Review

Recent developments in radiation oncology

Integrating radiation physics and molecular radiobiology advances into clinical radiotherapy practice and beyond

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Significant developments in radiation oncology have taken place in recent years as a result of advances in radiation physics and molecular radiobiology. From the conventional 2-dimensional (2D) radiotherapy to 3-dimensional (3D) conformal radiotherapy, we have now entered the era of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT). IMRT/IGRT allows conformal treatment of tumor and conformal avoidance of normal tissues leading to possible improvement of tumor control and decrease in treatment-related toxicity. Frameless stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) have now become a reality, offering more treatment options in radiation oncology. With technological advances in image guidance, brachytherapy especially in early stage prostate cancer has progressed and shown excellent long-term outcome data. Charged particle therapy, including proton therapy is a promising area for new development. Combining radiotherapy with the more traditional chemotherapy and hormonal therapy to novel targeted therapy and gene therapy is aimed to overcome radio-resistance, improve the radio-therapeutic index and provide better loco-regional and systemic control of cancer. A recent randomized trial in head and neck cancer has shown improved survival data when comparing combined radiotherapy and targeted therapy with radiotherapy alone. Recent advances in functional or molecular imaging offer new opportunity to improve targeting of tumor, for example, hypoxic region, and possibly to perform radiation dose painting with IMRT. Integrating PET/CT in radiotherapy has shown promise in assisting target delineation during treatment planning and assessing radiation treatment response. Cancer stem cell, gene expression profiling and nanotechnology with the implications on radio-resistance are new exciting areas requiring more research in future as we move toward personalized medicine.

Radiation oncology plays an important role in cancer care. Over recent years, significant developments have taken place in radiation physics, radiobiology and clinical radiation oncology. Technological advances have made possible the transition from orthovoltage and cobalt-60 machines to megavoltage and the recent image-guided linear accelerators. Progress has also been made from a simple hand calculation method of one or more opposed fields to multi-field three-dimensional conformal radiotherapy (3D CRT), intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT) and stereotactic body radiotherapy (SBRT). Stereotactic radiosurgery (SRS) has also advanced from an invasive framed system to a non-invasive frameless system using the image-guidance and stereotaxis technology. The other promising development is charged particle radiotherapy based on radio-physical and radio-biological properties. Integrating advances of molecular biology, for example, the use of targeted therapy or gene therapy, with radiotherapy has shown promising treatment outcome data in the treatment of cancer. Research on radio-resistance and methods in overcoming this will further serve as an impetus to advance the field of radiotherapy in the future. Radio-therapeutic advances incorporating physics, biology and clinical aspects have and will continue to have positive impact on patient care: better loco-regional control and decreased treatment-related toxicity leading to improvement in cure rate and quality of life of patients. In this perspective article, various aspects of the recent development in radiotherapy will be highlighted and addressed.

Three-Dimensional Conformal Radiotherapy/Intensity-Modulated Radiotherapy

The goal of optimal radiotherapy is to deliver a maximal therapeutic dose while keeping the dose received by the surrounding normal tissues below radiation tolerance. This goal is difficult to achieve with two-dimensional (2D) conventional radiotherapy using two or several opposed fields as large volumes of normal tissues will be irradiated. The continuum of evolution from 2D conventional radiotherapy, 3D CRT to IMRT has taken place as a
Recent developments in radiation oncology

Recent developments in radiation oncology

Head and neck cancer. IMRT has been shown to decrease xerostomia with parotid-sparing approach\textsuperscript{3-5} as shown in Figure 1. Xerostomia is an undesired radiotherapy sequela, which can affect patients' quality of life negatively. In addition, head and neck cancer and the draining lymphatic are in close proximity to many critical normal tissues, such as, mandible, parotid and submandibular glands, spinal cord, optic apparatus, and so on. The use of IMRT is ideal with the capability to spare these important structures.\textsuperscript{6,7} Despite smaller treatment field, there is no decrease in tumor control rate suggesting that the importance of 3D approach and better imaging used in radiotherapy when compared with historical controls\textsuperscript{8,9}. However, there are case series reporting the marginal recurrences with IMRT highlighting the importance of understanding lymphatics drainage, pattern of spread and accurate target delineation.\textsuperscript{10,11} We have also pioneered a new fractionation scheme with IMRT known as simultaneous modulated accelerated radiation therapy (SMART) boost.\textsuperscript{7} This is a fractionation schedule initially designed to overcome rapid repopulation in head and neck cancer. SMART boost allows us to treat the gross tumor and subclinical disease sites with different fraction sizes to different total doses (Fig. 1). It also allows the convenience of once a day treatment as compared with other altered fractionation schemes requiring twice or three times a day treatment to overcome rapid repopulation in head and neck cancers. Another fractionation scheme known as simultaneous integrated boost (SIB) using the same concept was also introduced at the same time.\textsuperscript{12} Re-irradiation for local recurrent head and neck cancer in the era of IMRT has become a reality.\textsuperscript{13}

Prostate cancer. Radiation dose relationship with prostate tumor control has been shown based on Class I evidence or randomized trials.\textsuperscript{14} However, high radiation dose is associated with an increased incidence of treatment-related toxicity. Radiation proctopathy is a limiting factor for radiation dose escalation.\textsuperscript{15} IMRT has been shown to decrease treatment-related toxicity in patients receiving dose-escalated radiotherapy.\textsuperscript{16-18} We have demonstrated that IMRT is clinically feasible, safe and efficacious as primary treatment modality for prostate cancer (Fig. 2), in post-prostatectomy setting, in combination with brachytherapy for high-risk patients, as well as in conjunction with hormonal therapy, gene therapy and chemotherapy.\textsuperscript{16,19-23} In addition, we have demonstrated the benefits of using the rectal balloon during the delivery of IMRT for prostate cancer (Fig. 2) to decrease prostate motion and distend lateral and posterior rectal walls from receiving high-dose radiation.\textsuperscript{24} The benefits of rectal balloon in reducing rectal toxicity using an endoscopic examination have been reported recently.\textsuperscript{25}

Brain tumor. During brain irradiation, many critical radiosensitive normal structures need to be considered and preferably protected. The best example is optic pathway apparatus including nerve, chiasm
Image-Guided Radiotherapy

IGRT is a new method of treatment delivery that integrates image-based tumor definition methods, patient positioning devices and radiation delivery image-guidance tools. It is optimally suited to improve treatment margin. It involves the process of image verification and localization during treatment delivery. As opposed to relying on external marks, IGRT assesses the position of the tumor and normal structures within the body. Recently, there is evidence from two randomized trials emphasizing the need of IGRT to improve local control when irradiating prostate cancer. Both trials found strong evidence that distended rectum on planning CT is associated with decreased biochemical and local control likely due to decreased biochemical and local control resulting from the conformal technique of IMRT delivered much lower doses of radiation to the auditory apparatus while still delivering full doses to the desired target volume.

With the advances in technology, including patient immobilization, better tumor/target delineation, image-guidance, radiation planning and delivery, SRS to extracranial sites has become a reality. Extracranial SRS or SBRT is defined by the American Society of Therapeutic Radiology and Oncology and American College of Radiology practice guidelines as a “treatment method to deliver in a high dose of radiation to the target, utilizing either a single dose or a small number of fractions with a high degree of precision within the body.” SBRT is aimed to yield more potent radiobiological and clinical effects. Applying linear-quadratic formula, Fowler et al. reported that the conventional 60 Gy in 30 fractions (2 Gy per fraction) and 60 Gy in three fractions (20 Gy per fraction) have biological equivalent doses (BED) of 72 Gy and 180 Gy respectively as well as can yield an estimated progression-free survival at 30 months of 15% and >99%, respectively. SBRT is therefore beneficial for treating more radioresistant tumors such as melanoma, sarcoma, renal cell carcinoma (RCC) and non-small cell lung carcinoma (NSCLC).

Clinical experience with SBRT has been reported especially in lung, spine and liver for both primary and metastatic lesions. A Japanese multi-institutional study showed that patients treated with SBRT have a similar survival rate but less treatment-related morbidity when compared with patients treated with surgery. Radiation Therapy Oncology Group (RTOG) is currently running a Phase II SBRT trial evaluating 60 Gy in three fractions (20 Gy per fraction) for early stage NSCLC in medically inoperable patients. Figure 3 shows a SBRT plan for a biopsy proven small NSCLC in a medically inoperable patient. Similar promising local control and favorable toxicity profiles were achieved using SBRT in primary hepatocellular carcinoma (HCC) and metastatic liver lesions, as well as primary RCC and metastatic RCC. Spinal SRS and SBRT have been reported with excellent symptoms palliation, local control and minimal side effects. In addition, retreatment after initial conventional radiotherapy is now feasible with SBRT.

Image-guided SBRT is an emerging treatment paradigm with new promise in radiation oncology. The promise to produce biologically potent dose in a short time and a non-invasive manner is exciting.
Recent developments in radiation oncology

Charged Particle Radiotherapy

Charged particle exemplified by proton beam therapy is another development in radiotherapy. The sharp increase in dose absorption called Bragg peak, near the end range of proton beam offers a theoretical advantage, as there is no further dose deposition beyond this peak. This depth-dose distribution with almost no exit dose allows the reduction of normal tissues volume receiving low dose radiation, thus lower integral dose when compared with IMRT. Proton beam therapy is thus especially attractive in the treatment of childhood malignancies whereby the main concerns include radiation-induced malignancies and late treatment-related adverse events, for example, growth and developmental delays. Using a model-based guidelines from the International Commission on Radiologic Protection, Mirabell et al. showed that proton planning decreased the estimated risk of radiation-induced malignancy when compared with photon planning. When compared with standard photon beam and IMRT plans, proton beam therapy used in cranial spinal irradiation with a posterior fossa boost for medulloblastoma could help to spare more substantial normal tissues. Clinical results are awaited to confirm the theoretical advantages of proton beam therapy in childhood malignancies. To date, there is no randomized trial comparing proton and photon beam therapy. Long-term efficacy data of proton beam therapy has been reported in choroidal melanoma and skull base sarcoma.

The biological effect of radiotherapy is highly dependent on its linear energy transfer (LET), that is, the rate of energy transferred by ionizing radiation along its path. This is characterized by the relative biological effectiveness (RBE) factor, which is the ratio of the dose of particle radiation to the dose of 60Co radiation producing the same biological end point. Despite the potential dosimetric advantages of Bragg peak, radiobiological proton beam (RBE = 1.1) is essentially the same as photon beam (RBE = 1.0). However, heavy charged particles such as carbon ions with high LET can cause direct damage to the critical cellular target and not as dependent on free radical intermediary. High-LET radiation has lower oxygen enhancement ratio (OER) and is less affected by hypoxia. Carbon ion therapy has been shown to be safe and effective for HCC producing three-year local control and overall survival rates of 81% and 50%,.

The challenges of charged particle RT include expensive cost, secondary neutron contamination which may lead to higher risk of second malignancy, more susceptibility to tissue in homogeneity (treatment planning and delivery requires greater degree of certainty—immobilization and image-guidance are essential) as well as more clinical evidence that proton beam is better for certain malignancies when compared with photon.

Brachytherapy

With the advances in imaging and 3D computer treatment planning, the field of brachytherapy has shown tremendous progress in recent years. Ultrasound-guided transperineal prostate brachytherapy with 3D treatment planning approach (Fig. 4) has demonstrated the best success story for the treatment of early stage prostate cancer: brachytherapy produced excellent treatment outcome comparable...
Recent developments in radiation oncology

Combined Genetherapy and Radiotherapy

Genetherapy involves the transfer of genetic materials to the somatic cells to gain therapeutic benefits. Cancer genetherapy is broadly grouped into various categories: cytotoxic “suicide” genetherapy, replacement genetherapy and immunomodulatory genetherapy. Combined radiotherapy and genetherapy is a novel cancer therapeutic approach, as explored in our institution against prostate cancer over last few years. The first genetherapy that we explored was intra-tumoral adenovirus-mediated HSV-\(\beta\kappa\) (Herpes simplex virus thymidine kinase) suicide genetherapy. The rationale behind the combined radio-genetherapy approach in the treatment of prostate cancer includes normal tissues tolerance with very high dose escalation, peripheral zone located immediately next to rectum harbors majority of cancer, the presence of radio-resistant very high grade tumor, risk for micrometastatic regional and systemic disease, and additional immunostimulation with this type of genetherapy. Potential benefits in this combined radio-genetherapy strategy to enhance antitumor effects via active vaccine approach are shown in Figure 5. Other advantages of this approach include that radiation improves transgene integration and transfection/transduction efficiency, radiotherapy and genetherapy target at different phases of the cell cycle, radiation may enhance the bystander effects of genetherapy, genetherapy may interfere with repair of radiation-induced DNA damage, and genetherapy may increase DNA susceptibility to radiation-induced damage.

Preclinical data have demonstrated the enhanced antitumor effects of this combined radio-genetherapy approach in terms of local tumor control, prolongation of survival and systemic control.\(^{59-61}\) This offers a new paradigm in spatial cooperation, whereby two local therapies are combined to elicit both local and systemic effects. Besides, these two treatment modalities have different toxicity profiles. This novel combined radio-genetherapy approach has been translated to a Phase I-II clinical trial.\(^{23,62}\) The concept is to add HSV-\(\beta\kappa\) genetherapy to the standard of care treatment (radiotherapy). The reported results on safety, prostate-specific antigen (PSA) and biopsy response were very encouraging.\(^{23,62}\) There was no clinical failure within the radiotherapy portals. In addition, the addition of radiotherapy to HSV-\(\beta\kappa\) genetherapy was noted to augment the immunostimulation of suicide genetherapy based on pathologic and systemic (peripheral blood) evidence.\(^{63,64}\)

Combined Molecular Targeted Therapy and Radiotherapy

In the era of molecular biology, searching for specific molecular targets in certain cancers followed by the use of specific inhibitors either in the form of monoclonal antibody or small molecule is known as molecular targeted therapy. The best success stories include HER2-neu and Herceptin (tranzucimab) as well as c-KIT and Gleevec (imatinib). Prior to this, combined chemoradiotherapy was aimed to enhance radiation effects and maximize the spatial cooperation of chemotherapy and radiotherapy. Combined chemoradiotherapy has been the gold standard for various cancers especially in the organ preservation approach, such as laryngeal cancers, esophageal cancers, lung cancers, anal cancers, and so on. In high risk prostate cancer patients, combined hormonal therapy and radiotherapy has been shown to provide better local and biochemical control as well as PSA failure-free survival and overall survival.\(^{65,66}\) Recently, there was a randomized trial demonstrating that the addition of C225 (cetuximab), an epidermal growth factor receptor (EGFR) inhibitor, to radiotherapy is superior to radiotherapy alone in the treatment of head and neck cancers in terms of local regional control, disease-free survival and overall survival.\(^{67}\) Similarly, a randomized trial has shown that combined temozolomide and radiotherapy improved survival in patients with glioblastoma multiforme when compared with radiotherapy alone especially in the tumors with high expression of methylguanine-methyltransferase (MGMТ).\(^{68,69}\) The Class I evidence lends support to the combined molecular targeted therapy and radiotherapy approach in many other malignancies in future especially very important targets continue to be discovered, for example, vascular endothelial growth factor (VEGF), AKT, mammalian target of rapamycin (mTOR), and HER family. One of the recent development was that cancer stem cell may be implicated in radio-resistance in glioblastoma multiforme.\(^{70}\) Combining specific inhibitors in cellular pathways of certain cancer stem cells, such as Wnt pathway, with radiotherapy may offer new
opportunity in overcoming radio-resistance and improving cancer cure with radiotherapy. Other advances in molecular biology have also contributed to individualize radiotherapy to cancer patients. These can be based on the molecular signatures of individual tumor, such as gene expression profiling, specific expression of markers, proteomics, and so on. We may even be able to predict which patient will benefit the most from radiotherapy, which patient will have severe adverse events caused by radiotherapy, which patient has radio-resistant cancer and many other possibilities. Nanotechnology will also play an important part in radiotherapy development, for example, using nano-shells to deliver radiosensitizers or to track real-time tumor motion to guide radiotherapy.

Imaging (PET/CT and Computer Visualization Techniques)

From the early days of fluoroscopy to the current image-guided delivery techniques, both radiation oncology and radiology have worked closely to optimize targeting of the tumor or tumor bed volume. Target delineation has traditionally been based on anatomic landmarks and abnormalities shown on a CT image. PET-CT, combining anatomic and physiologic or functional imaging information, has made significant impact on oncologic imaging. The incorporation of PET-CT (Fig. 6) in radiotherapy target delineation has improved the accuracy thus avoiding underdosing tumor or overdosing normal tissues, for example, in identifying biologically active areas on PET-CT but negative on CT, decrease in the target volume as PET-CT can differentiate between active tumor and collapse or consolidation of lung and others.71-73 The concept of biological target volume was first introduced by Ling et al.74 With the advances in molecular imaging, we are going to witness more translational research in radiation oncology using novel radio-tracers beyond FDG-PET, such as F-miso, to define sub-target of hypoxic regions.75 This concept can be applied to target delineation and thus dose-painting, for example, higher dose to hypoxic region as well as to monitor radiotherapy response.

Computer visualization techniques (CVTs) (Fig. 6) are an emerging technology with the ability to maximize the currently untapped advantages of IMRT.76 The visual speed and dynamic strategies inherent in CVTs improve IMRT by distilling vast amounts of anatomic, multimodal imaging (Fig. 6), textual/meaning, and surgical/outcome data into a large, rigorous, standardized evidence base of storable target delineation plans. This ability to standardize strategies will allow the collection of meaningful evidence based outcome data. Using CVTs approach has fostered evidence-based target delineation and enhanced the accuracy in delineating gross tumor volume (GTV), clinical target volume (CTV) including draining lymphatics and normal tissues/avoidance structures in various anatomical sites. This system has important values in teaching nodal delineation to the residents and practicing radiation oncologists as well as may serve as a tool to standardize nodal delineation among participants across specialties and training levels in multi-institutional trials addressing IMRT.

Conclusions

Integrating the advances in radio-physics and molecular radio-biology into clinical radiation oncology practice has truly made significant contributions to the field of oncology. Evolution of conventional radiotherapy to 3D-CRT, IMRT and now IGRT has improved the radio-therapeutic index leading better tumor control and less treatment-related adverse events. Advances in SRS, SBRT, charged particle therapy and brachytherapy will continue to offer more therapeutic options in delivering biologically more potent dose while keeping low dose to the surrounding normal tissues. Hopefully, this will further translate to improved cure and quality of life. Combining radiotherapy with other therapy beyond traditional chemotherapy, such as hormonal therapy, genetherapy, targeted therapy, and so on, holds promise to maximize both loco-regional and systemic control of cancer. Radiation oncology is entering an exciting new era with many significant developments that will impact positively in cancer management, now and future.

References


Recent developments in radiation oncology


