Evolution and progress in the application of radiation in cancer diagnosis and therapy

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Cancer is a ubiquitous health problem globally caused by poor food quality, environmental pollution, genetic factors, etc. Despite the manifold presumptive theories put forth for its causation, there is an extreme paucity of knowledge as regards the actual etiology of cancer, as well as any preventive or prophylactic therapy. The treatment options available include surgery, chemotherapy and radiation therapy (both internal and external). There have been technical and technological advancements in the fields of 'cancer surgery' and 'cancer chemotherapy', and radiotherapy in oncology is not too far behind. X-rays (from linear accelerators LINACs) and gamma rays (e.g. in Bhabhatron) are commonly used for radiation treatment of various types of cancers. New developments include proton beam therapy (PBT) and heavy ion beam therapy (IBT) (e.g. C^{+6} ion). These new developments of PBT and IBT offer significant advantages to treat paediatric patients, and to radiate deep-seated and radioresistant tumours. This article gives an overview of the various radiation therapies used worldwide, cost comparison of setting up these facilities, operational and treatment costs and advantages, limitations as well as the present status of different charged particle therapy facilities available worldwide.

Keywords: Accelerators, cancer, diagnosis, oncology, radiation therapy.

CANCER (a generic term for more than 100 different diseases characterized by uncontrolled, abnormal growth of cells) is one of the major killer diseases in humans whose origins are not yet well established despite extensive research in different international laboratories and hospitals all over the world. There are various kinds of cancers, e.g. breast cancer which accounts for 23% of all cancer cases in females, brain cancer, lung cancer, gastrointestinal (GI) cancer, cervical cancer, prostate cancer, etc. The treatment and prognosis are dependent upon the stage at which the cancer is detected, which in turn is governed by the accurate and sensitive cancer diagnostic methodology. Imaging techniques based on different radiations like X-rays and γ-rays are highly valuable, and are internationally recognized 'gold standards' for cancer diagnosis. X-rays, γ-rays, α-particles, protons and heavy ions are useful for radiation therapy before or after the surgery of a cancerous organ. Radiation therapy can be given by internal radiation (brachytherapy) or external radiation for the treatment of cancer. About 4% of people in developed countries are diagnosed with cancer each year, and more than 50% of these patients are subjected to radiation therapy, along with surgery, as a part of their treatment protocols. Radiation therapy may be used with curative intent, or as a palliative treatment, where cure is not possible. It can be used alone or in combination with other approaches (surgery and chemotherapy) to treat localized solid tumours (e.g. cancers of the skin, brain, breast, or cervix), and also to treat cancers such as leukaemia and lymphoma. Radiation therapy works by damaging the DNA (genetic material) of cells because radiation disrupts the growth of tumour cells by directly or indirectly ionizing the DNA. The cell with damaged DNA dies during division.

X-ray mammography is conventionally used for breast cancer diagnosis. However, this does not give a clear image for patients with dense tissues of their breasts, as well as, in particular, in young females. Positron emission tomography (PET) based on ^{18}FDG (fluorodeoxyglucose) is popular to unequivocally diagnose breast cancer in these cases, because of the detection and measurement of two 511 keV photons (gamma radiations) generated in the annihilation of the positron emitted by ^{18}F, with the surrounding electrons. Since FDG is preferentially taken up by the cancerous cells/tissues compared to the healthy ones, this approach allows the accurate diagnosis of breast cancer, albeit at higher cost at present. This approach is known as positron emission mammography (PEM), and two such facilities have been built worldwide in Coimbra, Portugal and Marseilles, France. Clinical studies performed recently have demonstrated the usefulness of PEM for diagnostic purposes in breast cancer cases[1]. The other advantages of PEM approach include detection of small lesions due to high image resolution, smaller examination time because of high detection efficiency of cerium-doped lutetium-yttrium silicate (LYSO: Ce)-based detector, and less amount of the radioactive isotope to be injected.

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This article gives the current status of various radiation therapy treatments (both external and internal), a few typical results reported internationally, cost comparison of the different radiation treatments, and summarizes some of the critical comments published in various international journals in recent years about the promises and pitfalls of proton and heavy ion-based radiation therapies[2].

Gamma radiotherapy

Radiation therapy based on the use of gamma rays from ^{60}Co (half-life of about 5.3 years) is commonly used for cancer treatments. ^{60}Co isotope is produced by irradiation of natural ^{59}Co with thermal neutrons in a nuclear reactor and is available indigenously. An indigenous 'Bhabhatron' tele-therapy unit has been developed and built at Bhabha Atomic Research Centre (BARC), Mumbai, to defray the cost of imported equipment, and is now available in a few cancer speciality hospitals in India[3,4]. Bhabhatron is a cobalt-radiotherapy unit equipped with 3D conformal treatment technique and radiolucent couch. This unit can be used to implement arc therapy and non-coplanar beam-based treatment plans. Such units have been provided to Vietnam (2010), Sri Lanka (2010) and recently to Mongolia (2015). In India, technology has been transferred to Panacea Medical Technologies Pvt Ltd, Bengaluru for mass production to provide such units to various cancer hospitals. The limited half-life of the radioisotope, however, necessitates periodic changing of the source. Tungsten and depleted uranium are used to shield the radiations in the off condition, because the radiation cannot be switched off when not in use. The cost of the radiation source and its availability are the bottlenecks to the widespread use of Co-based tele-therapy units. However, because Bhabhatron is an indigenous product, it is a matter of pride for India, and reduces the country's dependency on imported costly radiotherapy units. Under the Programme for Action on Cancer Therapy (PACT), the International Atomic Energy Agency (IAEA), Vienna, Austria estimated in 2015, that currently there is a deficiency of at least 5000 radiotherapy machines in developing countries. This shortage means that up to 70% of cancer patients in low and middle income (LMI) group countries do not receive this essential curative or palliative treatment.

Linear electron accelerator

Due to the limitation of periodic replacement of radioactive source, the use of linear electron accelerators (LINACs) has gained popularity worldwide[5,6]. Other advantages of LINAC technology are that the radiation can be focused well on the cancerous spot, and the machine can be switched off when not in use. At present, the initial cost of installation of a LINAC is at least ten times that of commercially available gamma radiator (Theratron), and therefore, the large amount of capital cost prohibits the widespread use of LINAC technology in the developing and under-developed countries. LINACs also require high maintenance, a stable source of power, and water for cooling.

LINACs accelerate electrons and produce high-energy photons (about 10 MeV), commonly known as X-rays, by striking a high atomic number material and are commonly used for cancer therapy. With X-ray energy of about 8 MeV, maximum dose is delivered to tissues located at a depth of 2–3 cm, and only 30% dose is delivered to tissues located inside a depth of 25 cm. Due to this non-optimal dose distribution, even a small increase in the maximum dose can be highly beneficial. For a typical tumour which is controlled with a 50% probability, a 10% increase of dose usually improves this probability by 15%–20%, so that the control rate increases from 50% to 65%–70%. Most electron beams generated clinically are in the 5–20 MeV range, and such beams are normally used to treat superficial tumours, due to the limited penetration depth. Electron beams have been used by radiation oncologists to treat cancer for more than 50 years and presently, more than 10,000 LINACs are used worldwide.

Intensity modulated multiple beams are used to irradiate the cancerous spot(s), nevertheless, the procedure always gives some dose to the healthy tissues. Intensity modulated radiotherapy (IMRT) makes use of 10–12 X-ray beams. The beams may be non-coplanar, and their intensity is varied across the irradiation field by means of variable collimators (also known as multi-leaf collimators, MLC). The absorbed dose has a roughly exponential absorption in matter after an initial increase. To increase the dose to the tumour, it is essential to 'conform' the dose to the target. In order to selectively irradiate deep-seated tumours, radiotherapists use multiple beams from several directions, usually pointing to the geometrical centre of the target. This is achieved using a mechanical structure containing the LINAC, which rotates around a horizontal axis passing through the isocentre ('isocentric gantry').

Two numbers of 6 MV (million volts) LINACs 'Siddharth' built jointly by Council of Scientific and Industrial Research (CSIR)-Central Scientific Instruments Organisation (CSIO) (Chandigrah) and Society for Applied Microwave Electronics Engineering and Research (SAMEER) (Mumbai) have been installed at the Cancer Centre and Welfare Home (CCWH), Kolkata and at Bharat Electronics Limited (BEL), Ghaziabad[7]. For these LINACs, 2.6 MW pulsed magnetron was developed at CEERI, Pilani; MLC for IMRT was developed at SAMEER and automated traction unit at Centre for Development of Advanced Computing (C-DAC), Mohali. The technology was transferred to a consortium of five PSUs, viz. BHEL, Hardwar; BEL, Ghaziabad; ECIL, Hyderabad; Instrumentation Ltd, Kota and Andrew Yule & Co., Kolkata. The cost of the indigenously built unit was about

Rs 2.4 crores compared to that of an imported unit of Rs 4 crores, with the added advantage of easy maintenance and less down-time. About 1000 LINACs are needed in our country and this indigenous production will increase their availability by 10–15 units per year. Indigenous LINACs were recently installed at the Mahatma Gandhi Institute of Medical Sciences (MGIMS), Wardha and at the Cancer Institute (WIA), Chennai. More than 140,000 patients have received treatment so far from these installations. During the second phase of this activity, it is envisaged to deploy four 6 MV LINACs for cancer treatment in four hospitals, viz. Indore Hospital (installed), Amravati (under commissioning) and hospitals at Chiplun and Benglauru (site preparation under progress).

Hadron therapy

Hadron therapy, also known as charged particle therapy (CPT) or ion beam therapy (IBT) uses protons or heavy ions like fully stripped carbon ions (C^{6+}) for cancer therapy. These particles allow a more conformal treatment, and also a high dose to be given to the tumour with millimetre accuracy, and also spare the healthy tissues. These charged particles have little scattering when penetrating in matter and give the highest dose near the end of their range in the famous 'Bragg peak', just before coming to rest. Furthermore, heavy ion radiotherapy is a non-invasive cancer therapy, and therefore, vital organs are preserved. This treatment also improves the quality of life (QOL) of a patient and allows him/her to return to normal life earlier than conventional cancer treatment methodology. Usually 1–2 nA current of protons is sufficient for irradiation. Helium ions are similar to protons in their biological radiation properties. Heavy ions have increased relative biological effectiveness (RBE) in the Bragg peak compared to the entrance region. This advantage is lost for very heavy ions (above oxygen), because in these cases RBE is already high in the entrance region and does not increase much further in the Bragg peak. The proposal of using protons and carbon ions in radiotherapy was put forth by Bob Wilson in 1946, who later became the founder and first Director of Fermilab, in Chicago, USA. More than 50% of the centres with proton and heavy ion treatment facilities are in USA and Japan. Proton energies above 250 MeV and carbon ions with 400 MeV/amu are required to treat tumours that are deeply seated in the body.

Between 1977 and 1992, first clinical experiments were done with helium and neon ions using the Bevalac available at the Lawrence Berkeley Laboratory in California, USA. These experiments produced encouraging results, particularly in skull base tumours and paraspinal tumours. A total of 433 patients were treated with ions heavier than helium, majority of them treated with neon ions, and some patients treated with carbon, silicon and argon beams. Two treatment rooms, both equipped with a fixed horizontal beam-line, were available with majority of the patients treated in a sitting position. For treatment planning, a CT scanner was modified to scan patients in the seated position.

Proton beam therapy

Proton beam therapy (PBT) is another type of external beam radiation therapy (EBRT) like γ-radiations and X-rays. As protons travel through body tissues, they interact with the nuclei and electrons of atoms. Their heavier mass leads to a smaller scattering angle, and this yields a sharper lateral dose distribution than photons. In addition, the dose-depth distribution for PBT is characterized by a sharp increase in dose deposited at the end of the particle range (known as the Bragg peak). Because the protons stop in the tissue immediately after the Bragg peak, there is no exit dose beyond the target.

A large number of patients have been treated worldwide using protons, because these can be produced with cyclotrons. PBT is particularly important in the management of childhood cancers that require radiotherapy, and for the treatment of skull-based malignancies and spinal tumours such as chordoma, and ocular and prostate tumours[8]. This is because PBT delivers a lower dose to tissues around the tumour than X-rays, that is likely to lead to less disturbance of growth, lesser deleterious psychosomatic effects, and a lower risk of second malignancy. PBT is also predicted to be useful for children with brain tumours because of its reduced impact on subsequent neuropsychological and IQ development. However, randomized controlled trials (RCT) are required at various PBT centres to examine and evaluate the long-term effects and benefits, so as to establish a strong clinical efficacy and toxicity of PBT, and answer the questions raised and clarify the doubts expressed by a few critics[9]. For example, in hypoxic tumours such as head and neck cancer, Edinburgh randomized trial studies to compare fast neutrons (with high RBE) and photons showed that local control was similar but late severe radiation morbidity was significantly high in the neutron-treated patients[10].

The conventional proton treatment was mainly given by passive scattering technique which was relatively insensitive to organ motion caused by respiration[11]. The development of advanced scanning techniques, which was first used at Paul Scherrer Institute in 1996, but deployed at other clinics after 2008, is another milestone for proton therapy. These scanning techniques provide the capability to cover a large field, conduct intensity-modulated proton therapy (IMPT), and treat tumours with complex geometry. For example, in cases of head and neck cancers, treatment often needs large fields to cover the primary tumour and neck lymphatics, and tumours that have complex target shape, and are close to organs at risk (OAR).

In USA, proton accelerators are used for a large number of the prostate cancer cases. The cost of proton therapy for prostate cancer is typically about twice as much as conventional radiation, three times that of surgery, and 4–5 times that of brachytherapy[9]. In June 2011, a study of prostate cancer patients receiving conventional radiation showed fewer gastrointestinal problems than a similar group treated with proton beams. Somewhat surprisingly, proton therapy had the highest GI toxicity of radiation modalities. The comments made about proton therapy for prostate cancer treatment in 2012 in USA are reproduced here[12]: 'Crazy medicine and unsustainable public policy', by Ezekiel Emanuel, a professor at the University of Pennsylvania, oncologist, and former adviser to President Obama. 'If the United States is ever going to control its healthcare costs, we have to demand better evidence of effectiveness and stop handing out taxpayer dollars with no questions asked.' 'Increased risk of hip fractures, bowel problems or other delayed effects associated with the proton therapy treatment for prostate cancer need to be evaluated.'

A review was recently published on PBT for management of breast cancer cost-effectiveness[13]. It mentions a number of compelling benefits which include non-invasive and painless treatment. In addition, PBT was effective for treating early stage breast cancer, quick recovery times with minimal side effects, less cosmetic damage compared to the burn marks caused by X-ray regular radiation, and treatment provided as an outpatient. Considering the above-mentioned advantages, the setting-up of proton therapy centres has grown substantially all over the world. The cost per quality-adjusted life year (QALY) was found to be better in case of proper-risk targets, e.g. those with left-breast cancer and high risk of developing cardiac disease.

As of now, PBT has been demonstrated to be safe and effective for primary eye tumours, paediatric tumours, skull base tumours, chordomas, spinal and pelvic chondrosarcomas, and head and neck cancers near the spinal cord, at the base of skull, and in the paranasal sinus region[14,15]. However, controversial discussions continue around the world, on the efficacy and cost-effectiveness of PBT[16–20].

Heavy ion beam therapy

Heavy ion radiotherapy is particularly suited for hard-to-reach tumours, or for tumours which are too large or are radio-resistant[21–23]. C-ion radiotherapy gives high linear energy transfer (LET) (78 keV/μm) at the distal part of the spread out of Bragg peak (SOBP), and shows good dose localizing properties. This therapy produces lesser side effects compared to traditional radiotherapies like photon and proton therapies, and the individual can return to work the same day. For example, the side effects of proton therapy include epidermal tissue fibrosis, bone necrosis, feeling of sickness, etc. Carbon ions provide a better physical dose distribution compared to that with protons because of reduced lateral scattering of the former. Also, carbon ions have higher relative biological effectiveness (RBE) and a lower oxygen enhancement ratio (OER) which are highly desirable for treatment of radio-resistant, hypoxic tumours. The densely ionizing nuclei offer additional radiobiological advantages, such as reduced repair capacity, decreased cell-cycle dependence, and stronger immunological responses compared to sparsely ionizing X-rays and protons. The presence or absence of oxygen within cells has a strong influence in the biological effects of radiation, and hypoxic tissues are known to be less radiosensitive. This effect is given in terms of OER, and depends very much on the LET of the radiation used. For low-LET radiation, such as X-rays or protons, hypoxia represents a serious limitation factor to the effectiveness of the treatment. For high LET, like carbon ions, this effect is limited and is, therefore, highly useful to treat hypoxic radio-resistant tumours. The location where the dose is deposited by carbon ions can be determined by means of on-line positron emission tomography (PET).

In view of the better RBE of carbon ions, these are advantageous for cancer treatment but are costlier by at least a factor of two compared to proton therapy. Heidelberg heavy ion beam therapy (HIT) in Germany is the world's first heavy ion beam cancer therapy centre with a movable radiation source known as gantry. Carbon ion beams of 400 MeV/u are required for the treatment of deep-seated tumours which are radio-resistant both to X-rays and protons. The first patient was treated at the Heavy Ion Medical Accelerator Centre (HIMAC) in Chiba, Japan, in 1994 with carbon ions and with a passive dose distribution system. About 2000 patients at Chiba[24] and 250 patients at GSI (Helmholtz Centre for Heavy Ion Research), Darmstdat, Germany affected by brain glioma, tumours of the cervico-cephalic area, lung, liver, prostate and uterine cervix tumours have been treated with very promising results on some special tumour sites, such as lungs and liver[21].

In the last decade, valuable clinical experience has been gained in heavy ion therapy at HIMAC and GSI. With increased utilization of heavy ions for radiotherapy, there will be a broader implementation of ions in clinical settings that allow for an optimal exploitation of the physical and biological potential of heavy ions. Among these technologies are inverse treatment planning for particles, gating for breath-dependent targets, the raster scan system for tumour conform beam application, and biologic plan optimization. Further research is still required to clarify what indications benefit most from heavy ion therapy and what is the ideal ion species and fractionation scheme. These questions can be answered only by clinical studies performed at dedicated ion facilities, available in a few selected countries.

The above-mentioned characteristics of C-ions have encouraged the medical fraternity to use them for the treatment of head and neck malignancies. C-ion doses of 64.0 GyE (Gray equivalent dose)/16 fractions/4 weeks, and 57.6 GyE/16 fractions/4 weeks were used for human salivary gland (HSG) tumour cells and the skin target volume respectively, at HIMAC and the National Institute of Radiological Sciences (NIRS), Japan. A RBE of 3.0 was assumed for C-ion RT (radiotherapy) to convert the dose of C-ions in terms of photon equivalent doses (GyE)[25]. In some of the cancers like adenoid cystic carcinoma, combined photon and carbon ion therapy (boost) has been used and shown encouraging results without severe late effects[26].

One of the requirements of heavy-ion therapy is the development of a light, compact, rotating gantry in a 360° circle, so that the patient can be irradiated from all directions without tilting the treatment couch. The gantry should also allow to deliver a concentrated radiation dose to the targeted tumour from multi-directions by precise control of the beam positions and angle so that critical organs such as spine and nerves are not irradiated. Two designs, i.e. isocentric and exocentric are under consideration. The isocentric geometry keeps the patient in the stationary condition, whereas the exocentric involves movement of the patient along with rotating gantry and requires less area. Except for one exocentric rotating gantry for the proton beam at Paul Scherrer Institute (PSI), Zurich, all others are considering the development of isocentric rotating gantry systems. The first one at Heidelberg Ion Therapy (HIT), Germany is 25-m long, 14 m in diameter and weighs 660 tonnes. The recently installed rotating gantry at NIRS, HIMAC facility, Japan in 2015 uses superconducting magnets instead of normal magnets[27], and this has helped reduce both the size (13 m long and 11 m diameter) and weight. The superconducting magnets use compact cryogenics technology based on the refrigerator-directly-cooling method; this technology eliminates the need for liquid helium to cool the superconducting coils below 4 K, and makes the rotating gantry safe and easy to handle in ordinary medical facilities. The present trend in the development of ion gantries is focused on space-savers with the isocentric layout.

High-frequency LINACs for carbon ion therapy are needed for effective treatment of organs, which move during the irradiation, because of the respiration cycle. Three strategies can be used. These include synchronization of the dose delivery with the patient expiration phase (respiratory gating); detection of organ movement by a suitable system and a set of feedback loops to compensate with on-line adjustments of the transverse and longitudinal locations of the following delivered spots (3D feedback); or painting the tumour many times in three dimensions so that each delivery gives a small contribution to the local dose and any possible delivery error can be corrected during the following ‘visits’ to the same voxel. An optimal delivery mechanism should be such as to allow the use of any combination of these three approaches, the most effective one being the combination of a 3D-feedback with repainting.

Table 1 gives the worldwide present status of accelerators for charged particle therapy[28,29]. At present, there are 64 proton and C-ion therapy centres available worldwide and 32 are under construction. However, carbon ion therapy is still under evaluation in a few research and academic institutes, and is far from being used routinely mainly because of the high cost involved. New results from the international research institutes equipped with C-ion RT, smaller footprint and lower cost would be helpful in future to make this technology acceptable worldwide. Only sparse data are available for combination therapies of carbon-ion RT, chemotherapeutic agents and other modifiers of the radiation response. Almost all clinical trials performed so far have utilized C-ion RT alone. Since modern treatment includes chemotherapy as essential part of the treatment, studies utilizing combination of carbon-ion RT with different chemotherapeutic agents will be highly valuable in future.

Cost-comparison of radiation therapies

Peeters *et al.*[30] estimated the capital cost of 139 million € for combined proton/carbon facility, 95 million euros for proton facility, and 23 million euros for the photon facility. CNAO (National Centre for Oncological Hadron Therapy) in Pavia, Italy started out-patient treatment in 2014, and has treated about 400 patients until March 2015. The fee for a patient for three kinds of treatment (protons or carbon ions) is € 12,000 for boost (up to 6 fractions), € 18,000 for radiosurgery (1–3 fractions) and € 24,000 for full course. Another report[18] estimates a capital investment of US$ 140 million for setting up proton beam therapy facility and an average cost of US$ 40,000 per treatment. A detailed evaluation indicated that cost difference between particle and photon therapies is relatively small for lung and prostate cancer, but larger for skull-base chordoma, and head and neck tumours[30].

Present status of Hadron therapy

At present, there are 64 operating centres of hadron therapy in the world as reported by Particle Therapy Co-operative Group (www.ptcog.ch) (11 March 2016) and a strong expansion is expected in future. Amongst these, 54 operating centres have proton available with the geographical distribution as: 16 (USA), 15 (Europe), 9 (Japan), 8 (various parts of the world). Ten centres provide carbon ion therapies with five in Japan, three in Europe

Table 1. Present worldwide status of charged particle therapy facilities (www.ptcog.ch) as on 11 March 2016

Country	Already available	Under construction	Planning stage (all-proton therapy machines)
Austria	–	1 (p + C-ion)	–
Canada	1	–	–
China	4 (2 C-ion, 2p)	3 (1 C-ion)	2
Czech Republic	1	–	–
Denmark	–	–	1
France	2	1	1
Germany	8 (2 C-ion)	–	–
India	–	1 (Chennai)	1 (Mumbai)
Italy	5 (1 C-ion)	–	–
Japan	14 (5 C-ion)	3	1
The Netherlands	–	2	2
Poland	1	1	–
Russia	3	1	1
Saudi Arabia	–	1	–
Slovak Republic	–	1	1
South Africa	1	–	–
South Korea	1	2 (1, p + C-ion)	–
Sweden	1	–	–
Switzerland	1	–	2
Taiwan	1	1	1
UK	1	2	–
USA	19	12	3
Total	64 (10 C-ion)	32 (31 p, 3 C-ion)	16 (p)

and two in China. Four of these centres (viz. Heidelberg in Germany, Pavia in Italy, Shanghai in China and Hyogo in Japan) have ‘dual accelerators’ which can accelerate both protons and carbon ions. Thirty-two more centres are under construction, and these include 25 with protons, two with carbon ions, and one with both. By 2019, more than 110 centres will become available in 22 countries (29 in USA, 20 in Europe, 16 in Japan, the others in various parts, including China, South Africa, Russia, South Korea, Taiwan and Saudi Arabia). More than 137,000 patients have been treated with particle therapy worldwide between 1954 and 2014, with 86% treated with protons, and 14% treated with C-ions and other particles. In 2014, about 10% of patients were paediatric, with another 10% treated for ocular melanomas. It may be noted that charged particle therapy continues to draw criticism because of its poor cost effectiveness, scarcity of data showing clinical superiority compared to photons, increased technical and clinical complexity, and difficult controversial possibility of comparisons based on randomized clinical trials. The Korea Heavy Ion Medical Accelerator (KHIMA) project proposed as an ion-beam synchrotron facility[28], will be installed at Gijang, Busan with completion in 2017. The proposed maximum energy of the ions is 430 MeV/u (for carbon) to cover various tumour depths up to 30 cm. It will take a few more years before hadron therapy becomes available in India. There are ambitious plans by Tata Memorial Cancer Hospital in Mumbai in this regard.

Brachytherapy

Brachytherapy (BT), also known as internal radiation therapy or implant therapy or short-distance radiation therapy or sealed radiation therapy, allows the treatment of cancer with a larger radiation dose that cannot be given with external beams[31–34]. Cancer cells are treated directly with radiation and normal tissues are spared or are subjected to very less radiation. Sources of radiation for brachytherapy include ^{90}Sr and ^{125}I (20–30 keV for LDR-BT), ^{106}Ru, ^{137}Cs, ^{198}Au, ^{192}Ir (380 keV for HDR-BT), ^{103}Pd in the form of thin wires, tubes (catheters), ribbons, needles, capsules or small seeds. Depending on the type of implant, the radiation source stays in place for minutes, hours, days or permanently. The implant may be inserted as interstitial (prostate cancer), intracavity (cervical cancer), intraluminal (oesophagus or bronchus) or on the surface (eye or skin tumour). Latest information about brachytherapy in India is available from the website of the Indian Brachytherapy Society (established in 2006; http://www.indianbrachytherapy.com). An International Group with acronym ‘EMBRACE’ (IntErnational study of MRI-guided BRachytherapy in locally Advanced CErvical cancer; https://www.embracestudy.dk) is actively pursuing advances in MRI-guided 3D brachytherapy for cervical cancer with active participation of two centres at Mumbai and Chandigarh in India.

Radionuclides such as ^{89}Sr (megastron), ^{153}Sm (lexidronam) and ^{186}Re-hydroxyethylidene diphosphonate, because of their bone-seeking character, were approved in USA and Europe, and are useful for the palliative care of painful bone metastasis[33]. These have been used in cases of prostate cancer and need further large randomized control trial studies in breast-cancer cases.

Discussion and conclusion

Cobalt tele-therapy units (e.g. Bhabhatrons) will continue to be the workhorse for radiation therapy in developing countries. The tele-cobalt units have disadvantages of penumbra and dose rate decay. The proponents who argue their replacement with other radiotherapy units (e.g. LINACs and PBT) consider the problem of periodic replacement and management of radioactive ^{60}Co source. Nevertheless, these machines are preferred in developing countries because they are less capital-intensive, and have less operational and maintenance cost. For large countries like India based on the incident spectrum of malignancies prevailing, the World Health Organization (WHO) recommended tele-cobalt equipments. K. A. Dinshaw (Tata Memorial Hospital, Mumbai) advocated the need to 'revisit the context of cost-effectiveness, cost-benefit, and cost-utility analysis in Indian perspective, and to strike the right balance between the science of technology and the art of medicine, with special relevance to radiotherapy in cancer treatments'. Despite the availability of advanced features like asymmetric collimator, motorized wedge, etc. it cannot compete with the LINACs because it requires a radioactive source which decays with time. LINACs are increasingly used these days despite higher cost compared to cobalt tele-therapy units.

Today, over 25 countries do not have any radiotherapy unit, and this does not allow cancer patients living in those countries to have radiation therapy treatment. However, even when radiotherapy is available in LMI (lower middle income) countries, it is often inadequate for the number of cancer patients in need of care. Most high-income countries have at least one radiotherapy unit available for every 250,000 people compared to one unit for more than 5 million people (sometimes 20 million) in nearly 20 LMI countries. In high-income countries, between 50% and 60% of patients diagnosed with cancer are given radiotherapy treatment. For those in LMI countries, radiotherapy remains an unattainable treatment option, with only 25% of radiotherapy patients having access to radiotherapy treatment. Although LMI countries represent around 85% of the world's population, they possess less than 40% of the world's radiotherapy facilities. According to Ravichandran[5], 'with judicious treatment planning and intelligent executions of treatments, proper results could be achieved with tele-cobalt machines if basic facilities such as simulator and mould room are available'.

Future challenges for radiation therapy include improved cost-effectiveness, smaller footprints, developments of new accelerators like synchro-cyclotrons, rapid cycling synchrotrons, fixed-field alternating gradient rings, cyclotron–LINAC combinations, etc. A close and strong national and international cooperation of physicists, engineers, biologists and physicians is essential to realize the benefits of these advanced technologies to the human race. As an example, electron beams of energies above 150 MeV can be generated with laser irradiation of gas targets where much less laser intensity is required compared to the case for ion acceleration. Such electron beams have a range of about 40 cm, and can be used to treat deep-seated tumours. Moreover, scattering of high-energy electrons in air is sufficiently small and, therefore, electromagnetic pencil beam scanning is possible for intensity modulated treatment where high lateral resolution is required. However, comparative studies of laser-accelerated ion irradiation (both electron and proton) with those generated with conventional radio-frequency accelerators need to be performed. The present authors strongly believe that the emergence of charged particle therapy from basic and fundamental research is a boon to those with cancer problems to improve their quality of life, and will also be highly useful for non-cancer diseases in future. A statement about the prohibitive cost of hadron beam therapy is worth recollecting[35]: 'Although most developing countries would find the costs required for a conventional accelerator-based hadron therapy center to be prohibitive, they might find a laser-based system to be more affordable given national budgets. These countries could potentially afford 5–10 million € to initiate a laser-driven beam center that can guide future innovation. Such start-up laser systems may not be able to provide 250 MeV protons for deep tumor therapy but they can establish the necessary foundation and suitably comprehensive thinking.' However, while enthusiasm to use PBT has grown in recent years, there are uncertainties regarding its cost-effectiveness to treat patients with prostate and breast cancers. Needless to say, there are always both proponents and critics of any new technology, and judicious choice needs to be made keeping in mind the requirements of a particular region and country. It is interesting to note that two PBT facilities will be available in India, in Chennai and Mumbai, in future. Additional care has to be exercised in patients with artificial cardiac pace-makers having complementary metal-oxide semiconductor (CMOS) circuitry and implantable cardioverter defibrillators (ICD) devices to avoid their malfunction by electromagnetic radiations[36]. Partial breast irradiation (PBI) is another new breast cancer therapeutic strategy compared to whole breast irradiation (WBI)[37]. However, PBI should only be performed in a well-defined subgroup of patients (young) with a low risk of local recurrence in order to gain benefit from the real advantages of this procedure.

According to the Atomic Energy Regulatory Board report[38], there were 362 radiotherapy centres, equipped with 308 medical linear accelerators, 238 telecobalt units, four cyber knife units, three tomotherapy units, eight gamma knife units, one super-gamma unit, 232 high dose rate (HDR) and 91 low dose rate (LDR) brachytherapy units in India in 2014. Also, the existing facilities are located in urban areas while the vast rural areas remain largely untouched. The Board of Radiation and Isotope Technology in the Department of Atomic Energy is playing an active role to provide radioactive sources for both internal and external radiation therapy. Because of urgent need of radiation therapy units, it appears that India will have to augment the facilities by import of both the cobalt-60 teletherapy and linear accelerators. The linear accelerators in the 6–10 MV energy range will be able to treat a large number of patients, and one cobalt teletherapy unit in every major centre will be highly useful for calibration purposes due to its predictable dose rate.

Endless debates and controversies continue among proponents and sceptics about the efficacy and cost-effectiveness of advanced radiation therapies vis-à-vis Co-60-based teletherapy. According to a recent publication[39], ‘Novel technology has decreased access to radiotherapy in resource-constrained developing countries. Tele-therapy and brachy-therapy machines with Co-60 radio-isotope as the source of radiation may be feasible, and inexpensive option for countries like India. Advanced techniques and LINAC-based therapy may be restricted for selective cases and should always be carried-out within the scope of clinical trials.’ A detailed economic analysis done to compare the costs of photon therapy, proton beam therapy and C-ion beam therapy summarizes that[30]: ‘depending on the indications selected for particle therapy, when a sufficient number of patients is available, and a facility is run efficiently, particle therapy may not be *too expensive to become true*.’ Another report mentioned[40]: ‘New particle beam centres should be funded with a provision for shared basic research, technical improvements and properly conducted trials. An enhanced level of global, or at least continental or national, governance of particle therapy is of paramount importance. Only then, will we be in a position to clarify the real gain of CPT and to bring an otherwise endless debate to an unequivocal conclusion.’ As has been correctly stated[41], ‘Hospital administrations must accept that a technology should neither be used for prestige nor for marketing, and their business models should be based on conservative, rather than optimistic, assumptions about patient accrual.’ In future, mix and match of the beams of various properties to individualize the best treatment for each patient should evolve[42]. As is rightly said, ‘Necessity is the mother of invention.’ Despite the proven health benefits of radiation therapies for cancer patients, concern exists about the late effects of radiations (e.g. secondary cancers in children) with modern treatment modalities such as passive proton therapy and IMRT, because these therapies produce large amounts of scatter, leakage and neutron radiation, and their effects are being evaluated with computational phantoms. The advanced radiation therapies[43–45] with principle of ALARA (as low as reasonably achievable) need to be pursued continuously.

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Received 17 March 2016; revised accepted 26 May 2017

doi: 10.18520/cs/v113/i03/413-421