Proceedings Article

□ Recent advances in tomotherapy, intensity modulated and image guided radiation therapy

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SUMMARY: *Remarkable advances are evolving in radiation therapy technology that optimize the treatment of patients with cancer, with irradiation alone or combined with other modalities (surgery, chemotherapy, hormones or biologically targeted therapies). Accurate delineation of tumor, target volumes and organs at risk is crucial to the quality of treatment planning and delivered accomplished with innovative technologies in radiation therapy. Quality assurance in all components of the treatment planning, delivery and verification will ensure optimal patient care and better treatment outcome. The increased complexity of this technology requires more rigorous training of all professionals involved in the radiation therapy process and more detailed and accurate quality assurance procedures to ensure an optimal treatment of our patients. There is an increased cost in the application of innovative techniques, but in a long run this is compensated by a lower cost in the overall treatment of a patient, as additional management of initial treatment failures or complications is three-fold higher than the cost of successful and uncomplicated initial treatment.*

KEY WORDS: *Image guided radiation therapy, Intensity modulated radiation therapy, Tomotherapy.*

□ Recenti progressi nella tomoterapia e nella radioterapia con intensità modulata e guidata dalle immagini

RIASSUNTO: *Si registrano notevoli progressi nelle tecnologie di radioterapia che ottimizzano il trattamento del paziente con tumore, con irradiazione singola o combinata con altre modalità (chirurgia, chemioterapia, ormoni o terapie per il target biologico). La precisa delineazione del tumore, dei volumi target e degli organi a rischio è fondamentale per la qualità del piano di trattamento e per la irradiazione con tecnologie innovative. Il controllo di qualità di tutti i componenti del piano di trattamento, della irradiazione e della verifica assicurano un trattamento ottimale del paziente e un miglior outcome. La maggiore complessità di queste tecnologie necessitano di un training più rigoroso per tutti i professionisti coinvolti nel processo di radioterapia e più dettagliate e precise procedure di controllo di qualità per assicurare un trattamento ottimale ai nostri pazienti. L'aumentato costo per l'applicazione di tecniche innovative è compensato dai minori costi del trattamento generale di un paziente, dal momento che ulteriori terapie dopo iniziali insuccessi nel trattamento o complicazioni comportano un costo tre volte maggiore di quello di un trattamento iniziale di successo e senza complicazioni.*

PAROLE CHIAVE: *Radioterapia guidata dalle immagini, Radioterapia con intensità modulata, Tomoterapia.*

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□ INTRODUCTION

Exciting advances have taken place in oncology in recent years, including enhanced knowledge of molecular biology and genetics, functional imaging (positron emission tomography scanning), image-guided radiation therapy, microvascular reconstruction, organ preservation and robotic surgery, increased use of monoclonal antibodies, as well as molecular targeted cytotoxic agents, which are increasingly applied to clinical situations. At the same time there have been remarkable technologic developments in radiation oncology, including the use of more powerful and versatile computers for treatment planning, sophisticated devices to improve precision of radiation dose delivery, data processing, and informatics. This has resulted in an increasing use of volumetric image-based treatment planning for the delivery of radiation therapy using three dimensional conformal (3DCRT), intensity modulated radiation therapy (IMRT) or image guided radiation therapy (IGRT), stereotactic radiation therapy (radiosurgery), stereotactic body radiation therapy, image-guided brachytherapy, radiolabeled compounds and special particle therapy (protons, heavy ions). Computer-based record and verify systems as well as advanced on-board imaging such as kV cone beam CT (CBCT), MV helical CT, and MV electronic portal imaging are increasingly used to enhance treatment delivery verification[13].

The definition of IGRT is not standardized, and lately has been defined as the use of imaging modalities, especially those incorporating functional or biological information for target delineation, and the use of imaging to adjust for target motion or positional uncertainty, and to adapt treatment to variations in target delineation[22]. A key element of IGRT, facilitated by the advent of fast multi-slice CT scanners is the use of 4D target localization, which incorporates into the radiation therapy treatment planning process images documenting internal organ motion.

Further, reproducibly positioning the patient is an important element of fractionated RT delivery. However, both systematic and random errors in patient set-up as well as movement or changes occurring in target and normal tissues between (*inter*-fraction) or even during (*intra*-fraction) treatment contribute to variation in daily target delineation and localization[12]. IGRT incorporates strategies to more accurately localize the target and optimize RT during the treatment course, ideally leading to more effective and less toxic therapy. Adjustments can take place between fractions (off-line) or while the patient is in the treatment position (on-line). Such corrections allow reductions of planning margins, sparing of normal tissue, or adaptation of treatment plans to optimize dose delivery, which has been defined as adaptive radiation therapy[28].

While targeting accuracy has always been a goal in radiation therapy, coupled with dose optimization, the impetus to adopt IGRT has taken on greater importance with the growing popularity of IMRT[22]. Some concerns about IMRT, however, include the longer treatment time per session and the presence of steep dose gradients, factors that increase uncertainties related to target localization which heighten the need for IGRT to compensate for them.

A second impetus for 3DCRT, IMRT or IGRT is the greater need to decrease toxicity. Concurrent chemoradiotherapy is now standard treatment in many disease sites, but is generally associated with higher acute toxicity. IGRT, especially using IMRT, by more precisely tailoring the radiation dose distribution to the target volume and sparing normal structures could reduce such toxicities and/or permit implementation of more aggressive treatment without increasing toxicity[22].

In addition, interest in hypofractionation is increasing, especially in sites where it may have distinct radiobiological and/or logistical advantages. Use of high fraction sizes requires optimal target definition and localization to ensure local tumor control and limit complication risks. Finally, as systemic therapies improve prolonging survival, the importance of reducing chronic treatment effects becomes greater. As toxicity is often the major factor limiting the applicability of RT, it is imperative to reduce toxicity so the therapeutic role of RT is both maintained and advanced.

□ TARGET AND NORMAL STRUCTURES DELINEATION

Ling and coll.[19] summarized imaging advances that have potential application in radiation oncology and emphasized the need to adequately identify gross, clinical, and planning target volumes as defined by ICRU Reports No. 50 and 62 (Figure 1). They proposed the concept of a biologic target volume (BTV), which can be derived from biologic images that will substantially improve target delineation, treatment planning, and radiation therapy delivery. They noted that in the future, radiation therapy clinical dosimetry

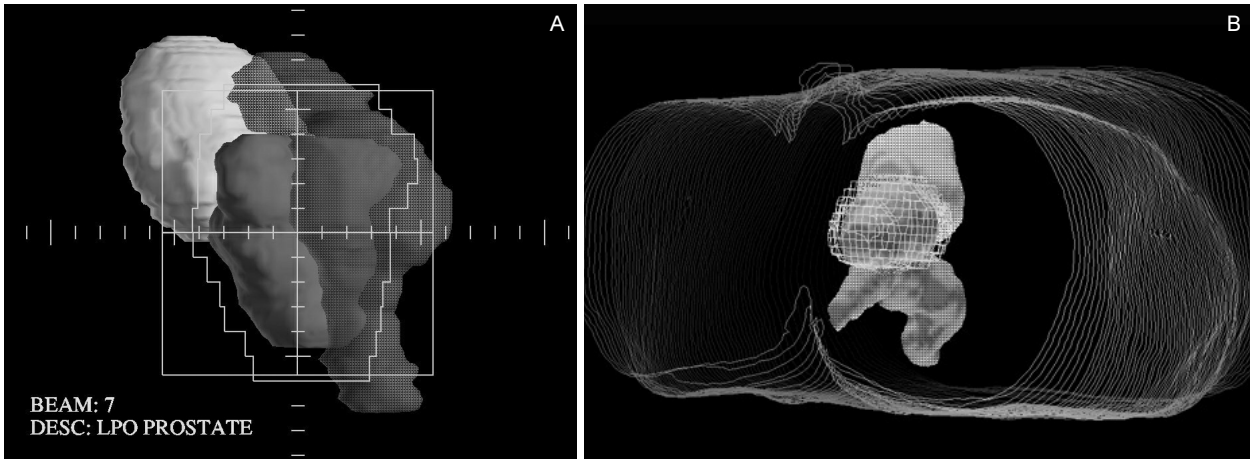

Figure 1. A. Three dimensional Beam's-Eye-View (BEV) display of volumes to treat localized carcinoma of the prostate. B. Room's Eye-View (REV) display of three-dimensional radiation therapy dose distribution for localized carcinomas of the prostate.

will incorporate both physical and biologic conformity and evidence-based multidimensional conformal therapy to improve the treatment of patients with cancer using 3DCRT, IMRT, or other techniques.

Central to all these advances is the need to carefully and continuously account for anatomical variations, different tumor locations and configurations, concerns with organs at risk in the irradiated volumes and motion of the patient or the internal target/organs during a course of fractionated radiation therapy.

Strategies to address motion have included elaborate patient immobilization techniques, careful simulation, accurate tumor delineation, setting up margins around the tumor volume(s), re-simulation and re-planning, real time target position monitoring and portal imaging.

Innovations in medical imaging, including computed tomography (CT) and magnetic resonance imaging (MRI), have been invaluable in these efforts, providing a fully three-dimensional model of the patient's anatomy and the tumor volume, which is sometimes complemented with functional imaging, such as positron emission tomography (PET) or magnetic resonance spectroscopy (MRS). The standard procedure for delineation of tumor volumes and organs at risk is computed tomography, in most instances with contrast agents for more accurate imaging of tumors or blood vessels. However, in specific instances magnetic resonance provides better imaging of soft tissues masses. For instance, several authors have noted that delineation of the prostate can be more accurately achieved with MRI, particularly in identification of the prostatic apex.

Respiration has been shown to introduce substantial uncertainty in target positioning when irradiating patients with intrathoracic or upper abdomen tumors, which ideally must be accounted for in treatment planning[17]. Several approaches to 4D target delineation have been described[1,8,22] facilitated with the advent of fast multi-slice CT scanners, which enable reconstruction of an "integrated target volume (ITV)", consisting of imaging data acquired in separate phases of respiration into a combined 3D volume containing the probable location of tumor. Allen and coll.[1] created a composite volume based on the tumor delineated on maximal inhalation and exhalation scans in 16 patients. This structure was significantly smaller than a 1 cm uniform expansion around the gross tumor volume (GTV) delineated on a free breathing scan, indicating that a standard approach using a 1 cm expansion leads to over-treatment of normal tissues.

Positron emission tomography scanning clinical applications in oncology include[1] differentiating benign from malignant lesions (albeit, not always accurately)[2], staging of malignant tumors[3], treatment planning including radiation therapy, and[4] monitoring treatment results and follow up[4,10,24]. Gregoire[9], in an editorial, pointed out the increasing use of PET scanning to determine tumor extent and as a guide for radiation therapy treatment planning in patients with cancer, spearheaded by the popularity of 3DCRT and IMRT. He thoughtfully discussed issues related to sensitivity and specificity of PET scanning in different anatomical locations, which affect the usefulness of this modality in clinical practice. The advent of PET/CT devices, markedly facilitates the acquisition

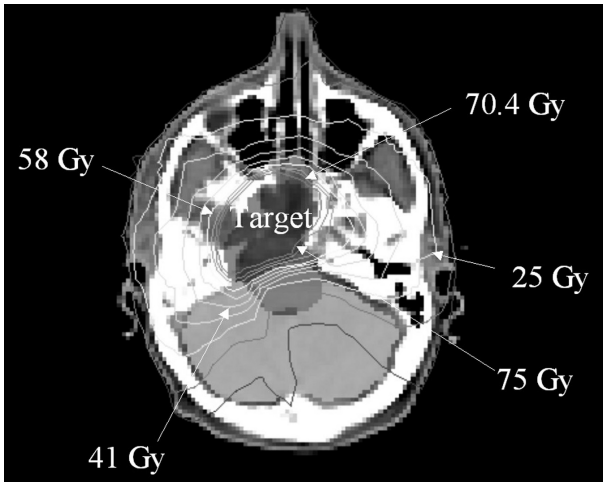

Figure 2. Cross section intensity modulated radiation therapy (IMRT) dose distribution for patient with head and neck cancer.

of anatomic and physiologic fused images under similar conditions for radiation therapy treatment planning. In the future it will be possible to expand the applications of PET in oncology by taking advantage of *in vivo* distribution of radionuclides such as ^{15}O, ^{11}C, and others mentioned in this review. Similarly, single photon emission tomography (SPECT) can be used to quantify *in vivo* distribution of receptor targeting compounds labeled with ^{111}In, ^{99m}Te, or ^{123}I.

Bourguet and Group de Travall Standards, Options and Recommendations project, developed guidelines for the use of FDG-PET scanning in the diagnosis of the primary tumor, treatment response, and examination for recurrence. The recommendations were made on the basis of data published up to February 2002. Systematic monitoring of the new scientific data on FDG-PET was set up to ensure updating of available reports[5].

□ THREE-DIMENSIONAL TREATMENT PLANNING

The ultimate goal of radiation therapy treatment planning is to biologically characterize and accurately delineate the target volume, plan an effective course of therapy, predict tumor and normal tissue response (TCP, NTCP), and monitor the outcome of treatment. 3DCRT uses a number of co-planar or non- coplanar radiation beams shaped to conform to the target volume, which sometimes has irregular configuration. In the past, to improve the conformality of radiation dose distribution, conventional beam modifiers (e.g., wedges, partial transmission blocks, and/or compensating filters) were sometimes used. This "*forward planning*" approach to 3DCRT is rapidly being replaced by "*inverse planning*", which for IMRT, can achieve even greater conformity by optimally modulating non-uniform photon fluence of individual beamlets that make up the radiation beam to achieve a specified dosimetric and clinical objective. IMRT dose distributions are created to conform more closely to the target, particularly for those volumes having complex/concave shapes, and shaped to avoid critical normal tissues in the irradiated volume (Figure 2).

3D treatment planning for conformal therapy typically involves establishing the patient's treatment position (including constructing patient repositioning/immobilization devices when needed), obtaining a volumetric image data set of the patient in treatment position, contouring target volume(s) and critical normal organs using the volumetric planning image data set, determining beam orientation and designing beam block apertures or multileaf collimation (MLC) settings, computing a 3D dose distribution according to the dose prescription, evaluating the treatment plan, and if needed, modifying the plan (e.g., beam orientations, apertures, weights, modifiers, etc.) until an acceptable plan is approved by the radiation oncologist. The approved plan must then be implemented on the treatment machine and the patient's treatment verified using appropriate quality assurance (QA) procedures.

The 3D treatment planning/conformal radiation therapy process demands greater involvement of the radiation oncologist to specify target volume(s) and critical structure(s) with far greater accuracy than previously. Moreover, conformal therapy also requires increased efforts of the radiation oncology physicist to insure adequate QA measures are in place, e.g., checks regarding use of multi-modality imaging (including fusion QA), patient set-up reproducibility checks, organ motion assessment, treatment delivery verification, etc.[27,28].

Using inverse planning for IMRT, tomotherapy and IGRT, will not guarantee an optimum treatment plan, since approximations are always introduced when moving from calculated intensity patterns to dose delivery. In addition, the results of inverse planning are strongly dependent on specification of dose-volume constraints and other parameters that guide the optimization process. Finding an optimum solution will depend on the physician's ability to set dose-volume

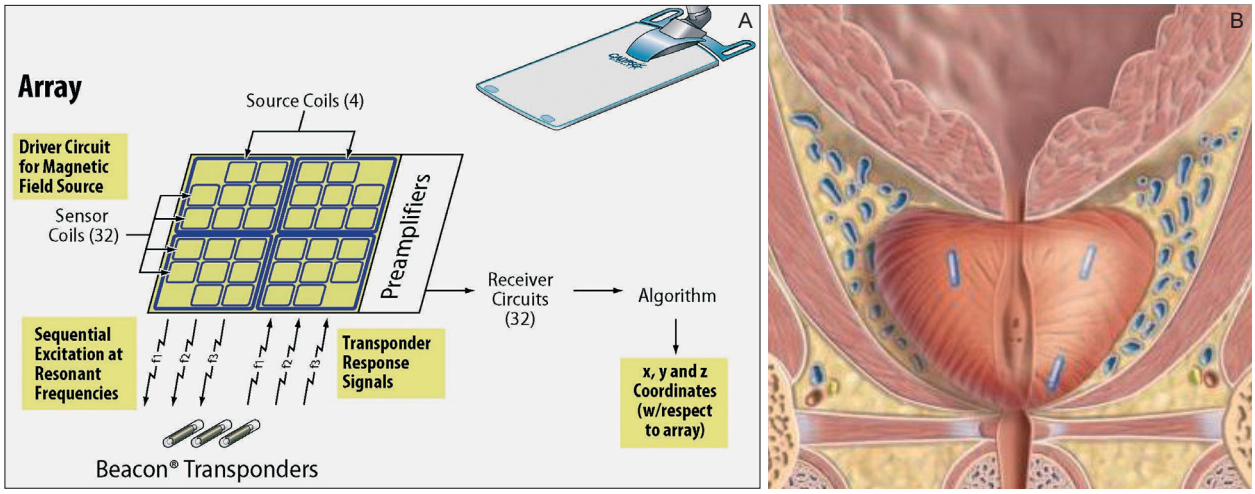

Figure 3. A. Diagramatic representation of radiofrequency tumor localization and monitoring system (*Calypso Corp.*). B. Drawing illustrating placement of transponders in prostate for Calypso system tumor localization and monitoring.

constraints. The planning system must have the capability to simulate each of the treatment machine motion functions, including gantry angle, collimator length, width and angle, MLC leaf settings, couch latitude, longitude, height, and angle. Patient surface and heterogeneity corrections are integral part of the dose calculations. Dose-volume histograms (DVH), in conjunction with three-dimensional or multiple plane dose calculations are essential in the evaluation of 3D treatment plans, although DVH's do not factually represent the inhomogeneities in dose distributions within the volumes of interest.

☐ TREATMENT VERIFICATION

Fiducial radiopaque markers, ultrasound, megavoltage electron portal imaging, kilovoltage or megavoltage CT scanning (available in modern IGRT linear accelerators equipped with cone beam CT or helical tomotherapy devices) are being used to image the anatomy of the patient and the target volume on a daily or weekly basis. Recently a novel device using radiofrequency transponders implanted in the patient allow a real time three-dimensional determination of the target position and coordinates, which are displayed on a screen (*Calypso Corporation, Seattle, WA, USA*) (Figure 3).

Electronic portal imaging devices (EPIDs) provide a means of generating an electronic image of a treatment field with the patient on the treatment table. Similar to conventional portal imaging, EPIDs produce images using the therapeutic (megavoltage) beam, which can be digitally processed for better visualization of the relevant anatomy and stored for off-line review[2,7,14].

☐ QUALITY ASSURANCE

To ensure the quality of radiation therapy it is mandatory to implement programs that test the functionality of the equipment and the precision of dose calibration, treatment planning, dose calculations and delivery used in the treatment of the patient. Dosimetric QA compares measured and calculated dose distributions for specific test treatment plans. The American Association of Physicist in Medicine (AAPM) and the European Society for Treatment and Research Organization (ESTRO) have published detailed reports describing acceptance testing, commissioning and procedures for periodic quality assurance procedures of hardware and software used in radiation therapy facilities[15,18,26]. Other elements of quality assurance include protocols and manuals documenting the operating procedures in the radiation facility, appropriate clinical and physics records, chart review sessions and audits of parameters of treatment and dose verification, with participation of radiation oncologists, physicist, dosimetrists therapists and other personnel to ensure the proposed treatment is being accurately carried out.

Because in general, with 3DCRT, IMRT or IGRT the margins around the target are smaller and the dose

gradient steeper it is necessary to exercise more care in the treatment of the patient. Therefore a QA program for these modalities must be more detailed and demanding, as it involves not only all of the elements described above but also performance of the multileaf collimator, leaf accuracy (for IMRT sub-mm accuracy is needed, speed, etc.) and the radiation exposure with the accelerator gantry in motion.

For IMRT treatment, which lacks a convenient portal imaging to verify patient position and accuracy of dose distribution, specific patient directed QA program is mandatory, including irradiation of anatomical phantoms with the proposed treatment parameters, using ionization chambers, film dosimetry (radiographic, radiochromic), thermoluminescent dosimeters, etc. and comparing this data with the dose distributions and DVH's generated by the treatment planning system[20].

□ INNOVATIVE RADIATION THERAPY TECHNOLOGY

In the past 20 years new techniques have been implemented to more accurately optimize the radiation doses delivered to the target volumes while sparing adjacent normal tissues. This has led to lower treatment morbidity and the potential for increasing radiation doses to the tumor, which results in higher local-regional tumor control, lower incidence of distant metastasis, improved survival and better quality of life of the patient.

Three-dimensional Conformal Radiation Therapy began to be used about 20 years ago, using an increasing number of radiation beams shaped using Beam's-Eye-View (BEV) treatment planning to conform the dose distribution to the configuration of the target volume. This approach has been widely used in the treatment of patients with tumors of the central nervous system, head and neck, thorax, pancreas, prostate[13], rectal, soft tissue sarcomas and other tumors, with excellent results.

Intensity Modulated Radiation Therapy is a variation of 3DCRT in which a computer-aided optimization process is used to generate customized non-uniform fluence of photons to attain specific dosimetric objectives in the irradiated volumes and fulfill an intended clinical goal. There are no secondary field-shaping or beam modifying accessories, other than the multileaf collimator. The ideal photon energy for IMRT is between 4 and 10 MV; at higher energies scattered radiation and neutron contamination are increased[20].

Because of the inherent characteristics of the IMRT dose distribution it is possible to deliver simultaneous integrated boost in a single treatment, which may offer added radiobiological advantage, with delivery of higher doses to the target volume in a shorter period of time. IMRT also allows for simultaneous treatment of the primary tumor and regions of sub-clinical disease. This feature can make it difficult or even impossible to use standard dose fractionation for both volumes[20]. Concern has been expressed that IMRT, with multiple beamlets, delivers low doses of irradiation to larger volumes of normal tissue, in addition to a larger number of monitors units, increasing the body exposure due to leakage radiation from the head of the accelerator, compared with other irradiation techniques, which may eventually result in an increased incidence of second malignancies[11].

Tomotherapy is a novel approach, initially proposed by Mackie and collaborators[21] which consists of intensity modulated photon irradiation delivered using a rotating slit-beam and a temporally modulated collimator that rapidly moves the leaves in and out of the slit beam. A variation of this technique is serial tomotherapy, in which narrow segments (usually 1.6 cm wide) are sequentially irradiated in the patient to achieve a defined composite dose distribution in the volume of interest.

Helical Tomotherapy (Hi-Art) is a more complex version, in which a fully integrated system includes treatment planning computational capability, a 6 MV photon accelerator mounted on a gantry, beam pulse modulator, radiation detectors and a megavoltage imaging device. As in a CT scanner, the radiation source and the collimator continuously revolve around the patient. Unlike the Peacock the Hi-Art Tomotherapy system moves the patient couch at the same time the gantry is rotating, providing a continuous helical geometry of the radiation beams[16] (Figure 4).

Given its relative recent clinical implementation, outcome data of patients treated with tomotherapy is limited. This will certainly change in the coming years given the number of dosimetric studies supporting its benefits[29,30]. Tomotherapy may be particularly beneficial in patients undergoing hypofractionated or stereotactic body radiation therapy.

Aoyama and collaborators[3] in a study in phantoms showed that helical tomotherapy results in a lower radiation dose to the non-target volumes compared to standard IMRT, although the dose is greater than that

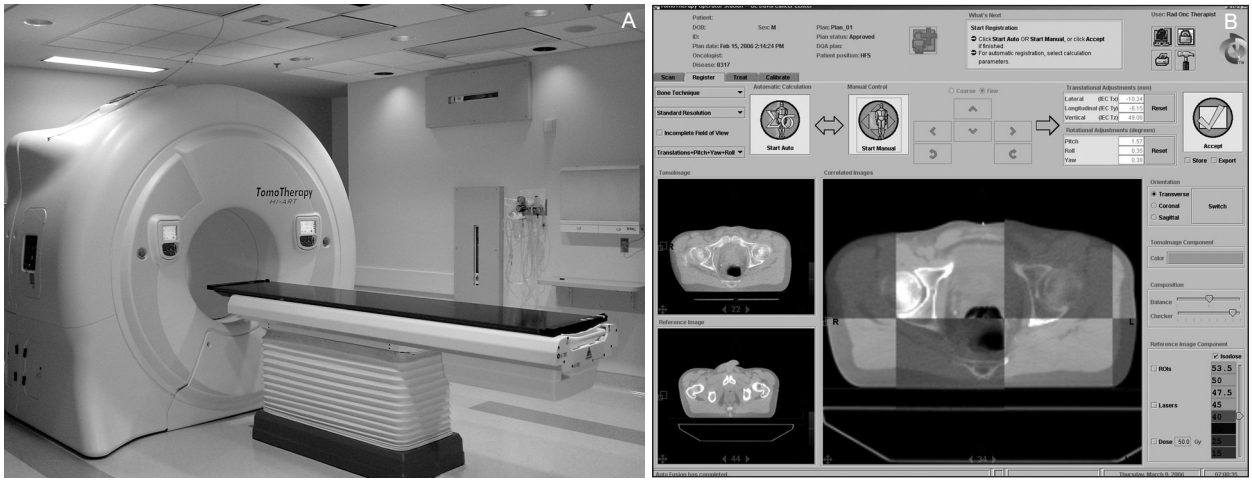

Figure 4. A. TomoTherapy Hi-Art system for IGRT (*TomoTherapy Inc.*). B. Megavoltage (MV) CT images of the pelvis obtained in TomoTherapy system. C. Dose volume histogram illustrating impact of adaptive IGRT on final irradiation dose administered to parotid gland (compared with initial treatment plan) in patient treated for carcinoma of oropharynx.

delivered by pencil beam proton irradiation[11].

MV Cone-Beam Systems (CBCT) incorporate 2D images using the treatment beam or a kilovoltage X-ray beam in linear accelerators[23]. Image acquisition and processing times were both on the order of 90 seconds. MV CBCT and conventional CT datasets were registered with millimeter and degree accuracy. No clinical outcome data have been published to date in patients undergoing MV CBCT scanning and treatment.

Robotic Radiation Therapy (Cyberknife) consists of a compact X-band 6 MV linear accelerator coupled to a multi-jointed robotic manipulator with 6 degrees of freedom[22]. The current generation of cyberknife technology incorporates two precisely calibrated diagnostic X-ray tubes fixed to the ceiling of the treatment vault and two nearly orthogonal aSi flat-panel detectors. After coarse alignment, projected images from the cameras are automatically registered with the DRRs from the planning CT. Changes in target position are relayed to the robotic arm which adjusts pointing of the treatment beam. During treatment, the robotic arm moves through a sequence of positions (nodes). At each node, a pair of images is obtained, the patient position is determined, and adjustments are made. Cyberknife treatment was initially based on tracking of the skeletal anatomy of the skull and upper spine, limiting treatment to tumors of the brain, head and neck and upper spine. Subsequently, the ability to track implanted fiducial markers and more recently, software development that enables respiratory tracking has expanded the clinical applications of this modality.

Image Guided and Adaptive Radiation Therapy. This approach has the potential to enhance the therapeutic ratio (dose to tumor or normal structures). However, due to the complexity of treatment delivery and variation in patient intra-fraction and inter-fraction body motion, risks for geographic misses exist (0.3, 35A); "closed loop" technology that provides continuous feedback to the irradiation system and allows for adjustment to be made for changes in the patient's position or target deformation or position, or normal structures location and configuration may be necessary in order to optimize the actual dose delivered in a multi-fraction radiation therapy course. Replanning of the radiation therapy (daily, weekly), accounting for dose distribution differences based on

anatomical variations will achieve a more realistic representation of actual dose delivered. However, repeated imaging, re-contouring, re-planning, and verification of quality assurance are very labor intensive and perhaps clinically not practical or cost effective, except under special circumstances. More research and development of robust deformable registration tools are still needed to make this so called "adaptive radiation therapy" practical[29].

□ COST BENEFIT AND UTILITY

There is a substantial financial investment in the acquisition of modern radiation therapy treatment planning systems and devices, in addition to the documented increased time and effort involved in the procedures necessary to maintain, operate the equipment and treat a patient with 3DCRT, IMRT, tomotherapy, IGRT, etc. As noted, there is significantly greater involvement of the radiation oncologist and physicist as well as more time required of the dosimetrist(s) and radiation therapists to supervise, generate, verify treatment planning and delivery. The complexity of the treatment techniques and the potential for errors that will undermine the therapeutic objectives and jeopardize the well being of the patient demand more training and continuing education for all professionals involved in the management of patients treated with these modalities.

Several publications[25] have documented the time and effort of modern radiation therapy which is only partially impacted by increased experience and proficiency of the staff. In USA this has been reflected with higher reimbursement for services that attempt to cover the greater use of equipment, facilities and human resources involved in the treatment of these patients. Further, as these modalities are frequently used in conjunction with cytotoxic or molecular targeted therapies that enhance the effect of irradiation, the overall management of the patient is more complex and time consuming. On the other hand, innovative radiation therapy and dose optimization has been documented to increase local-regional tumor control and survival with decreased incidence of distant metastasis and better quality of life of the patient. Perez and collaborators[25] in a study of patients with localized carcinoma of the prostate noted that the retreatment of a patient who has a tumor recurrence after initial treatment increases the total cost of therapy to about three to four times the cost of a patient treated successfully at initial treatment. Moreover, the cost of management of complications of treatment will also add to the overall cost of management of the patient.

□ CONCLUSIONS

Remarkable advances are evolving in radiation therapy technology that optimize the treatment of patients with cancer, with irradiation alone or combined with other modalities (surgery, chemotherapy, hormones or biologically targeted therapies). The increased complexity of this technology requires more rigorous training of all professionals involved in the radiation therapy process and more detailed and accurate quality assurance procedures to ensure an optimal treatment of our patients. Accurate delineation of tumor, target volumes and organs at risk is crucial to the quality of treatment planning and delivered accomplished with innovative technologies in radiation therapy. Quality assurance in all components of the treatment planning, delivery and verification will ensure optimal patient care and better treatment outcome. There is an increased cost in the application of innovative techniques, but in a long run this is compensated by a lower cost in the overall treatment of a patient, as additional management of initial treatment failures or complications is three-fold higher than the cost of successful and uncomplicated initial treatment.

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