Inorganics in Nuclear Medicine

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Abstract: More than 130 radionuclides are being used worldwide for therapeutic, diagnostic, and preventative purposes in the medical field. Using radionuclides, different organs can be imaged, and malfunction revealed. The most commonly used radionuclide in diagnosis by SPECT is technetium-99m (^{99m}Tc), with some 40 million procedures yearly, almost 80% of all nuclear medicine procedures in the world. The Positron Emission Tomography (PET) is sophisticated and more precise technique using isotopes, like ^{18}F produced in a cyclotron. The synthesis and use of organic molecules and their labeling with radionuclides are currently dominating in new radiopharmaceutical development. On the other hand inorganics (^{60}Co, ^{131}I and ^{192}Ir) are still playing unique role in nuclear medicine. In this article more commonly used radionuclides and their inorganic forms in nuclear medicine are described.

Keywords: Radiopharmaceuticals, Radiotherapy, Radioactive sealed sources, SPECT, PET, Inorganics.

1. INTRODUCTION

In Nuclear medicine radiation is used to gain diagnostic information about the functioning of a patient's specific organs, or to cure them. The use of radionuclides in solution form began in the late 1930s with attempts to treat blood diseases such as polycythaemia vera with the aid of phosphorus-32 (^{32}P) labeled sodium hydrogen phosphate [1]. At the same time, Iodine-131 (^{131}I) as sodium iodide was being trialled as a treatment for cancer of thyroid [2]. Using gamma (γ) emitting radionuclides, various organs such as thyroid, bones, heart, brain, liver, spleen etc, are imaged, and malfunction in organ revealed. Radiation is also used to cure diseased organs, or tumours. Over ten thousand hospitals worldwide use radionuclides in medicine, and about 90% of the procedures are for diagnostic purposes. The most common radionuclide used in diagnosis is technetium-99m (^{99m}Tc); the daughter product of molybdenum-99 (^{99}Mo). Approximately 40 million procedures are performed yearly, accounting for 80% of all nuclear medicine procedures worldwide [3]. Nuclear medicine was developed in the 1950s by physicians with an endocrine emphasis, initially using ^{131}I to diagnose and then treat thyroid disorder [4]. The Positron Emission Tomography (PET) is a sophisticatedand, more accurate technique using isotopes produced in accelerators. PET is a functional imaging technique that produces a three-dimensional (3-D) image of functional processes in the human body. PET's most important clinical role is in oncology, with fluorine-18 (^{18}F) as the prime radiotracer, since it has proven to be the most accurate non-invasive method of detecting and evaluating most cancers [5]. Several radionuclides have been developed and tagged into appropriate carriers for targeted radiotherapy and diagnosis. As radionuclide carriers, chelating chemical agents, monoclonal antibodies, peptides, biomolecules, biodegradable particles, colloids, etc., have been investigated as radiopharmaceuticals for therapeutic nuclear medicine. The synthesis and use of organic molecules and their labeling with different radionuclides are currently dominating in new radiopharmaceutical development [6]. On the other hand inorganics are still playing unique role in nuclear medicine [7]. Inorganics include metals, salts, compounds made from single elements and any other substance that don't contain carbon bonded to hydrogen. In this article more commonly used radionuclides and their inorganic forms in nuclear medicine are described. It includes decay characteristics, production mode and medical applications etc., of the radionuclides.

2. RADIONUCLIDES FOR DIAGNOSIS AND THERAPY

Radioisotopes are used in diagnostic studies via emission tomography (SPECT and PET). Diagnostic techniques use radiotracers which emit γ rays from within the body. These tracers are usually short-lived linked to chemical compounds which permit specific physiological functions to be checked. The radio labeled compounds are injected, inhaled or given orally. The first type is where single photons are detected by a γ-camera which can view certain organs from many different angles. In the second type a positron-emitting radionuclide is introduced, usually by injection, and accumulates in the target tissue. As it decays it emits a positron ($β^+$), which promptly combines with a nearby electron resulting in the simultaneous emission of two identifiable γ rays (511

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keV) in opposite directions. These are detected by a PET camera and give very accurate indication of their origin.

The major criteria for the selection of a radionuclide for therapy are suitable decay characteristics and biochemical behavior. Regarding the decay properties, the desired half life is between few hours and several days; the emitted particles (β^-, α, and Auger electron) of radiation should have an appropriate linear energy transfer (LET) value and range in the tissue. The ratio of target to non target tissue should be high.

2.1. Boron Neutron Capture Therapy

In 1935, Taylor and Goldhaber described that boron-10 (^{10}B) nuclei could capture thermal neutrons resulting in splitting of the boron-11 (^{11}B) nuclei into helium-4 (α particles) and lithium-7(^{7}Li) ions [8].

$$^{10}B + n_{th} \rightarrow [^{11}B] \rightarrow \alpha + {}^{7}Li + 2.31 \text{ MeV}$$
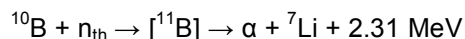
In 1936, Locher, a scientist at the Franklin Institute in Pennsylvania, realized the therapeutic potential of the reaction and products and proposed that boron neutron capture could be used for the treatment of cancer [9, 10]. Sweet first suggested the discovery for the most malignant brain tumors in 1951[11], and a trial of the therapy against glioblastoma multiforme using borax (sodium borate) as the boronating agent was reported in a collaboration between Massachusetts General Hospital and Brookhaven National Laboratory in 1954 [12].

Both α particles and ^{7}Li ions produce closely spaced ionizations in the immediate vicinity of the reaction, with a range of approximately 5–9 µm; the diameter of one cell. Their lethality is limited to ^{10}B containing cells. Boron Neutron Capture Therapy (BNCT), therefore, can be considered as both a physically and biologically targeted type of radiation therapy. The success of BNCT is dependent upon the selective delivery of sufficient amounts of ^{10}B to the tumor with only small amounts localized in the surrounding normal tissues [13]. Various ^{10}B delivery agents have been synthesized [14], but only two of these currently are being used in clinical trials. The first, primarily used in Japan is a polyhedral borane anion, sodium borocaptate or BSH ($Na_2B_{12}H_{11}SH$), and the second is a dihydroxyboryl derivative of phenylalanine, referred to as boronophenylalanine (BPA). The BPA has been used in clinical trials in the United States, Europe, Japan, Argentina and Taiwan. Following administration of either BPA or BSH by intravenous infusion, the tumor site is irradiated with neutrons, the source of which has been specially modified nuclear reactors. Up to 1994, low-energy (< 0.5 eV) thermal neutron beams were used in Japan [15], but since they have a limited depth of penetration in tissues, higher energy (>0.5eV<10 keV) epithermal neutron beams, which have a greater depth of penetration, have been used in clinical trials in the United States [16, 17], Europe [18, 19], and Japan [20, 21]. Boron containing nano particles and boron carbide particles delivery agents has also been evaluated [22].

The BNCT is a highly selective type of radiotherapy that can target the tumor at the cellular level without causing radiation damage to the adjacent normal tissues. By BNCT doses up to 60–70 Gy can be delivered to the tumor cells in one or two applications compared to 6–7 weeks for conventional external beam photon irradiation.

2.2. Cesium-137

The half life of Caesium-137 (^{137}Cs) is 30.1 years and disintegrates by beta (β^-) emission to metastable Barium-137m (^{137m}Ba) (94.4% of the time), emitting an electron with energy of 512 keV. ^{137m}Ba releases a γ photon as it returns to its ground energy state, with energy of 662 keV. Fission yield of ^{137}Cs is ~ 6% by fission reaction of various isotopes of thorium, uranium, and plutonium [23]. Generally ^{137}Cs is produced by fissioning uranium-235 (^{235}U) nuclei and then chemically separating the cesium from the irradiated nuclear fuel or targets. Separated ^{137}Cs sold internationally is produced only by the Production Association Mayak (PA Mayak) in the Chelyabinsk region of Russia and sold through REVISS; a U.K.-based company[24]. It is supplied as cesium chloride, a crystalline salt. Cesium-137 teletherapy units are designed for treatment of different source to skin distances (SSD) [25].

Radioactive sealed sources of ^{137}Cs as CsCl are manufactured either as an insoluble powder, ceramic microspheres or a solid ceramic rod. The radioactive material is then doubly encapsulated in stainless steel, with each layer welded shut. ^{137}Cs replaced radium-226 (^{226}Ra) for temporary interstitial / intracavity low dose rate brachytherapy due to its stable daughter product and improved radiation protection features.

The ^{137}Cs radioactive sealed source is widely used for the treatment of gynecological cancer [26]. Uses of

different strengths sources of ^{137}Cs are essential to achieve the desired dose distribution. In modern remote afterloading devices iridium-192(^{192}Ir) is preferred radionuclide.

Low dose-rate (LDR) systems use multiple radioactive sources, together with inactive spacers to get typical dose rates of about 0.4–2 Gy/h. On the other hand, high dose-rate (HDR) devices use a single source of ^{192}Ir, with a typical radioactivity of 10-20 Ci (370-740 GBq), delivering treatment dose rates exceeding 2 Gy/min. Oral tongue carcinoma is highly curable when treated with radiation therapy, especially via interstitial brachytherapy [27].

2.3. Chromium-51

Chromium-51(^{51}Cr) has a half-life of ~ 27.7 days, disintegrates by electron capture (EC) resulting in emission of γ photons with energy of 0.320 MeV (9.83%) [28]. The published literature shows that 2 production methods for ^{51}Cr are practiced. The first one is the direct neutron bombardment of enriched or natural $^{50}Cr(n,\gamma)^{51}Cr$ [29], while the second one is based on Szilard-Chalmers reaction using specially chosen chromium compounds [30, 31]. Sodium chromate (^{51}Cr) is useful for determining red blood cell (RBC) volume or mass, studying RBC survival time (in conditions such as hemolytic anemia), and evaluating blood loss [32]. The suggested dose range in the 70 kg patient for determination of RBC volume or mass is 0.37 - 1.11 MBq (10-30 µCi). For study of RBC survival time is 5.55 MBq (150 µCi) while evaluation of blood loss needs 7.40 MBq (200 µCi). This drug has not been found by Federal Drug Administration (FDA) to be safe and effective, and this labeling is not recommended by FDA of USA [33].

2.4. Cobalt-60

Cobalt-60 (^{60}Co) has a half-life of 5.27 y. [60]Co is produced in a reactor (Research or Power) by $^{59}Co(n,\gamma)^{60}Co$ nuclear reaction. It undergoes β⁻ decay emitting an electron and a neutrino and emits two γ rays with each decay; one at 1173 keV and one at 1333 keV [34]. Cobalt-60 teletherapy devices are used to treat malignant tumors in human body. The teletherapy radiation source is kept at a distance from the patient and a beam of radiation is directed to the tumor. Teletherapy machines contain 37 to 550 TBq (1,000 to 15,000 Ci) and, at least in the United States virtually all (247 of 248) use cobalt-60 (one uses cesium-137) [35]. The Gamma Knife® competes with linear accelerator machines for the treatment of centimeter-sized brain tumors in areas of the brain where conventional surgery generally is not possible. There are approximately 200 Gamma Knife® devices worldwide, including at least 104 in the United States. Elekta, a Swiss/Swedish company is the sole manufacturer of the Gamma Knife®, while MDS Nordion is the main source for the small cobalt-60 sealed sources. A Chinese company, Gamma Star, has begun to market a competing device and Elekta is now selling a new version of the Gamma Knife® with ^{192}Ir sources, instead of the 201 encapsulated ^{60}Co sealed sources used in previous models [35]. Cobalt-60 teletherapy machines provide relatively high energy γ rays for therapy which are ideally suited for treatment of head and neck carcinomas and other superficially located tumors, such as breast cancers and soft tissue sarcomas of extremities. [60]Co sources are not adequate for treatment of deep seated tumors and have the added disadvantage of decreasing output with decay of source and the need for source replacement within 5-7 years, due to 5.27 y half-life of [60]Co.

In 1962 Walstam [36] introduced the first concept of a remote afterloader equipped with [60]Co. Since its introduction, ^{60}Co has achieved tremendous success and has continued to evolve to support modern HDR brachytherapy needs. Cobalt-60 has been shown to be a good choice for treating gynecological, rectal, prostate, breast, esophagus, skin, and other body sites [37-41]. The treatment with ^{60}Co leads to lower dose to organs at risk (OAR) than with [192]Ir. Due to its higher mean energy of 1.25 MeV, less backscatter is produced and therefore, ^{60}Co shows a more linear radial dose function than ^{192}Ir with 0.37 MeV. Due to the long half-life of ^{60}Co, the source can be used for up to 5 years which means that during the recommended working life of a single ^{60}Co source, approximately 20 source exchanges of ^{192}Ir would have to be performed.

Copper-64

Copper-64(^{64}Cu) has a half-life of 12.7 h. It disintegrates by three processes; positron emission, electron capture, and β⁻ decays. The decay characteristics; β⁺ 653 keV (17.8 %); β⁻ 579 keV (38.4 %) allow the positron emission tomography (PET) imaging as well as targeted radiotherapy of cancer. The nuclear reactor production routes result in either low specific activity by $^{63}Cu(n,\gamma)^{64}Cu$ or high specific activity by $^{64}Zn(n,p)^{64}Cu$ reactions [42, 43]. Large quantities of ^{64}Cu with high specific activity are usually

produced using a cyclotron via $^{64}Ni(p,n)^{64}Cu$ nuclear reaction [44, 45].

It was supposed that Wilson Disease patient may have increased uptake of Cu in brain tissue and pathologic analysis of the brain tissue may show gliosis and neuronal loss in association with increased Cu deposition. $^{64}CuCl_2$ PET may serve as a straightforward, noninvasive and quite simple tool for the diagnosis of Wilson Disease [46]. Currently nanodevices/nanoparticles [47] have been used in biomedical field investigating new and improved diagnosis and therapy agents and with sufficient development, the ^{64}Cu is likely to become an important radionuclide in nuclear medicine in coming years.

2.5. Fluorine-18

Fluorine-18 (^{18}F) has a half-life of 109.7 min and decays by positron (β^+) emission. 97 % of the decay results in emission of a β^+ with a maximum energy of 0.633 MeV and 3% of the decay results in EC with subsequent emission of characteristic X-rays of oxygen. The principal photons useful for diagnostic imaging (positron emission tomography-PET) are the 0.511 MeV γ photons, resulting from the interaction of the emitted β^+ with an electron. ^{18}F atom decays to stable ^{18}O-oxygen. There are many charged particle reactions that are used to produce ^{18}F in accelerator [48]. The widely used method consists of irradiating a small volume of enriched $H_2^{18}O$ in a metal target with protons of energies from near threshold, approximately 3-20 MeV [49-51].

According to United States Pharmacopoeia (USP), Sodium Fluoride (^{18}F) injection is used for diagnostic positron emission tomography (PET) imaging of bone to define areas of altered osteogenic activity. With clinical experience in ~ 100 children, weight based doses (2.1 MBq/kg) ranging from 19 MBq to 148 MBq (0.5 mCi to 4 mCi) were used. Dose for adults are 300 MBq/mL to 450 MBq/mL (8 mCi/mL to 12 mCi/mL) as an intravenous injection. Fluoride (^{18}F) ion normally deposits in the skeleton in an even fashion, with greater accumulation in the axial skeleton (*e.g.* vertebrae and pelvis) than in the appendicular skeleton and greater accumulation in the bones around joints than in the shafts of long bones [52-55].

2.6. Iodine-123

Iodine-123 (^{123}I) has a half-life of 13 h and primarily a gamma-emitter. Iodine-123 decays by EC to emit a high-speed internal conversion electron, which is not a β^- particle, but this could little cellular damage due to the nuclide's short half-life and the relatively small fraction of such disintegration events. ^{123}I also disintegrates decays to emit a 0.159 MeV γ ray, which is quite suitable for gamma camera imaging. The ^{123}I is widely used for thyroid imaging to evaluate the anatomic and physiologic function of the thyroid disorders [56, 57].

The ^{123}I is mainly produced by two routes. The first one is the direct route and the second is through the xenon-123 (^{123}Xe) precursor. The advantage of ^{123}Xe production route is that the xenon can be isolated from the irradiated target material and allowed to decay in isolation, which gives the ^{123}I with almost negligible contamination from other radioiodine. The most common reaction used for the production of ^{123}I has been the $^{124}Te(p, 2n)$ ^{123}I reaction employing highly enriched ^{124}Te [58].

2.7. Iodine-124

Iodine-124 (^{124}I) is a proton-rich isotope of iodine with a half-life of 4.18 days. Its modes of decay are about 75% electron capture and 25% positron emission. The use of ^{124}I is becoming more widespread. Iodine-124 has potential as both a diagnostic and a therapeutic radionuclide. The main use of iodine-124 is to directly image the thyroid using positron emission tomography [59]. Iodine-124 can also be used as a PET radiotracer with a usefully longer half-life compared with fluorine-18. In this use, the nuclide is chemically bonded to a pharmaceutical to form a positron-emitting radiopharmaceutical, and injected into the body, where again it is imaged by PET scan (60-62).

The best nuclear reaction for the production of ^{124}I is the $^{124}Te(p, n)^{124}I$ reaction on enriched ^{124}Te [63].

2.8. Iodine-125

Iodine-125 (^{125}I) has a physical half-life of ~60d, and disintegrates by 27-32 keV Te X rays and 35 keV γ ray). It is a radionuclide of iodine, which has major uses in biological assays (*e.g.*, radioimmunoassay-RIA) and as a radioactive sealed source in radiation therapy as brachytherapy (prostate and brain tumors treatment). The neutron irradiation of ^{124}Xe by n,γ reaction produces ^{125}I in a nuclear reactor. The separation of Xe and I is carried out by dry distillation technique [64]. Due to better radiation penetration and shorter half-life

[123]I is preferred over ^{125}I for thyroid imaging. In addition to its use in biological assays [65], ^{125}I is generally used by radio-oncologists as brachytherapy to treat cancer at sites other than the thyroid, such prostate cancer and brain tumors [66, 67]. When the radioactive sealed source of ^{125}I is used in therapy, it is encapsulated in titanium (Ti) seeds and implanted in the area of the tumor, where it remains. The low energy of the γ spectrum of ^{125}I limits radiation damage to tissues far from the implanted seeds.

Iodine-125 was finally introduced in interstitial cancer therapy, such as prostate, lung cancer and lymph nodes in 1965 [68]. Since 1979 it has been applied for treatment of brain tumours. Even though the physical and biological characteristics make ^{125}I implants quite attractive for minimal invasive treatment damages, the place for stereotactic brachytherapy is still poorly defined [69].

2.9. Iodine-131

Iodine-131 (^{131}I) has a half-life of 8.025 days and disintegrates with β^- (100%) emission to stable [131]Xe (99%) and to 11.8 d [131m]Xe (1%), with an average β^- particle energy of 182 keV. The decay of ^{131}I is followed by emission of high intensity gamma ray at 0.365 MeV (81.5%). Other γ ray include 0.637 MeV (7.16%), 0.284 MeV (6.12%), 0.080 MeV (2.62%), and several weaker γ rays [70].

Saul Hertz in 1941 reported the therapeutic use of ^{131}I to treat hyperthyroidism from Grave's disease [71]. The usual sodium iodide-^{131}I dose range is 148 to 370 MBq (4 to 10 mCi) for the treatment of hyperthyroidism, [72]. Higher doses may be effective for the treatment of toxic nodular goiter and other peculiar situations. For thyroid carcinoma, the usual sodium iodide-^{131}I solution therapeutic dose is 3700 to 5550 MBq (100 to 150 mCi) [73].

The post-operative residual thyroid tissue ablation is performed by a usual dose of 1850 MBq (50 mCi) [74].

Sodium iodide-^{131}I solution given orally is rapidly absorbed and distributed within the extracellular fluid of the body. The iodide is accumulated in the thyroid via the sodium/iodide symporter, and subsequently oxidized to iodine. The β^- particles emitted by ^{131}I destroy the thyroidal tissue. The therapeutic effects of ^{131}I are a result of the ionizing radiation absorbed by the thyroidal tissue. Approximately 90% of local irradiation dose from ^{131}I is the result of β^- radiation and 10% is the result of γ radiation.

Iodine-131 is generally produced in a reactor by the neutron irradiation of tellurium according to the nuclear reaction $^{130}Te(n, \gamma)$ ^{131}Te $\beta^- \rightarrow$ ^{131}I. The iodine is separated from the TeO_2 target material by dry distillation technique above 750°C and Te metal by wet distillation methodology [75, 76] absorbed in dilute sodium hydroxide solution. [131]I is also a fission product with a yield of 2.878% from [235]U, An elaborate technology is required for separation of ^{131}I from fission products [77].

2.10. Iridium-192

Iridium-192 (^{192}Ir) is produced by (n,γ) reaction on [191]Ir in a nuclear reactor. [192]Ir has a half-life of 74.2 days and disintegrates to stable platinum-192 ([192]Pt) and emits β^- particles of maximum energy of 672 keV (46%) and γ rays of energies of 604, 468 and 308 keV. The iridium (>99.9 % purity) target is irradiated in a high flux reactor, providing more than $2x$ 10^{14} $n.cm^{-2}.sec^{-1}$ neutron flux density, because specific activity of the irradiated target should be more than 16.8-18.5 TBq/g (450-500 Ci/g). Activity of the ^{192}Ir HDR assembly should be more than 370 GBq (10 Ci) for effective therapy [78]. Low dose rate ^{192}Ir is manufactured in lengths of wire 10-14 cm long and 0.3 mm thick, which can be cut into the desired length for LDR applications. The wires are flexible and inert to body fluid.

The HDR ^{192}Ir sources are composed of platinum/iridium alloy having a 3.5 mm long, 0.6 mm diameter with a high specific activity of [192]Ir. It is coated in 1 mm of platinum, which attenuates any electrons emitted through decay. This capsule is welded to the end of a wire that allows it to be retracted and deployed from within a High Dose Rate remote afterloading device. Iridium-192 HDR brachytherapy is a suitable alternative in the treatment of localized prostate cancer who are not eligible for radical prostatectomy [79].

Traditionally, High Dose Rate after loaders have been based on Ir-192. The high specific activity of iridium allowed very small sources to be used interstitially despite its half-life period. Typically a source exchange is required each 3-4 months to keep the treatment times within the limits required by clinical practice and also because a maximum number of transfers is recommended by the manufacturer. The Cobalt-60 manufacturer claims important economic advantages because of the larger half-life period and the improved technology which allow for less source exchange frequency [80]. The Brachytherapy treatment

may improve the control of local tumor and prolong the survival of patient, when used in deep malignant brain gliomas, by temporary implanted high doses of ^{192}Ir radioactive sealed sources [81].

Catheter-based brachytherapy using ^{192}Ir seeds has shown valuable reduction in the rate of restenosis in patients with coronary in-stent restenosis [82].

Women with locally advanced or recurrent gynecological malignancies treated with the remote afterloader LDR MUPIT applicator can expect reasonable rates of local control that are not operator-dependent [83].

According to published reports, fractionated HDR brachytherapy represent one option for the primary treatment of cervical carcinoma [84].

2.11. Krypton-81m

Krypton-81m (**^{81m}Kr**) has a half-life of 13 sec and is a gas produced from the decay of rubidium-81 (^{81}Rb) having a half-life of 4.6 h [85]. The ^{81m}Kr gas has an ideal γ energy of 193 keV suitable for gamma imaging. Rubidium-81 decays by positron emission and electron capture. The main reaction for the production of ^{81}Rb is the proton reaction of natural krypton [86]. ^{81}Rb solution having certain concentration is fixed on to AG50W-X8 cation exchange column. The cation resin has a high affinity for Rb, while the daughter ^{81m}Kr is eluted by sterile air or sterile water. In the case of water, an adjustment is made with a sodium chloride solution of appropriate concentration [87]. ^{81}Rb/^{81m}kr generators are used either in gaseous form for ventilation imaging or in solution for lung perfusion imaging.

The short half-life of 13 sec implies that inhaled ^{81m}Kr disappears from the alveolar space at a much faster rate by decay than by exhalation. When a patient is breathing air with ^{81m}Kr at a normal respiratory rate, the regional alveolar ^{81m}Kr concentration is at steady state, closely proportional to regional ventilation. Deviation from proportionality occurs in lung compartments with very high or low regional ventilation in relation to resident alveolar volume [88]. This deviation occurs in children with a high ventilatory rate and a high ventilation/volume ratio [89]. During steady-state ^{81m}Kr ventilation, multiple planar imaging or SPECT acquisition can be performed. Very recently, Ventilation/Perfusion SPECT in combination with low-dose CT has been reported [90]. ^{81m}Kr has an advantage that ventilation and perfusion can be imaged

simultaneously as ^{81m}Kr has higher γ energy of 193 keV than technetium-99m (^{99m}Tc) of140 keV, which is used as a perfusion marker [91, 92]. As ^{81}Rb has a short half-life of only 4.6 h, the ^{81}Rb/^{81m}kr generator can be used for 1 day only. Very low radiation exposure to patients makes ^{81m}Kr an alternative to radioactive aerosols and particularly advantageous for use in young children [88].

2.12. Nitrogen-13

The physical half-life of Nitogen-13 (^{13}N) is 9.96 min, hence application is limited and requires an on-site cyclotron production technology. Nitrogen-13 decays by only positron emission (100%) to stable carbon-11 (^{13}C). The end point energy of the β$^+$ is 1.19 MeV. There are several charged particle reactions leading to the production of ^{13}N [93]. The widely used production route is the^{16}O(p, α)^{13}N reaction on water using 16.5 MeV protons [94-96]. Over the past 3 decades ^{13}N labeled ammonia has been used for most of the scientific investigations in cardiac PET imaging. Intravenous injection, typically 10-20 mCi (370–740 MBq) as a bolus is useful in these studies [97, 98]. Two methods are commonly used for ^{13}N-ammonia synthesis. In the first method, the ^{13}N-labeled nitrates/nitrites formed by proton irradiation of water are reduced by either titanium (III) chloride, titanium (III) hydroxide, or Devarda's alloy (an alloy of aluminum 44–46%, copper 49–51%, and zinc 4–6%) in alkaline medium [99]. After distillation, trapping, and sterile filtration, ^{13}N-ammonia is available for injection. In the second method, oxidation of ^{13}N to ^{13}N-nitrates/nitrites is prevented by the addition of ethanol as a scavenger to the target content [100]. The target content is passed through a small cation-exchange column to trap ^{13}N-ammonium ions, and ^{13}N-ammonia is then eluted with physiological saline and filtered through bacteria filter before its use.

2.13. Oxygen-15

Oxygen-15 (^{15}O) is the longest lived (Half-life: 122 s.) of the β$^+$ emitting radionuclide (99.9% β$^+$ emission) of oxygen. The end point energy of the β$^+$ is 1.72 MeV. Oxygen-15 disintegrates to stable ^{15}N. Various charged particle reactions leading to the production of ^{15}O have been described [101]. Oxygen-15 is commonly produced using a deuteron particle reaction on N gas or a proton particle reaction on enriched ^{15}N gas. [^{15}O]-water has also been produced by bombarding natural water using the ^{16}O(p, pn)^{15}O route, with a final purification on an ion exchange column [102]. Oxygen-

15 water is a freely diffusible agent with very high myocardial extraction across a wide range of myocardial blood flows [103]. The degree of extraction is independent of flow and is not affected by the metabolic state of the myocardium. Since oxygen is a freely diffusible tracer, but imaging is challenging due to its high concentration in the blood pool.

2.14. Palladium-103

Palladium-103 (^{103}Pd) has a 17-day half-life and X-ray photon emission at the main energies of 20.07 keV (19.83%), 20.22 keV (37.55%) and 22.71 keV (37.55%) [104].^{103}Pd is commonly produced by cyclotron irradiation of rhodium targets with accelerated protons. This approach allows production of carrier-free ^{103}Pd having near theoretical value of specific activity of 75000 Ci/g (~2.8 10^6 GBq/g) [105].

An alternative approach to ^{103}Pd production is reactor irradiation of isotopically enriched ^{102}Pd.

The low natural isotopic abundance of ^{102}Pd (1,02%) requires the use of moderate to highly enriched ^{102}Pd target material of no less than 50%. Moreover, the low cross-section of ^{102}Pd(n,γ)^{103}Pd nuclear reaction (thermal cross-section is 3.4 barn, resonance integral 10 barn) requires also the use of highflux nuclear reactors, like the HFIR (ORNL, Oak-Ridge, USA) or SM (RIAR, Dimitrovgrad, Russia), to produce high-specific activity ^{103}Pd [105]. The effectiveness of ^{103}Pd brachytherapy in Stage T1 and T2 adenocarcinoma of the prostate has been rvaluated [106]. A review of 123 early stage T1c and T2 prostate cancer patients implanted at Yale University with^{125}I (82 patients) or ^{103}Pd (41 patients) reveals a significantly lower overall complication rate with ^{103}Pd (0%) versus ^{125}I (13%) [107].

2.15. Phosphorus-32

The half-life of Phosphorus-32 (^{32}P) is 14.29 days and it decays solely with the emission of β$^-$ particles, with a mean energy of 0.695 MeV (Emax =1.71 MeV), to stable sulfur. In a reactor ^{32}P is produced by ^{31}P(n,γ) ^{32}P and ^{32}S(n,p)^{32}P reactions. No carrier added ^{32}P is produced by irradiation of sublimed sulfur targets filled in aluminum capsules in a reactor. Dry distillation technique is used for separation of sulfur from ^{32}P [108].

Sodium phosphate (^{32}P) solution must be injected carefully and after intravenous injection a saline flush must be followed to prevent venous thrombophlebitis.

An inadvertently administered subcutaneous injection of Sodium phosphate (^{32}P) may lead to radio-necrosis of the surrounding tissues.

For the palliative treatment of primary proliferative polycythemia and / or essential thrombocythemia, the usual initial intravenous dose is 100 MBq (2.7 mCi)/body surface area (m^2). The use of maximum radioactivity 185 MBq (5 mCi) is recommended, but initial activities of 74-260 MBq (2-7 mCi) have been applied. When hormone treatment, chemotherapy, radiotherapy or any other therapy have failed, the bone pain may be treated by doses of 370-555 MBq (10-15 mCi), administered at 3-4 month intervals, Reduction in bone pain may take a few weeks and it may be associated with increased treatment compliance and reduced used of analgesics. Small intravenous doses of sodium phosphate (^{32}P) generally did not cause pharmacodynamic effects. Phosphorus is nearly1% of total body weight and affects the functioning of bones, red blood cells and the nervous system. The selective accumulation of ^{32}P by the hematological tissues will exert a continuous exposure to the dividing cells which will have a significantly detrimental effect on their survival. The accumulation of phosphate by different tissues is dependent on the existing amount of tissue phosphate, the amount of new tissue matter and the vascularization of the tissue etc, [109]. The treatment of polycythemia rubra vera by using sodium phosphate (^{32}P) was first reported in 1955 [110].

Chromic phosphate (^{32}P) is indicated by intracavity instillation for the treatment of peritoneal and pleural effusions caused by metastatic disease. In the presence of large tumor masses, other forms of treatment may be indicated; however, chromic phosphate-^{32}P may control the effusion when other treatment has failed [111, 112] Bloody effusions may reduce the effectiveness of treatment. Chromic phosphate is indicated by interstitial injection for the treatment of cancer, such as cancer of the ovary (early-stage) and of the prostate [113].

Colloidal chromic phosphate (^{32}P) administered into a body cavity is phagocytized by free macrophages and fixed to the lining of the cavity wall, thus providing local irradiation to the affected area [114]. Usual adult and adolescent dose for Malignant effusions are; Intraperitoneal instillation, 370 to 740 MBq (10 to 20 mCi) and Intrapleural instillation, 222 to 444 MBq (6 to 12 mCi). For treatment of Carcinoma, the Interstitial injection, 3.7 to 18.5 MBq (0.1 to 0.5 mCi) per gram of estimated tumor weight [115]. The FDA has approved

three brachytherapy delivery systems for in-stent restenosis: Cordis Checkmate System™ (iridium-192 seeds for γ radiation), Novoste Beta-Cath System™ (strontium-90 for β⁻ radiation), and the Galileo Intravascular Radiotherapy System™ (phosphorus-32 wire for β⁻ radiation). These systems are intended for use in intracoronary brachytherapy only and all have similar labeling that limits the approved use of the devices to treatment of in-stent restenosis. No devices have been approved or recommended for approval for primary prevention of in-stent restenosis. There are currently no FDA-approved devices for brachytherapy of noncoronary arteries [116]. Lawrence and Tobias' were the first to use radioactive phosphorus (^{32}P) on neoplastic tissues. Later, ^{32}P was used for palliation of pain from bone metastases [117, 118].

2.16. Radium

Radium (Ra) has thirty three known nuclides, with mass numbers from 202 to 234 and all are radioactive [119]. Four radionuclides occur naturally in the decay chains of thorium-232, uranium-235, and uranium-238. These are ^{223}Ra (half-life=11.4 days), ^{224}Ra (half-life=3.64 days), ^{226}Ra (half-life=1600 years), and ^{228}Ra (half-life=5.75 years). Radium-226 is the most long lived radionuclide of Ra, which has a half-life of 1600 years and disintegrates into radon gas. In nature, radium is found in uranium and thorium ores in trace amounts as small as a seventh of a gram per ton of uraninite. In 1898 Marie Curie and Pieree Curie discovered Ra in the form of radium chloride [120]. Natural radium mostly comprises ^{226}Ra and emits mostly α particles, but other steps in its decay chain (the uranium or radium series) emit α or β⁻ particles, accompanied by γ rays [121]. The biological effects of radium were known to some extent from its discovery. Antoine Becquerel became ulcerated by carrying a small ampoule of radium in his waistcoat pocket for 6 hours. Pierre Curie observed skin lesion when attached a tube filled with radium to his arm for 10 hours. These observations raised the question that if Ra can destroy healthy tissue, could it also destroy cancerous tissue [122]?

Kelly, physicians of Johns Hopkins Hospital, a major pioneer used Ra for the treatment of cancer [123]. In 1906, Kelly treated his own aunt but she died shortly after surgery [124]. He used excessive amounts of Ra to treat various tumors and cancers, resulting in the deaths of some of his patients due to high doses of Ra [124]. Kelly inserted a Ra capsule near the affected area then sewed the radium "points" directly to the tumor [125]. Similar technique was used to treat Henrietta Lacks, the host of the original HeLa cells, for cervical cancer [126]. Radium chloride or bromide was commonly used to produce radon gas which was used as a cancer treatment and several of such radon sources were used in Canada during the 1920s and 1930's [127, 128].

Several treatments that were performed in the early 1900s are not used anymore because of the harmful effects like, anaemia, cancer, and genetic mutations caused by RaBr exposure [129].

Now-a-days ^{223}Ra and ^{224}Ra are used as therapeutic agents. Radium-223 dichloride is an α emitter used in the treatment of patients with prostate cancer that is resistant to medical or surgical treatments. This type of cancer lower testosterone and has spread to only bones with symptoms. Radium-223 dichloride is given intravenously slowly, over about 1 minute. The drug mimics calcium (Ca) and forms complexes with the bone mineral at sites of bone metastatses. It then emits α particles, causing the DNA destruction in nearby cells, resulting death of cancer cells in the bone. Radium-223 acts as an internal radiotherapy treatment agent. It is a mildly radioactive and commercially sold by the name of Alpharadin and now has the brand name Xofigo [130].

Although ^{223}Ra is generated in trace amounts by the disintegration of ^{235}U, it is generally made artificially by irradiating natural ^{226}Ra to neutrons to produce ^{227}Ra, which decays with a 42 min half-life to actinium-227(^{227}Ac). Actinium-227 has a half-life 21.8 years and decays via ^{227}Th (half-life 18.7 days) to ^{223}Ra. Hence the decay path makes a generator system of ^{227}Ac/^{223}Ra[131].

^{224}Ra has a half-life of 3.2 days and has been used for many decades to treat ankylosing spondylitits [132]. Recently in Germany, it has been reintroduced and reapproved for ankylosing spondylitits [132]. In the case of ^{224}Ra, long term follow up of patients receiving moderate levels revealed no significant difference in overall cancer incidence or life expectancy compared to a control population [133]. Radium-224 is a natural daughter product in the decay chain of natural ^{232}Th to ^{228}Th [134].

Brachytherapy can be traced historically with applications of ^{226}Ra sources, which involved exposure of the surrounding tissue. Treatment of oral tongue carcinoma has been quite successful when treated with radiation therapy particularly by interstitial

brachytherapy [135]. To make comparison simple, the patients treated by one of the three major sources, [226]Ra, ^{192}Ir and MS-HDR (^{192}Ir) were examined.

2.17. Rhenium-186

Rhenium-186 ([186]Re) has a physical half-life of 3.7 days and it emits a β[-] particle with a a mean energy of 349 keV, maximum energy of 1070 keV, and an average soft tissue range of 1.1 mm. [186]Re also emits 9% abundant γ emission of 137 keV. In a nuclear reactor low specific activity [186]Re can be made available from neutron irradiation of [185]Re [136]. Proton or deutron bombardment of enriched tungsten targets can produce high specific activity [186]Re [137-139].

The use of Re-186-labelled sulfur colloid particles for therapy of rheumatoid arthritis of the synovial joints is quite successful. [186]Re sulphur colloid is suitable for hip, shoulder, elbow, wrist, ankle and subtalar joints.The administered activity and the injected volume of [186]Re sulfide colloid depends on the volume of the joint to be treated [140]. The maximum activity of [186]Re at a single session should be ~ 370 MBq (10 mCi). The use of Re-186-liquid-filled balloons for restenosis therapy has also been evaluated [141]. Rhenium-186-labelled particles are sold commercially in European countries and the supplier recommends [186]Re sulfide colloid, for radiosynovectomy of medium size joints [142].

2.18. Rhenium-188

Rhenium-188 ([188]Re) has a half-life of 16.9 h and emits a β[-] particle with a maximum energy of 2.12 MeV, useful for therapeutic applications. It also emits a 155 keV gamma photon (15%) for gamma camera imaging.

Rhenium-188 can be produced with high specific activity by neutron irradiation of enriched[187]Re in a nuclear reactor [143]. However carrier-free [188]Re as perrhenate is usually obtained from the [188]W/[188]Re generator in the clinic at a certain time. Elution of generator after every 24 hours provides ~60% yields of [188]Re. Alumina based column chromatography generators for [188]W/[188]Re system is generally used and commercially available. Tungsten-188 ([188]W; $T_{1/2}$: 69 d), is reactor-produced by double neutron capture on tungsten-186, which is the parent isotope of [188]Re [144].

A simple method for preparation of Re-188-labelled sulfur colloid is reported [145], which provides a tight particle size range of 86% = 5 µm. The most activity is retained in the liver *via* intravenous or hepatic artery injection. Rhenium-188 sulfide preparations have shown usefulness when injected in tumors and used in radiosynovectomy [146, 147]. [188]Re sulfide colloid is commercially available for radiosynovectomy of large size joints [142].

Re-188-labelled agents for the use of [188]Re liquid-filled angioplasty balloons inflated at low pressure following coronary angioplasty for the inhibition of coronary restenosis by high dose delivery have been evaluated [148, 149]. Angioplasty balloons are filled at low pressure (2-3 atmospheres of inflation pressure) with a solution of [188]Re-perrhenate or Re-ISS-MAG$_3$ following high pressure angioplasty to deliver a dose of 2500-3000 rad at 0.5 mm of depth. Patient studies have been performed at several Institutions in the USA, Europe and Australia.

For vascular radiation therapy or for other applications which require a [188]Re liquid-filled balloons, the pooled experience obtained thus far from several collaborative clinical sites, a total volume of 1.5-2 mL of the rhenium-188 solution with a specific volume (up to 250 mCi/mL) which is required for use in the Catheterization Laboratory. Although the actual balloon volume will probably not be greater than 0.15 - 0.20 mL even for large coronary vessels, the extra volume is required for filling the lines, valves, etc., and to have sufficient back pressure in the inflation syringe [150].

2.19. Rubidium-82

The half-life of strontium-82 ([82]Sr) is parent nuclide with 25 d half-life, while the daughter rubidium-82 ([82]Rb) has a half-life of 1.25 min [151]. Strontium-82 decays via EC, while the daughter, [82]Rb decays 95.5% by β[+] emission, resulting in the production of annihilation radiation of two 511 keV γ rays; and 4.5% by EC, resulting in the emission of "prompt" γ rays of predominantly 0.777 MeV. Both decay modes of [82]Rb lead to the formation of stable [82]Kr nuclide. The only useful charged particle reaction for the production of [82]Sr using protons is the high energy reaction of metallic rubidium target material [85]Rb(p, 4n)[82]Sr [152]. The [82]Sr can also be produced in an accelerator by proton spallation of molybdenum (Mo) with a high-energy 800 MeV proton accelerator, followed by chemical purification technique [153]. Cardiogen-82 generator system contains accelerator-produced [82]Sr fixed on stannic oxide column properly shielded by lead (Pb) provides nonpyrogenic solutions of [82]Rb chloride for injection purposes [154]. The [82]Rb is eluted with 25-

50 mL physiological saline (0.9% NaCl) by a computer-controlled elution pump, connected by intravenous tubing to the patient. The $^{82}Sr/^{82}Rb$ generator is fully replenished every 10 minutes and 90% of available activity of ^{82}Rb can be eluted within 5 minutes since the last elution, making serial imaging every 5 minutes. Rubidium-82 has proven an efficient heart imaging agent for routine clinical usage [155,156]. The recommended adult single dose of ^{82}Rb-chloride injection is 1480 MBq (40 mCi) with a range of 1110-2220 MBq (30-60 mCi). Rubidium is analogous to potassium ion (K^+) in its biochemical behavior and is rapidly extracted by the myocardium proportional to the blood flow. Rubidium cation participates in the sodium-potassium (Na^+/K^+) ion exchange pumps that are present in cell membranes. The intracellular uptake of ^{82}Rb requires maintenance of ionic gradient across cell membranes. Rubidiumb-82 radioactivity is accumulated in viable myocardium reflecting intracellular retention, while the radiotracer is cleared rapidly from necrotic or infarcted tissue [154].

2.20. Strontium-89

Strontium-89 (^{89}Sr) has a half-life of 50.5 d and decays by β^- emission. The maximum β^- energy of ^{89}Sr is 1.463 MeV (100%). The maximum energy of $ß^-$ particles capable of penetrating in tissue is approximately 8 mm**.** High specific activity and no-carrier-added ^{89}Sr can be produced by irradiating the natural yttrium in the fast neutron flux of a reactor via $^{89}Y(n,p)^{89}Sr$ reaction. Low specific activity ^{89}Sr can also be produced via $^{88}Sr(n,\gamma)^{89}Sr$ reaction in a reactor [157]. Following intravenous injection of $^{89}SrCl_2$ behave like their calcium analogs, clearing rapidly from the blood and selectively localizing in bone mineral. $^{89}SrCl_2$ is retained in metastatic bone lesions much longer than in normal bone, where turnover is about 14 days. In patients with extensive skeletal metastases, more than 50% injected radioactivity is retained in the bones. Uptake of Sr by bone occurs preferentially in sites of active osteogenesis; thus primary bone tumors and areas of metastatic involvement (blastic lesions) can accumulate significantly greater concentrations of Sr than surrounding normal bone. ^{89}Sr is commercially available as a pharmaceutical brand name Metastron™ and is used as a bone pain palliation agent [158]. The recommended dose of $^{89}SrCl_2$ is 148 MBq/4 mCi, administered by slow intravenous injection in1-2 minutes. A dose of 1.5 - 2.2 MBq/kg, (40-60 µCi/kg) body weight may also be employed.

2.21. Strontium-90

Strontium-90 (^{90}Sr) is a long lived radionuclide and has a half life of 28.8 years. It decays by β^- emission with a maximum energy 546 keV to ^{90}Y. Yttrium-90 (^{90}Y) has a short half life of 64 hours with a β^- emission of 2.24 MeV. Ytrrium-90 exists in a secular equilibrium with ^{90}Sr and is the main source of electrons for therapeutic applications. Yttrium-90 decays to stable ^{90}Zr. ^{90}Sr is a fission product arising from the fission of ^{235}U, ^{238}U or other heavy nuclei. Various extraction techniques for ^{90}Sr from fission products have been described [159]. After 1 year of decay of burnt fuel rods, ^{90}Sr represents 3.7% by mass of the total fission product inventory. Typically, ^{90}Sr is combined with fluorine or chlorine to produce strontium fluoride ($^{90}SrF_2$) or strontium chloride ($^{90}SrCl_2$), respectively.

Strontium-90 is a bone seeking element, similar to calcium. After entering the organism, approximately 70–80% of the ^{90}Sr gets excreted. Only 1% activity remains in blood and soft tissues, while all remaining strontium-90 is deposited in bones and bone marrow [160]. ^{90}Sr radioactive sealed sources are prepared as a plaque - usually a silver disc coated in ^{90}Sr. The disc is placed in a cavity within a Pb larger disc, and a very thin metal 'window' covers its external surface.

Strontium-90 can also be used for endovascular brachytherapy, but typical use is in ophthalmic applicators for the treatment of pterygium [161, 162].

The safety and efficacy of strontium (Sr^{90}) beta radiotherapy as adjuvant treatment for conjunctival melanoma has been reported [163].

2.22. Technetium-99m

Technetium -99m (^{99m}Tc) has a half –life of 6 h and only emits 140 keV gamma ray, which is quite suitable for gamma cameras imaging. It is currently the most widely used radionuclide in diagnostic nuclear medicine. For the last 5 decades, it has dominated over all other nuclides used in nuclear medicine. ^{99m}Tc is the daughter product of ^{99}Mo ($T_{1/2}$ = 67 h) which can be obtained with low specific radioactivity either by irradiation of natural ^{98}Mo (usually as MoO_3) with thermal neutrons in a nuclear reactor [164] or with high specific activity from fission of ^{235}U, also in a nuclear reactor [165]. The majority of the world's supply of ^{99m}Tc is derived from $^{99}Mo/^{99m}Tc$ generators in which fission-produced ^{99}Mo is adsorbed to a small alumina column. These generators are can be eluted with small

volumes of physiological saline to yield highly concentrated solutions of very pure [99m]Tc [166]. Other separation techniques like, solvent extraction, sublimation, gel technology etc, were employed for isolation of ^{99m}Tc from low specific activity [99]Mo.

2.22.1. Technegas

Technegas is an ultra-fine suspension of carbon micro-particles labeled with [99m]Tc. A specially designed device called Technegas generator is employed for generation of technegas. In the generator a solution of sodium pertechnetate (Na[99m]TcO$_4$) is introduced into a crucible and evaporated till dryness. In an inert atmosphere of argon gas technegas is generated by heating crucible to 2550 °C. The Technegas particles are hexagonal platelets of metallic ^{99m}Tc closely encapsulated with a thin layer of graphite. The size distribution of technegas particles being around 30-60 nm with 80% of the particles being <100 nm. Technegas should be administered to the patient within 10 minutes of its preparation [167]. Once technegas inhaled by the patient the gamma camera is used for imaging in the ventilation part of a Ventilation/Perfusion SPECT scan. Technegas penetrates to the sub-segmental areas of the lung and is trapped by surfactant in the alveolar walls. Lung Scintigraphy has a superior sensitivity combined with adequate specificity and low rate of non-diagnostic tests. The low radiation dose, the possibility to quantify the degree of embolism and to use the test for follow-up of treatment of pulmonary embolism and its feasibility in very sick patients, contributes to the priority of lung scintigraphy over Computed Tomographic Pulmonary Angiography [168, 169].

2.22.2. Technetium-99m Labelled Colloidal Particles

Technetium-99m labelled colloidal particles, such as ^{99m}Tc-antimony trisulphide colloid, ^{99m}Tc-sulphur colloid, ^{99m}Tc-rhenium sulphide nanocolloid and ^{99m}Tc-tin colloid have been used for lymphoscintigraphy and/or sentinel lymph node (SLN) detection purposes. Technetium-99m labelled colloids slow elimination rates from the injection site and the uptake of radioactivity by lymph nodes is dependent on both particle size and the functional state of the reticuloendothelial system.

Technetium-99m-antimony trisulphide colloid prepared by slowly adding a solution of potassium antimonyl tartrate to a hot saturated aqueous hydrogen sulphide solution has a particle size of 3–30 nm [170, 171]. ^{99m}Tc-antimony trisulphide colloid provides

satisfactory lymph node scans [170-172], but several adverse reactions requiring medical treatment have been reported [173]. ^{99m}Tc-sulphur colloid (^{99m}Tc-SC) produced by the reaction of thiosulphate with acid is unsatisfactory for lymphoscintigraphy because of the relatively large particle size and range (100–1000 nm), thus, ^{99m}Tc-SC produced by is filtered through a 0.1–0.2 µm filter to obtain particles of smaller and even sizes, commonly used in clinical studies [174]. ^{99m}Tc-sulphur colloid produced by passing hydrogen sulphide gas through an acidic pertechnetate solution, produces particle sizes of less than 100 nm, and the product provides satisfactory lymph node scans [175, 176].

Technetium-99m (^{99m}Tc) rhenium sulphide nanocolloid is used for lymphoscintigraphy for the purpose of visualising the regional lymphatic system. It can be used for imaging and intraoperative detection of sentinel lymph node (SLN) in the breast cancer, prostate cancer, malignant melanoma, and carcinomas of vulvar, penile, and head and neck squamous cell. Imaging of regional lymphatic flow for individualised radiotherapy and lymphatic flow scintigraphy are performed for diagnosing lymphatic oedema in the limbs. It is also used in digestive exploration; gastroesophageal imaging. Subcutaneous injection is route of administration of ^{99m}Tc-colloidal rhenium sulphide, generally in the interdigital space of the hand or foot, or in the marginal area of a tumour.

Since colloids are made of small size, they can be rapidly taken up from interstitial fluids into the lymph capillaries having a discontinuous wall with pores and no basal membrane. Some of the colloidal particles are phagocytosed by bordering cells of the reticuloendothelial system during transport of the lymph through the lymph nodes. This process is repeated from one lymph node to the next lymph node. It is a metal colloid, which is partly phagocytosed and stored in the first lymph node group. Following administration, the radioactivity in the lymph node corresponds to 3.06 ± 0.10 % of the injected radioactivity at the first hour, and 3.83 ± 0.16 % at the third hour [177]. Rhenium sulphide nanocolloid comprises of two vials. One contains: Rhenium (as sulphide): 0.15 mg; Gelatin: 9.6 mg; Ascorbic acid: 7 mg; Water for injection: 1 mL, whereas second vial contains: Sodium pyrophosphate: 3 mg; Stannous chloride dihydrate: 0.1 mg [178].

[99m]Tc-Sn colloid has been used for liver and spleen scintigraphy [179, 180]. When injected, ^{99m}Tc colloidal tin circulates in the blood and accumulates in the liver and the spleen. An image will then help doctor to

determine the ability of these organs to eliminate foreign material like bacteria and denatured protein from the blood.

The particle size of ^{99m}Tc-tin colloid is dependent on the ratio between the ^{99m}Tc solution and the tin solution [181]. As the ratio of tin decreases, the size of colloidal particles increases. Technetium-99m-tin colloid has a particle size of 50–1500 nm. Uenosono *et al.* recommended 100 nm as a suitable colloidal size for detecting SLN in gastric cancer [182]. Formulation of tin colloid kit generally contains, Stannous chloride dihydrate: 0.3 mg, Sodium fluoride: 1.0 mg, Sodium chloride: 3.6 mg, and Povidone: 0.5 mg [183].

2.22.3. *^{99m}Tc-Pertechnetate*

Sodium pertechnetate (Na^{99m}TcO$_4$) solution is used in adults for imaging of brain including cerebral radionuclide angiography; thyroid, salivary gland, placenta localization; blood pool including radionuclide angiography and urinary bladder. In children Na^{99m}TcO$_4$ injection is used for imaging purposes of brain including cerebral radionuclide angiography; thyroid, blood pool including radionuclide angiography and urinary bladder; direct isotopic cystography for the detection of vesico-ureteral reflux [184, 184].

The ^{99m}TcO$_4$- ion distributes in the human body as the iodide ion, but is not organified when accumulated in the thyroid gland. It tends to accumulate in intracranial lesions with excessive neovascularity or an altered blood-brain barrier. It also accumulates in the thyroid/salivary glands, gastric mucosa, and choroid plexus. The ^{99m}TcO$_4$- ion is released unchanged from the thyroid gland. Since the ^{99m}TcO$_4$- ion remains in the circulatory system for sufficient time it can be used for blood pool measurement, organ perfusion, and major vessel studies. It gradually equilibrates with the extra vascular space and small fraction of ^{99m}TcO$_4$- ion is promptly excreted via the kidneys [178, 185].

Thyroid uptake and scintigraphy using ^{99m}Tc-pertechnetate is faster with minimum exposure to patient. Use of pertechnetate is more advantageous than with ^{131}I-iodide, since the ^{99m}Tc gives far better images quality [186].

When Na^{99m}TcO$_4$ is mixed with a tin compound, it binds to red blood cells and can therefore be used to scan disorder in circulatory system. It is useful to detect gastrointestinal bleeding sites.

Pertechnetate-^{99m}Tc is actively accumulated and secreted by the mucoid cells of the gastric mucosa

[187], and therefore, Na^{99m}TcO$_4$ is injected into the human body when looking for ectopic gastric tissue as is found in a Meckel's diverticulum with Meckel's Scans [188]

2.22.4. *^{99m}Tc-Pyrophosphate*

^{99m}Tc-Pyrophosphate (^{99m}Tc- PYP) Injection is a bone imaging agent used to demonstrate areas of altered osteogenesis. It is also a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction. ^{99m}Tc- PYP is given intravenously and 1-2 h post injection, an estimated 40-50 % of the injected dose had been taken up by the skeleton, and ~ 0.01-0.02 %/g of acutely infarcted myocardium. In one hour, ~ 11% remains in the vascular system, and after 24 h reduces to ~ 2-3 %. After 24 h post injection, the average urinary excretion was observed to be ~ 40 %.

^{99m}Tc- PYP has been used as a blood pool imaging useful for gated blood pool imaging and for the detection of sites of gastrointestinal bleeding. When administered intravenously 15-30 minutes prior to intravenous injection of Na^{99m}TcO$_4$ for *in vivo* red blood cell labeling, ~ 75% of the injected radioactivity is found in the blood pool. The modified *in vivo/in vitro* red blood cell labeling method has also been utilized for blood pool imaging [189, 190].

2.23. Thallium-201

Thallium-201 (^{201}Tl) has a physical half-life of 73.1 h, and decays by EC to mercury-201 (^{201}Hg). Useful Photons for the detection/imaging are 135.3 KeV (2.7%) and 167.4 KeV (10 %). The ^{201}Hg daughter of ^{201}Tl emits lower energy x-rays that are recommended for myocardial imaging, because the mean percent disintegration at 68.9 to 80.3 keV is much higher than the combination of other gammas mean percent disintegration.

High-energy protons are used for the production of thallium-201. Several methods have been investigated for production of ^{201}Tl.

1. ^{202}Hg (p, 2n) ^{201}Tl (proton energy 50→14 MeV)

2. ^{nat}Hg (p, xn) ^{201}Tl (proton energy 50→14 MeV)

3. ^{203}Tl (p, 3n)^{201}Pb --------- → ^{201}Tl (proton energy 28→20 MeV)

4. ^{206}Pb (p,x) ^{201}Tl (proton energy 60→15 MeV)

5.   Pb, Bi (p, spall)^{201}Tl (proton energy 800 MeV)

The most common route however is the ^{203}Tl (p, 3n) ^{201}Pb → ^{201}Tl reaction on enriched ^{203}Tl. The optimum proton energy range for production is 28→20 MeV, Therefore a medium-energy 30 MeV proton is needed. The production of no-carrier-added ^{201}Tl via irradiation of ^{203}Tl or ^{nat}Tl involves a 2-step process and complex wet chemical processing. At first ^{201}Pb is separated from the target matrix activity. Thereafter ^{201}Pb is allowed to decay for an optimum time of 32 h whereby ^{201}Tl grows in. The removal of the ^{201}Tl can be performed by anion-exchange chromatography or solvent extraction techniques [191].

Thallous chloride (^{201}Tl) is indicated in myocardial perfusion imaging for the diagnosis and localization of myocardial infarction [192-195].

Thallous chloride (^{201}Tl) is also indicated in studies of myocardial perfusion done under resting conditions and after physiologic or pharmacologic stress induced by exercise or infusion of dipyridamole, adenosine, or dobutamine respectively, to detect myocardium with abnormal perfusion reserve secondary to coronary artery disease [196-200].

Thallous chloride (^{201}Tl) is used for the detection and localization of parathyroid tissue in patients with documented hyperparathyroidism. Thallous chloride (^{201}Tl) may also be useful in preoperative screening to localize extrathyroidal and mediastinal sites of parathyroid tissue and for postsurgical reexamination [201-203]. However, the use of thallous chloride (^{201}Tl) as a parathyroid imaging agent generally has been replaced by technetium Tc-99m sestamibi.

Thallous chloride (^{201}Tl) is used for the detection and localization of various tumors, including thyroid carcinomas, malignant brain neoplasms, lymphomas, and mediastinal tumors, especially for postoperative detection of residual and recurrent tumors and differentiation of these from post-therapy fibrosis or necrosis [204-208].

Usual adult and adolescent administered activity (IV) are 37-74 MBq (1-2 mCi) and 74-148 MBq (2-4 mCi) for Planar and SPECT imaging, respectively. Parathyroid imaging is performed by injecting 75 MBq (2 mCi) and tumor imaging by 55.5 -111 MBq(1.5-3 mCi) Usual pediatric administered activity for Cardiac imaging andParathyroid imaging is1.11 MBq (30 µCi) per kg of body weight administered intravenously, with a minimum total dosage of 27.75 MBq (750 µCi) and a maximum total dosage of 111 MBq (3 mCi).

In Cardiac imaging, the Thallous chloride (^{201}Tl) appears to accumulate in cells of myocardium and other tissues in a manner analogous to that of potassium [209]. The initial biodistribution of Thallous chloride (^{201}Tl) in most tissues is primarily related to regional blood flow. Ischemic myocardial cells take up less ^{201}Tl than nonischemic cells, in proportion to the relative change [202, 203] in blood flow, especially during maximal stress (or pharmacologically induced vasodilation) when the differential in perfusion is most marked between regions supplied by normal coronary arteries and those supplied by stenotic vessels. Imaging equipment can record regional differences in thallium-201 uptake, and thus in myocardial perfusion, confirming the presence or absence of coronary disease [210, 211]

In Parathyroid imaging, the Thallous chloride (^{201}Tl) localizes in parathyroid adenomas, parathyroid hyperplasia, and other abnormal tissues, generally in proportion to organ blood flow at the time of injection [212].

Two other Technetium-99m labeled compounds MIBI and tetrofosmin are also used for same purpose. Usually MIBI/tetrofosmin labeled with 10-30 mCi of technetium-99m is injected to patient.^{99m}Tc-MIBI / ^{99m}Tc-tetrofosmin requires two injections, a stress study and a rest study. While only one injection of (~2mCi) ^{201}TlCl is sufficient for whole study. However images are inferior compared to ^{99m}Tc-MIBI / ^{99m}Tc-tetrofosmin [213].

2.24. Yttrium-90

Yttrium-90 (^{90}Y) has physical half-life is 2.7 days. It emits a β$^-$ particle with a maximum energy of 2.27 MeV, a mean energy of 0.935 MeV and an average soft tissue penetration range of 3.6 mm. The low specific activity ^{90}Y is produced in a nuclear reactor by neutron activation of the non-radioactive ^{89}Y, where ^{89}Y captures a neutron and becomes the radioactive β$^-$ emitter ^{90}Y [214]. For very high specific activity ^{90}Y (that is used for target therapy), a radionuclide generator system of Strontium-90 (^{90}Sr) is used and it is based on the fact that ^{90}Sr decays to ^{90}Y [215]. Various types of ^{90}Sr/^{90}Y generators have been developed including ion exchange based generator, Supported Liquid Membrane (SLM) based generator and Electrochemical generator. The best of these generators is the electrochemical system as it yields around 97–98% of ^{90}Y deposition [216-218].

Finally, for patients with rheumatoid arthritis (RA) that is unresponsive to glucocorticoids, nonsteroidal anti-inflammatory pharmaceuticals and disease-modifying antirheumatoid pharmaceuticals, cronicoligo or mono-arthritis can be cured by radionuclide synovectomy. Radiosynoviorthesis with ^{90}Y is an established concept for the treatment of persistent synovitis of the knee joint [219, 220].

Radiolabeled particles of various sizes have been applied for delivering a high localized radiation dose to tumors in different organs following intraarterial administration for more six decades [221]. Delivery of a highly selected distribution of radiation doses that are 20-30 times greater than that achievable by external beam therapy is possible by virtue of the preferential blood flow to the tumor relative to normal tissues [222]. Different types of particles and microspheres have been utilized including ^{90}Y-labeled-Y_2O_3 particles, ^{90}Y-ceramic microspheres, ^{90}Y-resin microsphere and ^{90}Y glass microsphere [223, 224].

TheraSphere consists of insoluble glass microspheres where ^{90}Y is an integral part of the glass [224]. The mean diameter of spheres ranges from 20-30 µm. Each mg of radiopharmaceutical contains between 22 000 and 73 000 microspheres. Hepatic artery radioembolization (RE) with ^{90}Y-loaded microspheres is an alternative treatment for patients with unresectable primary or secondary liver tumours, especially in cases of hepatocellular carcinoma (HCC) and metastatic colorectal cancer (mCRC) [224].

Yttrium [^{90}Y] silicate injection is a suspension for injection for intra-articular or intra-cavitary use. The active ingredient, yttrium [^{90}Y] silicate is present as a sterile colloidal suspension in water for injection. The solution also contains sodium silicate, and is buffered with hydrochloric acid to give a pH of 10.0 - 11.5. Each mL of solution contains yttrium: 0.24 - 0.39 mg/ml. The radioactive concentration is 92.5 - 370 MBq/ml (2.5 - 10 mCi/ml) and the specific activity is 259-1259 MBq/mg (7-35 mCi/mg) yttrium at reference time. Indications are therapeutic irradiation of synovial hypertrophy of the knee joints (isotopic radiation synovectomy) mainly for mono- or oligo-articular arthritis of chronic inflammatory rheumatism particularly rheumatoid polyarthritis. Yttrium [^{90}Y] silicate is also used for treatment of recurrent malignant effusions in those patients who have failed to respond to conventional radiation therapy or chemotherapy of the pleural and peritoneal cavities. The recommended injected radioactivity ranges from 111-222 MBq (3-6 mCi) per joint. Several radiation

synovectomies can be performed successively as well as simultaneously. Reinjection of radioactive Yttrium [^{90}Y] silicate colloid in one articulation can be performed after a period of 6 months in the event of relapse. The activity per administration typically ranges from 400 MBq to 3000 MBq (10.8 - 81.1 mCi) of ^{90}Y depending on clinical indication. Yttrium [^{90}Y] silicate Injection of colloid can be given via intra-articular, intrapleural or intraperitoneal [225]. Yttrium-90 hydroxyapatite is commercially available as a therapeutic agent to cure chronic kneesynovitisin rheumatoid arthritis, hemophilia or orthopedic troubles [142].

2.25. Xenon-133

Xenon-133 (^{133}Xe) has a half-life of 5.245 d and it disintegrates by β$^-$ and γ emissions. The photon of 81 keV finds application in detection and imaging studies. Xenon-133 is produced by fission of Uranium-235 [226]. Xenon-133 gas has been shown to be useful for diagnostic inhalation studies for the evaluation of pulmonary function, for lungs scanning and applied to assessment of cerebral blood flow.

Xenon-133 is a readily diffusible gas which is not utilized by the body. It passes through cell membranes, freely exchanges between blood and tissue, and tends to concentrate more in body fat than in blood, plasma, water or protein solutions. Xenon-133 gas is administered by inhalation from a spirometer or closed respirator device. The usual activity range employed for inhalation by an average patient of 70 kg is 74 to 1110 MBq (2 to 30 mCi) for pulmonary function including imaging and 370 to 1110 MBq (10 to 30 mCi) for cerebral blood flow studies [227, 228]. ^{133}Xe is historically an agent that was used for ventilation studies [229].

CONCLUSIONS

Sodium iodide (^{131}I) treatment of thyroid disorders is the only treatment that has continued to be developed up to the present day and has become fully established in routine clinical practice in developing as well as in developed countries. Some other radionuclides, such as ^{22}Na, ^{35}S, ^{59}Fe, ^{85}Sr, radioindium and ^{198}Au find rare medical applications in routine. Use of radioactive sealed sources (^{60}Co, ^{192}Ir and short lived radionuclides) will continue to play their important role in medical applications and even increase in the future. In the wake of the terrorist attack on September 11th 2001 in USA, there is a security concern over sealed

sources of cesium-137 as CsCl especially susceptible to be being used by terrorists. Its substitution by less hazardous technology as well as use of stable compound of ^{137}Cs is also recommended. Nanoparticles and nanocomposites, containing radioactive isotopes, are promising objects for a series of biomedical and chemical applications. Use of currently inorganic radioactive compounds will continue in near future and new compounds of ^{47}Sc, ^{64}Cu, ^{67}Cu, ^{105}Rh, ^{111}Ag, ^{153}Sm, ^{165}Dy, ^{166}Ho, ^{177}Lu and ^{199}Au may emerge, particularly in the field of radiotherapy.

REFERENCES

[1] Lawrence JH. Nuclear physics and therapy: Preliminary report on a new method for the treatment of leukemia and polycythemia, Radiology 1940; 35: 51-60. http://dx.doi.org/10.1148/35.1.51

[2] Hertz S, Roberts A. Application of radioactive iodine in therapy of Graves' disease, J Clin Invest 1942; 21: 624.

[3] Technetium-99m radiopharmaceuticals: manufacture of kits. Technical reports series, ISSN 0074-1914; no. 466. International Atomic Energy Agency, Vienna, Austria; 2008.

[4] Radiopharmaceuticals: Production and Availability. https://www.iaea.org/About/Policy/GC/GC51/GC51InfDocuments/English/gc51inf-3-att2_en.pdf

[5] Cyclotron produced radionuclides: guidance on facility design and production of [^{18}F] fluorodeoxyglucose (FDG). IAEA radioisotopes and radiopharmaceuticals series, ISSN 2077-6462; no. 3. International Atomic Energy Agency, Vienna, Austria; 2012.

[6] Lie-hang Sheng, New trends in development of radiopharmaceuticals. Ann Nucl Med Mol Imag 2013; 26: 1-4

[7] Chai-Hong Yeong, Mu-hua Cheng, and Kwan-Hoong Ng. Therapeutic radionuclides in nuclear medicine: current and future prospects. J Zhejiang Univ Sci B. 2014; 15(10): 845-863 http://dx.doi.org/10.1631/jzus.B1400131

[8] Taylor HJ, Goldhaber M. Detection of nuclear disintegration in a photographic emulsion, Nature 1935; 135: 341. http://dx.doi.org/10.1038/135341a0

[9] Barth RF, Soloway AH, Fairchild RG. Boron neutron capture therapy for cancer. Scientific American 1990; 263(4): 100-3, 106-7. Bibcode:1990 Sci Am. 263d.100B. http://dx.doi.org/10.1038/scientificamerican1090-100

[10] Locher GL. (1936). Biological effects and therapeutic possibilities of neutrons. Am J Roentgenol 1936; 3(1): 1-13.

[11] Sweet WH. The uses of nuclear disintegration in the diagnosis and treatment of brain tumor. New England Journal of Medicine 1951; 245(23): 875-878. doi:10.1056/NEJM195112062452301.PMID 14882442.

[12] Farr LE, Sweet WH, Robertson JS, Foster CG, Locksley HB, Sutherland DL, Mendelsohn ML, Stickley EE. Neutron capture therapy with boron in the treatment of glioblastoma multiforme. The American journal of roentgenology, radium therapy, and nuclear medicine 1954; 71(2): 279-293.

[13] Barth RF, Coderre JA, Vicente MG, Blue TE. Boron neutron capture therapy of cancer: Current status and future prospects. Clinical Cancer Research 2005; 11(11): 3987-4002. http://dx.doi.org/10.1158/1078-0432.CCR-05-0035

[14] Vicente M. Boron in medicinal chemistry. Anti-Cancer Agents in Medicinal Chemistry 2006; 6(2): 73.. http://dx.doi.org/10.2174/187152006776119162

[15] Nakagawa Y, Pooh K, Kobayashi T, Kageji T, Uyama S, Matsumura A, Kumad, H. Clinical review of the Japanese experience with boron neutron capture therapy and a proposed strategy using epithermal neutron beams. Journal of Neuro-Oncology 2003, 62(1-2): 87-99. http://dx.doi.org/10.1023/A:1023234902479

[16] Diaz AZ. Assessment of the results from the phase I/II boron neutron capture therapy trials at the Brookhaven National Laboratory from a clinician's point of view. Journal of Neuro-Oncology 2003; 62(1-2): 101-109. http://dx.doi.org/10.1023/A:1023245123455

[17] Busse PM, Harling OK, Palmer MR, Kiger WS, Kaplan J, Kaplan I, Chuang CF, Goorley JT. et al. A critical examination of the results from the Harvard-MIT NCT program phase I clinical trial of neutron capture therapy for intracranial disease. Journal of Neuro-oncology 2003; 62(1-2): 111-121. http://dx.doi.org/10.1007/BF02699938

[18] Kankaanranta L, Seppälä T, Koivunoro H, Välimäki P, Beule A, Collan J, Kortesniemi M, Uusi-Simola J. et al. L-Boronophenylalanine-mediated boron neutron capture therapy for malignant glioma progressing after external beam radiation therapy: A Phase I study. International Journal of Radiation Oncology Biology Physics 2011; 80(2): 369-376. http://dx.doi.org/10.1016/j.ijrobp.2010.02.031

[19] Kankaanranta L, Seppälä T, Koivunoro H, Saarilahti K, Atula T, Collan J, Salli E, Kortesniemi M. et al. Boron neutron capture therapy in the treatment of locally recurred head-and-neck cancer: Final analysis of a Phase I/II trial. International Journal of Radiation Oncology Biology Physics 2012; 82(1): 67-75. http://dx.doi.org/10.1016/j.ijrobp.2010.09.057

[20] Kawabata S, Miyatake SI, Kuroiwa T, Yokoyama K, Doi A, Iida Kyoko, Miyata S, Nonoguchi N et al. Boron neutron capture therapy for newly diagnosed glioblastoma. Journal of Radiation Research 2009; 50(1): 51-60. http://dx.doi.org/10.1269/jrr.08043

[21] Miyatake SI, Kawabata S, Yokoyama K, Kuroiwa T, Michiue H, Sakurai Y, Kumada H, Suzuki M et al. Survival benefit of boron neutron capture therapy for recurrent malignant gliomas. Journal of Neuro-Oncology 2008; 91(2): 199-206. http://dx.doi.org/10.1007/s11060-008-9699-x

[22] Barth R F, Vicente H, Graca M, Harling OK, Kiger WS, Riley KJ, Binns PJ, Wagner FM, Suzuki M, Aihara T, Kato I, Kawabata S. Current status of boron neutron capture therapy of high grade gliomas and recurrent head and neck cancer. Radiation Oncology 2012; 7: 146. http://dx.doi.org/10.1186/1748-717X-7-146

[23] Kocherov N, Lammer M, Schwerer O. "Handbook of Nuclear Data for Safeguards," International Atomic Energy Agency, INDC (NDS)-376, December 1997.

[24] Radiation Source Use and Replacement: Abbreviated Version. http://www.nap.edu/catalog/11976.html

[25] Cole A, Sinclair WK, Fletcher GH, Johnson GC, Physical studies on a short-treatment-distance cesium-137 teletherapy unit. Radiology 1960; 74:731-742. http://dx.doi.org/10.1148/74.5.731

[26] Nagalingam S, Ervin BP, Heikki T, Chapter 13. Brachytherapy: Physical and Clinical Aspects, In: Review of Radiation Oncology Physics: A Handbook for Teachers and Students http://www.irsn.fr/fr/professionnels_sante/documentation/documents/syllabus_chapitre_13.pdf

[27] Hareyama M, Nishio M, Saito A, Kagami Y, Asano K, Oouchi A, Narimatsu N, Somekawa Y, Sanbe S and Morita K: Results of cesium needle interstitial implantation for carcinoma of the oral tongue. Int J Radiat Oncol Biol Phys 1992; 25: 29-34. http://dx.doi.org/10.1016/0360-3016(93)90141-H

[28]   Firestone R, Shirley VS. (Ed.) Table of isotopes, 8th edition John Wiley & Sons Inc., New York.1996.

[29]   Chromium-51. Manual for reactor produced radioisotopes, IAEA-TECDOC-1340, IAEA Vienna. 2003.p. 35-40.

[30]   Dag Brune. Separation of ^{51}Cr by means of the Szilard-Chalmers effect from potassium chromate irradiated at low temperature. Acta Chem Scand 1967; 21: 2087-2094. http://dx.doi.org/10.3891/acta.chem.scand.21-2087

[31]   Karim HMA. Preparation of sodium chromate-^{51}Cr and chromic chloride-^{51}Cr for medical applications. Int J Appl Radiat Isot 1973; 24(10): 599-603. http://dx.doi.org/10.1016/0020-708X(73)90129-4

[32]   Eyre HJ, Rosen PJ, Perry S. Relative labeling of leukocytes, erythrocytes and platelets in human blood by 51-chromium. Blood 1970; 36 (2): 250-253.

[33]   Sodium chromate Cr-51. http://www.drugs.com/pro/sodium-chromate-cr-51.html

[34]   Cobalt-60 (^{60}Co$_{27}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, Vienna. 2003.p. 44-50.

[35]   Radiation Source Use and Replacement: Abbreviated Version (p. 35-36). http://www.nap.edu/catalog/11976.html

[36]   Walstam R, Remotely-controlled afterloading apparatus (a preliminary report), Phys. Med. Biol.1962 Oct 7: 225-228. http://dx.doi.org/10.1088/0031-9155/7/2/308

[37]   Atara N, Adeniyi A, Bidemi A and Oladapo C. High Dose Rate Brachytherapy in the treatment of cervical cancer: preliminary experience with cobalt 60 radionuclide source-A Prospective Study. Clinical Medicine Insights: Oncology 2010; 4: 89-94.

[38]   Leroy JK, Michael KB, Modern Brachytherapy for Localized Prostate Cancers: The Northwest Hospital (Seattle) Experience. Rev Urol. 2001; 3(1): 51-60.

[39]   Fourquet A, Campana F, Mosseri V, Cetingoz R, Luciani S, Labib A, Asselain B, Vilcoq JR. Iridium-192 versus cobalt-60 boost in 3-7 cm breast cancer treated by irradiation alone: final results of a randomized trial. Radiother Oncol 1995; 34(2): 114-120. http://dx.doi.org/10.1016/0167-8140(94)01492-L

[40]   Granero D, Perez-Calatayud J, Vijande J, Ballester F, Rivard MJ. Limitations of the TG-43 formalism for skin high-dose-rate brachytherapy dose calculations. Med Phys. 2014; Feb 41(2):021703. http://dx.doi.org/10.1118/1.4860175

[41]   Chauhan A, Kaur P, Annex E. Radical external beam radiotherapy with intraluminal high rate dose brachytherapy in patients with carcinoma esophagus. The Internet Journal of Gastroenterology 2008; 8(1). https://ispub.com/IJGE/8/1/11901.

[42]   Mushtaq A, Karim HMA, Khan MA. Production of no-carrier-added ^{64}Cu and ^{67}Cu in a reactor. J. Radioanal. Nucl. Chem. Articles. 1990; 141: 261-269. http://dx.doi.org/10.1007/BF02035793

[43]   Bukhari TH, Mushtaq A, Khan IU. Production of low and high specific activity copper 64 in a reactor J. Radioanal. Nucl. Chem. 2010; 284: 265-271. http://dx.doi.org/10.1007/s10967-010-0519-3

[44]   McCarthy DW, Shefer RE, Klinkowstein RE et al., "Efficient production of high-specific-activity ^{64}Cu using a biomedical cyclotron," Nuclear Medicine and Biology. 1997; 24: 35-43. http://dx.doi.org/10.1016/S0969-8051(96)00157-6

[45]   Alliot C, Michel N, Bonraisin AC et al., "One step purification process for no-carrier-added ^{64}Cu produced using enriched nickel target," Radiochimica Acta. 2011; 99: 627-630. http://dx.doi.org/10.1524/ract.2011.1821

[46]   Subramanian I,Vanek ZF, and Bronstein JM. "Diagnosis and treatment of Wilson's disease," Current Neurology and Neuroscience Reports, 2002; 2:317-323.

[47]   Zhao Y, Sultan D, Detering L, Cho S, Sun G, Pierce R, Wooley KL, Liu Y. Copper-64-alloyed gold nanoparticles for cancer imaging: improved radiolabel stability and diagnostic accuracy. Angew Chem Int Ed Engl. 2014 Jan 3; 53(1): 156-159. http://dx.doi.org/10.1002/anie.201308494

[48]   Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods. Technical Reports Series No. 468. International Atomic Energy Agency Vienna, 2009 p.106-116.

[49]   Kilbourn MR, Hood JT, Welch MJ. A simple ^{18}O water target for ^{18}F production. Int J Appl Radiat Isot 1984; 35: 599-602. http://dx.doi.org/10.1016/0020-708X(84)90102-9

[50]   Kilbourn MR, Jerabek PA, Welch MJ, An improved [^{18}O] water target for [^{18}F]fluoride production. Int. J. Appl. Radiat. Isot 1985; 36: 327-328. http://dx.doi.org/10.1016/0020-708X(85)90099-7

[51]   Tewson TJ, Berrydge MS, Bolomey L, Gould KL. Routine production of reactive fluorine-18 salts from an oxygen-18 water target Nucl Med Biol 1988; 15: 499-504. http://dx.doi.org/10.1016/s0969-8051(88)80005-2

[52]   Sodium Fluoride F-18 Injection; http://www.drugs.com/pro/sodium-fluoride-f-18-injection.html.

[53]   Even-Sapir E, Metser U, Flusser G, et al. Assessment of malignant skeletal disease: initial experience with 18F-fluoride PET/CT and comparison between 18Ffluoride PET and 18F-fluoride PET/CT. J Nucl Med 2004; 45: 272-278.

[54]   Harmer CL, Burns JE, Sams A, Spittle M. The value of fluorine-18 for scanning bone tumours. Clin Radiol. 1969; 20: 204-212. http://dx.doi.org/10.1016/S0009-9260(69)80174-1

[55]   Lim R, Fahey FH, Drubach LA, Connolly LP, Treves ST. Early experience with fluorine-18 sodium fluoride bone PET in young patients with back pain. J Pediatr Orthop. 2007; 27: 277-282. http://dx.doi.org/10.1097/BPO.0b013e31803409ba

[56]   Park HM. 123-I: almost a designer radioiodine for thyroid scanning. J Nucl Med 2002; 43: 77-78.

[57]   Hibbert A, Gruffydd-Jones T, Barrett EL, et al. Feline thyroid carcinoma: diagnosis and response to high-dose radioactive iodine treatment. J Feline Med Surg 2009; 11: 116-124. http://dx.doi.org/10.1016/j.jfms.2008.02.010

[58]   Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods. Technical Reports Series No. 468. International Atomic Energy Agency Vienna, 2009.p. 155-167.

[59]   Sharma HL, Zweit J, Downey S, Smith AM, Smith AG. Production of ^{124}I for positron emission tomography. J Labelled Compd Radiopharm 1988; 26: 165-167. http://dx.doi.org/10.1002/jlcr.2580260171

[60]   Wyszomirska A. Iodine-131 for therapy of thyroid diseases. Physical and biological basis. Nucl Med Rev Cent East Eur 2012; 15: 120-123.

[61]   Peterson ME. Radioiodine treatment of hyperthyroidism. Clin Tech Small Anim Pract 2006; 21: 34-39. http://dx.doi.org/10.1053/j.ctsap.2005.12.006

[62]   Peterson ME, Broome MR. Radioiodine for feline hyperthyroidism In: Bonagura JD, Twedt DC, eds. Kirk's Current Veterinary Therapy, Volume XV. Philadelphia: Saunders Elsevier, 2013.

[63]   Cyclotron Produced Radionuclides: Physical Characteristics and Production Methods. Technical Reports Series No. 468. International Atomic Energy Agency Vienna, 2009.p. 167-175)

[64]   Iodine-125 (^{125}I$_{53}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, VIENNA, 2003.p. 75-81.

[65] Yalow RS. Radioimmunoassay. Annu Rev Biophys Bioeng 1980; 9: 327-345.
http://dx.doi.org/10.1146/annurev.bb.09.060180.001551

[66] Georgakopoulos J, Zygogianni A, Papadopoulos G, et al. Permanent implantation as brachytherapy technique for prostate carcinoma-review of clinical trials and guidelines. Rev Recent Clin Trials 2012; 7: 173-180.
http://dx.doi.org/10.2174/157488712802281268

[67] Schwarz SB, Thon N, Nikolajek K, et al. Iodine-125 brachytherapy for brain tumours--a review. Radiat Oncol. 2012 Mar 6; 7: 30.
http://dx.doi.org/10.1186/1748-717X-7-30

[68] Kim JH, Hilaris B. Iodine 125 source in interstitial tumor therapy-clinical and biological considerations. American Journal of Roentgenology 1975; 123(1): 163-169.
http://dx.doi.org/10.2214/ajr.123.1.163

[69] Ruge MI, Kickingereder P, Grau S, Treuer H, Sturm V, Voges J. Stereotactic iodine-125 brachytherapy for brain tumors: temporary versus permanent implantation. Radiat Oncol. 2012 Jun 19; 7: 94.
http://dx.doi.org/10.1186/1748-717X-7-94

[70] IAEA Nuclear Data Services, NuDat 2.5, www-nds.iaea.org.

[71] Hertz S, Roberts A. Radioactive Iodine in the study of thyroid physiology: VII. The Use of Radioactive Iodine Therapy in Hyperthyroidism. J Am Med Assoc, 1946; 131: 81-86.
http://dx.doi.org/10.1001/jama.1946.02870190005002

[72] Kaplan MM, Meier DA, Dworkin HJ. Treatment of hyperthyroidism with radioactive iodine. Endocrine Clin N Am 1998; 27: 205-223.
http://dx.doi.org/10.1016/S0889-8529(05)70307-8

[73] Ernest L. Mazzaferri. Papillary thyroid carcinoma: A 10 year follow-up report of the impact of therapy in 576 patients. The American Journal of Medicine 1981; 70 (3): 511-518.
http://dx.doi.org/10.1016/0002-9343(81)90573-8

[74] Zidan J, Hefer E, Iosilevski G, Drumea K, Stein ME, Kuten A, Israel O. Efficacy of ^{131}I ablation therapy using different doses as determined by postoperative thyroid scan uptake in patients with differentiated thyroid cancer. Int J Radiat Oncol Biol Phys. 2004; 1; 59(5): 1330-1336.

[75] Iodine-131 $(^{131}I_{53})$ (Dry distillation method) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, Vienna 2003.p. 86-89.

[76] Iodine-131 $(^{131}I_{53})$ (Wet distillation method) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, Vienna 2003.p. 82-85.

[77] Iodine-131 $(^{131}I_{53})$ (Fission product) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, Vienna, 2003.p. 111-115.

[78] Production techniques and quality control of sealed radioactive sources of palladium-103, iodine-125, iridium-192 and ytterbium-169. Final report of a coordinated research project 2001-2005. IAEA TECDOC-1512. IAEA Vienna 2006.

[79] Paul R, Hofmann R, Schwarzer JU, Stepan R, Feldmann HJ, Kneschaurek P, Molls M, Hartung R, Iridium 192 high-dose-rate brachytherapy--a useful alternative therapy for localized prostate cancer? World J Urol. 1997; 15(4): 252-256.
http://dx.doi.org/10.1007/BF01367663

[80] Michael Andrássy, Yury Niatsetsky, José Pérez-Calatayud, Co-60 versus Ir-192 in HDR brachytherapy: Scientific and technological comparison. Rev Fis Med 2012; 13(2): 125-30.

[81] Liu Z, Yu X, Guo Y, Li S, Cui Y, Yu X, Yuan Z, Kang J. Interstitial brachytherapy using iridium-192 for malignant brain tumors: clinical results. Chin Med J 1999; 112(2): 139-142.

[82] Shirish K. Jani, Stephen Steuterman, Gerard B. Huppe, Guo Long Chu, Radiation Safety of personnel during catheter-based Ir-192 coronary brachytherapy. J Invasive Cardiol. 2000; 12(5) http://www.medscape.com/viewarticle/407459

[83] Gupta AK, Vicini FA, Frazier AJ, Barth-Jones DC, Edmundson GK, Mele E, Gustafson GS, Martinez AA. Iridium-192 transperineal interstitial brachytherapy for locally advanced or recurrent gynecological malignancies. Int J Radiat Oncol Biol Phys 1999; 15: 43(5): 1055-1060.

[84] Pötter R, Knocke TH, Fellner C, Baldass M, Reinthaller A, Kucera H. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993-1997) compared to the preceding period in the context of ICRU 38 recommendations. Cancer Radiother. 2000 Mar-Apr; 4(2): 159-72.
http://dx.doi.org/10.1016/S1278-3218(00)88900-3

[85] Elliot AT. in Textbook of Radiopharmacy: Theory and Practice (Sampson CB., Ed.) Gordon and Breach, New York 1990.

[86] Kovacs Z, Tarkanyi F, Qaim SM, Stoeklin G. Excitation functions for the formation of some radioisotopes of rubidium in proton induced nuclear reactions on natKr, 82Kr and 83Kr with special reference to the production of $^{81}Rb(^{81m}Kr)$ generator radionuclide, Appl. Radiat. Isot 1991; 42: 329-335.
http://dx.doi.org/10.1016/0883-2889(91)90134-M

[87] Rubidium-81/Krypton-81m Generator System In: Cyclotron produced radionuclides: physical characteristics and production methods.: International Atomic Energy Agency, Vienna, 2009. Technical reports series, ISSN 0074-1914; no. 468 p. 182-186.

[88] Valind SO, Rhodes CG, Jonson B. Quantification of regional ventilation in humans using a short-lived radiotracer - theoretical evaluation of the steady-state model. J Nucl Med 1987; 28: 1144-1154.

[89] Ciofetta G, Piepsz A, Roca I, Fisher S, Hahn K, Sixt R, et al. Guidelines for lung scintigraphy in children. Eur J Nucl Med Mol Imaging 2007; 34: 1518-26.
http://dx.doi.org/10.1007/s00259-007-0485-3

[90] Gutte H, Mortensen J, Jensen C, Johnbeck C, von der Recke P, Petersen C, et al. Detection of pulmonary embolism with combined ventilation/perfusion SPECT and low dose CT: head-to-head comparison with CT-angiography. J Nucl Med 2009; 50: 1987-1992.
http://dx.doi.org/10.2967/jnumed.108.061606

[91] Ohno Y, Koyama H, Takenaka D, Nogami M, Kotani Y, Nishimura Y, et al. Coregistered ventilation and perfusion SPECT using krypton-81m and Tc-99m-labeled macroaggregated albumin with multislice CT utility for prediction of postoperative lung function in non-small cell lung cancer patients. Acad Radiol 2007; 14:830-8.
http://dx.doi.org/10.1016/j.acra.2007.03.013

[92] Sando Y, Inoue T, Nagai R, Endo K. Ventilation/perfusion ratios and simultaneous dual-radionuclide single-photon emission tomography with krypton-81m and technetium-99m macroaggregated albumin. Eur J Nucl Med 1997; 24:1237-1244.
http://dx.doi.org/10.1007/s002590050147

[93] Cyclotron produced radionuclides : physical characteristics and production methods. International Atomic Energy Agency Vienna 2009. Technical reports series, ISSN 0074-1914; no. 468. p. 196-203.

[94] Tilbury RS, Dahl JR. [13]N species formed by the proton irradiation of water. Radiat Res 1979; 79: 22-33.
http://dx.doi.org/10.2307/3575019

[95] Helmeke HJ, Harms T, Knapp WH. Home-made routinely used targets for the production of PET radionuclides. Targetry and Target Chemistry (Proc. 7th Workshop Heidelberg, 1997), TRIUMF, Vancouver (1997) 241.

[96] Mulholland GK, Sutorik A, Jewett DM, Manager TJ, Kilbourn MR. Direct in-target synthesis of aqueous N-13 ammonia by proton irradiation of water under hydrogen pressure, J Nucl Med 1989; 30: 926.

[97]　Feinstein Institute for Medical Research (Chaly T). Highlights of Prescribing Information for Ammonia N 13 Injection for intravenous Use. 2011, Initial approval 2007 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/02 2119Orig1s001.pdf

[98]　Alessio AM et al. Validation of an axially distributed model for quantification of myocardial blood flow using ^{13}N-ammonia PET. J Nucl Cardiol 2013; 20: 64-75. http://dx.doi.org/10.1007/s12350-012-9632-8

[99]　Vaalburg W, Kamphuis JA, Beerling-van der Molen HD, Rijskamp A, Woldring MG. An improved method for the cyclotron production of ^{13}N-labelled ammonia. Int J Appl Radiat Isot 1975; 26: 316-318. http://dx.doi.org/10.1016/0020-708X(75)90169-6

[100]　Wieland B, Bida G, Padgett H, et al. In-target production of [^{13}N] ammonia via proton irradiation of dilute aqueous ethanol and acetic acid mixtures. Int J Rad Appl Instrum [A] 1991; 42: 1095-1098. http://dx.doi.org/10.1016/0883-2889(91)90018-V

[101]　Cyclotron produced radionuclides: physical characteristics and production methods. Vienna: International Atomic Energy Agency, 2009. Technical reports series, ISSN 0074-1914; no. 468.p. 203-209

[102]　Van Naeman J, Monclus M, Damhaut P, Luxen A, Goldman S. Production, automatic delivery and bolus injection of [^{15}O] water for positron emission tomography studies, Nucl. Med. Biol. 1966; 23: 413-416. http://dx.doi.org/10.1016/0969-8051(96)00014-5

[103]　Schelbert HR. Evaluation of myocardial blood flow in cardiac disease. In: Skorton DJ, Schelbert HR, Wolf GL, Brundage BH, eds. Cardiac Imaging. A Companion to Braunwald's Heart Disease. Philadelphia: WB Saunders; 1991:1093-1112.

[104]　ENDF/B-VI Decay data. [Accessed 11 Nov 2011]. http://t2.lanl. gov/data/endf/decayVI.html

[105]　Production techniques and quality control of sealed radioactive sources of palladium-103, iodine-125, iridium-192 and ytterbium-169. Final report of a coordinated research project 2001-2005. IAEA, TECDOC-1512, IAEA, VIENNA, 2006.p. 13-14.

[106]　Jerrold S, Stanley DC, Raymond JB, Ramon P, Juan O, Zucel S, William H, Alan C. Outpatient ultrasound-guided Palladium 103 brachytherapy for localized adenocarcinoma of the prostate: A preliminary report of 434 patients. Urology1998; 51(5): 796-803. http://dx.doi.org/10.1016/S0090-4295(98)00017-X

[107]　Richard EP, Zhe Chen, Kenneth R, Ravinder N. Long-term complications with prostate implants: Iodine-125 vs. palladium-103. Radiation Oncology Investigations 1999; 7(5): 278-288. http://dx.doi.org/10.1002/(SICI)1520-6823(1999)7:5<278::AID-ROI3>3.0.CO;2-3

[108]　[108]. Phosphorous-32 (^{32}P$_{15}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA Vienna, 2003.p. 158-166.

[109]　Summary of Product Characteristics Sodium Phosphate (^{32}P) 18.5-185 MBq/ml Injection http://www.mapmedical.fi/ cms/images/stories/docs/en/Sodium_Phosphate_32P.pdf

[110]　Lawrence JH, polycythemia physiology, diagnosis and treatment based on 303 cases.In Modern Medical Monographs Grune and Stratton; New York-London, 1955.

[111]　Package insert (Phosphocol by Mallinckrodt (rev. 1/81); Chromophosphotope by Squibb). http://www.drugs.com/mmx/phosphocol-p-32.html

[112]　Chromic Phosphate P 32 (Parenteral-Local) http://www.drugs.com/mmx/chromic-phosphate-p-32.html.

[113]　Powell JL, Burrell MO, Kirchner AB. Intraperitoneal radioactive chromic phosphate P 32 in the treatment of

[114]　ovarian cancer. South Med J 1987; 80(12): 1513-1517. http://dx.doi.org/10.1097/00007611-198712000-00007

[114]　Hladik WB, Saha GB, Study KT. Essentials of Nuclear Medicine Science. Williams & Wilkins, 1987.

[115]　Phosphocol P 32 package insert (Mallinckrodt rev. 8/90, recv'd 2/92). http://www.drugs.com/mmx/chromic-phosphate-p-32.html

[116]　Medical policy Excellus. https://www.excellusbcbs.com/wps/ wcm/connect/9347ef97-1087-4f0e-89bb-67c5c0e2438c/mp+intravasc_brachy+tac+14.pdf? MOD=AJPERES&CACHEID=9347ef97-1087-4f0e-89bb-67c5c0e2438c

[117]　Lawrence JH, Tobias CA. Radioactive isotopes and nuclear radiations in the treatment of cancer. Cancer Res 1950; 16: 185-193.

[118]　Friedell HL, Storaasli JP. The use of radioactive phosphorus in the treatment of carcinoma of the breast with widespread metastases to bone. Am J Roentgenol 1950; 64: 559-575.

[119]　Audi G, Wapstra AH, Thibault C, Blachot J, Bersillon O. (2003). The NUBASE evaluation of nuclear and decay properties (PDF). Nuclear Physics A 2003; 729: 3-128. Bibcode: 2003 Nu Ph A. 729.3A. http://dx.doi.org/10.1016/j.nuclphysa.2003.11.001

[120]　Curie P, Curie M, Bémont G. "Sur une nouvelle substance fortement radio-active, contenue dans la pechblende (On a new, strongly radioactive substance contained in pitchblende)". Comptes Rendus 1898; 127: 1215-1217.

[121]　Strutt RJ (7 September 2004). The Becquerel Rays and the Properties of Radium. https://books.google.com.pk/ books?id=alC0vvE-ZUwC&pg=PA220&lpg=PA220&dq= Strutt+RJ+The+Becquerel+Rays+and+the+Properties+of+Ra dium&source=bl&ots=3GBFvJofwO&sig=qF1VOIETs7O8nq w6pUJx__YBHpc&hl=en&sa=X&ved=0CDYQ6AEwBWoVCh MI8tupiuPVxgIVSjoUCh3f8Af8#v=onepage&q=Strutt%20RJ %20The%20Becquerel%20Rays%20and%20the%20Properti es%20of%20Radium&f=false

[122]　Redniss L. Radioactive: Marie & Pierre Curie: A Tale Of Love And Fallout. New York, NY: Harper Collins.2011.p. 70. ISBN 978-0-06-135132-7.

[123]　The Four Founding Physicians". http://www.hopkinsmedicine.org/about/history/history5.html

[124]　Dastur AE, Tank PD. "Howard Atwood Kelly: much beyond the stitch". The Journal of Obstetrics and Gynecology of India 2011; 60(5): 392-394. http://dx.doi.org/10.1007/s13224-010-0064-6

[125]　Aronowitz JN, Robison RF. "Howard Kelly establishes gynecologic brachytherapy in the United States". Brachytherapy 2010; 9(2): 178-184. http://dx.doi.org/10.1016/j.brachy.2009.10.001

[126]　Rebecca S (2 February 2010). The Immortal Life of Henrietta Lacks. Random House Digital, Inc. ISBN 978-0-307-58938-5 Retrieved 8 April 2013.

[127]　Radium. Encyclopædia Britannica. http://www.britannica.com/science/radium

[128]　Hayter C. "The Politics of Radon Therapy in the 1930s". An Element of Hope: Radium and the Response to Cancer in Canada, 1900-1940. McGill-Queen's Press. 2005. ISBN 978-0-7735-2869-7.

[129]　Harvie, DI. "The radium century". Endeavour 1999; 23(3): 100-105. http://dx.doi.org/10.1016/S0160-9327(99)01201-6

[130]　Larsen RH, Oyvind SB. "Radium Revisited" targeting of skeletal metastases by the alpha-emitter radium-223. http://www.bruland.info/PDF/195-202.pdf

[131]　Wick RW, Nekolla EA, Gøssner W, and Kellerer AM. Late effects in ankylosing spondylitis patients treated with 224Ra. Radiation Res 1999; 152: S8-S11. http://dx.doi.org/10.2307/3580103

[132]   4Ra treatment in ankylosing spondylitis. J. Nucl Med 2001 42S: 128P.

[133]   Nekolla EA, Kreisheimer M, Kellerer AM, Kuse IM, Gossner W, Spiess H. Induction of malignant bone tumors in radium-224 patients: Risk estimates based on the improved dosimetry. Radiat Res 2000; 153: 93-103.
http://dx.doi.org/10.1667/0033-7587(2000)153[0093:IOMBTI]2.0.CO;2

[134]   Radium Radiation Protection US EPA http://www.epa.gov/radiation/radionuclides/radium.html

[135]   Hideya Y, Takehiro I, Ken Y, Yasuo Y, Souhei F, Naoya K, Kimishige S. Comparison of three major radioactive sources for brachytherapy used in the treatment of node negative T1-T3 oral tongue cancer: Influence of age on outcome. Anticancer Research 2007; 27: 491-498.

[136]   Rhenium-186 ($^{186}Re_{75}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA Vienna, 2003.p. 179-185.

[137]   Zhang X, Li W, Fang K, et al. Excitation functions for $^{nat}W(p, xn)^{181-186}Re$ reactions and production of no-carrier-added ^{186}Re via $^{186}W(p, n)^{186}Re$ reaction. Radiochim Acta 1999; 86: 11-16.
http://dx.doi.org/10.1524/ract.1999.86.12.11

[138]   Shigeta N, Matsuoka H, Osa A, Koizumi M, Izumo, M, Kobayashi K, Hashimoto K, Sekine T, Lambrecht RM. Production method of no-carrier-added ^{186}Re. Radioanal Nucl Chem 1996; 205: 85-92.
http://dx.doi.org/10.1007/BF02040553

[139]   Szelecsenyi S, Takacs S, Tarkanyi F, Sonck M, Hermanne A. Study of production possibility of ^{186}Re via the $^{186}W(d,2n)^{186}Re$ nuclear reaction for use in radiotherapy. J Lab Cmpds Radiopharm 1999; 42: Suppl. 1 S912-S914.

[140]   EANM Procedure Guidelines for Radiosynovectomy. Eur J Nucl Med 2003; 30: BP12 BP16.

[141]   Robinson K, Pipes DW, Von BR, et al. ^{186}Re-Liquid-filled balloon catheter system for endovascular brachytherapy: dose-response efficacy study and biodistribution after coronary injection," Circulation Suppl. I 1998; 3432.

[142]   PARS Isotope Company, file:///C:/Users/M.%20PC/Downloads/parsisotopepdf20141007041005.pdf

[143]   Rhenium-188 ($^{188}Re_{75}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA Vienna, 2003.p. 186-188.

[144]   Therapeutic radionuclide generators: $^{90}Sr/^{90}Y$ and $^{188}W/^{188}Re$ generators. Technical reports series, ISSN 0074-1914; no. 470 International Atomic Energy Agency, Vienna 2009.

[145]   Wang SJ, Lin WY, Hsieh BT, Shen LH, Tsai ZT, Ting G, Knapp FF. Rhenium-188 sulphur colloid as a radiation synovectomy agent. Eur J Nucl Med 1995; 22: 505-507.
http://dx.doi.org/10.1007/BF00817272

[146]   Jungfeng Y, et al., [^{188}Re] Rhenium sulfide suspension: A potential radiopharmaceutical for tumor treatment following intra-tumor injection, Nucl Med Biol 1999; 26: 573-579.
http://dx.doi.org/10.1016/S0969-8051(99)00017-7

[147]   Venkatesan PP, Shortkroff S, Zalutsky MR, Sledge CB, Rhenium heptasulfide: A potential carrier system for radiation synovectomy, Nucl Med Biol 1990; 17: 357-362.
http://dx.doi.org/10.1016/0883-2897(90)90101-6

[148]   Knapp FF. Jr, Guhlke S, Beets, AL, et al. Rhenium-188 — attractive properties for intravascular brachytherapy for inhibition of coronary restenosis after PTCA. J Nucl Cardiol 1997; 4: S-118.
http://dx.doi.org/10.1016/S1071-3581(97)91584-1

[149]   Giedd KN, Amols H, Marboe C, et al. Effectiveness of beta-emitting liquid-filled perfusion balloon to prevent restenosis, Circulation 1997; 96: 1-220.

[150]   Knapp FF (Russ) Jr. Set-Up, general use and quality control of the ORNL Tungsten-188/Rhenium-188 generator system

and methods for concentration of Rhenium-188 to high specific volume solutions. January 9, 2009, Oak Ridge National Laboratory (ORNL) http://web.ornl.gov/sci/nsed/fcid/nuc_med/GENERATOR-SET-UP-USE-PROCEDURE-1-09-09.pdf

[151]   Radionuclide safety data sheet. Nuclide Sr-82/Rb-82 Generator. http://web.stanford.edu/dept/EHS/prod/researchlab/radlaser/RSDS_sheets/Sr-82.pdf

[152]   Cackette MR, Ruth TJ, Vincent JS. ^{82}Sr production from metallic Rb targets and development of an ^{82}Rb generator system, Appl. Radiat. Isot 1993; 44: 917-922.
http://dx.doi.org/10.1016/0969-8043(93)90045-C

[153]   Thomas KE. Strontium 82 production at Los Alamos National Laboratory. Int J Appl Radiat Isot. 1987; 38:175-180.
http://dx.doi.org/10.1016/0883-2889(87)90083-9

[154]   Cardiogen-82. http://www.drugs.com/pro/cardiogen-82.html.

[155]   Alvarez-Diez TM, Dekemp R, Beanlands R, Vincent JS. Manufacture of strontium-82/rubidium-82 generators and quality control of rubidium-82 chloride for myocardial perfusion imaging in patients using positron emission tomography. Appl Radiat Isot 1999; 50:1015-1023.
http://dx.doi.org/10.1016/S0969-8043(98)00170-5

[156]   Kim SH, Machac J, Almeida O. Optimization of rubidium-82 generator performance. Clin Nucl Med. 2004; 29: 135.

[157]   Strontium-89 ($^{89}Sr_{38}$); Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA Vienna, 2003.p. 206-216.

[158]   Strontium Chloride Sr-89. http://www.drugs.com/pro/strontium-chloride-sr-89.html.

[159]   Production of long lived parent radionuclides for generators: ^{68}Ge, ^{82}Sr, ^{90}Sr and ^{188}W. IAEA radioisotopes and radiopharmaceuticals series-2. International Atomic Energy Agency, 2010.p.49-78.

[160]   Strontium, US, Environmental Protection Agency. http://www.epa.gov/radiation/radionuclides/strontium.html.

[161]   Pokrajac B, Kirisits C, Schmid R, Schillinger M, Berger D, Peer K, Tripuraneni P, Pötter R, Minar E. Beta endovascular brachytherapy using CO2-filled centering catheter for treatment of recurrent superficial femoropopliteal artery disease. Cardiovasc Revasc Me. 2009; 10(3): 162-165.
http://dx.doi.org/10.1016/j.carrev.2009.02.005

[162]   van Ginderdeuren R, Evan L, Spileers W. 18 Years' experience with high dose rate strontium-90 brachytherapy of small to medium sized posterior uveal melanoma. Br J Ophthalmol 2005; 89: 1306-1310.
http://dx.doi.org/10.1136/bjo.2005.068460

[163]   Victoria MLC, Vasilios PP, Liu S, Ian S, John LH. The use of Strontium-90 beta radiotherapy as adjuvant treatment for conjunctival melanoma. Journal of Oncology Volume 2013 (2013), Article ID 349162, 7 pages
http://dx.doi.org/10.1155/2013/349162

[164]   A. Mushtaq A. Preparation of high specific volume solutions of Technetium-99m and Rhenium-188. Appl Radiat Isot 2003; 58: 309-314.
http://dx.doi.org/10.1016/S0969-8043(02)00353-6

[165]   Muenze R, Beyer GJ, Ross R, Wagner G, Novotny D, Franke E, Jehangir M, Pervez S, Mushtaq A. The fission-based 99Mo production process ROMOL-99 and its application to PINSTECH Islamabad. Science and Technology of Nuclear Installations, 2013, Article ID 932546, 9 pages.
http://dx.doi.org/10.1155/2013/932546

[166]   Mushtaq A, Pervez S, Hussain S, Mirza JA, Khan MM, Asif M, Siddique MU, Khalid U, Khan B, Khalid M. Evaluation of Pakgen ^{99m}Tc generators loaded with indigenous fission ^{99}Mo. Radiochim Acta. 2012; 100: 793-800.
http://dx.doi.org/10.1524/ract.2012.1945

[167]   Senden TJ, Moock KH, Gerald JF, Burch WM, Browitt RJ, Ling CD, Heath GA. The physical and chemical nature of

technegas. J Nucl Med 1997; 38(8): 1327-1333.

[168] Bajc M, Leblanc M, Lemb M. SPECT lung images demonstrate precise localisation & characterisation of defects. file:///C:/Users/M.%20PC/Downloads/ 090415%20TECHNEGAS%20SALES%20BROCHURE.pdf

[169] Bajc M, Neilly JB, Miniati M, Schuemichen C, Meignan M, Jonson B, EANM guidelines for ventilation/perfusion scintigraphy Part 1. Pulmonary imaging with ventilation/perfusion single photon emissionTomography, Eur J Nucl Med Mol Imaging 2009; 36: 1356-1370.
http://dx.doi.org/10.1007/s00259-009-1170-5

[170] Alazraki NP, et al., Lymphoscintigraphy, the sentinel node concept, and the intraoperative gamma probe in melanoma, breast cancer, and other potential cancers. Semin Nucl Med 1997; 27: 55-67.
http://dx.doi.org/10.1016/S0001-2998(97)80036-0

[171] Strand SE, Persson BR. Quantitative lymphoscintigraphy I: Basic concepts for optimal uptake of radiocolloids in the parasternal lymph nodes of rabbits, J Nucl Med 1979; 20: 1038-1046.

[172] O'Btien CJ., et al., Prediction of potential metastatic sites in cutaneous head and neck melanoma using lymphoscintigraphy. Am J Surg 1995; 170: 461-466.
http://dx.doi.org/10.1016/S0002-9610(99)80330-4

[173] Ponto JA. Adverse reactions to technetium-99m colloids. J Nucl Med 1987; 28: 1781-1782.

[174] Hung JC, et al., Filtered technetium-99m-sulfur colloid evaluated for lymphoscintigraphy, J Nucl Med 1995; 36: 1895-1901.

[175] Ege GN. Internal mammary lymphoscintigraphy. The rationale, technique, interpretation and clinical application: a review based on 848 cases, Radiology 1976; 118: 101-107.
http://dx.doi.org/10.1148/118.1.101

[176] Richards TB, Mcbiles M, Collins, PS. An easy method for diagnosis of lymphedema, Ann. Vasc Surg 1990; 4: 255-259.
http://dx.doi.org/10.1007/BF02009453

[177] Summary of product characteristics for NANOCIS, kit for the preparation of technetium (^{99m}Tc) colloidal rhenium sulphide injection (Nanocolloid), Danish Medicines Agency. March 16th 2011. https://www.google.com.pk/ webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=tc-99m+rhenium+sulfide+colloid&start=20

[178] Technetium-99m radiopharmaceuticals: manufacture of kits. International Atomic Energy Agency, 2008. Technical reports series, ISSN 0074-1914; no. 466, p.105-108.

[179] European Directorate for The Quality of Medicines, Technetium (^{99m}Tc) colloidal tin injection, European Pharmacopoeia, 5th edn, EDQM, Council of Europe, Strasbourg 2005. 853.

[180] Akhter M, Mushtaq A, Haider I, Aziz A, Karim HMA. Technetim-99m tin colloid; A simple method for the preparation and evaluation. J Radioanal Nucl Chem Letters 1990; 146: 415-420.
http://dx.doi.org/10.1007/BF02199264

[181] Higashi H., et al., Particle size of tin and phytate colloid in sentinel node identification, J. Surg Res 2004; 121: 1-4.
http://dx.doi.org/10.1016/j.jss.2004.02.011

[182] Uenosono Y., et al., Evaluation of colloid size for sentinel nodes detection using radioisotope in early gastric cancer, Cancer Lett 2003; 200:19-24.
http://dx.doi.org/10.1016/S0304-3835(03)00389-6

[183] Technetium-99m Radiopharmaceuticals; Manufacture of kits, Technical report series No. 466, International Atomic Energy Agency, Vienna, 2008.p. 102-104.

[184] TechneLite® (Technetium Tc 99m Generator) http://www.technelite.com/about_technelite.html

[185] Ultra-TechneKow™ DTE (Technetium Tc 99m Generator) file:///C:/Users/M.%20PC/Downloads/a880I0-in0000-

us0214.pdf

[186] Celso Darío Ramos, Denise Engelbrecht Zantut Wittmann, Elba Cristina Sá de Camargo Etchebehere, Marcos Antonio Tambascia, Cleide Aparecida Moreira Silva, Edwaldo Eduardo Camargo, Thyroid uptake and scintigraphy using 99mTc pertechnetate: standardization in normal individuals. Sao Paulo Med. J. vol.120 no.2 São Paulo Mar. 2002.
http://dx.doi.org/10.1590/S1516-31802002000200004

[187] Nuclear Imaging of Meckel's Diverticulum: A Pictorial Essay of Pitfalls. Huynh S, Amin R, Barron B, Dhekne R, Nikolaidis P, Lamki L. University of Texas Houston Medical School and Memorial Hermann - Texas Medical Center (TMC), St. Luke's Episcopal Hospital and Texas Children Hospital, Houston, Texas. Last Modified September 5, 2007.

[188] Robert D, Robin R, Abass A. The Role of Cimetidine-Enhanced Technetium 99m-Pertechnetate Imaging for Visualizing Meckel's Diverticulum. The Journal of Nuclear Medicine 1991; 32(7): 1422-1424.

[189] Technetium TC 99M Pyrophosphate; http://www.drugs.com/ pro/technetium-tc-99m-pyrophosphate.html

[190] MPI Pyrophosphate Kit Kit for the Preparation of Technetium Tc 99m Pyrophosphate Diagnostic-For Intravenous Use. http://www.nuclearonline.org/PI/ Nycomed%20PYP.pdf

[191] Standardized High Current Solid Targets for Cyclotron Production of Diagnostic and Therapeutic Radionuclides, Technical Reports Series No. 432, IAEA, Vienna (2004) CD-ROM.

[192] Parker JA, Markis JE, Royal HD. Assessment of regional wall motion and perfusion by multigated myocardial scintigraphy after intracoronary Tl-201. Radiology 1985; 154: 783-786.
http://dx.doi.org/10.1148/radiology.154.3.3969484

[193] Berman DS, Kiat H, Maddahi J, et al. Radionuclide imaging of myocardial perfusion and viability in assessment of acute myocardial infarction. Am J Cardiol 1989; 64: 9B-16B
http://dx.doi.org/10.1016/S0002-9149(89)80003-7

[194] Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. Circulation 1991; 83: 363-381.
http://dx.doi.org/10.1161/01.CIR.83.2.363

[195] Wackers FJT. Comparison of thallium-201 and technetium-99m methoxyisobutyl isonitrile. Am J Cardiol 1992; 70: 30E-34E.
http://dx.doi.org/10.1016/0002-9149(92)90036-X

[196] Boucher CA, Okada RD. Thallium-201 myocardial perfusion imaging without exercise. Chest 1984; 86: 159-61.
http://dx.doi.org/10.1378/chest.86.2.159

[197] Lette J, Waters D, Lapointe J, et al. Usefulness of the severity and extent of reversible perfusion defects during thallium-dipyridamole imaging for cardiac risk assessment before noncardiac surgery. Am J Cardiol 1989; 64: 276-281.
http://dx.doi.org/10.1016/0002-9149(89)90519-5

[198] Bairey CN, Rozanski A, Maddahi J, et al. Exercise thallium-201 scintigraphy and prognosis in typical angina pectoris and negative exercise electrocardiography. Am J Cardiol 1989; 64: 282-287.
http://dx.doi.org/10.1016/0002-9149(89)90520-1

[199] Kaul S. Superiority of quantitative exercise thallium-201 variables in determining long-term prognosis in ambulatory patients with chest pain: a comparison with cardiac catheterization. J Am Coll Cardiol 1988; 12: 25-34.
http://dx.doi.org/10.1016/0735-1097(88)90351-8

[200] Esquivel L, Pollock SG, Beller GA, et al. Effect of the degree of effort on the sensitivity of the exercise thallium-201 stress test in symptomatic coronary artery disease. Am J Cardiol 1989; 63: 160-165.
http://dx.doi.org/10.1016/0002-9149(89)90278-6

[201] Maisey MN, Britton KE, Gilday DL. Clinical nuclear medicine. 2nd ed. Philadelphia: J.B. Lippincott, 1991: 256-257.
http://dx.doi.org/10.1007/978-1-4899-3358-4

[202]   Thallous Chloride Tl 201 package insert (Amersham-US), Rev 5/95, Rec 11/95. http://www.nuclearonline.org/PI/Nycomed%20Tl-201%20Tl%20Chloride.pdf

[203]   Thallous Chloride Tl 201 package insert (Du Pont-US), Rev 7/91, Rec 11/95. http://www.drugs.com/mmx/ thallous-chloride-tl-201.html

[204]   Hoefnagel CA, Delprat CC, Marcuse HR, et al. Role of thallium-201 total-body scintigraphy in follow-up of thyroid carcinoma. J Nucl Med 1986; 27(12): 1854-1857.

[205]   Ganz WI, Serafini AN. The diagnostic role of nuclear medicine in the acquired immunodeficiency syndrome. Nucl Med 1989; 30: 1935-1945.

[206]   [206]Tonami N, Hisada K. Thallium-201 scintigraphy in postoperative detection of thyroid cancer: a comparative study with I-131. Radiology 1980; 136(2): 461-464. http://dx.doi.org/10.1148/radiology.136.2.7403524

[207]   Ochi H, Sawa H, Fukuda T, et al. Tl-201-chloride thyroid scintigraphy to evaluate benign and/or malignant nodules. Cancer 1982; 50: 236-240. http://dx.doi.org/10.1002/1097-0142(19820715)50:2<236::AID-CNCR2820500213>3.0.CO:2-V

[208]   Waxman AD. Thallium-201 in nuclear oncology. Nucl Med Ann. Raven Press, New York. 1991; 193-209

[209]   Pohost GM. The value of thallium-201 imaging [editorial]. N Engl J Med 1990; 323(3): 190. http://dx.doi.org/10.1056/NEJM199007193230309

[210]   Stratmann HG, Mark AL, Walter KE, et al. Prognostic value of atrial pacing and thallium-201 scintigraphy in patients with stable chest pain. Am J Cardiol 1989; 64: 985-990. http://dx.doi.org/10.1016/0002-9149(89)90795-9

[211]   Brown KA. Prognostic value of thallium-201 myocardial perfusion imaging: a diagnostic tool comes of age. Circulation 1991; 83: 363-381 http://dx.doi.org/10.1161/01.CIR.83.2.363

[212]   Gupta SM, Belsky JL. Use of oral phosphate to enhance visualization of enlarged parathyroids on scanning [letter]. J Nucl Med 1985; 26(1): 100

[213]   Kailasnath P, Albert JS. Comparison of Tl-201 with Tc-99m-labeled myocardial perfusion agents: Technical, physiologic, and clinical issues. Journal of Nuclear Cardiology 2001; 8: 482-498. http://dx.doi.org/10.1067/mnc.2001.115078

[214]   Khalid M, Mushtaq A. Preparation and in vitro stability of (n, γ) yttrium-90 hydroxyapatite. Appl Radiat Isot 2005; 62(4): 587-590. http://dx.doi.org/10.1016/j.apradiso.2004.08.046

[215]   Yttrium-90 (^{90}Y$_{39}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, Vienna 2003.p. 244-247.

[216]   Chinol M, Hnatowich DJ. Generator-produced Yttrium-90 for radioimmunotherapy. J Nucl Med 1987; 28: 1465-1470.

[217]   Wike JS, Guyer CE, Ramey DW, Phillips BP. Chemistry for commercial scale production of Yttrium-90 for medical research. Appl Radiat Isot 1990; 41: 861-865. http://dx.doi.org/10.1016/0883-2889(90)90064-N

[218]   Therapeutic radionuclide generators: ^{90}Sr/^{90}Y and 188W/188Re generators. Technical reports series, ISSN 0074-1914; no. 470. International Atomic Energy Agency, Vienna 2009.p.51-105.

[219]   Schmid E, Selbach HJ, Voth M, et al. The Effect of the β-emitting Yttrium-90 citrate on the dose-response of dicentric chromosomes in human lymphocytes: a basis for biological dosimetry after radiosynoviorthesis. Radiat Environ Biophys 2006; 45: 93-98. http://dx.doi.org/10.1007/s00411-006-0045-4

[220]   Gencoglu EA, Aras G, Kucuk O, et al. Utility of Tc-99m human polyclonal immunoglobulin G scintigraphy for assessing the efficacy of Yttrium-90 silicate therapy in Rheumatoid Knee Synovitis. Clin Nucl Med 2002; 27: 395-400. http://dx.doi.org/10.1097/00003072-200206000-00001

[221]   Muller, J. H.; Roessier, P. H. Acta Radiol. 1951, 35, 449. http://dx.doi.org/10.3109/00016925109136677

[222]   Harbert JC, Ziessman H A. Nuclear Medicine Annual; Freeman LM,Weissman HS. Eds. Raven Press: New York, 1987; p 295.

[223]   Ehrhardt GJ, Day D E. Int J Radiat Appl Instrum. Part B Nucl Med Biol 1987; 14: 233-242. http://dx.doi.org/10.1016/0883-2897(87)90047-X

[224]   Deleporte A, Flamen P, Hendlisz A. State of the art: Radiolabeled microspheres treatment for liver malignancies. Expert Opin Pharmacother 2010; 11(4): 579-586. http://dx.doi.org/10.1517/14656560903520916

[225]   Technical Leaflet Yttrium [^{90}Y] Silicate Injection http://abush.health.gov.il/units/pharmacy/trufot/alonim/1028.pdf

[226]   Xenon-133 (^{133}Xe$_{54}$) Manual for Reactor Produced Radioisotopes, IAEA TECDOC-1340, IAEA, Vienna, 2003.p. 248-251.

[227]   Xenon Xe 133 Gas. http://www.drugs.com/pro/xenon-xe-133-gas.html

[228]   Hoshi H, Jinnouchi S, Watanabe K, Onishi T, Uwada O, Nakano S, Kinoshita K. (1987). Cerebral blood flow imaging in patients with brain tumor and arterio-venous malformation using Tc-99m hexamethylpropylene-amine oxime--a comparison with Xe-133 and IMP. Kaku igaku. The Japanese journal of nuclear medicine 1987; 24(11): 1617-1623.

[229]   Jones R L, Sproule BJ, Overton TR. Measurement of regional ventilation and lung perfusion with Xe-133. Journal of nuclear medicine 1978; 19 (10): 1187-1188.