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Tomotherapy: A novel approach to tumor therapy- An overview

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Abstract
Radiation therapy has been used in the treatment of cancer for decades, and the major challenges have been constant: How can physicians be certain that the radiation reaches the tumor site? How can radiation be delivered effectively to kill cancer cells and minimize exposure to healthy tissue? One effective method of delivering radiation is through a machine - a linear accelerator - that focuses an external beam at a specific part of the body. Tomotherapy means "slice therapy" and gets its name from tomography, or cross-sectional imaging. This linear accelerator is the first to integrate a CT (computed tomography) scanner to acquire real-time images – 3D x-rays – to verify the tumor site immediately before treatment. Treatments become more precise because the radiation is altered for any patient movement and the changing shape of the tumor. Our radiation oncologists are now able to make adjustments "on-the-fly". This approach is called Adaptive Therapy. The machine's design also allows it to continuously deliver radiation from all angles around the patient. Tomotherapy features beam-modulating technology that divides a single radiation beam into many smaller, narrow "beamlets" that precisely conform to tumors and minimize damage to surrounding healthy tissue. This translates into fewer side effects and may allow patients to complete their course of treatment in a shorter period of time.

Keywords: tomotherepy and tumor

Introduction
Cancer is the most significant health care problem in the western world surpassing heart disease as the leading cause of loss of potential years of life [1]. In Canada, about 134,000 people are diagnosed annually with cancer. This represents more than one in three people who will develop cancer during their lifetimes. Radiation will be used to treat approximately 66,000 new cancer patients per year of whom 33,000 will be treated with an attempt to cure the disease. Treatment of cancers remains a challenging task because, despite increased experience with the use of chemotherapeutic agents, therapy is often not curative.

Selection of a treatment regimen for an individual patient is empirical and is based largely on the results of clinical trials of tumor therapy and drugs in similar cases. Tumor therapy trials must compare efficacy in tumors of similar susceptibility (i.e. similar stage) for any observed differences to be meaningful. The relationship between growth rates, tumor size and treatment effectiveness implies that tumor size and location(s) are crucial prognostic determinants. Thus various approaches for "staging" tumors have been developed [2]. A tumor can be diagnosed by various tools like CT scans, MRI and Ames test etc. There are various types of tumor therapy which can be implied on the basis of tumor stage (ing) diagnosed e.g. monodrug therapy, combination drug therapy and multimodal therapy. Multimodal approach for tumor treatment includes surgery, chemotherapy and chemo-radiotherapy, the latter one is again classified in two wings like conventional radiotherapy following chemotherapy and tomotherapy. Among them Tomotherapy is most recent one and has dual approach to diagnose as well as to treat tumor with radiation.

Tomotherapy is a new modality of radiation treatment that combines the use of very sophisticated computer-controlled radiation beam collimation with an on-board computed tomography (CT) scanner to image the treatment site. It provides unprecedented accuracy in beam delivery allowing for an increase in tumour dose, thereby increasing the likelihood of cancer cure while at the same time reducing treatment complications in healthy tissues.

Tomotherapy, or "slice therapy," gets its name from tomography, or cross-sectional imaging. Tomotherapy is IMRT with helical/spiral computed tomography scanning delivery. The small beams of radiation are delivered from every point on a spiral.

The tomotherapy Hi·Art System® (tomotherapy Inc., Madison, WI) combines a multileaf collimator and a computed tomography (CT) scanner, verifies the location of the patient's tumor immediately before or after treatment and allows immediate update of the treatment plan to account for any changes in the patient's anatomy or position.

Historical aspect of tumor therapy

The popular introduction of IMRT started in the mid 1990s when the NOMOS Corporation (Swickley, Pennsylvania, USA) introduced the PEACOCK [3]. This comprised of the MIMiC, a tertiary "bolt-on" multileaf collimator (MLC), and a dedicated inverse treatment planning system. In February 2001, the University of Wisconsin Comprehensive Cancer Center installed the world's first clinical tomotherapy research system. The prototype was replaced in 2004, and now carries a full patient load. The TomoTherapy HI·ART System® received initial 510(k) approval from the U.S. Food and Drug Administration (FDA) on January 28, 2002, for use as an integrated system for the planning and delivery of intensity-modulated radiation therapy (IMRT) for the treatment of cancer. The approval document further specified that the planning station for the HI·ART System® was designed to be used by the toxicologist/oncologist to prescribe a radiation therapy plan for a particular patient. The HI·ART System® then calculates the treatment plan which the Toxicologist/Oncologist reviews and approves. On November 12, 2003, the FDA issued another 510(k) approval for a modified version of the HI·ART System® and a third 510(k) approval for this product was issued on November 3, 2004. The first patient was treated using this machine in July 2003. The concept of helical tomotherapy extends back to 1990, when researchers at the University of Wisconsin-Madison were investigating ways to deliver IMRT. In present time Tomotherapy is under clinical trial Phase I and Phase II.

Certain aspect of cancer biology helps in understanding the rationale behind treatment protocols and the limitations of chemotherapy. Discovery of qualitative differences between normal and cancerous cells would facilitate development of more selective therapies i.e. therapies that have lower toxicity for normal tissues. Selectivity is currently based primarily on quantitative differences. That is, both normal and cancer cells have essentially the same ongoing biochemical processes but the rates and timing may be very different. For most solid tumors, the lower limit of clinical or radiological detection is about 1 gram of tissue, or approximately 10^9 cells [4]. Recognizing the need to continue aggressive treatment in the face of apparent complete remission (<10^9cells) was one of the factors leading to success in the treatment of many acute childhood leukemias and lymphomas. Unfortunately, for most solid tumors, a drug-resistant subpopulation emerges and eventually leads to relapse. Now, Tomotherapy is given to acieve total tumor cell kill.

Types of tomotherapy

(1) Serial Tomotherapy, (2) Adaptive Tomotherapy and (3) Helical Tomotherapy

Serial tomotherapy

In this Radiation delivery consists of a machine that rotates around the patient while the beam is on and the leaves rapidly move in and out depending on whether that beamlet is aimed at the target or at normal tissues. After two simultaneous slices have been delivered, the patient is translated by two slice thicknesses and the next two slices are delivered until the total treatment volume is covered, hence the nomenclature, "serial tomotherapy".

Adaptive tomotherapy

Adaptive radiotherapy encompasses several specific processes, each of which represents a separate capability of helical tomotherapy. The key processes of adaptive radiotherapy include 3-D imaging which is utilized to generate an optimized intensity- modulated treatment plan, setup verification via MVCT, delivery modification to account for setup errors, treatment delivery, dose-reconstruction, and deformable dose registration [5, 6]. Adaptive tomotherapy uses information obtained during previous fractions, to correct or modify an ongoing treatment. For instance, dose reconstruction provides feedback to correct errors during delivery. These processes can be viewed as a closed-circuit loop, as illustrated in Figure 2. In order for this approach to adaptive radiotherapy to be successful, the MVCT images obtained from the helical tomotherapy unit must be of sufficient quality for tumor identification and targeting.

Helical tomotherapy

General Design Considerations

The helical tomotherapy machine is a combination of a helical CT scanner and a linear accelerator. It uses the slip ring technology of diagnostic CT scanners and, therefore, the unit is capable of continuous rotation around the patient while the couch is moving into the gantry, thus providing smooth helical delivery as shown in Figure 1. Mounted on the rotating gantry and attached to the slip ring is a compact (~40 cm long) 6 MeV S-band (3 GHz) linear accelerator generating a 6 MV photon beam.

The ability to perform repeated MVCT imaging during the course of treatment and to make corresponding corrections in the treatment delivery will allow dose escalation with less risk of normal tissue complications or geometric miss of the target. For example, in planned lung cancer studies, intra-treatment MVCT imaging performed, thus verifying tumor location relative to delivered radiation dose that is more accurate than a pre-treatment CT scan. Aggregate information from these acquired MVCTs can then beutilized to modify subsequent treatments.

There are several critical steps in this process. One of these is the use of sophisticated 3-D imaging using computorized tomography (CT), magnetic resonance imaging (MRI), single photon emission tomography (SPECT), or positron emission tomography (PET). These imaging modalities have evolved dramatically over the last decade and provide information about tumor location and tumor extent, with each modality providing unique information that is especially relevant for specific tumor types.

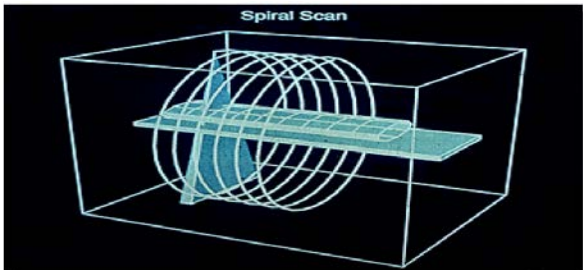

Fig 1

The process of helical tomotherapy

Due to the integration of several technologies into a single piece of equipment, helical tomotherapy allows the development of a number of processes that are either very difficult or simply not possible with other radiation therapy devices.

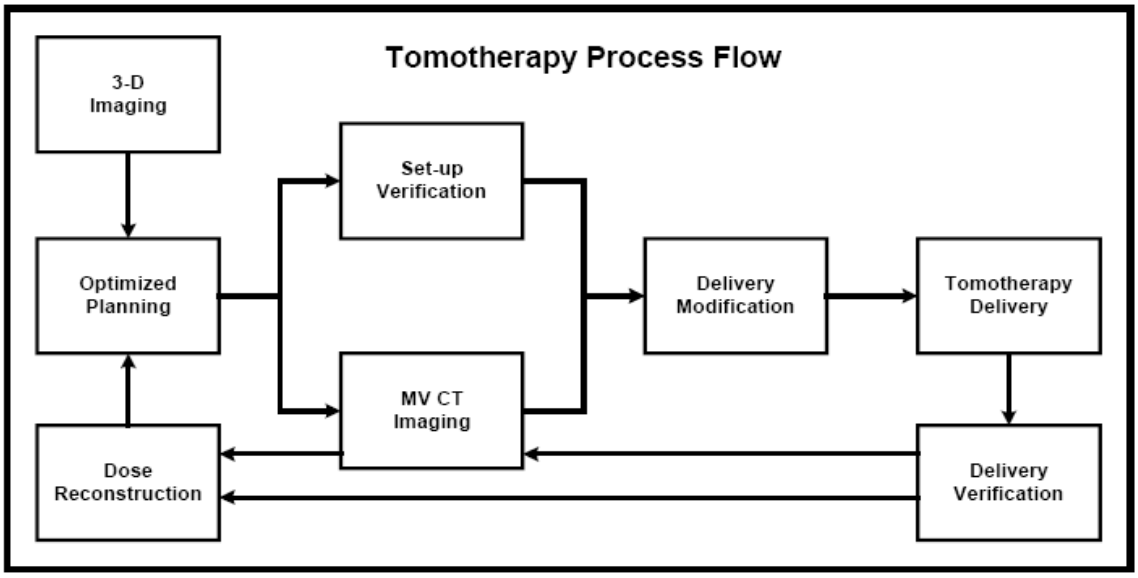

Fig 2: A schematic flow diagram illustrating the various steps of the helical tomotherapy process

A summary of the major components of the tomotherapy processes is illustrated in Figure 2. What follows is a somewhat more detailed description of the steps in the tomotherapy process.

(1) 3-D Imaging.

This step of the process is analogous to the generic first step of radiation therapy planning as shown in Figures 1 and 2. This imaging is generally performed with standard diagnostic imaging equipment or CT-simulators. Under special Circumstances or emergency situations (e.g., out of regular working hours), the megavoltage CT capabilities on the tomotherapy unit could be used to generate this image data for treatment planning and dose delivery purposes on short notice.

(2) Definition of Target Volume and Organs at Risk.

With this 3-D image data set, the radiation oncologist needs to contour the target volume as well as the organs at risk. This could be done at the CT-simulator or on a conventional 3-D treatment planning computer after the image data set has been transferred to the treatment planning system.

(3) Data Transfer to Tomotherapy Planning Computer.

The 3-D data set along with the contours of the target volume and the organs at risk are transferred to the tomotherapy treatment planning computer which will perform the delivery optimization calculations.

(4) Optimized Planning.

To calculate an optimized treatment plan, the radiation oncologist needs to define the planning constraints or objectives, e.g., the prescribed dose to the target volume and the dose limitations to various organs at risk. The tomotherapy treatment planning system provides "inverse planning" capabilities and determines the leaf positions for all the gantry angles and couch positions. The computation is carried out until all the constraints are satisfied or have been optimized.

(5) Creation of Verification Data.

Verification information for tomotherapy consists of the expected beam intensity at the detector array for each gantry angle and couch position. This intensity pattern is referred to as a "sinogram" because each point irradiated in the patient maps a sine wave pattern at the CT detector as the gantry revolves. Sinograms can actually be obtained for various processes including a CT sinogram as described above, an MLC sinogram, a registration sinogram, a verification sinogram and a planned detector sinogram. Conceptually, they are very similar; however, each is implemented in a very specialized manner to address a specific task. For example, the registration sinogram is a 2-D array containing the signal measured by the detector when a loose helical scan is performed of the patient. This sinogram is used to register the position of the patient and aids the determination of the patient position for each fraction and whether or not dose delivery adjustments are required. Verification data can also be generated for a specific measurement phantom situation which can be used to assess the accuracy of the MLC delivery configuration that is intended for a particular patient treatment. This allows measurements to be made in the phantom to confirm the accuracy of the dose intended for the patient.

(6) Transfer of Planning Data to the Treatment Unit.

Once the multileaf delivery configuration has been established by the treatment planning optimization calculation, the leaf positions for each gantry angle and couch position are transferred to the tomotherapy unit for delivery implementation.

(7) Phantom Verification.

This step of the process is described above under Creation of Verification Data and involves treating a phantom with the clinical multileaf collimator configuration and performing the actual measurements to verify its accuracy.

(8) Pre-Treatment Megavoltage CT.
A pre-treatment CT scan is performed for the verification of the patient position and the location of the internal anatomy. This allows for the relocation of the patient or for the replanning of the multileaf collimator configuration to ensure dose delivery to the right tissues within the patient.

(9) Delivery Modification.
Modification of the treatment configuration is performed dependent on the information obtained from the pre-treatment megavoltage CT. Automated delivery modification which involves the actual recalculation and resetting of leaf positions is not implemented in the first releases of tomotherapy, partly because this requires additional approval by the U.S. Food and Drug Administration and Health Canada.

(10) Tomotherapy Delivery.
Once the above steps confirm the accurate location of the patient and the internal anatomy, the dose is delivered according to the planned multileaf configuration with the leaves moving in and out while the beam is on, the gantry is rotating and the couch is moving simultaneously.

(11) Delivery Verification.
While the patient is being treated, the detector array is actively measuring the radiation transmitted through the patient (for each pulse of the linac). This is used to determine actual radiation incident on the patient and can be used to verify dose delivery during or after treatment.

(12) Dose Reconstruction.
Using the incident radiation fluence delivered to the patient and the CT information that was obtained before the treatment, the dose actually deposited in the patient can be computed and compared to the planned dose. If necessary, corrections can be made to subsequent fractions.

Mechanism of action of tomotherapeutic treatment
Radiation Damage and Cell Kill - Ionizing radiation kills cells by interacting with critical cellular molecules, such as deoxyribonucleic acid (DNA). The interaction of ionizing radiation with the molecular infrastructure of the cell results in chemical reactions. Damage to the DNA is either direct (DNA strand cleavage) or indirect, mediated by free radicals. Most cells die a reproductive death after irradiation and will therefore die at a rate consistent with the cell cycle duration. Slowly proliferating tissues respond slowly, whereas rapidly proliferating tissues and most tumors respond more quickly. There are many factors that influence the radiation response of cells in normal tissues and tumors. Some important factors that account for radio responsiveness are the number of clonogenic cells, redistribution or reassortment of cells in the cell cycle, repair of radiation injury, repopulation by stem cells, and the oxygenation status. Proliferating cells are more radiosensitive and have a greater cell loss/turnover rate. Normal tissues and tumors that are rapidly proliferating are more likely to be irradiated at the radiosensitive phase of the cell cycle. Cells are most sensitive to ionizing radiation during M (mitosis) and G2 phases of the cell cycle and most resistant in late S phase (DNA synthesis). The redistribution or reassortment of cells in the cell cycle is one reason behind fractionation of the radiotherapy dose. Dividing the radiation dose into multiple fractions allows cells to reassort to more sensitive phases of the cell cycle before the next treatment. Almost all tumor cell lines undergo some repair of sublethal and potentially lethal radiation damage [7]. Repair of radiation damage will decrease tumor control, but increases normal tissue tolerance. Hence, another reason the radiation dose is fractionated is because normal tissues are included in the radiotherapy field.

Tomotherapeutic doses
Radiation Doses and Volumes - Different doses of radiation are needed for tumor control, depending on the type and initial number of clonogenic cells present. Clonogenic cells are capable of producing a copy or clone. If these cells are malignant a tumor is generated or regenerated. For example, larger doses are needed to eradicate a 2 cm tumor volume as compared to microscopic disease that may be present after incomplete surgical resection. A clinical tumor can comprise several compartments: macroscopic (visible or palpable), micro-extensions into adjacent tissues, and subclinical disease which is presumed to be present, but not detectable. Radiotherapy treatment portals must adequately encompass all three compartments plus a margin to compensate for geometric inaccuracies during the treatment period. Geometric inaccuracies are divided into inherent mechanical imprecision in the treatment machine and those related to defining the target. The latter includes target determination, target localization and reproducibility of patient positioning at each treatment. Defined volumes in radiotherapy treatment planning include the gross tumor volume (GTV), the clinical target volume (CTV), and the planning target volume (PTV) [8]. The GTV is defined as all known gross disease including affected lymph nodes. The CTV includes the GTV plus a margin for suspected microscopic tumor extension. The PTV provides a margin around the CTV to compensate for variation in daily treatment set-up or other anatomic movement such as breathing. Radiation doses are measured in units of absorbed dose, Gray (Gy). A Gray is equal to 1 J/kg energy absorbed in tissue.

Modern dose delivery
One of the unique features of radiation therapy, compared to other forms of cancer treatment, is that the radiation can be delivered in an anatomically and geometrically specific fashion by using radiation field collimation and beam shaping. Today, linear accelerators (linacs), generating electron energies between 4 and 25 MeV, are generally used for producing x-ray beams for the treatment of tumours. Conventionally, these machines have collimators that produce rectangular fields between 4 x 4 cm2 to 40 x 40 cm2. The newer machines have collimators, which are divided into multiple segments from two opposite sides. The "leaves" in these "multileaf collimators" are motor-driven and computer-controlled and can project shadows at the level of the patient that are 0.5 or 1 cm in width.

Radio biologically-based clinical applications
The areas of interest include cranial, head and neck, lung, breast, pancreas, prostate, and gynecologic applications."

Breast cancer
Three-dimensional treatment planning and intensity-modulated planning were performed on five left and five right breasts [9]. Plans were compared using multiple dose distributions and dose volume histograms for the planning target volume (PTV), ipsilateral lung, coronary arteries, and

contralateral breast. Results showed significant improvements in the doses to critical structures were achieved using intensity modulation. Compared with a standard-wedged plan prescribed to 46 Gy, the dose from the IM plan encompassing 20% of the coronary artery region decreased by 25% for patients treated to the left breast; the mean dose to the contralateral breast decreased by 42%; the ipsilateral lung volume receiving more than 46 Gy decreased by 30%; the volume of surrounding soft tissue receiving more than 46 Gy decreased by 31%. Dose homogeneity within the target volume improved greatest in the superior and inferior regions of the breast (approximately 8%), although some decrease in the medial and lateral high-dose regions (approximately 4%) was also observed. They concluded that intensity modulation with a standard tangential beam arrangement significantly reduces the dose to the coronary arteries, ipsilateral lung, contralateral breast, and surrounding soft tissues.

The greatest improvement was seen in the patients with the most pendulous breasts. Researchers concluded that an IMRT planning approach is feasible for prone-position breast RT and improves dose homogeneity, particularly in women with larger, pendulous breasts.

Head and neck cancer

In a prospective study to assess the respective advantages of the various high conformality treatments in radiotherapy, 26 patients presenting with head and neck cancers were treated with IMRT; 18 whole IMRT and eight mixed IMRT and 3D CRT [10]. Results showed that delivered dose plans showed a systematic and highly significant improvement in terms of target coverage compared to referenced 3D CRT. IMRT provides a better degree of confinement of high dose levels in the neighborhood of target volumes compared with 3D CRT. Irradiation of parotid glands or spinal cord improved, as well.

Lung cancer

Treatment planning was performed for 18 patients with Stage I to IIIB inoperable non-small-cell lung cancer using four different RT techniques [11]. The radiation therapy techniques included IMRT, optimized three-dimensional conformal RT (3D CRT) using multiple beam angles, limited 3D CRT using only 2-3 beams, and traditional RT using elective nodal irradiation (ENI). Requiring a minimum dose of 70 Gy within the PTV, researchers found that IMRT was associated with a greater degree of heterogeneity within the target and, correspondingly, higher mean doses and tumor control probabilities (TCPs), 7-8% greater than 3D CRT and 14-16% greater than ENI. IMRT and 3D CRT offered similar results in node-negative cases (mean lung and esophageal normal-tissue complication probability [NTCP] of approximately 10% and 2-7%, respectively). In node-positive cases, however, IMRT reduced lung NTCP by 30%, compared to 3D CRT. They concluded that IMRT can deliver RT doses 25-30% greater than 3D CRT and 130-140% greater than ENI when meeting all normal-tissue constraints in node-positive patients.

Prostate cancer [12]

Studied 1100 patients with localized prostate cancer treated with 3D CRT or IMRT. Therapeutic outcome was measured by prostate-specific antigen (PSA) relapse-free survival, local tumor control and biopsy findings. They report that the results indicate higher than conventional radiation doses associated with improved local tumor control and improved biochemical outcomes and biopsy findings. IMRT was also associated with minimal rectal and bladder toxicity.

Total scalp irradiation using helical tomotherapy

Conditions treated with total scalp irradiation include dissecting cellulitis1 and malignancies such as angiosarcoma of the scalp. Homogeneous irradiation of the scalp poses technical and dosimetric challenges due to the extensive, superficial, curved nature of the treatment volume. Problems with these techniques include dose heterogeneity in the target due to varying source-to-skin distance (SSD), angle of beam incidence and field matching, and significant dose to the brain and eyes.

Spine

In a small trial, 22 spinal lesions were treated. Treatment was planned using IMRT fields in 15 cases, dynamic arcs in five, and conformal beams in two. Researchers stated that shaped beam and IMRS/IMRT may delay neurological deterioration, improving quality of life. They noted the lack of complication suggests that higher doses can be delivered to improve the control rate in patients with metastases.

Advantages of tomotherapy

Tomotherapy overcomes several limitations of IMRT and other forms of radiation therapy. Its unprecedented precision allows clinicians to deliver high doses of radiation extremely efficiently, sparing healthy tissue and shortening each treatment from 30 minutes to five minutes.

The advantages of IMRT are noted as most obvious when “a critical structure (e.g., the optic nerve) invaginates a target by creating a concavity in its surface (taken here as the planning target volume, or PTV) or when the critical structure is completely surrounded by that target.

“Intensity-modulated radiation therapy (IMRT) makes possible conformal radiation dose distributions to the target while reducing exposure of adjacent non target structures, beyond the capabilities of traditional two-dimensional or even state-of-the-art three-dimensional treatment techniques.”

This high-precision radiotherapy utilizes computer-controlled x-ray accelerators to deliver precise radiation doses that conform to the 3D shape of the tumor.

Tomotherapy allows real-time imaging of patients to verify set-up and detect variations in positioning. This provides an optimal means of delivering co-planar therapy and Conformal Avoidance.

Limitation of tomotherapy

- As with all major technological advances, the initial cost is an issue.
- Limited number of installed sites. 6 in US and none at major cancer center.
- First generation of IGRT technology.

Conclusion

This new process of planning and treatment delivery shows significant potential for improving the therapeutic ratio. Also, although inefficient today, it is expected that IMRT, when fully developed, will improve the efficiency with which external beam RT can be planned and delivered, and thus potentially lower costs. Helical tomotherapy mounted on a ring gantry provides significant advantages over today's state-of-the-art radiation treatment. First, it provides on-line imaging which allows for treatment adaptation on a daily

basis accounting for the tissue locations on each set-up. The dose reconstruction capabilities provide an ability to determine the dose actually delivered to the patient, also on a daily basis. The tomotherapy unit fits into a significantly smaller room compared to modern linear accelerators since it does not involve a couch rotation. Because of the CT detectors with an added beam stopper and the ring mounting, the primary beam is virtually fully attenuated, thereby reducing the shielding requirements of the treatment bunker. Both the reduced room size and the reduction of shielding will provide significant cost savings in the implementation of this technology. Because tomotherapy is a single energy linac, fully integrated with a treatment planning system, it is expected that once the technology becomes routine, it will be significantly easier to commission in comparison to today's multi-energy and multi-modality (photons and electrons) linacs.

Future perspective

With its novel physical design and method of delivering IMRT, helical tomotherapy holds great promise for the future enhancement of Radiation Oncology. Along with adaptive radiotherapy (shared by no other current approach), development and refinement of the concepts of conformal avoidance and radiobiological dose optimization offer promising opportunities for cancer specialists and for the cancer patients who stand to benefit from this new technology.

The future of tomotherapy will be broadened by the use of radiation in conjunction with molecular therapies. Many fields are to be further explored with respect to developments of radioprotection and sensitization of tumor cells by tomotherapy. Administration of tomotherapy for treatment of pets with cancer will become integral skills in many small animal hospitals. Tomotherapy can be a rational means of improving the patients' quality and/or quantity of life.

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