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Addressing the burden of cervical cancer through IAEA global brachytherapy initiatives

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Abstract

PURPOSE: Brachytherapy (BT) is an essential component of definitive therapy for locally advanced cervical cancer. Despite the advantages of the dose distribution with BT in cervical cancer, there is paucity of specific skills required for good-quality BT applications. Furthermore, replacing BT with other modern external beam techniques as a boost can lead to suboptimal results in cervix cancer.

METHODS AND MATERIALS: Review of available IAEA resources, research and cooperation programs available from the IAEA was completed. These opportunities can be used to address challenges in Brachytherapy.

The International Atomic Energy Agency (IAEA) provides support for BT through various means that includes education and training, both long term, short term and continuing medical education of professionals, providing expert visits to support implementation, development of curricula for professionals, e-learning through the human health campus, contouring workshops, 2D to 3D BT training, and virtual tumor boards. In addition, the IAEA provides support for implementing quality assurance in radiotherapy to its member states and provides guidelines for comprehensive audits in radiation therapy (QUATRO), and produces safety standards and training in radiation safety. In addition, mapping BT resources, making the case for investment and support for setting up BT services and radiotherapy centers are also available. The IAEA Dosimetry Laboratory provides calibration services to Secondary Standards Dosimetry Laboratories for well chambers

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used to confirm the reference air kerma rate of Co60 and Ir192 high-dose-rate BT sources, as well as for Cs137 low-dose-rate sources.

Furthermore, the IAEA supports research and development in radiotherapy (and BT) through coordinated research activities that include controlled randomized clinical trials, Patterns of Care studies among others. Partnerships with professional organizations and funding bodies, as well as through the United Nations Joint Global Programme on Cervical Cancer Prevention and Control support radiotherapy activities, including BT in countries worldwide.

CONCLUSION: The IAEA supports brachytherapy implementation, training and research and provides resources to professionals in the area.

Keywords

Brachytherapy; Cervix cancer; IAEA

Introduction: The role of brachytherapy in the treatment of cancer

Cervical cancer leads to most gynecologic cancer deaths worldwide and is a significant burden especially in low- and middle-income countries (LMICs). Brachytherapy (BT), given in a timely manner, is an essential component of definitive therapy for locally advanced cervical cancer and is one of the most critical treatment components to cure (1) cervical cancer. BT applicators provide a high dose to the cervix while limiting doses to organs at risk. This cannot be accomplished by external beam alone because of the proximity of organs at risk. Despite the favorable dose distribution with BT in cervical cancer, physician training and experience in BT applications has been an impediment to widespread, even in high-income countries (HICs) (2) and trainees report inadequate exposure to BT. The challenges became more evident with the decline in the rates of cervical cancer in these countries. As a result, there are efforts to replace BT with other modern external beam techniques even though these techniques have been shown to lead to an inferior overall survival as compared with BT in patients with cervical cancer (3). BT can be delivered using low-dose-rate (LDR), high-dose-rate (HDR), or pulsed-dose-rate modalities. Over time, HDR has replaced LDR because of its ease of delivery for the patient and the limited exposure to the ancillary staff. While safer and more convenient, commonly used HDR sources such as ¹⁹²Ir have a much shorter half-life than ¹³⁷Cs, an LDR source. However, more recently Cobalt-60 is also being used as a source for HDR, with a much longer half-life (5.3 years) than ¹⁹²Ir (74 days).

Global issues in brachytherapy

Global BT faces many challenges, from access to equipment and training to quality assurance (QA), among others.

Access to BT in LMICs

Development of cancer care capacity has not kept up with the growing demand in LMICs. Over half of patients with cancer in LMICs do not have access to radiation therapy, a number as high as 90% in low-income countries (4). Several LMICs either lack radiation

capacity altogether or have access to external beam radiation but not BT (5). Accurately characterizing radiotherapy infrastructure in LMICs is difficult because of the absence of robust published data. However, the IAEA's Directory of Radiotherapy Centres (DIRAC) (6) is a global data resource that includes data on BT.

In addition, methodologies for assessing cancer control capacity in countries do not always include radiotherapy, although this is not always the case (7). Quantification of BT capacity is even more limited in assessments.

Training of professionals

A BT implant of good quality is necessary for optimal outcomes in patients with cervical cancer. However, this requires additional skills and training of professionals. In addition, the availability of in-room imaging like a fluoroscopic c-arm or ultrasound (US) may be required for correct tandem placement (8,9).

Hence, modern BT is a very technology-intensive treatment modality (10). The various professionals in the BT team also need education and training specific to BT such as in the use of advanced hybrid applicators with intracavitary and interstitial components; using in-room imaging devices such as US, fluoroscopy, or MRI; real-time treatment planning systems based on US or MRI; cross-sectional, multimodality organ contouring; volumetric dose prescription and plan evaluation; and dedicated QA/quality control (QC) procedures and equipment.

These requirements put additional pressure on all human resources in the BT team. Most errors in BT treatment delivery result from human error, miscommunication, or misunderstanding of equipment operation (11). For this reason, the BT team needs adequate dedicated training. The AAPM Task Group-59 report and the IAEA Human Health Report No. 12 recommend that the treatment team comprises a radiation oncologist with special expertise in BT; a medical physicist with expertise in BT; and a treatment-unit operator who could be the radiation oncologist, medical physicist, dosimetrist, or a radiation therapist (12,13).

Training in BT is often neglected when implementing this treatment modality, especially in LMICs (14). Lack of reference centers offering training in this subdiscipline; competing priorities in other areas of radiotherapy; and lack of continuous professional development are some of the issues. In addition, the professional recognition of the medical physics profession still remains a concern in many countries (15).

Quality assurance in brachytherapy

BT is a complex process involving many different but interrelated steps and various pieces of equipment are used to deliver the treatment to the patient. These include hybrid endocavitary/interstitial applicators, interstitial needles, and plastic tubes; afterloader machines and radioactive sources; imaging devices for applicator guidance and dose calculation; computerized treatment planning systems; dosimetry measuring instruments; accessories; and IT infrastructure for data transfer and management. Adequate human resources (medical and support staff) are also critical to carry out all the specialized steps

throughout the BT procedure. Finally, treatment delivery is usually performed in a short timeframe with no scheduled delay between applicator insertion and dose delivery. All the steps of the procedure are performed sequentially while trying to minimize the duration of the procedure.

These characteristics of the BT procedure make it even more essential to have a robust quality management system (QMS) to consistently ensure safe, effective and efficient treatment. This QMS is based on a detailed knowledge of the process map, well-established protocols, a QA component to prevent errors, a QC component to detect and standardize response to errors, and an incident management mechanism to report events.

Some reports clearly show a link between the quality of radiotherapy and the oncologic outcomes. For example, a review of clinical trials showed clinical failure rates significantly higher after inadequate vs. adequate radiotherapy (16). This is especially important for BT for cervix cancer (8,9). The need for a QMS (formally established) is clear, to create and maintain a high standard for patient treatment.

Both ASTRO and AAPM provide the tools needed to implement a QMS for BT (11,12,17,18).

Unfortunately, many clinics in LMICs face challenges in establishing or maintaining a QMS (19). These challenges include the lack of commitment of top management or the lack of a quality policy at a hospital level; the lack of locally adopted treatment guidelines and QA/QC protocols; the lack of adequately trained staff; and the lack of adequate resources due to competing priorities.

Other challenges

In addition to QA and training of human resources as outlined previously, there are other challenges to BT delivery in LMICs that need to be considered when planning a BT program.

BT sources for HDR need to be replaced periodically based on the half-life of the source. This process requires approvals from the national regulatory bodies because of safety and security concerns associated with radioactive sources (20). The source is shipped to the country from abroad. Once the source is received at the closest port to the center, it requires further customs clearance before transport to the radiotherapy center and installation into the afterloader. This process requires resources and prior planning, otherwise BT services come to a standstill.

In addition, having access to appropriate and timely machine servicing contracts is critical (21). Prolonged machine downtime can lead to delays in treatment that can lead to inability to deliver curative treatment, especially for cervical cancer where overall treatment time is related to local control (22). In the recent study looking at machine downtime, it was found that LMICs are more likely to have machine downtime than HICs with prolonged waiting times for spare parts (23). In sub-Saharan Africa, up to 70% of medical equipment lies idle because of errors made during acquisition or installation and a lack of adequate training and technical support. Of the equipment in use, 25–35% is not operable because of a lack of

local capacity for repair and maintenance (24). In summary, implementing and maintaining these necessary processes for BT requires a significant, sustained commitment from the involved parties.

Furthermore, geographic access to BT is a challenge. Often in LMICs, there are few centers equipped with BT. Patients must travel long distances for treatment. These patients may not have the resources to support themselves during their time away from home without a stable income, forcing them to abandon treatment. It is therefore extremely important to provide resources for patients to enable them to complete treatment and achieve the highest chance of cure (25).

Ensuring access to safe, effective, and quality brachytherapy—The role of the IAEA

The role of the IAEA is to promote the peaceful use of nuclear applications and to help its member states to begin the process of implementing nuclear techniques in several fields. The IAEA is involved in several initiatives focusing on safety in radiotherapy delivery throughout the world that address provider-based, equipment-based, and systems-based interventions (26). In addition, the IAEA supports many initiatives to support quality radiotherapy and medical physics, including BT, some examples are discussed further (27).

Mapping BT resources

The DIRAC (6) has been maintained by the IAEA since 1959. The database collects data on teletherapy and BT units, imaging devices for treatment planning, treatment planning systems, dosimetry, and QA equipment. Despite the limitations of such a comprehensive registry, DIRAC provides the best and most robust data available on BT in LMICs.

Because BT is such an essential component of treatment in cervical cancer, it is interesting to assess the distribution of BT units worldwide. The DIRAC database includes data on 7477 radiotherapy centers operating about 14,374 teletherapy and 3309 BT installations (including around 500 ^{137}Cs LDR installations). Around 50% of these installations are located in North America and Western Europe, and only 3% in Africa. There is a clear imbalance between the available resources and the countries' needs, given the higher incidence of cervical cancer in LMICs.

In Africa, 120,000 cervix cancer cases are diagnosed per year and only 101 BT installations are available to treat these cases. One hundred additional BT afterloaders would be required for an adequate throughput. In addition, geographic access is a challenge for patients seeking BT treatment because of the uneven distribution of the resources. Around half of the radiotherapy centers do not offer BT services. Other authors have reported similar results for particular geographic settings (25,28).

The IAEA has also recently initiated an exciting project to improve the knowledge about the delivery of BT services worldwide. Information about equipment, indications, and workflow is being collected and processed for future dissemination. This project will provide

information to decision makers on various technological needs, thus ensuring optimal planning of cost-effective BT services.

Establishing a curriculum for professionals working in BT

Renewed interest in BT at a global level coincides with the greater recognition of cervix cancer as a significant public health issue and the availability of novel treatment techniques. However, BT is a complex irradiation technique that requires significant theoretical education but also practical training.

The IAEA has a long history of providing assistance to train professionals involved in BT to its member states. It has produced a comprehensive set of curricula for professionals in the field of radiotherapy (radiation oncologists, medical physicists, radiation therapy technicians, and oncology nurses), covering all aspects of the education including BT (29–34). The agency has also produced educational materials (35) and supported fellowships, and expert visits for the implementation of BT programs.

However, finding adequate training centers to teach the practical aspects of BT is challenging. In HICs, there is a trend to centralize the provision of BT services, making difficult to offer enough time to all residents to complete a minimum number of procedures. In LMICs, the lack of training programs, together with other structural and human resource deficiencies, make formal BT training difficult.

In addition, it is very challenging to assess the learning outcomes for BT. The theoretical concepts are usually well captured, but the exposure to the practical exercise is not well evaluated and the resident logbook is often an underutilized tool (36–39).

For this reason, the IAEA is now working in a new document describing the competencies needed for professionals working in BT. A working group has been established and the available evidence will be reviewed. Identification of Entrustable Professional Activities and the competencies required to perform these procedures will be determined based on the CanMEDS 2015 framework. Furthermore, an electronic e-learning platform will host multimedia material to support a blended approach to the training process.

Establishing a robust BT auditing methodology—The role of the IAEA dosimetry laboratory

A robust QA system is essential for safety and quality of radiotherapy. The IAEA provides support for implementing QA in radiotherapy worldwide and provides safety standards and training in radiation safety. The agency developed QA methodology and provides QA missions to support radiotherapy centers worldwide (40–42). The methodologies used are the basis for subsequent internal audits in various countries and regions, such as seen in Europe (43). The methodology and guidelines for comprehensive audits in radiation therapy (40) are implemented through the Quality Assurance Team for Radiation Oncology (QUATRO). By the end of 2019, 100 QUATRO missions have been implemented in 51 countries. This methodology is being updated and will include a complete dedicated section on BT.

The IAEA supports the establishment of QA programs at institutional and national level.

With regard to remote audits and calibration, the IAEA, in collaboration with WHO, offers a cost-free postal dosimetry audit service for teletherapy machines in over 2700 radiotherapy centers as well as a postal calibration service for dosimeters and BT units (44,45).

The dosimetry laboratory provides calibration services to Secondary Standards Dosimetry Laboratories for well chambers used to confirm the reference air kerma rate of Co60 and Ir192 HDR BT sources, as well as for Cs137 LDR sources (27).

Making the case for investment in BT

Although assessment of need is an important first step in a country's planning for investment in BT, calculating investment costs and designing a complete service is challenging. The IAEA provides expertise, tools, and support to address questions related to health economic analyses. For example, installation of a BT suite (building, plus one HDR BT afterloader, plus one C-arm, TPS, and ancillary equipment) requires a capital investment of around US\$ 1 million in LMICs. A BT suite can treat up to 666 cervical cancer cases, that is, eight insertions per day, assuming working 8 h per day, eight fractions per day, and three fractions per case, with a total operational cost of US\$ 473,000 per year. The addition of BT to EBRT in cervical cancer improves overall survival at 5 years from 40% to 60%, and cause-specific survival from 50% to 70% (46). The use of MRI-guided BT further improves local control and survival (47). Countries without access to BT can only offer palliative treatment to women diagnosed with locally advanced cervical cancer. Adding BT to external radiotherapy, up to 466 patients of the 666 treated can be cured. This represents 4660 patients in the lifetime of an HDR BT afterloader (10 years), while the costs of BT are US\$ 710 per patient in LMIC.

IAEA Technical Cooperation Projects

Assistance to the member states can also be provided through well-designed technical cooperation projects. The IAEA has helped many countries in establishing or upgrading radiotherapy programs, including improvement of BT services. The usual components of these projects include education and training, provision of experts, and procurement of equipment.

Establishing and upgrading BT is a usual component in national, regional, and interregional technical cooperation projects. Of a total of 1678 fellowships between 1994 and 2017, 617 (37%) had a BT component. The projects in human health, mostly related to cancer, traditionally represent 28% of the projects in the 120 million Euro Technical Cooperation Fund (48).

IAEA global research programs in BT

It is critical to collect good-quality data on patterns of care and outcomes for all patients being treated with BT to better understand and plan future steps in improving access, quality of treatment, and techniques. However, often registries are either completely lacking in LMICs or considerably limited. Furthermore, developing research programs without basic

research infrastructure tends to be very challenging (49,50). Needless to say, serious efforts are needed in this area and should be prioritized while planning a radiation/ BT program. There are now examples of collaborative programs in LMICs that are establishing a foundation for research programs with emphasis on local capacity building (51,52).

The IAEA supports research and development in radiotherapy (and BT) through coordinated research activities. These coordinated research activities enable researchers in LMICs to access a platform of controlled quality clinical research with a full range of projects (from preclinical to Phase III trials, health economics trials, patterns of care, and cost-effectiveness analyses <http://cra.iaea.org/cra/explore-crps>).

IAEA research activities facilitate acquisition and dissemination of new knowledge and technologies, as well as the adaptation to the needs of the LMIC. Evidence generated from Coordinated Research Projects (CRPs) can support evidence-based adapted recommendations for all settings, including low resource settings. The IAEA supports research through implementation of CRPs through the Human health program. The IAEA CRPs in human health have a broad scope that include QA and medical physics, radiation biology, diagnostic imaging, patterns of care studies, hypofractionation, and randomized controlled Phase III studies. In addition, educational CRPs assess the effectiveness of educational initiatives and their sustainability in a scientific manner. There are several examples of cervix cancer studies (53,54) including BT fractionation and radiobiology (55).

New CRPs in development include image-based treatment planning in cervical cancer, QA in HDR BT, spatially fractionated radiation therapy, and modern radiotherapy techniques in cervical cancer. In addition, research in medical physics of BT includes CRPs on the following: image-guided BT for cervix cancer: an implementation study (56); development of methodology for dosimetry audits in BT (57); modern techniques in BT of cancer with special reference to the developing countries (58).

IAEA partnerships in global BT

In response to the increase in global cancer incidence, the IAEA has increased its efforts to coordinate initiatives with international institutions to tackle these global challenges. Cervical cancer is preventable and curable and yet remains the second most common cancer in women in LMICs where 80% of new cases are diagnosed. To address these issues in a coordinated manner, a UN Joint Global Programme on Cervical Cancer Prevention and Control was initiated. The aim is to support sustainable national comprehensive cervical cancer control programs and achieve equitable access with increased coverage of screening and treatment for cervical precancer and increased capacity of health systems to diagnose and treat cervical cancer, including provision of palliative care. This program allows for a joint work plan that is supported by the findings on joint missions in the countries. The program activities range from preventive measures such as HPV vaccination, to diagnosis, treatment, and palliation (59).

Radiotherapy activities, both teletherapy and BT, are supported by the IAEA in accordance with its mandate. Participating organizations have increased from the original seven UN agencies (IAEA, WHO, IARC, UNAIDS, UNFPA, UNICEF, and UN Women) to include

NGOs such as UICC and others. The program has now extended to an additional 10 countries in Africa, after completion of all the joint programming missions in the original six countries. The activities in radiotherapy, which are mainly in BT, include interventions funded through the various IAEA programs such as activities planned through the IAEA Human Health program's PUI initiative in cervix cancer for example planned on-site education and training in BT in Morocco and Tanzania, as well as educational modules through IAEA Human Health program and training activities through the IAEA interregional technical cooperation cervical cancer project.

In addition, other partnerships with professional organizations and banks support activities in BT, such as the recent IsDB partnership that will support IAEA activities in over 20 countries. The IAEA also has formal partnerships with various professional groups, for example, ESTRO, among others, who support IAEA's initiatives and its mission. The IAEA also supports collaboration between 14 centers and the IAEA through a pilot virtual tumor board telemedicine project for radiation oncologists in Africa (AFRONET) that was initiated in 2012. Cervix cancer is one of the most commonly discussed cancers on the platform. This initiative also provides an opportunity for quality improvement through clinical peer review and is being expanded to other regions such as Francophone Africa, Asia-Pacific region, Latin America, and Russian-speaking countries.

Conclusions

Expansion of global access to treatment for cancer is essential to address the high mortality and inequity in LMICs. This is of utmost importance in cervix cancer because of the high impact of this condition at the community level. The IAEA has a significant role to play in supporting safe, quality radiotherapy in general and BT in particular. Finding solutions to many of the barriers that result in lack of access to treatment for many patients is essential to achieve health equity (60) and can be achieved through the many global initiatives and partnerships.

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