190 The Future of Radiosurgery and Radiotherapy

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Radiotherapy and radiosurgery will continue to play an important role in stereotactic and functional neurosurgery in the future.

- There have been tremendous technological advances in radiosurgery and radiotherapy treatment machines over the past few decades; this progress will continue, allowing improved targeting of radiation, improved sparing of normal tissues, and broader applicability of radiosurgery and highly focused radiotherapy.
- Integrated imaging with fast feedback to the treatment equipment and, in some cases, to the treatment planning system will assure more accurate delivery of radiosurgery and radiotherapy treatment.
- Advances in technology will allow complex problems to be solved more efficiently, so that radiosurgery and radiotherapy planning and delivery techniques of the future will provide straightforward and comfortable treatments to the patient without being excessively labor-intensive for medical personnel.
- The practice of radiosurgery and radiotherapy will also be enhanced by further improvements in anatomic, functional, and metabolic/biological imaging techniques, with gains in types of information obtainable as well as in spatial and temporal resolution. Radiosurgery for functional indications such as movement disorders may become more widespread as functional imaging allows very precise noninvasive localization of targets. We will gain a better understanding of how to appropriately target infiltrating gliomas. Various imaging datasets will be easily correlated with each other and readily integrated into the radiation treatment planning process. Imaging will more routinely become "four-dimensional," taking into account the variable of time, to allow precise targeting of mobile, shrinking, or biologically changing targets.
- There will be continued gains in knowledge to allow refinements in case selection, target delineation, and selection of appropriate combinations of radiation with surgery, chemotherapy, molecular targeted therapy, gene therapy, and other new modalities, for both intracranial and extracranial indications. In some cases, new applications for radiosurgery will be developed, such as its use for refractory temporal lobe epilepsy, which is being compared with temporal lobectomy in a prospective randomized trial.
- There has been a long interest finding drugs to act as radiosensitizers to render tumors more sensitive to radiation or radioprotectors to render normal tissues less sensitive to radiation. One radioprotector, amifostine, is being using to a limited extent currently, but more agents are likely to become available in the future to protect against, treat, or mitigate radiation effects [1,2]. Perhaps neural progenitor or stem cells or molecular targeted therapy will be used to mitigate or treat brain and spinal cord radiation injury and edema [3].
- Multidisciplinary collaboration and interaction will expand, maximizing benefits to patients from the advances in all of these areas.

Many of the topics mentioned earlier are discussed in other chapters in this section; this chapter will focus specifically on the future of radiotherapy and radiosurgery in terms of equipment, integrated imaging, motion management, and treatment planning systems.

Frame-based radiosurgery equipment. Although frameless radiosurgery is becoming increasingly popular, frame-based radiosurgery will continue to be used for many years to come. A stereotactic frame provides rigid immobilization of the area to be treated and defines a three-dimensional coordinate system to apply an action such as externally applied radiation to an internal target. The advantage of the frame is that once the coordinate system has been rigidly established, the isocenter of the radiation beam can be easily placed anywhere inside the target by merely shifting the patient in the frame along x-, y-, and z-directions without the need for any rotational corrections, because the system is by default Cartesian. Most commonly used frames are nonrelocatable, such as the Leksell G frame for Gamma Knife radiosurgery or the BRW (Brown–Roberts–Wells) head ring for linear accelerator based delivery; generally the frame is directly fixated onto the patient skull via four metal screws or pins. Relocatable frames commonly use a combination of a dentition mold, Velcro straps, and thermoplastic mask for immobilization, such as the GTC (Gill–Thomas–Cosman) frame. They facilitate dose fractionation and are less invasive, but also less precise than nonrelocatable frames.

Figure 190-1
Micro MLC (Image courtesy of BrainLAB AG)

Frame-based radiosurgery can be performed using any high-energy radiation source (photons produced by a linear accelerator, gamma rays, or protons). Linear accelerator (linac) radiosurgical units commonly use noncoplanar converging arc beams aimed at the target or dynamic rotation with simultaneous couch and gantry rotation. Linac radiosurgery systems have tended to move away from multiple arcs with circular tertiary collimator cones toward the use of mini- or micro-multileaf collimators (MLCs) (*Figure 190-1*) to continuously change beam shaping during the course of arc travel to conform dose distributions to the target contour. Examples of such systems include the Novalis system from BrainLAB AG (Feldkirchen, Germany) (*Figure 190-2*) and the XKnife™ system from Integra Radionics (Burlington, Massachusetts). The use of MLC shaped-beam radiosurgery tends to allow more uniform dose distributions and time-efficient treatment with few isocenter shifts for large or complex targets. In addition, the MLC allows intensity modulation of the radiation beams directed from multiple fixed angles. Traditional arc delivery has generally been limited to constant-speed gantry rotation with constant dose rate, i.e., constant dose per degree of rotation. Variable gantry speed with adjustable dose rate was recently made possible (RapidArc™, Varian Medical Systems, Inc., Palo Alto, California). The capability of varied dose rate delivery will significantly improve the efficiency and quality of traditional arc beam delivery in the near future. Most systems allow a combination of fixed intensity-modulated beams with arc beam delivery.

Figure 190-2
Novalis system (Image courtesy of BrainLAB AG)

Future systems will have refined delivery techniques allowing highly conformal treatment to be performed efficiently and accurately.

While other manufacturers are moving away from frame-based radiosurgery, Elekta (Stockholm, Sweden) has intentionally maintained the use of a stereotactic frame with the Leksell Gamma Knife, setting the gold-standard for intracranial radiosurgical accuracy. The Gamma Knife uses 192 or 201 cobalt-60 sources in a quasi hemispherical distribution to produce 1.25 MeV gamma ray beams aimed at a fixed isocenter with a dose rate on the order of 300 cGy/min at the isocenter. The patient is moved to align the target with the fixed isocenter. Elekta recently completely redesigned the Gamma Knife with the ambitious aim of producing an ultimate radiosurgery tool with excellent dosimetry performance and radiation protection, unlimited cranial reach, fully automated one-push-button treatment, outstanding patient comfort and safety, and superb reliability and serviceability. The resulting PERFEXION™ Gamma Knife (➜ *Figure 190-3*) is a prime example of how complex technology and elegant engineering solutions can simplify workflow and increase efficiency [4]. The large tungsten collimator body with built-in collimators and the couch patient positioning system allow comfortable, efficient treatment of one or more targets any place in the head. Previously, targets in extreme locations sometimes required uncomfortable patient positioning, stereotactic frame repositioning, or, rarely, abandonment of treatment. These problems have been virtually entirely eliminated. In addition, the treatment delivery has become much more efficient. The in-room time is now only a few minutes longer than the total beam-on time, whereas complex treatments on older Gamma Knife models required up to twice the

Figure 190-3
Perfexion Gamma Knife

beam-on time. This is the sort of advancement that is needed for future radiosurgery and radiotherapy equipment, making complex treatment more widely applicable, easier, and efficient.

One notable innovation in Gamma Knife PERFEXION™ is its first-time introduction of independent source group motions; in all previous Gamma Knife models, all of the sources are fixed in position. Since linear accelerators predominantly use a single beam transporting line with a single radiation source for radiation production, the delivery of linac radiosurgery will most likely continue to favor a single isocenter or a small number of isocenters with enhanced beam arcing or modulation capabilities. In contrast, the Gamma Knife will continue to extend itself on the delivery paradigm of superposition of a large number of isocenters to create conformal dose distributions. With the introduction and future refinement of independent source group motions, the Gamma Knife system will gain substantial beam-shaping capability while maintaining its classic scheme of multi-isocenter delivery. Future development will further explore this new beam-shaping capability for clinical applications such as improving the dose gradient for better sparing of critical structures.

Nonframe-Based Radiosurgery and Radiotherapy Equipment

With the exception of the Gamma Knife, the distinction has blurred between equipment used for radiosurgery versus radiotherapy; an increasing number of systems allow delivery of one, a few, or many fractions of highly focused radiation without a stereotactic frame. To achieve high focal precision, the majority of nonframeless systems employ special or dedicated linear accelerators that possess submillimeter isocenter tolerance, milli- or micro-MLC (e.g., 3–5 mm leaf width), a high output dose-rate of 800–1000 cGy/min or even more, as well as add-on or on-board image guidance systems.

The Novalis system from BrainLAB AG (Feldkirchen, Germany) (*Figure 190-2*) is an example of a versatile linear accelerator system for frame-based cranial radiosurgery, or cranial or exracranial frameless radiosurgery, or hypofractionated fractionated radiotherapy [5,6]. The system is comprised of a 6 MV Varian linac with a built-in micro-MLC that has 14 pairs of 3-mm leaves at the center flanked on each side by 3 pairs of 4.5-mm leaves and 3 pairs of 5.5-mm leaves. As a result, the treatment fields range from 0.3 × 0.3 cm^2 to 10 × 10 cm^2. The current system allows radiation delivery via fixed open fields, intensity-modulated fields, conventional fixed-field arcs, or dynamic conformal arcs with the MLC leaves moving while the gantry rotates. Future systems will likely allow finer MLC resolution for larger-sized fields and incorporate variable speed gantry rotation to enhance overall treatment delivery accuracy and efficiency.

The CyberKnife® (*Figure 190-4*) is a current and evolving robotic single-dose or fractionated radiosurgery system produced by Accuray, Inc. (Sunnyvale, California) [7,8]. Instead of a conventional linear accelerator that has a rotating gantry, a compact x-band 6 MV linear accelerator is mounted on an industrial robot arm with six degrees-of-freedom. During the course of treatment, the patient lies on a treatment couch and the robot arm aims at the target from hundreds of directions, using complex, nonisocentric beam patterns. For target localization, dual kV X-ray imagers are mounted on the ceiling (vs. beneath the floor for the Novalis system). Treatment proceeds in a repetitive stop, image, align, and shoot sequence. For targets within the head, a thermoplastic mask is typically used, but perfect immobilization is not required. The system is able to treat anyplace in the body, virtually free of patient size and positioning constraints. The imaging that makes this possible is described below in the section on "Integrated imaging." Future systems will allow more beam directions but also choose beam directions more efficiently to decrease delivery time, improve treatment clearance and patient safety with regard to the moving robot, and reduce scattered dose and integral radiation dose outside of the target. Future systems will also automatically adjust for rotational setup errors, further improve the target tracking accuracy, perform corrections in true real time, and allow deformable target corrections.

Figure 190-4
CyberKnife

In contrast to Novalis shaped-beam delivery, the CyberKnife system still uses a limited number of tertiary cones to define beam diameters ranging from 5 to 60 mm. Recently, Accuray has introduced several mechanisms for automatic cone switching plus an integrated system that automatically adjust the cone diameters. With increasing research on shaped-beam delivery, we envision that the future system will merge flexible beam-shaping, perhaps with the addition of micro-MLC, with the six-degrees-of-freedom robotic arm with unrestricted beam angles and source-to-target distance.

The Tomotherapy unit (Tomotherapy, Inc., Madison, Wisconsin) is another futuristic radiosurgery/radiotherapy system (*Figure 190-5*) [9]. A compact 6 MV linac accelerator mounted on a rotating slip ring delivers treatment in an axial fan-beam arrangement through 64 open or shut slit apertures as the patient couch moves through the bore of the machine, creating a beam passing through the patient in a spiral trajectory. Complex dose distributions can be created via the helical beam path around the patient. Currently, the system couch does not permit active or real-time six-degrees-of-freedom patient positioning correction, particularly in pitch, yaw, or roll angular rotations. Therefore, the initial treatment setup position needs to match the reference planning position as close as possible. With a 2p ring-and-detector configuration, the future system may overcome this limitation via treatment planning optimization on the fly, constant dose verification, and adaptive manipulation of the dose delivered to the patient.

In addition to the above specialized systems, major linear accelerator manufactures have begun to introduce combination systems in attempt to integrate a wide-range of applications into one machine with high-definition, multiple beam energies, and dual-modalities (electrons and photons), such as the Trilogy™ System from Varian Medical Systems, Inc. (Palo Alto, California). The name Trilogy implies the ambitious combination of three modern radiotherapy technologies: intensity modulated therapy, image guided therapy, and stereotactic single-dose or multi-fraction

Figure 190-5
Tomotherapy

radiosurgery. This system has a versatile 4–23 MV linear accelerator tube used with either tertiary cones or a built-in MLC. The system's on-board imaging capability is described later. Other creative treatment delivery systems have been developed and will be developed in the future with the aim of providing accurate radiosurgery/radiotherapy to one or more targets with increasingly complex dose constraints and yet increasing ease of use compared with past systems.

Ongoing advances in accelerator engineering are making protons and heavier ions, such as carbon, more affordable for use in clinical radiosurgery and radiotherapy. The depth dose profile of protons and heavy particles consists of increasing dose with depth of penetration up to a sharp maximum near the end of their range, called the Bragg peak, with essentially zero dose deposited in tissue distal to the sharp edge of the Bragg peak. This offers potential for improved dose distributions, and heavy particles have the additional potential advantage of increased radiobiological effectiveness [10]. Whereas gamma-ray and photon-based radiosurgery systems rely on a large number of convergent beams to create rapid fall-off of dose outside of the target, proton and heavy particle radiation units use a small number of beams with extremely sharp fall-off of dose at the distal edge of the target. This could be advantageous for tumors requiring high dose in close proximity to critical structures such as the optic chiasm or spinal cord. Particle machines are already becoming more widely available. Future particle systems will create more compact and cost-effective systems applying concepts from photon/electron beam radiotherapy such as beam intensity modulation, real-time feed-back adaptation, and improved range modulation capability to maximize the therapeutic ratio of charged particle delivery [11]. With wider availability of particle therapy, critical evaluation of clinical experience and clinical trials will be needed to determine appropriate case selection.

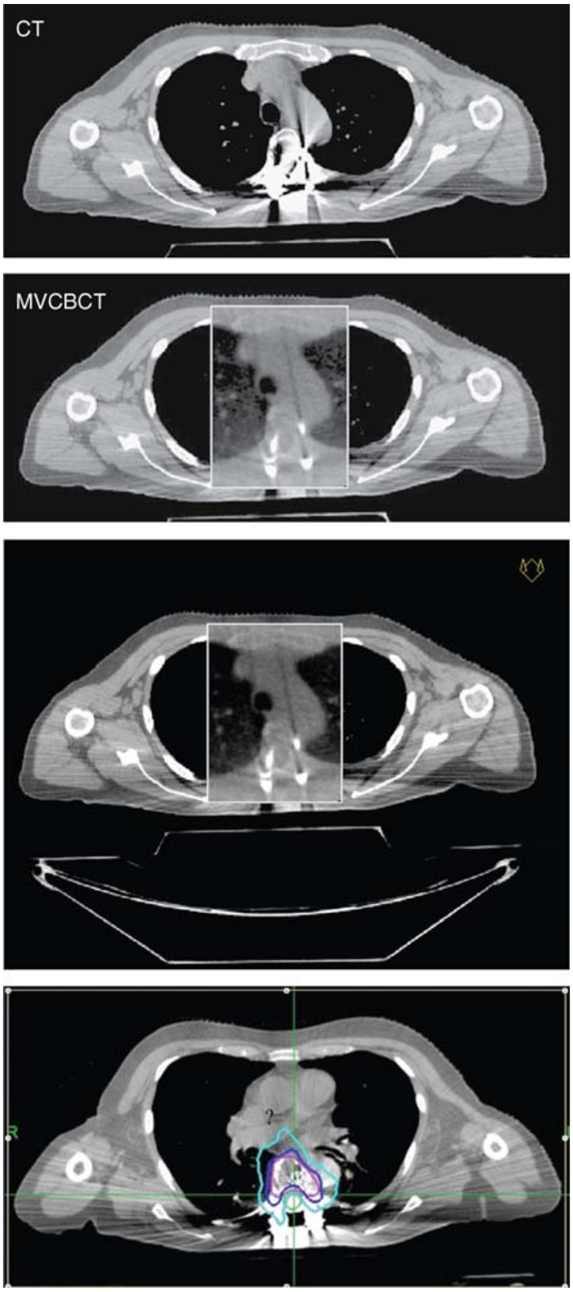
Integrated Imaging

Nonframe-based radiosurgery/radiotherapy is more versatile but of course has the tradeoff of more uncertainty in terms of targeting accuracy. Such systems require the use of imaging to confirm accurate positioning prior to starting treatment and, in some cases, during or after each treatment fraction. The CyberKnife takes the futuristic approach of adjusting the treatment to small variations in the patient's positioning rather than requiring the patient to be precisely positioned for treatment and rigidly maintained in that position throughout treatment. Orthogonal X-ray images captured by flat-panel detectors are obtained prior to commencement of treatment and every minute or so during the treatment. Within tens to hundreds of milliseconds, these images are compared with a pre-calculated library of digitally reconstructed radiographs based on thin-cut treatment planning computed tomography (CT) scan to detect small deviations in positioning. The comparison is based on the skull for intracranial targets, spine bony anatomy for spinal or paraspinal targets, soft tissue targets visible by X-ray, or implanted radio-opaque fiducial markers. The first set of images is used to establish patient positioning within an acceptable range prior to commencement of treatment. Repeat imaging during the course of treatment allows for the robot to alter treatment delivery as needed to adjust for measured small patient movements in x-, y-, and z-directions. Future systems will become more responsive to real-time changes, adjust for rotational setup errors, and further reduce the reliance on implanted fiducial markers.

During frameless radiosurgical treatment with the Novalis system, a pair of X-ray images are taken with kV X-ray imagers mounted beneath the floor of the treatment room. The images are compared with the digitally reconstructed radiographs generated from the CT studies used for treatment planning. Because the patient is immobilized without a frame, the patient setup position generally differs from the reference treatment planning positions in both translational and rotational variables. To correct for this, the Novalis system uses a robotic couch that moves with full six degrees-of-freedom for any shifts along x-, y-, and z-axis and also any rotations around these three axes, i.e., roll, pitch, and yaw.

To provide full three-dimensional imaging information, CT imaging can be built into radiosurgery or radiotherapy treatment machines. This yields much more information than a pair of two-dimensional images, and has the potential for allowing more accurate treatment as well as adjustment of treatment to tumor shrinkage or other anatomic changes during the course of treatment. The Tomotherapy unit incorporates a kV X-ray tube and xenon detectors into the rotating ring that also delivers treatment, and a CT scan can be performed daily prior to and after treatment to ensure accurate daily setup. Cone-beam CT acquires imaging data on the actual treatment machine with a large rotating field rather than conventional CT which acquires data slice by slice. Cone beam CT scans can be performed with kV energy used for conventional diagnostic imaging or with MV energy used for radiation treatment. MV cone-beam CT may be advantageous to minimize metal artifact from spine stabilization hardware (➲ *Figure 190-6*) or hip prostheses [12]. The Varian Trilogy System and Elekta Synergy System have a side-mounted kV X-ray unit and flat panel imager enabling conventional port films or cone-beam CT imaging. Recently, an on-board imaging device was added to the side of the Novalis linear accelerator to allow for in-room cone-beam CT acquisitions for three-dimensional soft-tissue targeting. Future systems will allow for full integration of rapid two-dimensional planar radiographs with relatively slow three-dimensional cone-beam CT imaging acquisition. Another setup confirmation approach called digital tomosynthesis creates tomographic images based on limited angles of rotation, potentially decreasing time and dose exposure, yet providing sufficient three-dimensional information [13].

Figure 190-6
MV cone beam CT for spine



Radiosurgery and radiotherapy systems of the future will employ adaptive image-guidance, allowing imaging information to be used to automatically correct patient positioning with an adjustable couch or adapt the treatment plan and treatment delivery based on setup variations or changes that occur during the course of treatment [14]. Another important area of development will be in the application of nonionizing radiation such as magnetic resonance imaging or ultrasound for real-time on-line imaging or delivery verification. This will eliminate increasing concerns about radiation exposure to the patient when more frequent imaging studies are needed for tracking or managing target changes throughout the treatment course.

Motion Management

Various approaches have been taken to apply radiosurgery to mobile targets such as small lung or liver tumors that move with respiration [15]. These movements can be large and somewhat complex, and the radiation tolerance of normal lung and liver tissue is quite limited, so that it is often unacceptable to simply treat with a large enough margin to encompass moving targets with static fields. With passive tracking delivery, the radiation beam may turn on only when the tumor movement is restrained (e.g., with assisted breathing control) or when the tumor moves into a favorable state (e.g., with respiratory-gated treatment). Recent integration of "four-dimensional" CT imaging capability (taking into account time) will refine the treatment planning process for traditional tracking delivery by better modeling the delivered dose and motion patterns. The CyberKnife was the first system to implement active tracking – beam movement in synchrony with the target movement. The flexible and responsive six-degrees-of-freedom robotic arm of the CyberKnife and the active tracking method created a happy marriage since the robotic arm can easily "breathe" together with the patient. This has dramatically shortened treatment time and improved the overall dose accuracy [16]. Other approaches for treating moving, deforming targets will become available in the future, such as adaptive MLC shaping, so that such targets will be treated easily and accurately.

Treatment Planning

Future treatment planning will become simpler and more automated and yet also more powerful, with added capability of adapting a plan as needed during the course of treatment in response to changes in anatomy, organ motion, tumor shrinkage, and detected setup variations. As radiation treatment planning has become increasingly sophisticated over the past decade, it has also become much more labor intensive with the advent of "inverse planning" necessitated by treatment machines capable of creating very complex dose distributions. Inverse planning typically requires the outlining of many normal structures of interest as well as one or more targets and specification of dose/volume constraints for each structure. The computer then develops a complex treatment plan to accomplish those goals. Plans often require multiple iterations, with the planner adjusting dose constraints or adding factitious "tuning structures" to try to force the inverse planning algorithm to come up with a desired solution. Future software will automate many of these steps to make this process much less labor intensive, and it will incorporate algorithms to conform high-dose areas to targets and lessen integral dose to normal tissues. The planning software will also automatically optimize treatment time without sacrificing target coverage or normal tissue sparing. With the many degrees-of-freedom of complicated systems, intelligent optimization of a large number of free parameters will be necessary to ensure that treatment planning and delivery will not be unnecessarily complex or lengthy.

Currently, treatment plans are evaluated chiefly by examining dose-volume histograms for various structures; future software will estimate probabilities of tumor control, acute effects, and late normal tissue complications based on generic patient data, with the capability of entering individual patient-specific parameters. Treatment planning of the future will also incorporate biological information and feedback from imaging obtained during the course of radiation to optimize and adapt the treatment plan as needed [17,18]. Imaging obtained during the course of treatment will allow treatment plans to be adapted automatically or semiautomatically to various factors such as detected setup variations, daily organ variation, tumor shrinkage, patient weight loss, and biological response to treatment. Biologically-guided and adaptive image-guided radiotherapy will become routine practice.

Conclusions

The use of radiosurgery has burgeoned, first for intracranial targets and more recently for extracranial targets. Radiosurgery and radiotherapy equipment will advance rapidly to allow accurate and efficient delivery of complex dose distributions to fixed, mobile, deformable, or changing targets in a wide variety of body sites. Frameless systems will incorporate more advanced integrated or on-board imaging to help ensure targeting accuracy. Treatment planning systems will become much more sophisticated and more automated, and they will integrate imaging and other data to allow image-guided, biologically guided, and image-adaptive radiotherapy. Many developments-in-progress have come at a cost of increased labor intensiveness in the short run, but further technologic advances are now yielding significant efficiency gains. This trend will continue, as evidenced by machines such as the Gamma Knife PERFEXION™. Equipment and treatment planning software for the delivery of radiosurgery and radiotherapy will continue to become more sophisticated but also more integrated, automated, efficient to use, and widely available, benefiting patients, medical personnel, and healthcare systems.

References

1. Brizel DM. *Pharmacologic approaches to radiation protection.* J Clin Oncol 2007;**25**:4084-9.
2. Moulder JE, Cohen EP. *Future strategies for mitigation and treatment of chronic radiation-induced normal tissue injury.* Semin Radiat Oncol 2007;**17**:141-8.
3. Oh BC, Liu CY, Wang MY, et al. *Stereotactic radiosurgery: adjacent tissue injury and response after high-dose single fraction radiation. Part II: Strategies for therapeutic enhancement, brain injury mitigation, and brain injury repair.* Neurosurgery 2007;**60**:799-814;
4. Lindquist C, Paddick I. *The Leksell Gamma Knife Perfexion and comparisons with its predecessors.* Neurosurgery 2007;**61**:130-40;
5. Chen JC, Rahimian J, Girvigian MR, et al. *Contemporary methods of radiosurgery treatment with the Novalis linear accelerator system.* Neurosurg Focus 2007;**23**:E4.
6. Teh BS, Paulino AC, Lu HH, et al. *Versatility of the Novalis system to deliver image-guided stereotactic body radiation therapy (SBRT) for various anatomical sites.* Technol Cancer Res Treat 2007;**6**:347-54.
7. Adler JR Jr, Chang SD, Murphy MJ, et al. *The Cyberknife: a frameless robotic system for radiosurgery.* Stereotact Funct Neurosurg 1997;**69**:124-8.
8. Hara W, Soltys SG, Gibbs IC. *CyberKnife robotic radiosurgery system for tumor treatment.* Expert Rev Anticancer Ther 2007;**7**:1507-15.
9. Welsh JS, Patel RR, Ritter MA, et al. *Helical tomotherapy: an innovative technology and approach to radiation therapy.* Technol Cancer Res Treat 2002;**1**:311-6.
10. Schulz-Ertner D, Tsujii H. *Particle radiation therapy using proton and heavier ion beams.* J Clin Oncol 2007;**25**:953-64.
11. Karger CP, Jakel O. *Current status and new developments in ion therapy.* Strahlenther Onkol 2007;**183**:295-300.
12. Morin O, Gillis A, Chen J, et al. *Megavoltage cone-beam CT: system description and clinical applications.* Med Dosim 2006;**31**:51-61.
13. Wu QJ, Godfrey DJ, Wang Z, et al. *On-board patient positioning for head-and-neck IMRT: comparing digital tomosynthesis to kilovoltage radiography and cone-beam computed tomography.* Int J Radiat Oncol Biol Phys 2007;**69**:598-606.
14. Jaffray D, Kupelian P, Djemil T, et al. *Review of image-guided radiation therapy.* Expert Rev Anticancer Ther 2007;**7**:89-103.

15. Giraud P, Yorke E, Jiang S, et al. *Reduction of organ motion effects in IMRT and conformal 3D radiation delivery by using gating and tracking techniques.* Cancer Radiother 2006;**10**:269-82.
16. Seppenwoolde Y, Berbeco RI, Nishioka S, et al. *Accuracy of tumor motion compensation algorithm from a robotic respiratory tracking system: a simulation study.* Med Phys 2007;**34**:2774-84.
17. Mageras GS, Mechalakos J. *Planning in the IGRT context: closing the loop.* Semin Radiat Oncol 2007;**17**:268-77.
18. Stewart RD, Li XA. *BGRT: biologically guided radiation therapy-the future is fast approaching.* Med Phys 2007;**34**:3739-51.