Editorial

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Novel Technologies in Radiation Oncology: Care for Better Future

Radiotherapy (Radiation Oncology)

Radiotherapy (RT) is the treatment of neoplastic disease by ionizing radiation. It is also useful in the treatment of certain benign diseases. Radiation alone can be delivered with a radical intent in a curative setting in early stage of the disease. Its combination with surgery can vary diversely from being delivered during (intraoperative), before (neoadjuvant) or after resection (adjuvant), or with systemic therapy, sometimes for organ preservation (such as in larynx, breast, urinary bladder, anal canal etc).[1-3] Moreover, it can provide symptomatic relief in cancers that are locally advanced or disseminated, by reducing or eliminating pain from bone metastases etc. in 60% of cases.[4] RT also has an effect on the dissemination of the tumor in that local/regional therapies are, in effect, 'stopping metastases at their source'.[5] More recently, the possibility of the abscopal effect has been raised on the basis of a remission in out-target lesions after localised RT.[6]

History of Radiotherapy

After the discovery of X-rays in 1895 by Wilhelm Conrad Roentgen, the scenario changed rapidly, for their role in the treatment of malignant and benign diseases. Antoine Henri Becquerel started to study the phenomenon of radioactivity and the natural sources of radiation. In 1898, Maria Sklodowska-Curie and her husband Pierre Curie discovered radium as a source of radiation. Three years later, Becquerel and Curie reported on the physiologic effects of radium rays. Period from 1930 to 1950, was characterised by continuous scientific progress to treat patients affected by deep cancers. This era (also known as Orthovoltage era) was mainly characterised by the use of the radium-based interstitial irradiation (brachytherapy) and by the development of super voltage X-ray tubes able to deliver energy from 50 kV to 200 kV. The second one, the introduction of electron beam therapy, an useful therapeutic option able to deliver higher and variable energies for treating tumors up to a depth of 5 centimetres. The studies, which were conducted during the successive three decades (Megavoltage era), were also committed to the production of more and more innovative radio-therapeutic devices capable of treating cancers in the deep tissues. This period saw the introduction of the Cobalt teletherapy, producing high-energy γ-rays, and of more potent electron linear accelerators (also known as LINACS), able to deliver megavoltage X-rays. The new devices were able to deliver a higher dose of energies than the previous ones, making possible the treatment of deeper tumors with a greater skin sparing. Due to the difficulties of managing these sources and thus the perilousness of excessive radiation within the tissue surrounding cancer, innovative multi-field plans of irradiations were designed. Another important progress in radiotherapy was achieved by the end of the 1990s when the introduction of more sophisticated computer planning systems allowed the development of a 3D conformal radiotherapeutic device (Stereotactic Radiation Therapy), able to treat in a more proficient and safer way with the aid of multileaf collimators(MLC). RT techniques have changed significantly over the past few decades due to the improvements in engineering and computing, evolving from conventional irradiation using simple treatment fields towards highly conformal RT techniques, such as Intensity-Modulated Radiotherapy (IMRT), Intensity-Modulated Arc Therapy (IMAT) and Stereotactic Radiotherapy (SRT, SRS), which aim to improve the outcome by escalating the dose to the target and minimizing the toxicity to normal tissue and critical organs. So, nowadays, certain tumors (i.e. breast and prostate cancer) receive shorter courses of RT as a secure and well-tolerated alternative to the longer conventional schemes; this often holds an enormous advantage for patients and also for healthcare costs.[z] Indeed, high-precision extremely hypo-fractionated RT has been called virtual surgery, since in many situations it can have a radical curative effect locally that's almost like surgery. From the biological point of view, such a high dose per fraction induces different radiobiological mechanisms of cell killing and thereby introducing a novel concept of Radioablation. Technological advances have mainly been the outcomes of integration of imaging information in every phase of the treatment, from the point of simulation to planning to treatment delivery. Indeed, Treatment Planning Systems (TPS) provide sophisticated image registration and fusion algorithms.[8] Moreover, treatment planning optimization is becoming more radiobiology-oriented, integrating local radiation damage models.[9] At present, the precise identification of target volumes for treatment planning is particularly grounded on the fusion of radiological/metabolic imaging, like Magnetic Resonance Imaging (MRI) or Positron Emission Tomography (PET), with Computed Tomography (CT) scan simulation.[10,11] Tumor localisation immediately prior to and through treatment delivery by means of image-guided techniques is becoming crucial for clinical practice and a fundamental prerequisite for high-precision RT.[12,13] As a part of comprehensive RT treatment process, Adaptive RT (ART) techniques make it possible to alter the treatment plan during the course of RT so as to account for anatomical and biological changes.

Novel Techniques in Radiotherapy

A. Treatment techniques: state of the art

1- Intensity-Modulated Radiotherapy(IMRT): Intensity modulation was introduced in the early 1990s as a further refinement in the delivery of Three-Dimensional Conformal Radiation Therapy (3D-CRT). IMRT was made possible by the use of computer-controlled MLCs and mMLCs and advanced treatment planning optimization algorithms that are able to create the desired dose variation inside the radiation field. As opposed to standard planning techniques, where the dose distribution can only be modified by means of a trial and error approach (changing for instance the field weight, angle and shape), with IMRT, the radiation oncologist designates the doses and dose/volume constraints for the tumor and the surrounding normal organs and the TPS determines the optimal fluence of each field leading to a tailored dose distribution (inverse planning).In the past, IMRT was usually delivered using a conventional LINAC with a static field geometry. Developments in IMRT techniques have focused on reducing treatment times with arc therapy by converting multiple static field IMRT into continuously rotating gantry intensity modulation.[14]

2- Stereotactic Body Radiotherapy(SBRT): SBRT is very much a technology-driven treatment modality. SBRT systems are capable of delivering very conformal treatment plans with a steep dose gradient outside the target. This technique makes possible the delivery of a secure, sound and proficient treatment across a wide range of anatomic locations, in proximity to critical organs, and even adjacent to or within prior RT fields. Essential requirements for SBRT are the veritableness of target delineation, and thus the implementation of inter- and intra-fraction tumor motion compensation strategies (especially for tumors within the lung and in the upper abdomen).The wider availability of in-room imaging and advanced treatment delivery systems means that more institutions are now offering SBRT.[15] At present, there are a variety of systems available for SBRT.

3- Particle beam therapy: Proton therapy has been used internationally for cancers of the eye, base of skull and spine, particularly in paediatric patients.[16,17] Indeed, proton therapy in children has been shown to have a lower incidence of vision and hearing impairment, of neurocognitive degeneration and of second cancers, than is the case with other RT modalities. Moreover, heavy particles, such as Carbon ions, are particularly indicated for severely radio-resistant tumors because their biological effectiveness is greater than that of photons and protons. According to the Particle Therapy Co-Operative Group (PTCOG, www.ptcog.com), which constantly updates the statistics on cancer treatment with particle therapy, ten carbon ion therapy facilities are in operation to date (July 2017). The National Institute of Radiological Sciences Chiba, Japan, has been treating cancer with high-energy carbon ions since 1994, with almost greater than 10,000 patients treated by August 2016 and, thus, is the centre with the greatest experience in carbon ion treatment worldwide.[18,19] For the first time, at the National Centre for Oncological Hadron therapy in Pavia, Italy, carbon ions delivered with active scanning together with breathing synchronisation and rescanning modalities have been used to treat patients with tumors of the liver and pancreas.[20]

B. Tumor localisation in treatment planning

As mentioned earlier, the more precise radiation delivery becomes, the more important it is to accurately identify the extension of both the tumor mass and also the normal tissue and critical organs involved in the neoplastic degeneration. This is essential so as to optimize irradiation geometry by delivering the radiation dose to the tumor itself while minimizing the dose delivered to surrounding tissue and organs at risk (OARs). The integration of radiological/metabolic imaging, like MRI and PET, with the CT scan simulation can provide useful information for accurately visualizing the tumour volume. PET with different tracers has made it possible to acquire metabolic information and identify the foremost radio resistant sub-volumes within the tumor. Automatic or semiautomatic (needing manual revision) segmentation algorithms can speed up the delineation of OARs and they offer reliability and repeatability in delineating the structures.

C. Tumour localisation in treatment delivery

1- Image Guided Radiotherapy (IGRT): Technological innovations have made possible the direct integration of imaging technology into the radiation treatment device to augment the precision and accuracy of radiation delivery by controlling the delivery of the dose within the body. A broad range of IGRT modalities are now available and usually used. There are several methods for localizing the target during each and every treatment fraction: by localizing surrogates, including implanted fiducial markers, external surface markers or anatomical features (through planar imaging, fluoroscopy, kilovoltage CT (kV-CT) or megavoltage CT (MV-CT), MRI, ultrasound and x-ray imaging, electromagnetic localisation, optical surface imaging and then on. Depending on the imaging methods used, the IGRT systems may broadly be divided into radiation based, non-radiation based and hybrid systems.[21] Of all soft-tissue based IGRT techniques, cone beam CT (CBCT) is the most widely used. It consists of acquiring multiple projection radiographs (for head and neck imaging ~350, for thoracic/pelvic imaging up to 600) before the RT fraction and within a gantry rotation of 180°–360°. A volumetric image with high spatial resolution and sufficient soft-tissue contrast is reconstructed and registered to the reference planning CT to figure out the true target position. Translational and rotational positioning errors are often corrected online before Irradiation.[22] To mitigate the consequences of tumor motion because of respiration on image quality and registration uncertainty,[23] CBCT are often acquired in conjunction with breath-hold strategies[24] or during a respiratory triggered approach (4D-CBCT).[25] Moreover, ultrafast 'snapshot' volume imaging is ready to be deployed clinically.

2- Breathing adaptive radiotherapy: Real-time monitoring of patient position significantly reduces intra-fraction movement, due either to physiological movement as in the case of the prostate, or due to respiration when tumors are located in the lung or upper abdomen. Electromagnetic technologies such as implanted radiofrequency markers have been successfully used for the prostate.[26] Marker-based real-time image guidance has been in clinical use within the CyberKnife systems for over a decade. For its use to become widespread, real-time IGRT will probably need markerless solutions.[27] A variety of kilovolt-based and MV-based possibilities have been proposed. Cine MRI, which is available with the new MRI-guided radiation therapy systems, is able to provide non-invasive target localisation during RT treatment .[28]

3- Adaptive Radiotherapy (ART): The term ART usually pertains to: 1) modifying the treatment plan during a course of RT to account for temporal variation in anatomy (e.g. tumor shrinkage, weight loss, internal motion or change of OARs), 2) adoption of the delivered dose based on early tumor response and 3) adaptation of the treatment strategy based on early response (e.g. adding chemotherapy or hypoxic sensitizers). ART is very much dependent on the anatomical information provided by IGRT. An appealing approach is the integration of molecular imaging in to anatomical information with the aim of identifying radiation-resistant regions within the tumor, such as clonogen density, proliferation or hypoxia, as different tumor regions have different radiosensitivity, which may make a heterogenous dose distribution desirable in order to obtain greater tumor control.

D. Biological advances in tumor targeting

The efficacy of RT is restricted by the intrinsic radio-resistance of tumor cells, which suggests an increased risk of local tumor recurrence, therefore there is urge to overcome radio-resistance and improve radio-sensitivity explains why there is such great interest in identifying new molecules that have a synergistic effect with radiation. One way to enhance the efficacy of RT that is already in use is to give chemotherapy or targeted agents concomitantly in order to modify the radio-sensitivity of the tumor cells at the molecular level. This field of radiation and cancer biology is rapidly expanding to provide a selective improvement within the tumor response to radiation, including T-cell checkpoint inhibitors, hypoxic radiosensitizers and cytotoxins, antiangiogenic agents, DNA repair inhibitors, signal transduction blockers, chemokine inhibitors and oxygen metabolism modifiers. Thus, there is a huge gap between the many exciting ideas emerging from pre-clinical studies in modern radiation and tumor biology and the lack of clinical trials testing these new concepts. Furthermore the Immunotherapy field offers exciting prospects along with Radiotherapy. Identifying biomarkers that can predict the sensitivity or resistance of tumors to radiation therapy and the risk of developing toxicity is another promising area of the research. In radiation oncology, 'omics' could even be able to predict the treatment response by screening for genetic polymorphism or by genetic polymorphism analysis, and assessing the potential of epigenetic factors, post translational modification, signal transduction and metabolism. An example within the plethora of 'omics studies' was published recently: a patient-specific molecular signature of radiation sensitivity to identify the optimum RT dose; a gene expression-based radiation sensitivity index and the linear quadratic model to derive the genomic-adjusted radiation dose (GARD).[29]

Conclusion

As can be seen, radiotherapy has undergone tremendous progress over years in terms of improved technology which leads to exact target localization, highly conformal dose delivery with powered image guidance and breath hold techniques too. With this all tools, we can give long term survival with reduction of late side effects which ultimately leads to better quality of life. But, we need to be very cautious in selecting patients for the highest technology and we also need highly skilled professionals to deliver such treatments.

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