7. Radioisotopes in Medicine

Radionuclides were first used for therapeutic purposes almost 100 years following the observation by Pierre Curie that radium sources brought into contact with the skin produced burns. Already by 1915, sealed sources of radium-226 and radon-222 were in use. By the 1950s radiotherapy had become much more widespread due to the development of remote source handling techniques and the availability of reactor produced radionuclides such as cobalt-60.

Ionising radiation from radionuclides kills cells by damaging the DNA thereby inhibiting cellular reproduction. The energy of the radiation (in the form of photons, electrons, heavy particle, etc.) required to damage DNA should be greater than a few electron volts (eV) corresponding to the binding energy of the outer electrons [1].

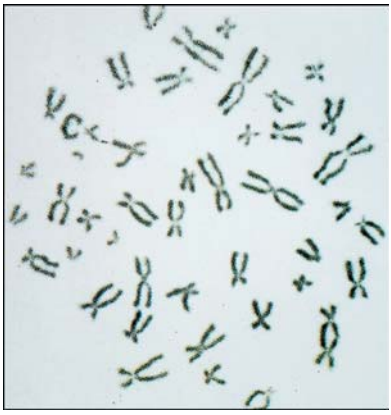

Fig. 7.1. A collection of normal chromosomes with their single centres (indicated by a X shape). An anomalous chromosome with a double centre (XX) can be seen at the bottom right-hand corner. © CEA-IPSN

Imaging

Nuclear diagnostic imaging techniques provide information about physiological and biochemical processes and compliment other imaging methods such as conventional radiology, nuclear magnetic resonance, and ultrasound. They have a very important role to play in identification of heart disease, brain disorder, lung and kidney function, and a range of cancers.

Gamma Imaging

One of the main applications in medical applications is the use of gamma cameras to detect diseases in the heart, brain, bone, lung, and the thyroid. More than 20,000

Table 7.1. Main isotopes used for gamma imaging

Organ	Nuclide
Lung	^{81m}Kr, ^{99m}Tc, ^{133}Xe
Bone	^{99m}Tc
Thyroid	^{99m}Tc, ^{123}I, ^{131}I
Kidney	^{99m}Tc, ^{111}In,, ^{131}I
Brain	^{99m}Tc, ^{123}I, ^{133}Xe
Liver, pancreas	^{99m}Tc, ^{111}In
Abdomen	^{67}Ga, ^{99m}Tc
Blood	^{99m}Tc, ^{111}In
Heart	^{82}Rb, ^{99m}Tc, ^{201}Tl

gamma cameras are in use throughout the world in some 8500 nuclear medicine departments [2]. The main radionuclide in use is ^{99m}Tc, however other nuclides are also in use as summarised in Table 7.1.

Positron Emission Tomography (PET)

There are some 250 PET cameras in use today mainly for the diagnosis of cancer. The radio-pharmaceutical mostly used is the ^{18}F compound fluoro-deoxy-glucose which is similar to glucose in behaviour, ahough the development of alternatives based on ^{64}Cu, ^{86}Y, and ^{124}I is underway.

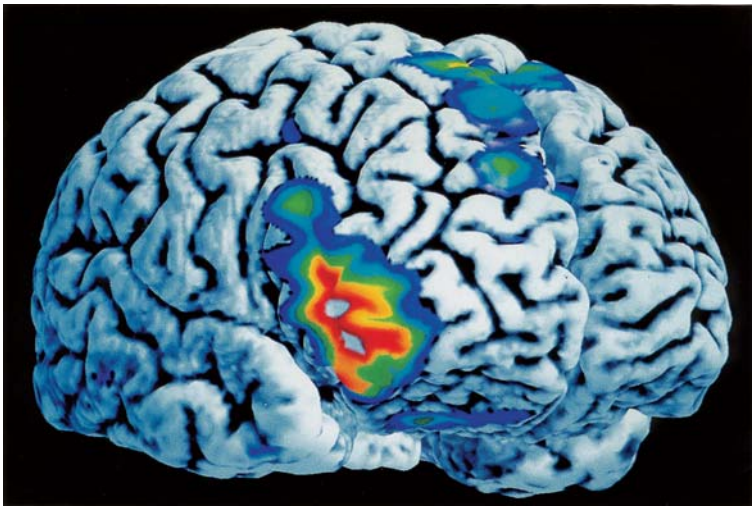

Fig. 7.2. Superposition of magnetic resonance imaging (which shows the morphology of the brain) and positron emission tomography showing the active areas (coloured zones) in the brain. Courtesy of the Montréal Neurological Institute, McGill University

External Beam Radiotherapy

In external beam radiotherapy, where radiation is delivered from outside the body, photon energies of millions of electron volts are required to penetrate the tissue and reach the tumours inside the body. Radiotherapy is also being carried out with sealed sources of ^{60}Co with some 1500 units in operation. A new process, known as the Gamma Knife, is being introduced especially for brain tumour treatment.

Brachytherapy

Today, hundreds of thousand of patients are treated each year based on brachytherapy (Brachys is the Greek word for near) in which sealed sources of radiation are brought into the body and placed in or near the tumour to be treated leaving the surrounding healthy tissue undamaged. Using these brachytherapy implants, radionuclides with photons energies as low as 20 keV can be used. The radionuclide palladium-103, for example, used for prostate implantation has an average energy of only 21 keV. Some gamma ray emitters commonly used are ^{192}Ir, ^{137}Cs, ^{125}I, ^{103}Pd and have an effective range of a few centimetres. Beta emitters include ^{90}Y, ^{188}Re, and ^{32}P with effective ranges of a few millimetres in tissue [3].

The technique is particularly successful for the treatment of prostate cancer at an early stage. In the U.S. almost 57,000 patients were treated for prostate cancer in 1999 using brachytherapy seed implants based on ^{103}Pd, ^{125}I, ^{137}Cs and ^{192}Ir.

Immunotherapy

In the last ten years, the technique known as radio-immunotherapy has been under investigation. In this technique, a radionuclide is chemically attached to an antibody which is then injected into the bloodstream. The antibodies go to the source of the tumour and the attached radionuclides, for example ^{131}I, emit charged particles to kill the tumour cells. The development of therapeutic substances for radiotherapy is being actively pursued by many companies and research organisations. Techniques are being developed which combine the radioisotopes ^{90}Y, ^{131}I, ^{153}Sm, and ^{213}Bi with monoclonal antibodies and smaller molecules such as peptides. The three main applications of radionuclides for therapeutic purposes, however, remain a) sealed sources for prostrate therapy, b) sources for intravascular therapy and c) radio-pharmaceutical therapy. It is expected that these therapies will see rapid growth in the near future.

Ion Beam Therapy

In December 1997, the GSI heavy ion radiotherapy started with the irradiation of the first two patients. The distribution of biological effective dose (isodose contours from carbon ion deposition) is shown in Fig. 7.3 superimposed on the image of the brain. The tumour, situated in the centre of the brain, is treated directly by depositing the ion beam energy in this region.

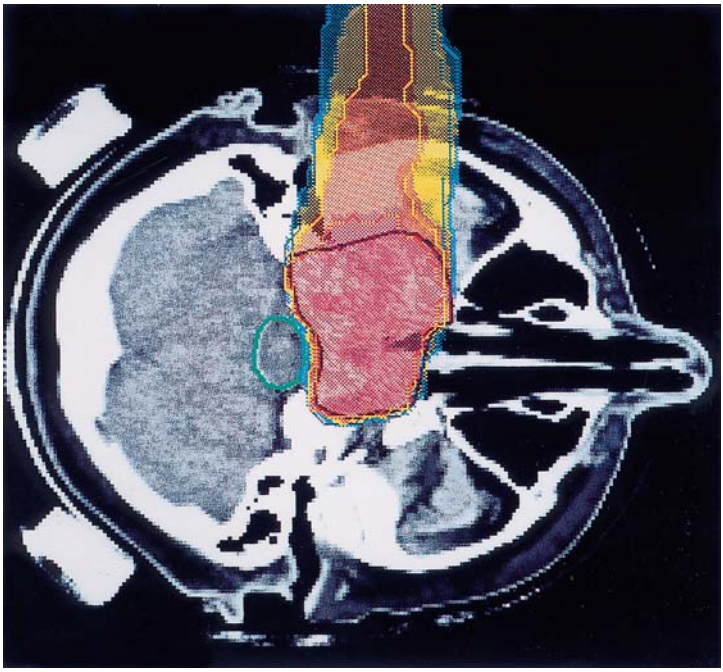

Fig. 7.3. Distribution of biological effective dose (isodose contours from carbon ion deposition) is shown superimposed on the image of the brain. © Gesellschaft für Schwerionenforschung mbH

Boron Neutron Capture Therapy

In Boron Neutron Capture Therapy (BNCT), a boron containing compound is administered intravenously to the patient. The boron accumulates preferentially in the malignant tumour. The patient is then irradiated with a beam of intermediate energy neutrons of a few keV, directed towards the tumour bed. The neutrons lose their energy through neutron scatter in the overlying tissue, whereby the thermalised neutrons are then captured by the ^{10}B atoms. These immediately disintegrate into two highly energetic particles: Li- and He-nuclei, which in principle can destroy the cancer cells, whilst sparing the healthy cells.

The American biophysicist G. L. Locher first came up with the idea of the NCT treatment in 1936. Pioneering work in the development of BNCT was carried out in the 1950s and 1960s at Brookhaven and MIT in the USA.

However, initial clinical results were disappointing. With hindsight, this was due to the non-accumulation in the tumour of the boron compounds used at the time and also the use of low energy neutrons, which in order to be able to give a high enough dose at depth, produced very high doses at shallower depths in healthy tissue. Nevertheless, in the late 1960s and early 1970s, improvements in both drug delivery and construction of higher energy neutron beams, led to a major improvement in this therapy [4].

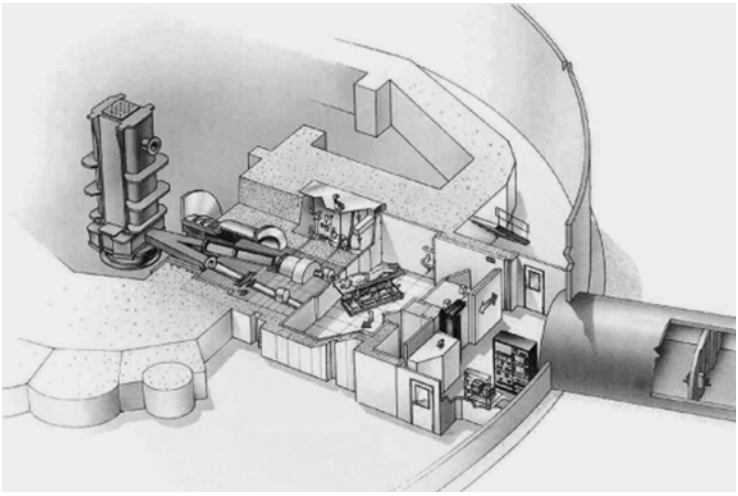

Fig. 7.4. BNCT: Clinical facility in Petten, showing the irradiation room, which has been built to reflect as closely as possible, a hospital-type environment. The clinical facilities have been installed at the High Flux Reactor (HFR) of the Joint Research Centre of the European Union (EU) in Petten. Courtesy R. Moss

Since October 1997, the first European clinical trial on BNCT is being performed at the High Flux Reactor of the Joint Research Centre of the European Commission, under the guidance of clinicians from the University of Essen and in collaboration with NRG Petten and five other hospitals. A Phase I clinical trial for the post-operative BNCT treatment of patients with glioblastoma multiforme, targets this highly aggressive brain tumour, which affects around 15,000 people in Europe every year.

The trial is the first of its type in Europe and is also the first time that a clinical application has been realised on a completely multi-national scale, whereby a unique facility localised in one country (The Netherlands), is operated by radiotherapists from another country (Germany), and treats patients coming from different countries (France, Germany, Austria, Switzerland and The Netherlands).

Since the start of BNCT trials at Petten, four other centres are performing BNCT in Europe (in Finland, Sweden, Czech Republic and Italy). Elsewhere in the world, BNCT is also carried out in Japan, USA and Argentina.

Radioactive “Bullets” – Alpha-Immunotherapy

Form the early 1980s, a new form of treatment for cancer therapy based on the use of radioactice isotope “bullets” in diseased cells began to attract increasing interest. Previouly, treatment mainly involved the use of relatively low energy beta emitters. More recently, isotopes emitting alpha particles have been recognised as more effective and selective against blood-borne cancers, widespread tumours, and residual cells remaining after surgical intervention. Production of suitable alpha emitters,

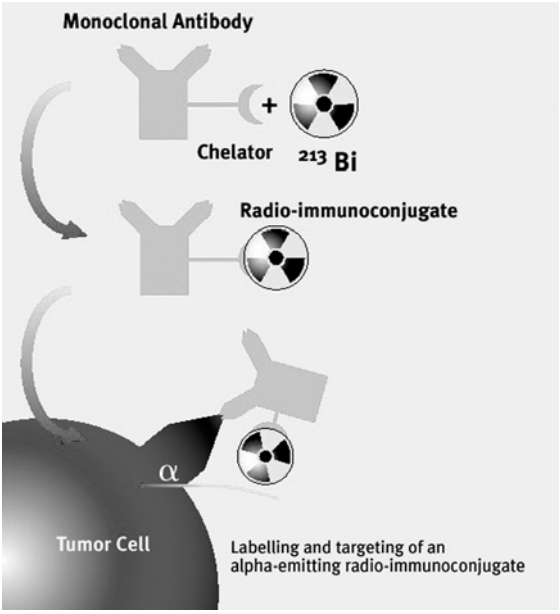

Fig. 7.5. ^{213}Bi is coupled to a monoclinical antibody using a chelation agent. The alpha emitting radionuclide is then close enough to the cancerous cell to destroy it with little damage to the surrounding tissue.

their stable coupling to suitable carriers, and safe use of such tools in hospitals have become the main goals.

Treatment of cancer by radio-immunotherapy involves injecting the patient with a radioactive isotope "bullet" connected to a specific carrier such as a monoclonal antibody, with the aim of selectively destroying targeted tumour cells. During radioactive decay, photons, electrons, or even heavier particles are emitted and damage or kill cells along their trajectory.

Alpha-emitting radionuclides are amongst the most promising radionuclides for the treatment of blood-borne cancers and micro-metastatic cancers cells. Because of their short range (60 to 100 micrometer) and high linear energy transfer values, alpha-emitters can deliver such a high radiation dose over the distance of a few cell diameters that they will effectively kill the cells. When alpha-emitters are conjugated to tumour-seeking monoclonal antibodies (a protein molecule that attaches to the cell), the resulting product is expected to be an efficient cancer drug. Other smaller molecular weight carriers such as peptides and fragments of the antibodies are being investigated because they can enter into larger sized tumours.

A number of alpha-emitting isotopes have been considered, but most gave rise to various drawbacks that preclude large-scale implementation. The preferred option today is the use of bismuth-213 (^{213}Bi), which has a half-life of 45 minutes. Actually ^{213}Bi is mainly a beta emitter with half-life of 46 m. This nuclide decays however to ^{213}Po, a very short-lived (half-life 4.2 μs) nuclide, which decays by alpha emission. So effectively ^{213}Bi is an alpha emitter with a half-life of 46 m. Actinium-225 (^{225}Ac), which has a half-life of 10 days and is the parent nuclide of ^{213}Bi, does not occur

in nature. The actinium isotope can, however, be obtained in small quantities from nuclear waste.

The first European clinical trials of such alpha-immunotherapy started in April 2000 in Basel on patients with glioblastoma and, since early 2001, in Heidelberg on patients with non-Hodgkin’s-lymphoma. The results vary from highly promising indications to cautious optimism, depending on the type and status of the disease. At the Memorial Sloan-Kettering Cancer Center in New York, clinical trilas are also continuing on patients with acute myeloid leukaemia. Other aspects of pre-clinical trials are being studied in Germany, Belgium and France. Clinical trial on leukaemia patients showed that the alpha particles were 100–1000 times more cytotoxic than beta particles, which have also been used, and caused much less damage to surrounding healthy tissue [5].