Recent Advances in Radiotherapy For Head and Neck Cancer: A Comprehensive Review

Amrit Kaur Mann[1], Indira AP[2], Maria Priscilla David[3]

ABSTRACT

Oral cancer is a health problem worldwide and is considered to be the fifth most common among other cancers. In order to improve the efficacy of treatment for head and neck cancer newer multimodality approaches are being used with combinations of surgery, radiotherapy and chemotherapy. Nearly fifty percent of all cancer patients receive radiotherapy with combinations and forty percent contributes as curative treatment with radiotherapy alone. Conventional radiotherapy is a standard approach for locoregionally advanced disease and is associated with a wide variety of well-known acute and long-term toxicities. These chronic toxicities (i.e. Xerostomia, dysphagia, and fibrosis) can negatively impact patient's quality of life. Hence technical advances in radiotherapy during the last few years has revolutionized the treatment of Head and Neck cancers. With the dawn of new technologies, radiotherapy seems to be hopeful in patients with malignancies. The most noticeable clinical gain has been a distinct reduction in long-term morbidity in these patients. Thus this article aims to present the advancements in radiotherapy which include three dimensional conformal radiotherapy.

Keywords: Head and Neck Cancer, Image Guided Radiotherapy, Intensity Modulated Radiotherapy, Oral cancer, Radiotherapy

INTRODUCTION

Radiotherapy (RT) plays an important part in the management of head and neck cancer. The radiation dose needed for the treatment of cancer is based on location and type of malignancy. Majority of the patients with head and neck cancer treated with a curative intent receive a dose between 50-70 Gy. In addition to antitumor effect, ionizing radiation causes damage in normal tissue located in the field of radiation. This becomes particularly evident in head and neck region, complex area composed of several dissimilar structures that respond differently to radiation; mucosal lining, skin coverings, subcutaneous connective tissue, teeth and bone/cartilage.[1] The oral complications that arise are primarily responsible for determining the patient's quality of life.[2]

Acute changes produced by RT are observed in the oral mucosa such as erythema, pseudomembrane covered ulcers, reduced salivation and changes in the composition of saliva, decreased taste acuity and skin (erythematous desquamation). Late changes can occur in all tissues. Various efforts to improve the efficacy of treatment for squamous cell carcinoma of head and neck have led to the use of multiple approaches.[1]

Radiotherapy (RT) is one of the most effective treatment for malignancies.[3] External beam radiation therapy has been the cornerstone of therapy for early stage and locoregionally advanced Head and Neck cancers.[4,5] RT is effective both as a primary modality and as an adjuvant to surgical treatment following surgery.[3] Though conventional radiotherapy is used as a treatment modality, its side effects out beat its benefits. The possibility of "geographic miss" which is bound to occur in conventional radiotherapy, where a small portion of tumor is excluded results in treatment failure. Over the past few decades, conventional radiotherapy which used simpler rectangular treatment fields has changed significantly to conformal radiotherapy techniques.[6-8] Modern day radiation therapy for cancers of the head and neck is oftenly administered with linear accelerators that produce high-energy external radiation beams. This beam of radiation pierces the tissues and carries the radiation dose deep in the area of the body where the cancer resides. These have resulted in improving the dose delivered to the tumor bearing tissues which reduces the radiation to the organ at risk thus improving radiation therapy.

Three-dimensional (3D) conformal radiotherapy

New developments in radiation oncology have helped to improve attitude of patients and find more effective treatment. With the introduction of Three-dimensional (3D) conformal radiation therapy which uses reconstructed matched computed tomograms (CT) and Magnetic Resonance images (MRI) during treatment plan reduces the risk of geographic miss. The distribution of the beam can be conformed to the tumor size and shape using customized showed dense block or by multileaf collimators which has 40 pairs of tungsten measuring 1 cm in width. These can be adjusted to define the x ray beam thus reducing the dose of radiation up to 50% to normal tissues and this in turn reduces late damages.[6]

Intensity-modulated radiotherapy (IMRT)

It is one of the recent adaptations of RT.[3] It is being used widely to treat Head and Neck cancers, cancer of the prostrate, central nervous system, breast, thyroid, lung, as well as in gastrointestinal, gynaecologic, pediatric malignancies and certain types of sarcomas.[9]

Intensity-modulated radiation therapy (IMRT) is an improved mode of high-precision radiotherapy that utilizes computer controlled linear accelerators to deliver precise radiation doses to a malignant tumor or to specific areas within the tumor.[9] This technique is delivered using linear accelerators with static or multi-leaf collimators or volumetric arc modulated therapy.[6]

[1]Post Graduate Student, [2]Professor, [3]Professor and Head of Department, Department of Oral Medicine and Radiology, M.R. Ambedkar Dental College and Hospital, Bangalore, India

Corresponding author: Dr. Amrit Kaur Mann, M.R. Ambedkar Dental College and Hospital. 1/36, Cline Road, Cooke Town. Bangalore – 560005, India

How to cite this article: Amrit Kaur Mann, Indira AP, Maria Priscilla David. Recent advances in radiotherapy for head and neck cancer: a comprehensive review. International Journal of Contemporary Medical Research 2017;4(4):927-932.

In this technique, the equipment can be rotated around the patient where the beam moves multiple times that may vary with intensity, resulting in three dimensionally sculpted radiation. It allows for the radiation dose to conform to the three-dimensional shape of the tumor, by modulating or regulating the intensity of the radiation beam in multiple trivial volumes. This permits increased radiation doses to be focused to regions within the tumor, while decreasing the dose to surrounding normal critical structures. In this advanced technique, the treatment is cautiously planned by using 3-D computed tomography (CT) or magnetic resonance image (MRI) of the patient along with computerized dose calculations to determine the dose intensity pattern that will best conform to the tumor shape. A powerful computer program optimizes the treatment plan based on clinician's dose instruction, and information about tumor size, shape and location in the body. This boosts the IMRT doses that are delivered at various target sites in a single phase and obviates the need for field matching, thus minimizing dosimetric uncertainties.[6]

The advantage of IMRT is that, it spares the important vital structures such as salivary gland, mucosa of digestive tract, optic nerves, pharyngeal constrictors, brain stem and spinal cord. It also spares the oral and hypopharyngeal muscles which helps in normal deglutition and hence reduces radiation induced dysphagia. The ability of IMRT to spare cochlea reduces the incidence of radiation induced loss of hearing.[6] The highly conformal dose distributions attained by IMRT could improve tumor control rates in advanced cases, particularly those arising from the nasopharynx and sino-nasal regions because they facilitate the delivery of high doses to the tumor that is closely related to adjoining critical organs like the brainstem and optic nerves, without exceeding the normal tissue tolerance.[10]

The precise, relevant and reproducible delineation of primary and secondary targets in head and neck cancer radiotherapy represents a major challenge. In this respect the use of IMRT may be refined further by improving technical delivery. Currently, the most commonly used method involves delivery of radiation fields at fixed gantry angles using a multileaf collimator. An emerging method of IMRT delivery involves tomotherapy, which combines radiotherapy and computed tomography to deliver beams from 360 degrees modulated by a multileaf collimator. The improved imaging facility conferred by the CT enables targeted regions to be observed prior to, during and after treatment, allowing delivery of IMRT with even greater accuracy.[4] However, toxicity associated with IMRT is inevitable. The success of such highly conformal planning process such as IMRT is highly sensitive to two major factors:

1. Description of tumor/target volume in 3 dimensions by the clinician around which the high dose distribution is developed through conformal planning
2. Daily variations in setup that could result in the tumor sneaking outside of the high dose distribution of the conformal plan, thus missing the intended treatment dose altogether.[10]

The disadvantage is that as with any precision technique, it is possible to be either highly precise or precisely inaccurate. The greatest risk can be to miss the tumor altogether while attempting to be very precise in defining targets and sparing normal structures.[3] IMRT is a relatively complex technique to perform well and variations in daily setup can have an adverse impact on the success of treatment.[4]

Volumated Intensity modulated Arc Therapy (VMAT)

Volumated intensity modulated arc therapy (VMAT) is newer technique of delivering IMRT. VMAT delivers IMRT-like distributions in a single rotation of the gantry, varying the gantry speed and dose rate during delivery in contrast to standard IMRT, which uses fixed gantry beams. This technique has been implemented in the Eclipse treatment planning software under the name Rapid Arc(RA) Planning. Studies using RA demonstrate shorter planning and treatment time, lesser monitor units for treatment delivery, better dose homogeneity and normal tissue sparing.[3,11,12] There is a lack of data in regard to clinical implementation of this technique.[3]

The toxicity associated with treatment of head and neck carcinoma, for example painful mucosal reaction, thick discharges that are difficult to clear, dysphagia, exaggerated gagging along with a sensation of claustrophobia due to lying under the mask contributes to setup instability on the table and could be associated with unrecognized intra fraction motion. This aspect can vary from patient to patient. There is increase in treatment time per fraction from approximately 5 to 10 minutes for a conventional treatment to 20 to 30 minutes with IMRT. Longer a patient is on treatment table, the more likely he/she will move and hence the unreliability of positioning during setup and treatment. Advantage is emerging radiation techniques such as VMAT that are capable of producing conformal plans that are analogous to IMRT.[10]

Adaptive Radiotherapy (ART)

ART is the process of altering the treatment plan in response to changes observed during radiation treatment. Deformation of targets, normal structures as well as patient anatomy may happen during a 6-7 week course of radiotherapy. For example large exophytic tumours of HPV origin and nasopharyngeal tumours often experience significant tumour regression during the course of treatment. It may be possible to replan and adjust for interval regression of the exophytic component of the disease to limit the occurrence of oral mucositis. These situations are currently being investigated by several groups to alleviate the problems of target deformation during a treatment course. Besides physical deformation in targets there could also be a biological variation with redistribution of tumour cells through the phases of cell cycle and reoxygenation of previously hypoxic cells, converting radio resistant cells to radio sensitive in some cases and vice versa. Disadvantage being changes in the patients anatomy from weight loss and tissue oedema may also occur during treatment. Soft tissue resolution is quite limited compared to bony anatomy.[10]

Image Guided Radiotherapy (IGRT)

With further inventiveness, by making use of advances in imaging techniques, IGRT arose to out beat the limitations. It is often used in conjunction with intensity-modulated radiation therapy (IMRT), proton beam therapy, or stereotactic body radiotherapy (SBRT).

The most basic and historical form of IGRT comprises of 2 dimensional portal images acquired in perpendicular/orthogonal planes to confirm the position of the isocenter, as well as the distinct fields. In most cases, these images are produced by the megavoltage (MV) beam of the treatment machine or less often by a devoted ancillary kilovoltage unit. Bony anatomical landmarks of the spine and skull are typically used as reference for alignment. These images are obtained prior to treatment. IGRT is used to treat Head and Neck cancers and tumors in areas of the body that are prone to movement, such as the lungs, as well as tumors located close to critical organs and tissues.[10]

Currently more advanced IGRT techniques are available for patient orientation and target positioning. Image guidance can be used for improved tumor delineation and to correct intra and inter fraction movement during radiotherapy. Computerized tomograms with image guidance provide three dimensional views of tumor and normal anatomy.[6] Recent advances in 3-dimensional or volumetric imaging have mentioned some of these issues and cone beam CT has emerged as an efficient system for in-room localisation. Basically this consists of a compact CT scanner that is combined into the linear accelerator unit. A scan can be acquired rapidly, generally within 1-2 minutes, just before treatment of the patient in the treatment position. This scan is usually of lower resolution than a diagnostic CT scan but provides adequate bony and soft tissue resolution for anatomic alignment. The CBCT localisation scan is then superimposed on the treatment planning CT scan using a software based registration algorithm to confirm the accuracy of setup, and any necessary shifts are made to obtain an accurate match.[10]

IGRT can be a useful tool that can detect and correct the geographic miss that can occur in treatment delivery. This technique can be fused with Positron emission tomography, which aids in delineation of gross tumor volume by using radio-active tracer namely Fluorine 18 labelled fluoromisonidazole have been shown to highlight the hypoxic areas of tumors. The PET images could be fused with the planning CT scans and used for biologic dose optimisation.[3]

Studies have shown that escalating the radiation dose to the hypoxic areas have established feasibility of this approach in terms of acute toxicity. The restrictions are that bony image quality is often quite vague especially with megavoltage imaging, and small displacements may not be readily or reproducibly identified, and clinical judgement is often required to interpret these images. In addition, soft tissue alignment and deformations cannot be appreciated with 2D imaging.[10]

Chemoradiotherapy

Adding concurrent chemotherapy to Radiotherapy (chemo radiotherapy) is now recognized to improve outcome in advanced head and neck cancer patients compared with once daily radiotherapy alone and has become a standard approach for non metastatic diseases. Furthermore, the addition of chemotherapy to radiotherapy following surgery for resectable Head and Neck cancer with high risk features shows improved loco regional control and disease free survival. The randomized trial with chemo radiotherapy represents an important advance in head and neck cancer. Some studies used once daily radiation, others twice daily. Some studies used Cisplatin or Mitomycin alone, whereas others used 5-FU or Carboplatin. The dose per delivery schedule of platinum varies dramatically from every three weeks (100mg/m^2) to low dose daily (6mg/m^2) administration. However, the most common global practice appears to include the administration of Cisplatin concurrent with the radiation, either low dose weekly at 32-40 mg/m2 or every 3 weeks, with doses of 75-100 mg/m.[2,4]

The recently reported results have led to the increase in common use of chemo radiotherapy as a standard of care for advanced Head and Neck cancer patients not receiving definite surgery. Nevertheless, many questions remain unanswered, not least of which is the specific chemo radiotherapy scheduled to recommend outside the context of controlled clinical trials.[4]

Particle Radiation therapy

Charged particle beams consisting of protons and carbon ions have the Bragg peak and allow highly localised deposition of energy that can be used for increasing radiation doses to target while minimising irradiation to adjacent normal tissues.[13,14]

It is one among the other types of radiation therapy. Charged particles like protons deposit little energy until they reach their end of their range at which point most of the energy is deposited in a small area until they near the end of their range at which point the rate of energy loss increases resulting in what is term as the Bragg peak. Intensity modulated proton (IMPT) allows modulation of the fluence and position of Bragg peak, permitting three dimensional dose distributions. Combination of photon and proton therapy for advanced malignant sinonasal tumours demonstrated good results when used IMRT alone. The present role of proton therapy lies in the treatment of tumor close to the skull base or spinal cord and in pediatric patients. Proton therapy provides maximum benefit in terms of normal tissue sparing. The advantage is reduced dose bath effect and normal tissue sparing and better homogenicity. The disadvantage being the distribution of proton therapy on a wide scale is restricted by the limited availability of proton therapy machines due to the financial resource required.[3]

Thermo radiotherapy

It involves the application of localized high temperature at the tumor site which is said to improve the radiation treatment outcome. Currently scientific research has been conducted on this treatment modality.[6]

Radioimmunotherapy

Radioimmunotherapy is a form of radiotherapy where cytotoxic radionuclides such as Yttrium 90, Iodine 131 are linked to antibodies in order to deliver toxins directly to the tumor targets.[6]

It is also known as Targeted Radiotherapy. The efficiency of their radioisotopes is that it has longer path length and thus large tumors may receive a higher dose of radiation to a greater depth. Another important factor is that conjugation or the chemicals linkage to the radioisotope to the tumor antibody, which allows the therapy to be delivered to the tumor cell.[6]

Radioimmunotherapy has proved to be effective for treatment of lymphomas, whereas its application in oral cancer has been reported to be under clinical trials using monoclonal antibodies. The advantage of radioimmunotherapy is that each cell does not have to be bound by the antibody to receive cytotoxic radiation. Thus the adjacent tumor cells though do not receive antigenic determinants, can be destroyed by radiation. Thus the evidence of immunogenicity of oral cancer may help in the success of Immunotherapies.[15]

Stereotactic radiotherapy

This is an important new development in the treatment of brain tumors. Stereotactic radiation uses a single high dose of radiation sent into cancerous tissue with very narrow beam of radiation.

Type of RT	Brief description- about principle/ specificity	Application	Advantages	Limitations
Intensity modulated Radiotherapy	It is an improved mode of high precision radiotherapy that utilises computer- controlled linear accelerators to deliver precise radiation doses to a malignant tumor or to specific areas within the tumor.	Widely used to treat Head and Neck cancer, cancers of the breast, central nervous system, thyroid, lung as well as in prostate.	It allows the radiation dose to conform to the three-dimensional shape of the tumor, by modulating or regulating the intensity of the radiation beam in multiple trivial volumes, thus sparing the important vital structures.	It is possible to be either highly precise or precisely inaccurate.
Volumated Intensity Modulated Arc Therapy (VMAT)	It delivers IMRT like distributions in a single rotation of the gantry, varying the gantry speed and dose rate during delivery.	Head and Neck cancers	It is capable of producing conformal plans that are analogous to IMRT.	Increase in treatment time per fraction.
Image-guided radiotherapy (IGRT)	Used in conjunction with IMRT, that comprises of two dimensional portal images that are produced by the mega-voltage beam.	Used to treat tumors in areas of the body that are prone to movement such as lungs, critical organs and tissues.	It can detect and correct the geographic miss that can occur in treatment delivery.	Bony image quality is often quite vague especially with megavoltage imaging and small displacements may not be readily identified.
Chemoradiotherapy	Intravenous administration of chemo-therapeutic drugs with radiation.	Advanced Head and Neck cancers and non metastatic diseases.	Head and Neck cancer patients not receiving definite surgery	Known adverse effects of the chemo-therapeutic drugs.
Particle radiation therapy	Charged particle beams consisting of protons and carbon ions have the Bragg peak and allow highly localised deposition of energy that can be used for increasing radiation doses to the target tissues.	Head and Neck cancer and advanced malignant sinonasal tumors.	Minimises irradiation to the adjacent normal tissues, reduce dose bath effect and better homogenicity.	Limited availability of proton therapy machines.
Radioimmunotherapy	Cytotoxic radionucleotides such as Yttrium 90, Iodine 131 are linked to antibodies inorder to deliver toxins directly to the tumor targets.	Head and Neck cancers and in the treatment of Lymphomas.	Each cell does not have to be bounded by the antibody to receive cytotoxic radiation.	Possibility of allergic reactions.
Boron neutron capture therapy	The boron compound is injected in the patient and the area is irradiated with a neutron beam causing boron B10 to be transformed into B11, which would disintegrate releasing an α particle and 7Li, which have high linear energy transfer (LET), thus killing the cancer cells with almost no damage to the surrounding normal tissues.	Head and neck cancers and in salivary gland tumors.	Distribution of high radiation dose only to the tumor cells while sparing the surrounding normal cells. It has the potential to more effectively target multicentric deposits of tumor than is possible with stereotactic radiosurgery of primary and metastatic brain tumors.	There is a need for more selective and effective boron agents that, when used either alone or in combination.

Table-1: Summary of various radiotherapy modalities

This is a precise technique that is painless. An example of this technique is the Gamma Knife. It is a radical type of surgery that uses highly targeted radiation to treat brain abnormalities which is proven safe and effective, with good outcomes. Gamma Knife procedures offer new hope, less risk and quicker recovery. The data from computed tomography scans, Magnetic resonance imaging and arteriograms to pinpoint abnormal areas within the brain and destroy them using multiple beam of low dose gamma rays which converge to produce a high dose of radiation at the exact side, thus protecting the tissues along the route of the lesion which is safe and effective.[6]

Carbon ion Therapy

Carbon ion radiotherapy can offer better dose conformitory to a target volume than other modalities.[16] In addition high linear energy transfer (LET) radiation such as carbon ion beams, as greater biological effectiveness than low LET radiation, such as X rays and proton beams. Because of its better dose distribution and cell killing potency, carbon ion radiotherapy is a promising modality in the treatment of patient with malignancy.[16-18]

Boron Neutron Capture Therapy (BNCT)

A new form of radiation therapy for cancer that is based upon the selective uptake of non-radioactive boron compounds. The boron compound is injected in the patient and when the required amount of boron reached the tumor site, the area could be irradiated with a neutron beam causing boron B10 to be transformed into B11, which would disintegrate releasing an α particle and 7Li, which have high linear energy transfer (LET), thus killing the cancer cells with almost no damage to the surrounding normal tissues.[19]

The BNCT delivery agents currently used in clinical trials are sodium borocaptate (BSH) and boronophenylalanine or BPA.

The merits of BNCT include distribution of high radiation dose only to the tumor cells while sparing the surrounding normal cells and also has the potential to effectively target multicentric deposits of tumor than is possible with stereotactic radiosurgery of primary and metastatic brain tumors. Critical issues regarding BNCT are that there is a need for more selective and effective boron agents that, when used either alone or in combination. Furthermore, their delivery must be optimized to improve both tumor uptake and cellular micro-distribution and also the radiation dosimetry for BNCT is based on the micro distribution of B10, methods are needed to provide semi-quantitative estimates of the boron content in the residual tumor.[19]

Sanctuary Therapy

Sanctuary therapy is a form of treatment with radiation that offers promise of effectively treating a high risk site of metastasis which could escape the attention of the oncologists. The therapy consists of prophylactic treatment with radiation at a level of 2000 to 3000 rads to the area of site of interest. The term "sanctuaries" refers to the belief that these organs are sanctuaries for tumour cells, since many chemotherapeutic agents do not cross the so called lipid barriers.[20]

Intraoperative Electron Radiation Therapy (IOERT)

IOERT excludes the irradiation of normal tissues and the critical structures in and around the target volume, hence called precision radiotherapy as the clinician views the tumour directly. As the dose falls off rapidly below the target site sparing the underlying healthy tissue, electron radiation can be applied directly on the tumour, which is vulnerable for destruction during intraoperative procedures. IOERT has proven to be beneficial when used in conjunction with endovascular brachytherapy which in turn reduces integral dose and treatment time.[21,22]

CONCLUSION

The field of radiotherapy has undergone an amazing series of developments since its inception over years. Stepwise improvement in head and neck cancer therapy are beginning to show favourable impact on the complex malignancy. Novel strategies aim at improving quality of life and disfigurement, which is an essential aspect of cancer treatment. Treating a locally advanced head and neck cancer still remains a challenge because of the high rate of loco-regional failures and the potential for serious complications following treatment. The advent of new technologies in radiotherapy offer promise in sparing normal cells/tissues thereby minimising toxic and side effects. Thus these advanced techniques are a boon in the treatment of Head and Neck cancers both to the clinician and the patient by improving the mortality and morbidity of this devastating disease.

REFERENCES

1. Vissink A, Jansma J. Oral sequelae of head and neck Radiotherapy. Crit Rev Oral Biol Med. 2003;14:199-208.
2. Vissink A, Burlag F R, Coppes R P. Prevention and treatment of the consequences of Head and neck Radiotherapy. Crit Rev Oral Viol Med. 2003;14:213-224.
3. Bhide S A, C.M. Nutting, Advances in radiotherapy for head and neck cancer. Oral Oncology. 2010;46:439–44.
4. Harari P M. Promising new advances in head and neck radiotherapy. Annals of Oncology. 2005;16:13-19.
5. Trotti A, Bellm L A, Mucositis incidence severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: Radiotheroncol. 2003:66;253-262.
6. Baig M, Current advances in radiotherapy of head and neck malignancies. Journal of International Oral Health. 2013; 5:119-23.
7. International commission on radiation units: Prescribing, recording and reporting photon beam therapy. Supplement to ICRU report 50. Bethseda; International commission on radiation Units and measurements, MD, ICRU: 1999.
8. Bhide S, Clark C, Results of Intensity Modulated radiotherapy in laryngeal and hypopharyngeal cancer: a dose escalation study. Radiotheroncol. 2007;82:S74-5.
9. B. Jorie, B Oak, Intensity Modulated Radiation Therapy, Radiological Society of North America. 2014, 1-5.
10. Parvathaneni U, Laramore GE, Liao JJ, Technical Advances and pitfalls in Head and Neck Radiotherapy. Journal of Oncology. 2012, p 1-13.
11. Vanetti E. Volumetric modulated arc radiotherapy for carcinomas of the oropharynx, hypopharynx and larynx: a treatment planning comparison with fixed field IMRT. Radiotheroncol. 2009;92:111-7.
12. Verbakel W F. Volumetric intensity modulated arc therapy vs conventional IMRT in head and neck cancer: a comparative planning n dosimetric study. Int J radiot oncol biol phys. 2009;74:252-9.
13. Okonogi N, Oike T Current advances in radiotherapy for newly diagnosed glioblastoma multiforme. J Neural Neurophysiol. 2014:5;4.
14. Jakel O, Schlagel W. Radiation therapy with charged

particles. Semin Radiat Oncol. 2016:249-259.
15. Pontus K.E, Radioimmunodetection and radioimmunotherapy of head and neck cancer. Oral Oncology. 2004; 40:761–772.
16. Suit H, Delaney T, Goldberg S. Proton vs carbon ion beams in the definitive radiation treatment of cancer patients. Radiother Oncol.2010;95:3-22.
17. Blakety E A. Cell inactivation by heavy charged particles. Radiant Environ Biophys. 1992;31:181-196.
18. Castro J R, Saundero WM; Treatment of cancer with heavy charged particles. Int J Radiant Oncol Biol Phys. 1982; 8:2192-2198.
19. Bajoria A.A, Kamath G, Asha ML, Babshetand M, Sukhija P. Boron neutron capture therapy – redefining radiotherapy. International Journal of Current Research. 2014;6:8834-8838.
20. Federick W, George W. Current status and recent advances in radiotherapy of lung cancer. CHEST. 1977;71:635-637.
21. Gunderson LL, Willet CG, Calvu FB. Current Clinical Oncology, Intraoperative Electron Beam Irradiation: Physics and Techniques, 2nd ed. NY, USA: Humana Press. 2011,51-71.
22. Calvo FA. Intraoperative radiation therapy. In: Perez CA, Brady LW, Halperin EC, eds. Principles and Practice of radiation Oncology. Boston, USA: Lippincott; 2004:428-56.

Source of Support: Nil; **Conflict of Interest:** None

Submitted: 29-03-2017; **Accepted:** 02-05-2017; **Published:** 15-05-2017