World Radiopharmaceutical Therapy Council Survey: A Preliminary Report on the Practice of Nuclear Medicine in Developing Countries with Special Emphasis on Radionuclide Therapy.

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Global Survey of Radionuclide Therapy in Developing Countries

Introduction

Radionuclide therapy has become an important component of the clinical applications in Nuclear Medicine complementing diagnostic in-vivo imaging and in vitro analysis. Its role in Nuclear Medicine, however, is still limited because of constraints imposed by various factors. The World Radiopharmaceutical Therapy Council initiated in 2007 a study on the status of radionuclide therapy in developing countries. The study was made through a survey instrument sent to representatives of national or regional Nuclear Medicine societies with direct or electronic contact made with some of them to clarify or complete certain important points. The survey included preliminary information on the education and training of physicians and the organizational set-up of Nuclear Medicine facilities; and more particularly, the various therapeutic applications of radiopharmaceuticals as they are done in the respondent countries.

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Material and methods

Methods

A questionnaire was developed by the proponents of the study and tested initially with a small group of respondents. After revisions were introduced, the questionnaire was sent electronically to targeted contacts in different countries. Responses were collected, compiled and tabulated for initial presentation and review at the 2nd International Conference on Radiopharmaceutical Therapy (ICRT) held in Ulaanbaator, Mongolia in September 2007.

Materials

Part 1 centered on the status and structure of Nuclear Medicine in the country. It asks whether Nuclear Medicine is an independent specialty or subsumed to other specialities (e.g., Radiology, Internal Medicine, etc); and whether Nuclear Medicine exists as an independent association or attached to bigger professional societies. Furthermore, it asks for the composition of the NM society (physicians, technologists, radiopharmacists, physicists or other scientists) and the estimated number of membership of each sector. It then inquires on specific practices related to the administration of radiopharmaceuticals for diagnostic and therapeutic purposes and the requirements for those allowed to do so. Moreover, it looks into the specific training of those who are practising Nuclear Medicine and the certification required of them. Finally, it asks for some quantification of the number of procedures done within the country, the percentages done in private facilities, the percentages of out-patient therapies, and the number of beds available for in-patient treatments.

Part 2 of the questionnaire was on therapy-specific issues. For thyroid therapy, it asks for information regarding radioiodine therapy for hyperthyroidism and thyroid cancer, the availability and number of procedures done, the doses (or range of doses) used, the constraints encountered in its use (especially the costs), and other data on the practice of radioiodine treatment for both benign or malignant thyroid diseases. This part also inquires on the other treatment applications in bone pain palliation, liver cancer, lymphomas, joint diseases, neural crest and

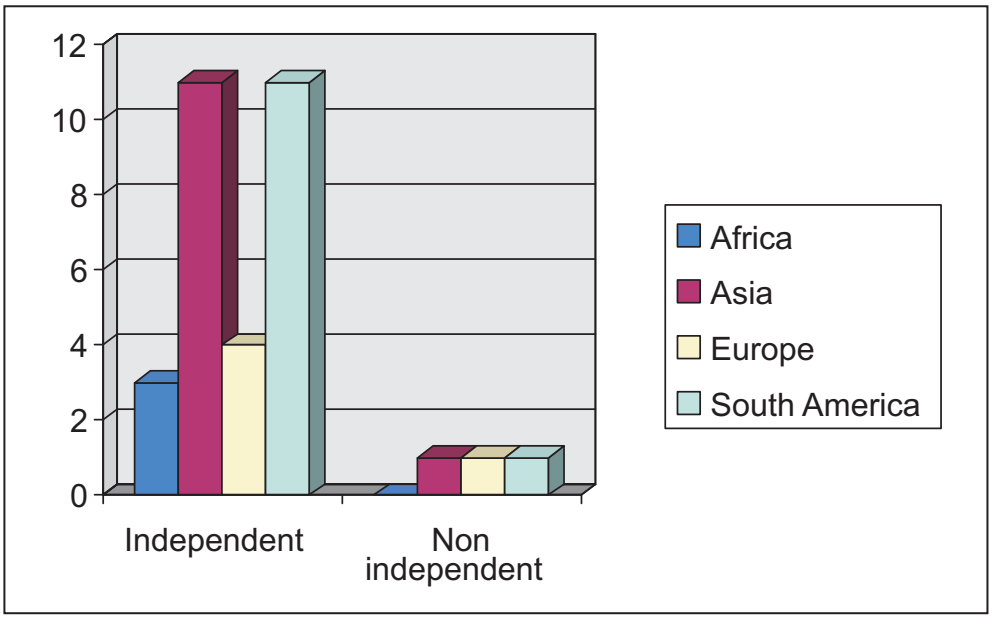

Figure 1. Existence of Nuclear Medicine as an Independent specialty

S.No	Region	Country
1	Asia	Bangladesh, China, India, Indonesia, Iran, Kazakstan, Korea, Philippines, Singapore, Sri Lanka , Thailand, Vietnam
2	Europe	Bulgaria, Croatia, Cyprus, Estonia, Macedonia, Romania, Slovakia,
3	Africa	Algeria, Libya, South Africa, Tunisia,
4	South and Central America	Argentina, Bolivia, Brazil, Chile, Colombia, Dominican Republic, Ecuador, El Salvador, Mexico, Peru, Uruguay

neuroendocrine tumours, and treatment by radio-guided antibodies and other radiopharmaceuticals. Under each treatment modality, issues as to availability, awareness, costs, clinical demands, expertise and restrictions were asked of respondents. Under this part, the use of rhenium generator was raised together with its utility in various applications and availability. Finally, the potential role of the WRPTC in the development and the promotion of the clinical use of all the procedures mainly in developing countries were raised.

Results

Some 22 national societies in as many countries and one regional organization (Latin America) responded to the questionnaires. All regions of developing countries are represented: Africa, Asia, Eastern Europe and South America. Detailed list of countries is attached (Table 1). Data have been gathered and analysed and displayed as follows:

Status of Nuclear Medicine:

1a. Existence of Nuclear Medicine specialty

In most of the countries, Nuclear Medicine is an independent specialty (Figure 1). In few countries it is part of Radiology or Internal Medicine. However, these figures are not so representative since in many countries in Africa as well as in Asia, Nuclear Medicine does not exist at all, or if it does, it is as a separate or a sub/specialty.

1b. National societies of Nuclear Medicine

National societies of Nuclear Medicine exist in more than 70% of respondent countries (Figure 2). It may exist independently or is subsumed into other specialty societies like Radiology or Internal Medicine. In some countries, there exist separate organizations for nuclear physicians, technologists, scientists and other allied professionals.

2 - Professional staff

Physicians and technologists are the most important sectors performing clinical nuclear medicine in the respondent countries. Both categories comprise 84% of the total (physicians = 43%; technologists and allied professionals = 41%); scientists comprise the remaining 15%. The total numbers of professionals in the participating countries are as follows: MD= 3649; Technologists = 3540; PhD = 960; Total = 8549

3 - Who performs diagnostic Nuclear Medicine?

In most countries (more than 65% of respondents), the clinical procedures are done either by physicians or by technologists (or allied professionals but only under physician supervision). In some countries clinical diagnostic Nuclear Medicine is performed exclusively by nuclear physicians. In still fewer countries, clinical Nuclear Medicine could be done by radiologists, oncologists, cardiologists or other scientists.

4 - Who performs Nuclear Medicine therapy?

In most of the countries (more than 74%), Nuclear Medicine therapy is done only by Nuclear Medicine

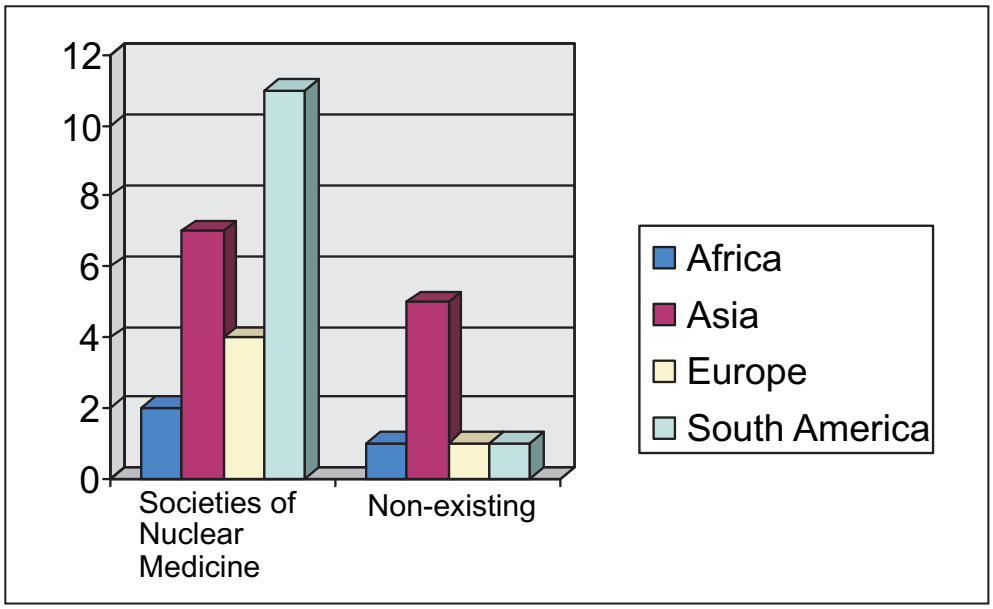

Figure 2. Existence of National Nuclear Medicine Societies.

physicians. That is the most prominent observation regarding the practice of therapeutic nuclear medicine. However, other practitioners like oncologists, endocrinologists, radiologists or rheumatologists may also perform therapeutic procedures specific to their respective specialties (e.g., radioiodine therapy for benign thyroid diseases by endocrinologists, radiosynovectomy by rheumatologists). It is very uncommon practice for a scientist or a technologist doing therapeutic nuclear medicine by themselves; most often they assist the nuclear physicians in doing the therapy.

5 - Education in Nuclear Medicine

In most respondent countries (more than 78%), education in Nuclear Medicine is provided for physicians as formal post-graduates studies (i.e., after the usual medical degree course). This period, commonly referred to as residency or registrarship, lasts between 2 and 4 years and culminates into a Postgraduate University Degree in Nuclear Medicine or Specialty Board Examination for appropriate certification. In some countries, within this residency or registrarship some other medical specialty training is a pre-requisite (e.g., rotations in Internal Medicine, Endocrinology or in Radiology and its subspecialty multimodality imaging like ultrasound, CT, MRI, etc).

A governmental certificate of radioprotection is also required and is often included in the formal training of Nuclear Medicine. In very few countries, only the governmental certificate of radioprotection is required to perform clinical Nuclear Medicine.

While most countries do not allow non-Nuclear Medicine physicians to practice Nuclear Medicine, there are situations where they have come to be involved in Nuclear Medicine imaging. In these situations (e.g., with very few, or inadequately-trained, practicing nuclear physicians) informal training or exposure to Nuclear Medicine seems to suffice. In these countries with only informal training or exposure is available, clinical training is required.

Radiation safety training is also mandatory to physicians who have not had formal training. As mentioned above, it is possible for non-specialists in Nuclear Medicine (endocrinologists, rheumatologists) to practice therapeutic nuclear medicine in some countries which lack manpower in clinical nuclear medicine; but only after following clinical radiation safety training. This requirement is imposed either by the government or by the concerned Nuclear Medicine facilities.

6 - Setting of Nuclear Medicine Practice

While Nuclear Medicine is practised more in the public (or governmental) setting, there are more than 50% of the respondent countries having private facilities and allowing private practice. In fact, private facilities have different levels of clinical nuclear medicine activities varying from 10% - 70%. Most of the facilities (whether public or private) perform Nuclear Medicine therapy on outpatient basis.

The number of beds devoted to radiopharmaceutical therapy even varies as most of them are located in Nuclear Medicine departments. However, in-patients facilities for radiopharmaceutical therapy exist in other departments like those of Oncology and Endocrinology. In a majority of the countries, Nuclear Medicine therapy is practiced mostly on out-patient basis especially for the radioiodine treatment of Graves' disease.

7 - Types of Therapeutic Procedures

By far, the treatment of benign thyroid diseases remains the most frequent indication for therapeutic Nuclear Medicine. The treatment of hyperthyroidism comprises at least 60% (in some places, reaching 80%) of the total therapeutic Nuclear Medicine procedures). Thyroid cancer is the second most frequent indication (30%) followed by bone pain palliation (5%), and radiosynovectomy (1%). Lymphomas, solid tumours, haematological diseases and others are done only on occasions. Intra-arterial application of radiopharmaceuticals for the treatment of cancer, intra-

pleural, intra-pericardial, intra-peritoneal, intra-thecal applications and direct intra-tumoral or intra-cystic applications are rarely done. MIBG therapy for neural crest tumors, treatment of neuroendocrine and other tumors with radio-labeled peptides, radioimmunotherapy of lymphoma are done only in very few centres in some of the more advanced developing countries.

8 - Radiopharmaceuticals

Iodine-131 is the most-frequently used radiopharmaceutical for therapy in Nuclear Medicine, used in about 90% of therapeutic procedures (benign and malignant thyroid diseases). Yttrium-90, Rhenium-186, Rhenium-188, Samarium-153 represent the remaining radiopharmaceuticals used as indicated

Discussion

Human resources in Nuclear Medicine

The use of Nuclear Medicine procedures is getting more and more widespread and their importance is still growing day after day. They require more often specialized team in Nuclear Medicine with sufficient background in radiation safety and adequate clinical education. Nuclear Medicine is globally well-practised in most of the respondent countries with dedicated training facilities. Post-graduate studies (residency) in Nuclear Medicine last from 2 to 4 years and are completed in many countries together with certification in radiation safety.

The Nuclear Medicine physician is the central person involved in the development of Nuclear Medicine in many countries. There is a direct relation between the number of Nuclear Medicine physicians in a given country and its level of development and variety of procedures possibly done locally. National societies of Nuclear Medicine exist in most of the countries (72%) with varying numbers and categories of membership (regular, affiliate, associate, etc) reflecting the different sectors involved (physicians, technologists, radiopharmacists, physicists and other scientists). To be sure, these allied medical professionals can have their own associations existing side-by-side with the national society. However, in some countries, Nuclear Medicine is organised as a section of another society (most often that of Radiology). Notwithstanding, nuclear physicians and technologists represent the two most important categories of staff extensively involved in the practice of Nuclear Medicine with a total of 70% more or less equally distributed in each category. It is noteworthy that Nuclear Medicine has been assimilated into the clinical specialties and that tendency is expected to be reinforced in the coming years with new therapeutic procedures and the expansion of PET imaging.

Technologists are more and more required for the practice of clinical nuclear medicine. It is likely that this category of staff will assume an ever-increasing role with the implementation of regular and new quality assurance programmes in Nuclear Medicine departments. On the other hand, physicists and radiopharmacists constitute only around 20% of society membership, or even not represented at all, (except in some countries like China, India or Iran). Their contribution and impact in the quality and outcomes of clinical Nuclear Medicine procedures are measures of the strength of departments of Nuclear Medicine. In the few countries where there is apparent lack of qualified Nuclear Medicine physicians, clinical Nuclear Medicine could be performed by non-specialists. These non-specialists in Nuclear Medicine are required more often to undergo some training programs in radiation safety or radioprotection.

Setting of Nuclear Medicine

Nuclear Medicine is practised either in public or private hospitals. The percentages of practice between public and private institutions are highly variable and probably dependent on the existing facilities and local regulations. However, since private facilities are present almost everywhere their contribution is evident and indicates their growing importance and influence in national health systems. It is expected that in the future more and more private facilities will fill the gap between what are needed and what can be offered.

Specific Therapies in Nuclear Medicine

Nuclear Medicine therapy requires a rigorous practice and needs specialised and skilled staff to carry out an increasing array of procedures. In most respondent countries, the treatment of hyperthyroidism and thyroid cancer are, by far, the two most frequent therapeutic procedures performed in every department. Radioiodine therapy for hyperthyroidism and radioiodine ablation in thyroid cancer constitute around 90% of the total procedures done in these countries.

The treatment of hyperthyroidism with radionuclides is a simple procedure and can be done on an out-patient basis. The most frequent way of calculating the activity to be administered to the patient is represented by the empiric method. The use of fixed doses, varying from low dose [5-10 mCi], medium dose [10-15 mCi], and high dose [15-30 mCi] is followed frequently by those giving radioiodine therapy with others doing dosimetric calculations based on gland size and uptake measurements. The choice between using fixed doses versus calculated doses depends basically on the philosophy of the physician whether he aims to render the patient euthyroid as far as possible, or hypothyroid to be immediately followed by substitution therapy. Thyroid uptake and software calculation of the activity are done only in few countries. The tendency to use the empiric method is probably due to the lack of medical physicists and the length of the procedure.

The second most frequent therapeutic Nuclear Medicine procedure is the treatment of thyroid cancer. This indication represents an increasing number of therapies and confirms the classical interest of Nuclear Medicine in thyroid cancer. In almost all countries, radioiodine treatment of thyroid cancer requires hospital facilities with dedicated beds. Majority of these hospital units are managed by nuclear physicians and are supplied with additional equipments for safety and radioprotection. Doses to ablate remnants typically consist of 100 mCi while doses to ablate metastatic disease range from 150-200 mCi. Endogenous stimulation (i.e., withdrawal of thyroid hormone followed by a rise of TSH) is more often used than recombinant TSH due to the high cost of the rTSH. In a few places, I-131 therapy of thyroid cancer can be done by non-nuclear physician specialists like radiation oncologists or endocrinologists.

The remaining indications for therapeutic Nuclear

Medicine comprising 10% of the total procedures are bone palliation therapy (5%) and radiosynovectomy (1%). For bone pain palliation, Samarium-153 EDTMP is the most common radiopharmaceutical used. Other radionuclides used are Phosphorus-32, Strontium-89 and Rhenium-188. For radiosynovectomy or radiosynoviorthesis, Yttrium-90 or P-32 colloids are commonly used. By far, the knee joint is the most frequent site treated by this procedure. The most common constraint causing the slow development of radiosynoviorthesis is the insufficient training of nuclear physicians or rheumatologists on this procedure and the lack of awareness among referring physicians.

Hepatocellular carcinoma (HCC) is one of the dreaded and most common cancers in the world, constituting more than 5% of all cancers. It is the third leading cancer killer after lung and stomach cancers. The disease is highly prevalent in most of the developing and least-developed countries of Asia and Africa. Most HCCs are un-resectable when diagnosed, requiring palliative therapy. A number of palliative therapies have been developed. Radionuclide therapy forms an important aspect of the palliative treatment of liver cancer. Radio-conjugates like I-131/Re-188 Lipiodol, Y-90 labeled Microspheres (Glass bead TheraSpheres) and Y-90 labeled SIR-Spheres (Polymerase beads) are being used in few centers in the developing countries. Interestingly, many developing countries like Mongolia, Vietnam, Colombia, Philippines, India, Pakistan have developed expertise in the in-house preparation of Re-188 Lipiodol and its use in the treatment of HCC. Re-188 Lipiodol has clear advantage over other radio-conjugates like TheraSpheres and SIR-Spheres with regard to cost as well as efficacy. Unfortunately lack of industry support has prevented this product from gaining widespread popularity. It is hoped that WRPTC may play an important leadership role in promoting and popularizing the use of Re-188 Lipiodol therapy for liver cancer.

The remaining therapeutic procedures are seldom done and only in very few respondent countries. The treatment of lymphomas, solid tumours, haematological diseases and others are done only occasionally. The use of radionuclides for intra-arterial application in the treatment of cancer (liver cancer), and its intra-pleural, intra-pericardial, intra-peritoneal, intra-thecal applications and direct intra-tumoral or intra-cystic applications are also done even more episodically. The therapy with MIBG for neural crest tumors, the treatment of neuro-endocrine and other tumors with radiolabeled peptides, and the radioimmunotherapy of lymphoma are done only in few places. This is mostly due to non-availability of radiopharmaceuticals in the developing countries and their prohibitive cost when imported.

Cost of Radiopharmaceutical Therapy

Radiopharmaceutical therapy is, admittedly, expensive, with the respondent countries showing great variability in the cost of the procedures. Radioiodine therapy for hyperthyroidism is charged anywhere from as low as US$ 25 (for a 10 mCi dose) in Uzbekistan to US$ 1,095 (for a 30 mCi dose) in Libya. The average cost in most countries, however, hovers $ 173 for a 10 mCi dose, $ 265 for a 20 mCi dose, and $ 298 for a 30 mCi dose. These costs are charged on outpatients.

In-patient charges for ablation of thyroid cancer remnants and metastasis increase exponentially to cover room and board and possibly whole body imaging. A 3-day admission using 200 mCi ablation dose would cost an average of $ 1,070 in most countries. Thyrogen intervention alone costs a substantial $ 1,245, thus effectively discouraging its widespread use in most developing countries.

Costing for bone pain palliation across the respondent countries also revealed great differences in the price of different radiopharmaceuticals, with P-32 being the cheapest to use at $ 286 per dose, and Sr-89 the most expensive at $ 1,865 per dose. Radiosynovectomy using Y-90 costs $ 1,480; haematological diseases $ 1, 090; neural crest tumours treated with MIBG would cost $ 2,580. By far, the most expensive therapy is the radioimmunotherapy of lymphoma: whether with I-131 Tositumomab (Bexxar) costing $ 10,200 or with Y-90 Ibritumomab (Zevalin) at $ 22,280. It may be noted that in many developing countries like India, Indonesia, Malaysia, Pakistan, Peru, etc., with active nuclear energy programs, several reactor-produced radionuclides like I-131, P-32. Sm-153 EDTMP could be available at fraction of the price quoted above. The prices submitted by the respondent countries are as of 2007 and may be exclusive of professional fees (in countries where the health systems allow separate charging). Notwithstanding, these figures indicate a major constraint faced by patients in most developing countries.

On the role of Rhenium generators

The particular and potential role of the Tungsten/Rhenium-188 generator has been especially discussed and highlighted on several occasions and meetings of Nuclear Medicine therapy. The physical properties of Rhenium-188 as well as its reasonable cost are its advantages. However, its use as a therapeutic agent throughout the world has not been realized as expected and most of the studies done using Rhenium-188 are in the framework of projects or evaluation studies supported by research funds. One of the greatest advantages of this radionuclide is its on-site availability within the nuclear medicine facilities on demand. One generator, when procured could last for over six months or more. Besides, the multi-modality applications of Rhenium make it even more attractive. For example Re-188 may be used in the treatment of HCC (Re-188 Lipiodol), bone pain palliation (Re-188 HEDP), Radiosynovectomy (Re-188 Colloid), intravascular radionuclide therapy to prevent restenosis (Re-188 perrhenate), etc. It is hoped that the nuclear medicine community, especially in developing countries would soon realize the potentials of Re-188 as a therapeutic agent.

On the role of WRPTC

The WRPTC [The future World Association of Radionuclide and Molecular Therapy (WARMTH)] is viewed by the respondent countries as having a distinct role to play in the promotion of radiopharmaceutical therapy particularly in developing countries. Aside from holding consensus conferences like the International Conferences on Radiopharmaceutical Therapy (ICRPs), it can conduct multi-centre studies and coordinated researches; formulate treatment guidelines, protocols and standards; identify nodal institutions for optimal resource management by way of channelized referrals; and identify experts for training the manpower in respondent countries or in developing

distance education for radiopharmaceutical users. Moreover, the WRPTC can act as advocate to radiopharmaceutical companies to produce cheaper products; act as consultant for international institutions and governments of UN Member States; and as a channel for unified communication among radiopharmaceutical consumers.

Conclusion

WRPTC has initiated a timely survey of the status of Nuclear Medicine practice in general and, more particularly, therapeutic applications in a number of developing countries scattered throughout the world. The survey revealed a number of information related to the availability, distribution, education and training of its human resources as well as the organizational set-up of Nuclear Medicine facilities. Data indicate the development and progress achieved so far with the invaluable contribution of scientific organizations and international agencies. Nuclear Medicine therapeutic applications have been largely in the realm of the thyroid because of the widespread use and availability of Iodine-131 combined with its very reasonable cost. While important strides have been made for the propagation of other Nuclear Medicine therapeutic applications, there remain a lot of issues to be addressed particularly on such matters as cost and availability, awareness of the referring medical community, human resources development and training.

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