REVIEWS

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Advances in Radiation Therapy

Postępy w radioterapii

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Abstract

Unbelievable progress in radiotherapy is currently being made. There are two aspects of this improvement. The first is the incredible technological development. The radiotherapeutic workshop has been enriched by new, precise planning methods which make use of three-dimensional imaging, such as IMRT, IGRT, ADRT, and many others. Correct and precise imaging of irradiated structures plays the most important role in the pretreatment process. Also, imaging should be of the best achievable quality. Parallel advances in computers have also influenced imaging technologies. The second factor is the change in the perception of radiotherapeutic implementations in oncological treatment. We now observe highly specialized treatment targeted to the particular type of tumor. A tumor's location and its biology determine the choice of the right treatment method and the prime therapeutic equipment. Modified radiotherapy sequences in some treatment schedules is taken into consideration as well as its concurrent or sequential use with chemotherapy. Better therapeutic results are being achieved due to the concurrent use of radiotherapy (additive effect) and chemotherapy (radio-potentiating effect). It is no wonder that these new treatment plans are being increasingly incorporated into medical oncological practice **(Adv Clin Exp Med 2007, 16, 5, 695–700).**

Key words: target volume, treatment planning, imaging, concurrent treatment.

Streszczenie

Radioterapia onkologiczna jest jedną z najprężniej rozwijających się metod leczenia onkologicznego. Z postępem w tej dziedzinie mamy do czynienia w dwóch aspektach. Pierwszy z nich to niezwykły rozwój technologiczny. Do warsztatu lekarza radioterapeuty wprowadzono nowe metody dokładnego planowania leczenia z wykorzystaniem trójwymiarowego obrazowania, np. IMRT, IGRT, ADRT i inne. W radioterapii prawidłowe i precyzyjne zobrazowanie struktury, która ma być napromieniana jest bardzo ważne. Niezwykle istotne jest, aby obrazowanie charakteryzowało się najlepszą jakością z możliwych do osiągnięcia w danym czasie. Równolegle dokonujący się postęp w dziedzinie komputeryzacji pozwolił między innymi na poprawę możliwości obrazowania. Drugi aspekt to zmiana koncepcji zastosowania radioterapii w leczeniu nowotworów. Obecnie można mówić o zjawisku kształtowania się w obrębie samej radioterapii wysoko specjalistycznego leczenia ukierunkowanego na konkretny typ nowotworu. Umiejscowienie guza nowotworowego i jego biologia zaczęły determinować wybór odpowiedniej metody leczenia i sprzętu terapeutycznego. Pod uwagę bierze się, odmienną niż do tej pory, kolejność wdrażania radioterapii do poszczególnych schematów leczenia oraz jej jednoczesne lub sekwencyjne skojarzenie z chemioterapią. Potwierdzeniem tego są uzyskiwane obecnie lepsze wyniki leczenia za pomocą radioterapii (działanie addytywne) i chemioterapii (promienioczulanie cytostatykami) łącznie. Nie dziwi zatem to, iż coraz częściej w praktyce znajdują zastosowanie tzw. schematy leczenia skojarzonego (**Adv Clin Exp Med 2007, 16, 5, 695–700**).

Słowa kluczowe: objętość tarczowa, planowanie leczenia, obrazowanie, leczenie skojarzone.

One can now without any hesitation pose the thesis that radiotherapy is one of the most dynamically developing methods of oncological treatment. There are two aspects of its progress. The first is the amazing technological development which can be recently observed. The development of radiotherapy is exceptionally fast, as is the parallel progress in computerization, which is now inseparably connected with it [1]. It is undeniably important in radiotherapy that the irradiated structure pictured correctly and precisely. It is therefore essential that the image should have the best possible quality attainable. Advances in computerization have allowed improvements in image capabilities. Within the span of a few years, radiotherapy has evolved from planning therapy based on plain, two-dimensional x-ray images and hand calculations of the necessary parameters for irradiation, then to more complicated three-dimensional imaging (computed tomography, magnetic resonance) and the introduction of complex computer algorithms, to the creation of exceptionally sublime treatment plans based on the latest methods of imaging which evaluate the tumor's biology (tumor metabolism, tumoral antigens). New methods of increasingly precise treatment planning using three-dimensional imaging [1–3] have been introduced as tools in the radiotherapist's workshop. The realization and simultaneous evaluation of such ultra-precise plans can be performed only on accelerators especially equipped for this purpose. Another aspect is the change in the perception of radiotherapy in oncological treatment. At the present stage we can talk about performing highly specialized treatments directed at a given type of tumor [4]. The choice of the proper therapeutic method and therapeutic equipment has begun to be determined by the location and biology of the tumor. In the therapy of head and neck tumors, much sooner than in other locations, the method of intensity-modulated radiotherapy has come into use, thanks to which critical organs (salivary glands) can be spared. Various strategies are now considered in organs afflicted by neoplasms which show little (prostate gland) or great (lungs) mobility in order to eliminate any errors resulting from such movement that can occur during realization of the treatment plan [5–7]. Special schedules of dose fractioning, i.e. shortening the time of the therapy but allowing the application of the proper dose in the given area (breast), have been prepared. Moreover, new schedules of combining radiotherapy with other cancer treatment methods, e.g. chemotherapy, have been gaining increased recognition [4, 8, 9].

Current Radiotherapy Options

The radiotherapy of the 21st century is not only conformal planning and treatment realization on linear accelerators, but also modern methods of irradiation of the area of the so-called target volume. External-beam irradiation methods are intensity-modulated radiotherapy, image-guided radiotherapy, adaptive radiotherapy, intra-operative radiotherapy, four-dimensional radiotherapy, stereotactic radiotherapy based on modulation of the radiation, and molecular irradiation. Brachytherapy now includes new kinds of applicators and three-dimensional imaging in its planning and treatment delivery. The aim of all these methods is to deliver the most homogenous dose to a target volume whilst sparing the surrounding normal tissue, at the same time achieving the largest dose-treatment ratio possible. Moreover, involuntary movements of the patient during treatment delivery as well as visceral motions, especially in the area of the chest and pelvis (respiration and digestion), have been taken into account.

Intensity-modulated Radiotherapy – IMRT

Intensity-modulated radiotherapy is, as its name suggests, a technique which allows changing the intensity of radiation within the beam, which means changing the intensity of radiation in various parts of the field during treatment delivery of the „fraction". The field is characterized by the presence of one or several areas receiving the proper dose intensity with simultaneous absence of hypo-irradiated areas. This enables shaping the dose within the target structures with simultaneous application of the correct treatment dose to the area of the tumor and to sites of metastases [1, 2, 5]. The change in the shape of the radiation field while delivering the fraction is a novelty of this technique. Advanced software used for treatment planning allows modulating the dose [10–12].

Image-guided Radiotherapy – IGRT

Image-guided radiotherapy, the latest technological achievement, is distinctly focused on the target. It can undergo geometric modifications during the application depending on the results of image tests (flat or volumetric) controlling the process [5]. There are two ways of evaluating radiation: directly, on a therapeutic accelerator in the "on-line" mode with correction of the centering before each of the fractions, or with correction of the centering in the "off-line" mode based on a limited number of tests, without correlation with the time of applying the fraction. This allows introducing daily corrections for differences in the positions and mobility of organs [13, 14].

Adaptive Radiotherapy – ADRT

Adaptive radiotherapy (ADRT) is, in turn, a method during which it is possible to make some changes in the target volume in the treatment plan after treatment has begun and to adjust it to the conditions determined based on the image control performed at the beginning of the treatment session. Modulation of the daily dose based on the reconstruction of the daily dose in real time is also possible [1, 2, 5]. After a few initial fractions, the target is averaged and the irradiation is continued appropriately for the averaged area [15, 16].

Intra-operative Radiotherapy – IORT

Intra-operative radiotherapy consists of precise radiation by means of special spherical applicators of small areas affected by the disease from a surgical access. A single photon fraction of 50 keV from a miniature radiation source is usually applied to the tumor or its residual bed. The idea of this method is to increase the dose in the treated area. This raises the probability of local treatment. The possibility of applying the applicator at any anatomical location and performing the radiation in any operation theater without using any special screens are the advantages of this method [17–20].

Four-dimensional (4D) Conformal Radiotherapy

The next step in radiotherapy is four-dimensional conformal radiotherapy, which takes into account every possible movement (the patient's, physiological) that may occur during treatment delivery. In 4D radiotherapy the time of radiation during which changes in the shape and location of the irradiated volume appear is defined as the fourth dimension. The idea of this method is to synchronize the radiation with, especially, large intra-fractional movements of the target. Radiotherapy of breast cancer, lung cancer, and liver cancer may be performed in 4D because of the appearance of large visceral motions [1, 2, 6]. The treatment can be implemented in various ways. Respiratory gating, i.e. turning the beam on and off during the breathing phases, and dynamic target tracking, i.e. monitoring the "glowing" markers of the target with subsequent current-beam adjustment (gantry movement, correction of the table or the collimator), are well known nowadays [21].

Intensity-modulated Stereotactic Radiosurgery

The introduction of intensity-modulated stereotactic radiosurgery represents a great advance in radiotherapy. This technique is realized on a therapeutic accelerator with the use of two characteristic elements: a multileaf microcollimator and a stereotactic frame immobilizing the patient. Because of the necessity of applying a large single dose on a small area, this technique requires immense precision at each of the stages of treatment planning and delivery. The stereotactic method was first applied in the irradiation of brain tumors; the development of this technique now allows irradiation of any anatomic area. It can now be a significant alternative to conformal static techniques. Modern radiotherapeutic systems now allow the application of the treatment to any anatomic area with one or many fractions in a proper schedule [22, 23].

Molecular Radiation

Molecular radiation, which is marginally mentioned possibly because of it lack of general availability and high costs, has unquestionable advantages. The therapy, using molecules of, for example, heavy carbon ions, is a new radiation method characterized by exceptional efficiency and precision [24]. The dose concentration in the irradiated area with simultaneous diminished irradiation of the healthy tissue in the entrance canal, precise placement of the dose in the target volume with a simultaneous sharp fall in intensity at the borders with healthy tissue, and the increased biological efficacy in the case of resistant neoplasms are unquestionable. This therapy significantly increases the chances of curing those neoplasms which are exceptionally resistant to radiation and located deep within the patient's body. Molecular irradiation is applied in cases of small anatomic area (neoplasms of the head and neck, pituitary gland, eye-ball). Unfortunately, using molecular irradiation, i.e. ionic, proton, or neutron radiation, is limited because of the high costs of its generation and technical problems related to its collimation and shielding the surrounding structures. It should also be remembered that heavy-ion therapy is not a universal method of treatment of all forms and kinds of neoplasms.

Treatment Verification

Evaluation of the correctness of treatment is as important as the choice of the proper therapeutic method. The methods aimed at verifying treatment are also undergoing changes. In conventional radiotherapy, portal images regularly taken on a therapeutic accelerator, e.g. once a week, are one of the control elements. Electronic portal images of so-called flat-image character show bony landmarks, field margins, and air structures. Present verification is performed by computer programs and measures any deviation, defining its level. Sometimes target surrogates, for example gold markers implanted in the organs to make them better visible on the pictures, are applied. This allows one to estimate movement of the irradiated area in relation to the beam or bone structures, especially when verification is performed on-line on an accelerator [25, 26].

The next available method is three-dimensional volumetric imaging, which can be performed by means of Doppler ultrasound (clinically the most often used in the area of the pelvis minor) or x-rays using various voltages. CT on rails, having a very good image quality equal to that of diagnostic CT, can be an additional device in the bunker. Another control opportunity is provided by tomotherapy (megavoltage CT, MV CT, consisting of an imaging device and a linear accelerator), this being a combination of two simultaneous procedures: treatment and its verification by megavolt computed tomographic images. Performing tomography using a wide and divergent cone beam is the next method (cone beam CT, CB CT). The examination can be made by means of a kilovolt or megavolt beam. The systems where the imaging is made by the kilovolt beam are an OBI (on-board imager) and an XVI (X-ray volume imager) integrated with an accelerator [1, 5, 27].

Brachytherapy

Technological progress has significantly improved brachytherapeutic methods [28]. The possibility of spatial reconstruction of the tumor together with installing the applicator by means of computed tomography and magnetic resonance are the main advances [29]. Treatment planning in real time (real-time brachytherapy) with the use of image-guided therapy is the future of brachytherapy [2, 30]. Proper application of the radiation sources and planning their positions are performed by ultrasound or computed tomography directly before treatment delivery [31, 32]. The necessary corrections are made continuously. After introducing the changes and verification, the irradiation is performed immediately. Such treatment planning prevents changes in organ positioning in relation to the radiation sources. Imaging has also been improved in brachytherapy. Fusion images, such as the melding of pictures from different imaging techniques (e.g. magnetic resonance and computed tomography), of static or dynamic character, are used more and more often in the planning procedure. Functional treatment, i.e. biological, allowing the determination of areas with a poor degree of oxygenation or with increased cell proliferation in the area of the tumor [32], is also used in the planning process. Radioactive elements marked by isotopes (indium, In^{111}) as well as high-resolution magnetic resonance imaging with intravenous paramagnetic ferric oxide of different affinity are applied to localize the target better. These methods enable defining the places affected by neoplastic processes to the highest degree in a prominently selective way. Studies on the use of new radioactive isotopes are continuing. Elements such as americium (Am^{241}) and ytterbium (Yb^{169}) can be used in the future.

The Changing Role of Radiotherapy

Apart from the immense amount of technological innovation, one also sees a change in the perception of applying radiotherapy in oncological treatment. The limitation of indications for treatment by ionizing radiation took place due to more detailed pathological examination of the diagnostic preparations and postoperative material. The change in the order of applying radiotherapy in selected treatment schedules and paying more attention to its character in oncological treatment is a very important fact [9, 33]. According to the contemporary direction of clinical research, combined treatment with chemotherapy is considered to have a significant role. This is demonstrated by the better treatment results due to the additive effect of radiotherapy and chemotherapy and the radiosensitization effect with cytostatic drugs (cervical cancer). Thus it is not surprising that such treatment schedules are being increasingly applied in practice. Their growing popularity has provoked a change in the sequence of applying radiotherapy in various therapeutic schemes. Ionizing radiation can be applied as a so-called neoadjuvant, i.e. in the initial, inductive form. This means that radiotherapy can be performed at the beginning of integrated therapy and its task is to enable continuation of the subsequent part of the treatment in a radical form in order to increase the probability of cure as much as possible. Neoadjuvant therapy is carried out, for example, in cases of locally advanced breast cancer, cervical cancer, and anal cancer. It turns out that this kind of procedure changes the prognosis significantly, and the elimination of mutilating and complicated surgeries is an additional advantage. Such treatment can be simultaneous, e.g. in the case of advanced larynx cancer with organ sparing, or it can be applied in a proper sequence interchangeably with the application of the proper cytostatic drug and, sometimes, with surgery, for example in the case of anal cancer with sparing the organ and removal of the tumor (pre- and post-operational radio-chemotherapy). Radiotherapy as a preserving method can, in general, be an alternative to radical surgical operations, such as cystectomy in bladder carcinoma. Additionally, in connection with cytostatics it allows achieving a high percentage of multi-year survivals. The role of radiotherapy as a method complimentary to surgical treatment is also recognized. The method of irradiating part of the breast using various techniques (accelerated partial breast irradiation, APBI) after previous sparing surgical treatment is a novelty [34]. The introduction of accelerated fractionation in the organ location mentioned above (radiation twice a day) and radiation of only a selected fragment of the organ is a novelty from the radiotherapeutic point of view [3, 4].

The authors conclude that reports in recent years have shown that the modern treatment planning methods and modified therapeutic schedules mentioned above are bringing positive results more and more often, but a credible evaluation of the efficacy of such treatment can first be made in a few years. It is worth remembering, however, that new technologies and operation guidelines should not be introduced into practice uncritically. A commonsense approach tells us that the most important elements of a correctly conducted therapy are: precise imaging, defining the target volume, dose application, quality assurance, and the skills and knowledge of the doctor. The new therapeutic schedules, although currently being clinically applied, are still far from being recognized as therapeutic standards. From among the vast and increasingly available therapeutic resources, a method should be chosen which suits the individual situation. The aim which should always be in view during the constant search for new methods is the pursuit to improve curability in oncological patients.

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