Europe will further evaluate its benefit in larger patient populations

3.2. Application of ^{188}Rhenium Labeled Agents for Therapy of Infectious Disease

Another unique application being pursued with ^{188}Re involves *in vivo* targeting of infectious disease with radiolabeled peptides [210-225]. Radioimmuno-targeting of antibodies radiolabeled with beta (^{188}Re) and alpha bismuth-213, ^{213}Bi)-emitting radioisotopes is a unique approach designed for the potential treatment of infectious disease. Target organisms include bacterial infections [217, 223], fungal infections (*Cryptococcus neoformans*, *Histoplasma capsulatum*) [210, 215-216], viral [211-215] and even HIV infections [217]. Although this seminal approach developed for treatment of certain infectious diseases with therapeutic radioisotopes has not entered the clinical arena, such a strategy may offer important possibilities for clinical therapy of special cases of viral and fungal disease which cannot be adequately treated by conventional technologies. Although the results of these impressive pre-clinical studies evaluating the effectiveness of treating infectious disease with ^{188}Re-labeled antibodies, at the current time no clinical studies have yet been reported. These authors have also explored a similar approach for patient treatment of metastatic melanoma with the ^{188}Re-PT1-6D2 antibody targeted to melanin expressed on the surface of melanoma tumor cells [226].

DISCUSSION

This goal of this paper has been to present a brief overview of the important established and developing clinical applications of ^{188}Re which have been pursued in nuclear medicine, oncology and for other applications. Impressive results describing new ^{188}Re radiolabeling strategies, radiopharmaceutical develop-ments, preclinical testing and clinical introduction of new ^{188}Re-laebed therapeutic agents have been reported over the last three decades. More extensive information on the development and clinical evaluation of ^{188}Re-labeled agents can be found in several reviews [106, 196, 227-230]. Current principal clinical efforts in this area are focused on the use of ^{188}Re-HEDP for bone pain palliation and the use of a variety of ^{188}Re-labeled arterial occlusive agents for therapy of inoperable HCC. Other developing future important clinical applications using ^{188}Re are expected to evolve for the therapy of non-melanoma skin cancer, unique treatment strategies for infectious disease, for augmentation of the therapeutic effectiveness of chemotherapeutic agents for cancer therapy, and possible development of new ^{188}Re-PSMA targeting agents for the treatment of recurring prostate cancer.

CONCLUSIONS

The routine, widespread use of ^{188}Re-labeled therapeutic radiopharmaceuticals in clinical practice will be dependent on regulatory issues and the expected increased availability of GMP sterile, pyrogen free ^{188}W/^{188}Re generators and labeling substrate "kits". In addition, the availability of ^{188}Re in centralized radiopharmacies and the further development and commercial availability of regulatory approved ^{188}Re agents are important factors which are expected to evolve as interest in the clinical use of ^{188}Re increases.

AUTHOR STATEMENTS

The authors declare no conflicts of interest.

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