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Recent Technological Advances in Radiotherapy

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Abstract

Intense and rapid technological advances in computer software, imaging and engineering projected to radiotherapy over the past decades. As the main objective of radiotherapy is sterilization of tumor cells at a defined target with adequate safety margins, treatment planning and dose delivery systems allowed the precise radiation dose to the target volume, sparing the adjacent structures. The breakthrough development of computer-controlled multileaf collimators and adaptation of computer tomography-based planning enabled three-dimensional conformal therapy. Intensity-modulated radiotherapy, volumetric modulated arc therapy, image-guided radiotherapy, adaptive radiotherapy, stereotactic radiotherapy, intraoperative radiotherapy, brachytherapy, charged particle radiotherapy, and hyperthermia are the technological reflection of these improvements. As radiotherapy is one of the most technology-driven treatment modalities in the management of cancer, future innovations and knowledge gained from clinical trials will help to improve new treatment strategies.

Keywords: 3D conformal radiotherapy, intensity-modulated radiotherapy, image guided radiotherapy, stereotactic radiotherapy, intraoperative radiotherapy, proton beam radiotherapy

INTRODUCTION

Radiotherapy is an important component of cancer treatment that remains as an integral part for local control. Delivering high dose to the tumor region is important for treatment achievement while the complications also increase with the dose given to the region of the organ irradiated. Over the past decade, advances in technology leading significant developments at computer software and imaging algorithms, sophisticated dose calculation methods in radiotherapy planning, and delivery techniques have allowed adaptation to tumor volume with better tumor delineation, decreasing nearby normal tissue irradiation while increasing targeted tumor dose accurately with the opportunity of improved survival.

Conformal Radiotherapy

In the early 1970s, the introduction of computer tomography (CT) was a key to the development of the modern three-dimensional (3D) planning that is crucial to conformal therapy because it made available a complete 3D description of the anatomy of each patient that could be the basis for planning (1). Similar to CT, magnetic resonance imaging (MRI) and positron emission tomography (PET) have also replaced plain radiography in radiation treatment planning for their direct visualization of soft tissue structure and tumors with precise location in defining the target volume.

Conformal therapy describes radiotherapy treatment that aims high-dose volume shaped to closely "conform" to target volumes while minimizing the dose to critical normal tissues. Although these features are the general aim of any radiotherapy treatment, normally, the term conformal radiotherapy is applied to treatment plans in which the target volumes are defined in three dimensions using contours drawn on many slices from a CT with multiple beam directions used to cross fire on the targets, and the individual beams are shaped to create a dose distribution that conforms to the target volume at desired dose levels. Radiation oncologist and medical physicist can avoid and mini-

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Table 1. ICRU report 50 target volume definitions (3)

Abbreviation	Name	Description
GTV	Gross tumor volume	Volume of macroscopic tumor that is visualized on imaging studies
CTV	Clinical target volume	Volume that should be treated to a high dose, typically incorporating both GTV and volumes that are assumed to be at risk as a result of microscopic spread of the disease
PTV	Planning target volume	Volume that should be treated to ensure that the CTV is always treated, including considerations of systematic and random daily set-up errors and inter- and intratreatment motion

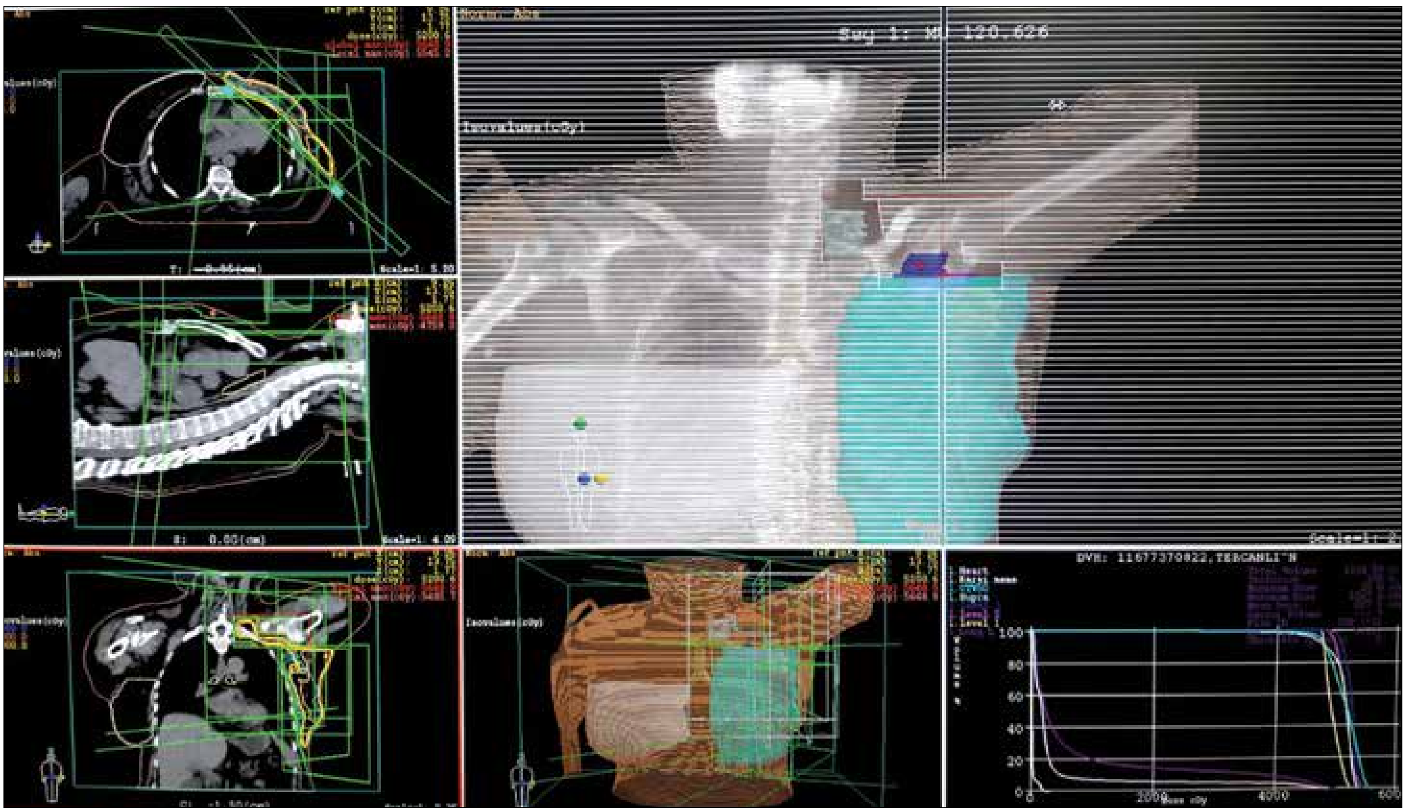

Figure 1. Three-dimensional conformal radiotherapy plan of a patient with breast cancer. Organs at risk and PTV doses are evaluated
PTV: Planning target volume

mize the dose delivered to normal tissues by the correct definition of normal tissues. For ideal results, image guidance, accurate patient set-up, and immobilization for the management of motion and other changes to ensure accurate delivery of the planned dose distributions to the patient are required and very important for conformal treatment (2).

3D Conformal Radiotherapy

The first conformal treatment planning technique based on the use of 3D treatment planning, multiple cross-firing with carefully shaped fixed fields is 3D conformal radiotherapy (3DCRT).

For 3DCRT, preparatory aspects include positioning and immobilization of the patient in the treatment position at CT scan. Gross tumor volume (GTV), clinical target volume (CTV), organ at risk (OAR), and planning target volume (PTV) with daily set-up errors margin are defined with the images of 1 to 3 mm thick slices. Table 1 summarizes the target volumes described in detail in the International Commission on Radiation Units (ICRU) report 50 (3). A medical physicist makes a plan by using a treatment planning system to decide the type of energy, number of beams with their angles and directions, and collimator angle and to shape the target volume with multileaf collimators (MLCs). The dose received by the target and normal tissues is evaluated by dose volume histograms and isodose curves with protocols. Once the plan is approved, the set-up process is performed with matching planning and treatment imaging (Figure 1) (4).

Intensity-Modulated Radiotherapy

After the clinical practice of conformal radiotherapy, the idea of modulating intensity across each radiation beam in order to determine the shape of the target and surrounding organs assisted by computer-based optimization algorithm is determined (5, 6).

Dividing the beam into numerous independent intensity beamlets allows for the modulation intensity of each beam of radiation so that each field can have multiple areas of high- and low-intensity radiation across the treatment area shaped with MLC and improved computer plan optimization called inverse planning. Conventional planning, in which the beam parameters are given first and the dose distributions are calculated, is "forward" planning. By contrast, intensity-modulated radiotherapy (IMRT) planning, in which the beam intensities are calculated to provide the given objectives and constraints on dose distributions to the target volume and OARs, is termed "inverse" planning (7).

There are several studies with IMRT at head and neck, prostate, breast, lung, brain, gynecologic, and gastrointestinal cancers with less toxicities, sparing the adjacent organs nearby the target volume (8, 9). In a study, 3DCRT and IMRT plans for breast cancer were compared according to dose-volume histogram analyses in terms of PTV homogeneity and conformity indices as well as OARs dose and volume parameters. As a result, IMRT decreases the irradiated volumes of the heart and ipsilateral lung in high-dose areas while increasing irradiated volumes in low-dose areas in patients with breast cancer treated on the left side (10).

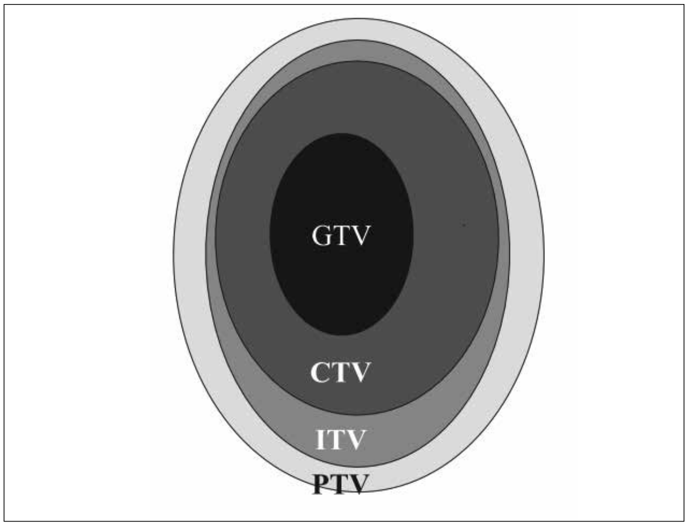

Figure 2. Target volume definition by the ICRU report 62 (16)

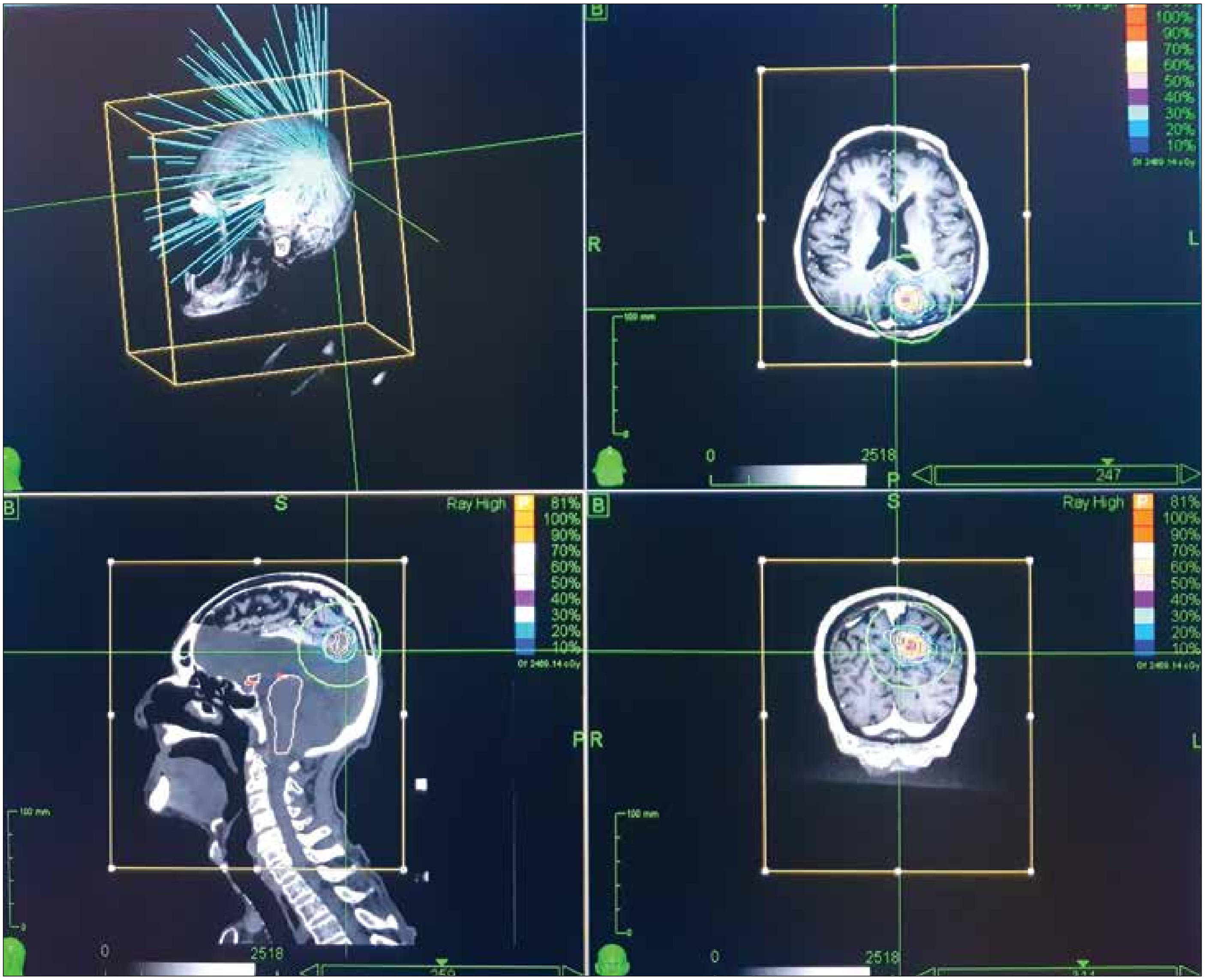
Figure 3. SRS of a patient with brain metastasis
SRS: Stereotactic radiosurgery

Volumetric Modulated Arc Therapy

Volumetric modulated arc therapy (VMAT) is a new technique for increasing the efficiency of treatment in which a full 360° of beam directions for optimization with the entire dose volume is delivered in a single source rotation by regulating the dose rate and dynamic MLC as IMRT has increased treatment time by requiring a larger number of beam directions and increased monitor units (MU). The type of rotational system leads different levels of dose distributions to different parts of the tumor. VMAT can spare OAR better than IMRT with similar conformity and better homogeneity that leads to reducing time and MU that is important at uncomfortable immobilization, such as head and neck cancers (11, 12). VMAT and IMRT with the increase in low-dose radiation to the surrounding normal tissue could theoretically increase the risk of secondary malignancy compared with conventional techniques. In fact, the risk should be lower with VMAT, which uses fewer MU, than with conventional fixed field IMRT; this could be counteracted by the increase of normal tissue volume receiving low-dose wash. With highly efficient treatment delivery, VMAT is studied in many tumor types (13).

Image-Guided Radiotherapy

Image-guided radiotherapy (IGRT) is a companion to conformal radiotherapy that allows the treatment team to account for daily changes in target anatomy for positioning and setting up the patient by integrated megavoltage or kilovoltage diagnostic imaging, cone beam CT (CBCT), or radiographic fiducials (14).

Cone beam CT (CBCT) takes projection radiographs with gantry rotation and helps to determine the correct target position before the RT fraction by registering volumetric image to the reference planning CT.

Respiratory motion is a significant source of error in radiotherapy treatment planning for the thorax and upper abdomen sites. In a four-dimensional (4D) CT technique, there is a breathing motion in radiotherapy treatment planning, where multislice CT scans are collected simultaneously by digital spirometry over many free breathing cycles to create a 4D image set, and where tidal lung volume is the additional dimension (15). Internal target volume is defined by the ICRU report 62 as a volume for the internal movement of organs during radiotherapy (Figure 2) (16). There are different methods, such as breath-hold techniques, with either active, in which the airflow of the patient is temporarily blocked by a valve (active breathing control), or passive techniques by the patient's voluntarily breath-hold gating; the radiotherapy beam synchronously with respiration to predict the phase of the respiration cycle while the patient breathes freely is called respiratory gating (17, 18).

The future of IGRT is now MRI systems and linear accelerators for radiotherapy (MR-linacs), which defines a single device that can simultaneously produce diagnostic quality MRI images and deliver highly conformal IMRT-based treatments with better tumor visualization, online adaptation, and potential for image biomarker-based personalized RT (19).

Adaptive Radiotherapy

While radiotherapy course lasts several fractions and weeks to complete, there can be dosimetric variation at organs, patient weight loss, size and shape of the target as early tumor shrinkage, and change in OAR that causes difference at dose distribution and treatment accuracy (20). The adaptive radiotherapy principle is used to measure variations during treatment and equalize planned dose distribution with final delivered dose distribution, with the help of image guidance, dose verification, and plan adaptation. This adaptation performs a decrease in late morbidity and an improvement in tumor control.

Stereotactic Irradiation

Stereotactic irradiation (STI) is an advanced radiotherapy method that converges multiple ionization radiation beams to the target from various directions, achieving high doses on the target and gradient dose falloff into the surrounding normal tissues. The word "stereotactic" means the target localized to a 3D coordinate system with either a rigid head frame or internal fiducial markers, such as bony landmarks or implanted markers. The optimal treatment delivery plan for STI has a high conformality that approaches the prescription dose at target volume while decreasing the high dose exposed to the normal tissue.

Stereotactic irradiation (STI) is classified as stereotactic radiosurgery (SRS) using a single fraction and stereotactic body radiotherapy (SBRT) delivering treatment in a number of fractions (21-22). In the 1950s, SRS is initially termed as radiosurgery by Lars Leksell who designed the first unit working with a stereotactic frame and multiple hemispherical patterned cobalt-60 sources (23). In the 1980s, after linac advancements and modifications, linac-based robotic systems are adapted to stereotactic radiotherapy. It is indicated in intracranial lesions, such as brain metastases, meningiomas, acoustic neuromas, arteriovenous malformations, vestibular schwannomas, and pituitary tumors. Doses range from 12 to 20 Gy according to closure to the critical structures and the type of tumor (Figure 3) (24-26).

Stereotactic body radiotherapy (SBRT) is an image-guided high-dose radiotherapy for each 3-5 fraction at extracranial tumors. It has a process of patient immobilization, CT image acquisition, target delineation with the fusion of diagnostic images, dosimetric planning, quality assurance testing, guidance images for target relocalization, and real-time monitoring for the management of even breathing-related motion and patient stability.

With SBRT, patients with inoperable non-small cell lung cancer who received stereotactic body radiation therapy had a survival rate of 55.8% at 3 years, high rates of local tumor control, and moderate treatment-related morbidity (27). Prostate cancer, gastrointestinal cancer, and oligometastases are the other studied indications (28).

Intraoperative Radiotherapy

Intraoperative radiotherapy (IORT) is delivering radiation directly to the visualized tumor bed during surgery by exclusion of dose-limiting normal structures and significantly increasing dose with less morbidity. Doses differ on the extent of disease at resection to 10-20 Gy. The process is performed in the operating room with mobile X ray or electron beam devices with the help of applicators ranging in diameters. In malignancies with high local relapse rates, such as retroperitoneal sarcoma, gynecologic, pancreatic, and colorectal cancers, the addition of IORT to conventional treatment improved local control and survival (29). As local recurrences frequently occur at or near the adjacent tumor bed in breast cancers, IORT alone or with external beam radiotherapy can be an alternative for improved local control (30, 31).

Brachytherapy

Brachytherapy is an internal radiation therapy by placement of a radioactive source using applicators immediately adjacent to or within the tumor, providing a localized high dose of radiation. With the improvement of 3D imaging and conformal radiotherapy for optimizing the dose distribution, brachytherapy is an accurate and reliable treatment option for gynecologic cancers, prostate cancers, breast cancers, skin cancers, sarcomas, and ophthalmic diseases (32, 33).

Proton Beam Radiotherapy

Proton therapy is the most studied charged particle radiotherapy based on proton particles with recent major advances in particle accelerator technology that stops at a given depth depending on their initial energy (pristine Bragg peak), which allows to spare normal tissues distal to the tumor target from incidental irradiation. As the precision of methods for delivering photon therapy has improved over the past several decades, methods for planning and delivering proton therapy are evolving as well for treatment of tumors located nearby sensitive organs, such as ocular tumors, nasal tumors, skull-based tumors, and treatment of pediatric cases, where damage of the surrounding tissues can have severe consequences (34, 35).

Hyperthermia

Hyperthermia (HT) is an effective modality for the treatment of cancer by heating tumor tissues to temperatures ranging between 39°C and 45°C. The biological rationale for HT is reoxygenation, inhibiting the repair of sublethal and lethal damages and complementary cytotoxicity. Technological advances over the last decade in both hardware and software have led to potent and even safer locoregional HT treatment delivery, thermal treatment planning, thermal dose monitoring through non-invasive thermometry, and online adaptive temperature modulation. Combination with radiotherapy offers a unique immunomodulating prospect with superficial HT at skin, head and neck, and breast cancers and intracavitary HT for rectal cancer, esophageal cancer, and prostate carcinoma with substantial clinical benefits (36, 37).

CONCLUSION

Technological advances with the integration of imaging and computer software in every phase of radiotherapy include simulation, MLC modulation of radiation beams, improved inverse treatment planning, image guidance, robotics, motion management strategies, and stereotactic treatments managed highly tailored dose distribution with maximum sparing of the surrounding structures, resulting in high tumor control rates and overall outcomes. Data from technology will progress in the future, and clinical studies of dose escalation, volume, fractionation, and avoidance of normal tissue lead to improving treatment response. Moreover, MRI- or PET-guided radiotherapy, targeted radiotherapy with nanoparticles, and combined immuno-radiotherapy treatments appeared to be the new future aspects.

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