

REVIEW

Radiation therapy : state of the art and the future

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Summary : Technical innovation in radiation therapy (RT) such as stereotactic irradiation, intensity modulated RT, image-guided RT, and brachytherapy using remote controlled after-loading system have made it possible to deliver ideally distributed radiation dose to the target with great accuracy, while sparing the adjacent organs at risk. As a result, tumor control rate by RT improved markedly and became excellent alternative to surgery for asymptomatic or mildly symptomatic brain tumors, early stage lung cancer, and low-risk prostate cancer. In locally advanced stage of cancer, randomized controlled trials established the chemoradiation therapy as a standard treatment option for patients with head and neck cancer, lung cancer, esophageal cancer, and cervical cancer. RT is also a valuable treatment for palliation of local symptoms caused by cancer with consistently high response rates. Minimally invasive therapy has come to be emphasized its needs in the background of increased tendency of elderly patients with cancer, and advances in conformal dose delivery technique raise the RT at a more important position in cancer therapy. However, adequate number of RT profession is indispensable to utilize highly-sophisticated RT technology. Substantiality of an education system for radiation oncologist, RT technologist, and medical physicists is our current most important issue. *J. Med. Invest.* 57 : 1-11, February, 2010

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INTRODUCTION

The number of patients treated with radiation therapy (RT) is rapidly increasing due to the spread of high-precision RT and diagnostic imaging systems, which facilitate low invasiveness in the treatment of cancer. Technical innovation of irradiation has made it possible to target high radiation doses to the lesion with great accuracy, resulting in high tumor control rates and making RT an alternative to surgery for various cancers. In this paper the

course of development of present and future irradiation techniques are discussed, and the role of RT as the current standard treatment for cancer is reviewed.

FROM TWO-DIMENSIONAL RADIATION THERAPY TO THREE- AND FOUR- DIMENSIONAL RADIATION THERAPY

Conformal radiation delivery technique

The dose-effect relationship in both tumor and normal tissue is characterized by a sigmoid curve, as shown in the Figure 1. The cure probability of RT depends on the difference between tumor cell kill and the development of normal tissue toxicity due to radiation. A radiation dose which can maximize

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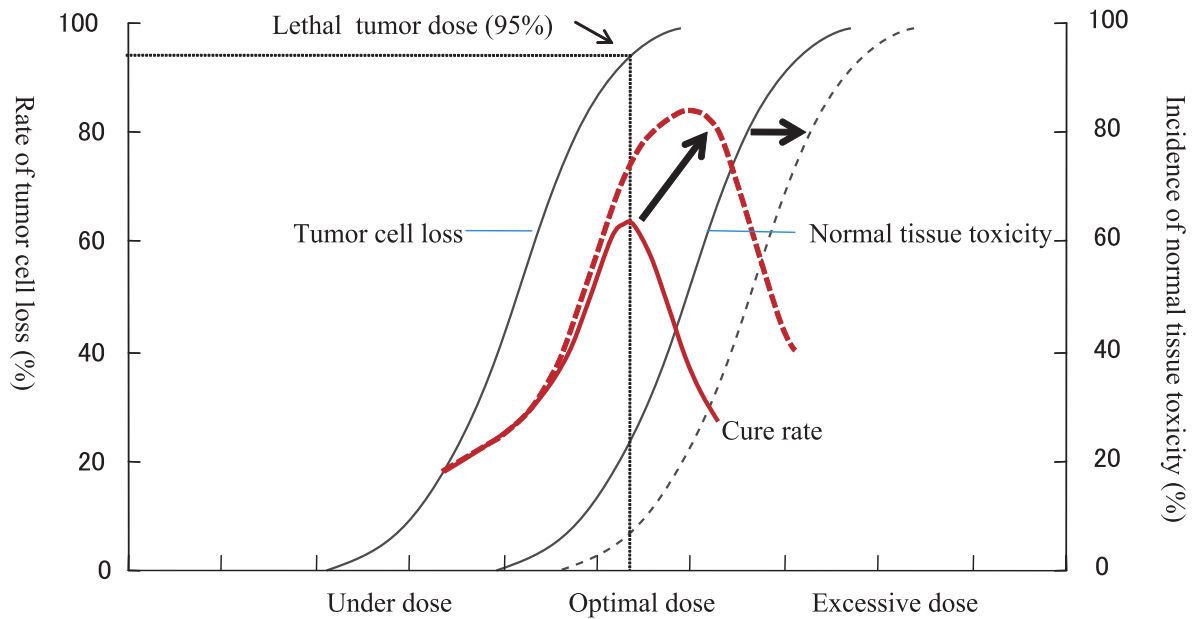


Figure 1. Dose effects on tumor and normal tissue

A radiation dose which can maximize the difference between tumor and normal tissue damage represents the optimal dose for the patient in radiation therapy, and a cure rate becomes greatest with the optimal dose. If normal tissue toxicity curve can be shifted to higher dose area by innovative technical development of irradiation, a cure rate improves (arrows).

the difference between tumor and normal tissue damage represents the optimal dose for the patient. If we can reduce the radiation dose to the surrounding normal tissues adjacent to the tumor, by improving dose conformity, the sigmoid curve for normal tissue damage can be shifted to a higher dose area. This makes it possible to escalate the tumor dose, resulting in an improvement in the cure rate. Currently, radiation delivery techniques are primarily centered on external beam RT and brachytherapy. Technical innovation of both of these techniques always aims to improve dose distribution conformity with the objective of decreasing normal tissue toxicity. The precision of external beam RT, which is the main delivery method for high-energy ionizing radiation to lesions from outside of the body, has been markedly improved by innovative technical development of various imaging modalities and irradiation devices. Formerly, the irradiation field was defined two-dimensionally by referring to bony structures on X-ray films. However, the first step in current RT planning is the definition of the target volume, which has been internationally defined by the International Commission of Radiation Units and measurements (ICRU) Report 62 (1) (Fig. 2). In the concrete process of RT planning, the contours of the target and organ at risk (OAR) are delineated on the RT planning system (RTPS) using data

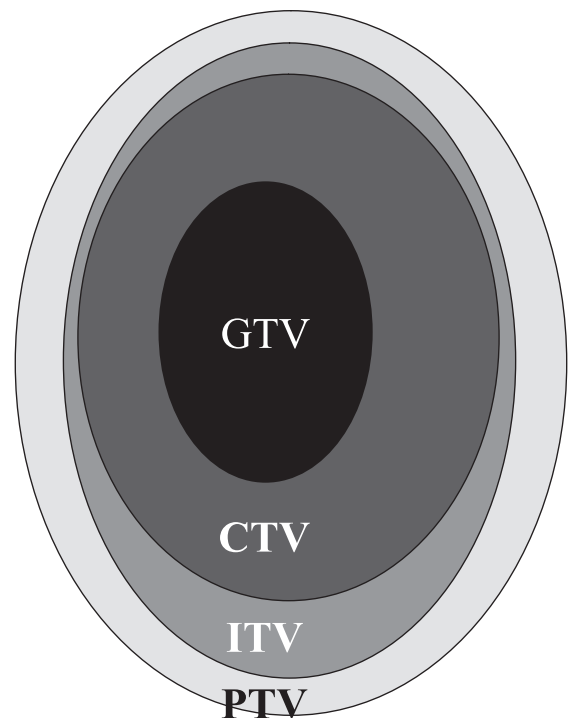


Figure 2. Target definition by ICRU Report 62 (1) in radiation therapy

Gross tumor volume (GTV) : tumor volume obviously delineated on imaging, Clinical target volume (CTV) : target volume including subclinical tumor extension, Internal target volume (ITV) : target volume including internal movement of tumor, Planning target volume (PTV) : target volume including set-up margin around ITV

on anatomical position and X-ray transmittance derived from CT. In the next step the setting of a number of beams, their angle and relative dose allocation is performed, and finally the absorption dose for the target and OAR is calculated. Biology-based planning using functional imaging, such as magnetic resonance imaging and positron emission tomography, is used according to necessity. A multi-leaf collimator (MLC) located at the nozzle of the external beam RT device is online with RTPS. Three-dimensionally conformed irradiation of the target becomes possible due to MLC formatting of irradiation according to the shape of the target in each beam. The final irradiation method is determined after evaluation of the dose distribution chart and dose volume histogram of the target, and all OAR in the patient body. A three-dimensional RT planning image for uterine cervical cancer is showed in Figure 3.

Every organ in the human body has internal movement (IM), and thus the target of the RT is also moving and changing its shape during irradiation. A new concept of internal target volume (ITV) is advocated as a volume to compensate for IM in ICRU report 62. Lung cancer that develops in the organ with the largest IM shows respiratory motion of up to 2 cm (2). Four-dimensional CT (4DCT) was developed as a new technology to define the ITV of the tumor in the lungs and liver, organs that both have large IMs. In 4DCT, anterior abdominal motion is monitored as a surrogate of respiratory motion during CT scanning. All CT data has information on the respiratory phase derived from simultaneously monitored respiratory motion (Fig. 4a). CT images are all sorted according to the 10 bins corresponding to the 10 phases of the full breathing cycle, and these images include information on

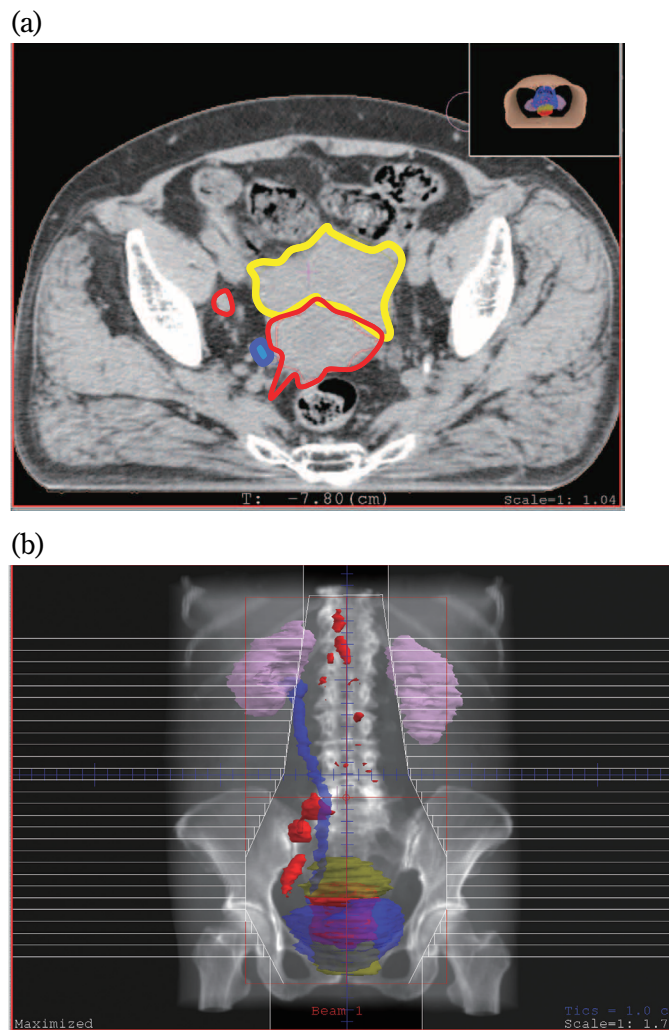


Figure 3. 3 dimensional radiation therapy planning for uterine cervical cancer with paraaortic lymph nodes metastases (a) Contours of target (red line : primary lesion and regional lymph nodes metastases) and organ at risks (yellow line : urinary bladder, blue line : right ureter) are delineated on CT images. (b) Radiation field formed by multi-leaf collimator on a digitally reconstructed CT image.

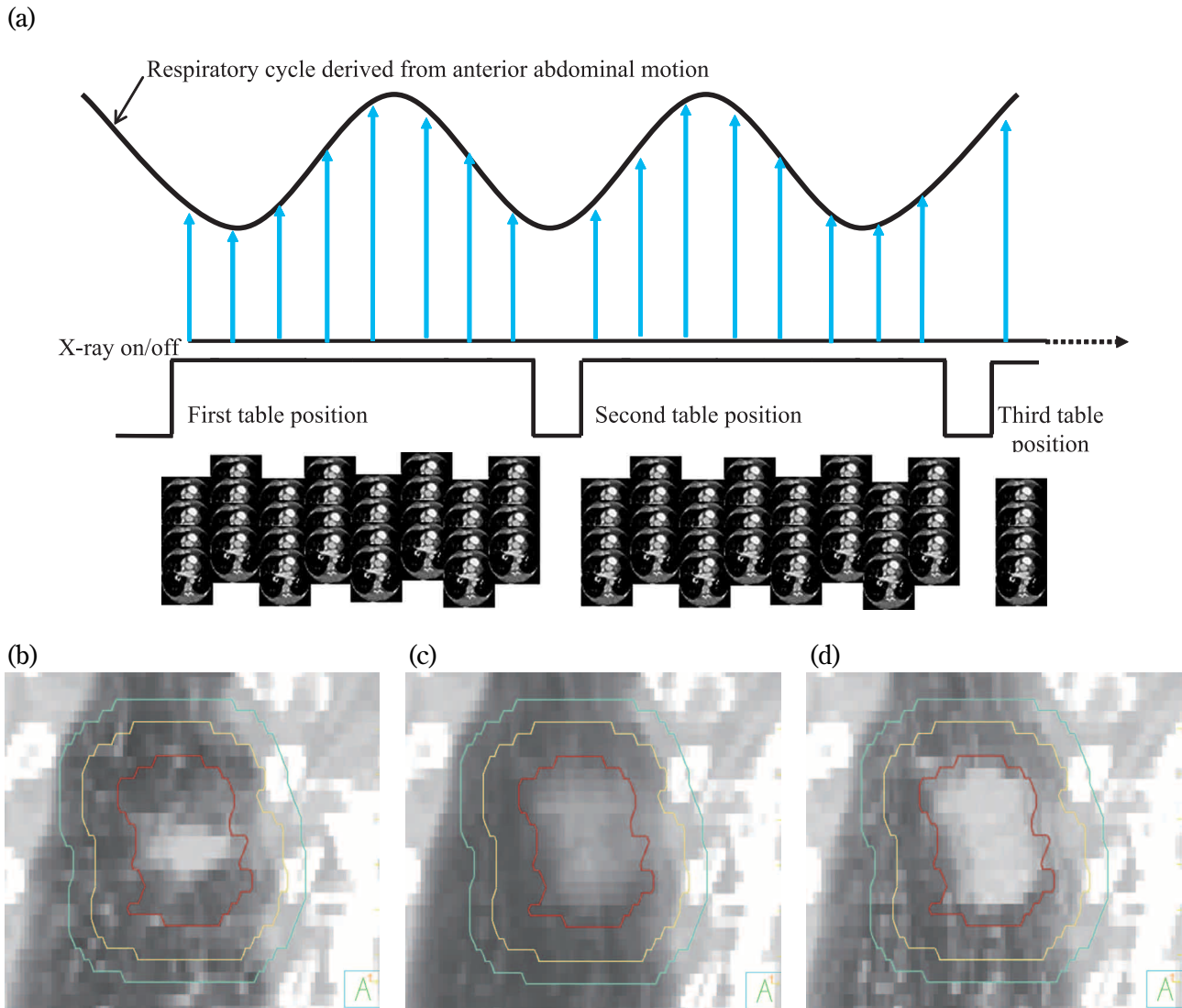


Figure 4. Respiratory motion tracking with retrospective gating

(a) Information on respiratory phase is attached to computed tomography (CT) images by performing CT scan simultaneously monitoring respiratory motion of the target during one respiratory cycle. All CT images are sorted according to 10 bins corresponding to 10 phases of the full breathing cycle for radiation therapy treatment planning. (b) A reconstructed sagittal plane image derived from fast spiral CT under free breathing: This image can show the target only at a point of time in respiratory phase. (c) A reconstructed sagittal plane image derived from 4 dimensional CT (4DCT) based phase average CT (d) Internal target volume definition on a reconstructed sagittal plane image of 4DCT based maximum intensity projection (red line: gross tumor volume (GTV) in 10 respiratory phases, yellow line: ITV defined by adding subclinical tumor extension around GTV, blue line: planning target volume defined by adding set-up margin around ITV)

the position and shape of the target in all respiratory phases. A contour of the ITV is defined on maximum intensity projection images to clearly delineate its border. (Fig. 4d) Dose calculation is performed using phase average CT, whose density is adjusted depending on the real speed of tumor motion (Fig. 4c). Radiation therapy that is planned, based on such an ITV defined on 4DCT, can cover the target's motion over the treatment time and is thus termed four-dimensional RT (4DRT). Intercepting radiation that can irradiate a target at any given position during respiratory motion is one of treatment methods that falls into the category of

4DRT. Intercepting RT can reduce the ITV by reducing IM, resulting in a dose reduction to the OAR. Also, there is a new concept in dealing with target movement known as chasing RT. This modality can irradiate a target while chasing it. Computer software supporting chasing irradiation technology is under development.

Stereotactic irradiation

Stereotactic irradiation (STI) is a highly precise treatment method that focuses a narrow ionizing radiation beam on the target from various directions. STI involves the use of an immobilization system

that can minimize isocenter deviation in the patient's body, or a coordinate system fixed to the patient, to within ± 2 mm in a treatment for brain tumors and to within ± 5 mm for the treatment of tumors located in other body organs (Fig. 5). If a target volume is small, STI enables the delivery of a large dose of radiation to the target in a single fraction or a small number of fractionations, resulting in an enhanced antitumor effect. The main target for STI is the metastatic brain tumor, because it can be clearly defined on imaging systems and the majority of these tumors are detected when they are small. However, since 2004 insurance policies have started to cover solitary lung cancer and liver tumors with a diameter of less than 5 cm for STI treatment. STI is classified as stereotactic radiosurgery (SRS) that can complete a treatment using a single fraction, and

stereotactic RT (SRT) that can deliver radiation in a number of fractions. Dose fractionation increases the total radiation dose that normal tissues can tolerate before developing late radiation morbidity. Therefore, SRT seems to be superior to SRS, at least in theory. However, the fractionation method has not yet been standardized due to some practical difficulties such as responsibility of staffs. The standardization of an appropriate fractionation schedule for SRT has not presently been achieved.

Intensity modulated radiation therapy

Intensity modulated RT (IMRT) is an emerging irradiation technique that has achieved a marked improvement in three-dimensional dose convergence on a target, by modulation of the beam intensity distribution within a field. IMRT can deliver a

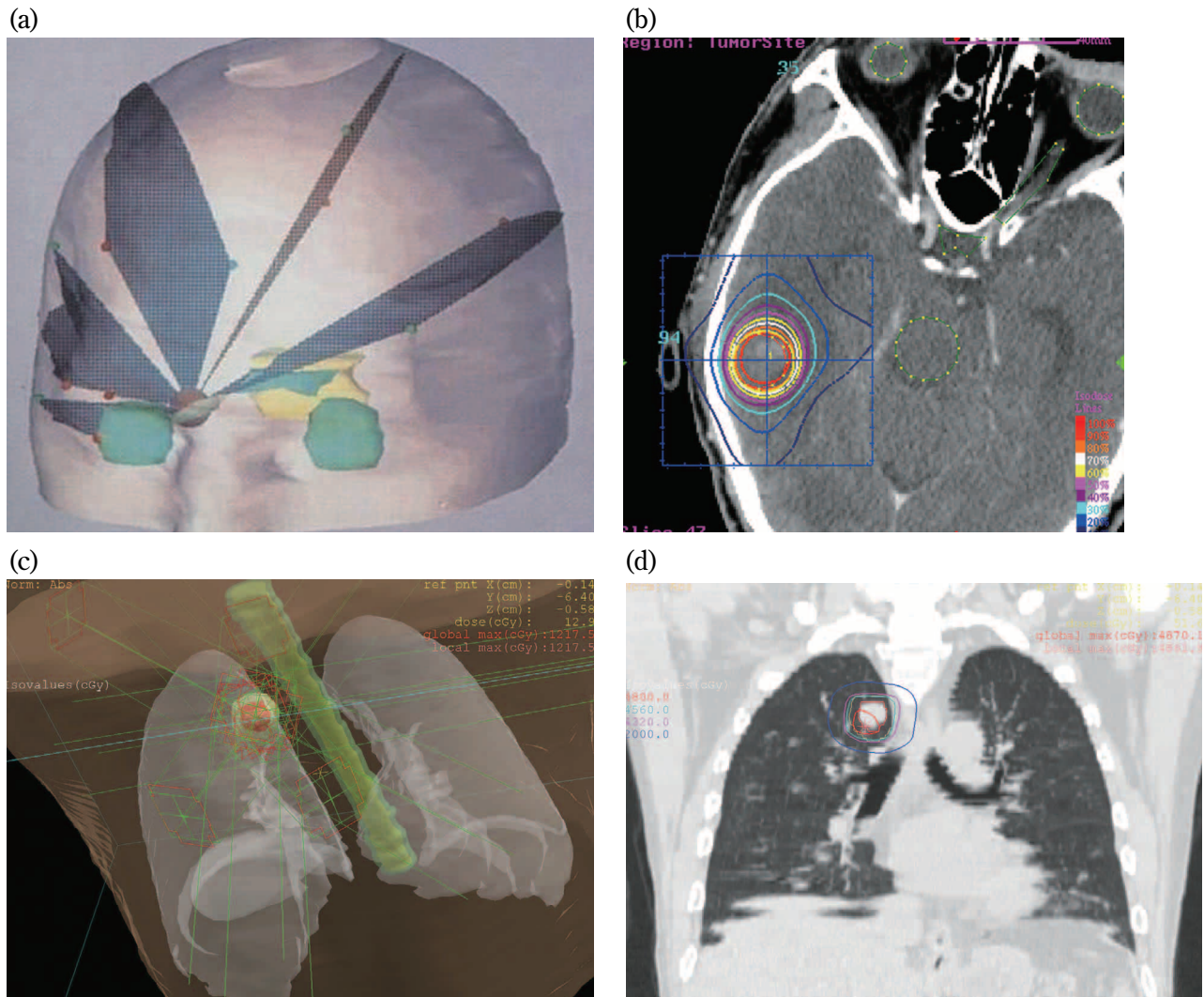


Figure 5. Stereotactic irradiation

- (a) Tracks of radiation beams in small volume multiple arcs radiation therapy (SMART) using linear accelerator for brain tumor
- (b) Dose distribution demonstrated on a CT axial image in SMART for metastatic brain tumor.
- (c) Beam arrangement in non-coplanar static multiple portals irradiation for lung cancer
- (d) Dose distribution demonstrated on a coronal CT image in stereotactic radiation therapy for lung cancer

higher radiation dose to a target while reducing the dose to the surrounding normal tissue (3-6). This modality can produce a horseshoe shaped dose distribution and it is useful, especially in head and neck tumors and prostate cancer, whose target is always abutting on OAR (Fig. 6). In IMRT, optimal intensity modulation is produced by continuous irradiation using various irregular fields with the MLC configuration being based on intensity maps calculated using RTPS. A newly developed technology in the field of IMRT, known as volumetric modulated arc therapy (VMAT), has been predicted to become widely deployed in Japan. In VMAT, modulation of

beam intensity is achieved by regulating the dose-rate and the MLC dynamically with a rotating gantry in a linear accelerator. VMAT requires shorter treatment time than conventional IMRT, and can be completed within approximately 1.5 min. Shortening the treatment time makes it possible to reduce the effect of target deviation during a treatment, and results in improvement in the accuracy of irradiation and a reduction in the low-dose radiation exposure to patients. Moreover, the primary advantage of VMAT in the clinic is its ability to increase treatment throughput, which is a very important consideration given the expected increase in patients.

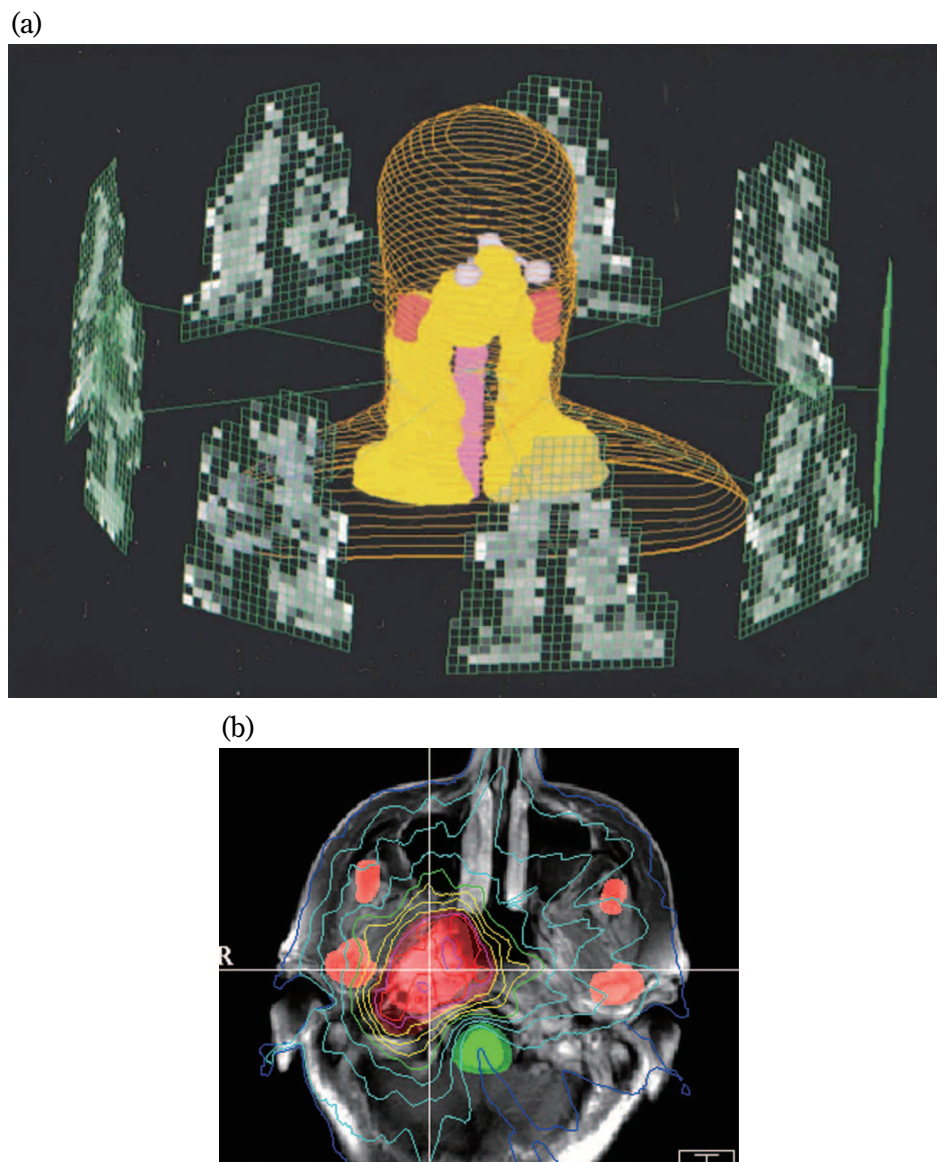


Figure 6. Intensity modulated radiation therapy

(a) A case of head and neck tumor treated by intensity modulated radiation therapy (IMRT) with 9 beams (cited from reference 7), Intensity modulation shown on a figure is performed in every beam. (b) Dose distribution chart on an axial image of CT in IMRT (green : cross section of the spinal cord, orange : cross section of the salivary glands), IMRT realize conformal dose distribution to the target, and irradiated dose to the adjacent normal tissue can be reduced. IMRT becomes an effective irradiation method for the patients where the organs at risk such as spinal cord and salivary glands locate beside the target.

Image-guided radiation therapy

High precision RT, such as IMRT, that can deliver a three dimensionally conformed dose distribution to a target shape requires a higher level of irradiation accuracy. In IMRT, even a tiny deviation in the target position can cause serious target dose deficiency, in terms of tumor control. Image-guided radiation therapy (IGRT) is a technology that was introduced to obtain higher precision irradiation. In RT planning, the planning target volume (PTV) is created by adding the necessary three-dimensional safety margins to the clinical target volume (CTV) to deliver an adequate dose to the CTV. Target position error covered by the PTV-margin at irradiation is classified as a set-up error that arises during patient positioning, and an organ motion error due to the IM of organs including the target. It is further classified as an inter-fractional error that arises between every irradiation, and as an intra-fractional error that arises during each irradiation. The PTV-margin must be calculated using actual error data from patients in each institution. First, the systematic error that is a mean value of deviations

in the target position, and a random error that is standard deviation of the deviations in the target position, must be calculated as shown in the Figure 7. Next, the standard deviation of the systematic error (Σ) and the square root of the square of the mean of the random error (σ) is calculated by group analysis of all patient data. The PTV-margin is determined using an equation such as $2.5\Sigma+0.7\sigma$ as advocated by van Herk et al. (7) using values of Σ and σ calculated for each set-up error and organ motion error, and for inter-fractional and intra-fractional. The PTV-margin significantly influences the final target volume. For example, an increase in the diameter by 1 mm results in a 10% increase in volume according to mathematical calculation, assuming that the target is a complete sphere with a diameter of 6 cm. If the PTV becomes larger and the radiation dose to the surrounding normal tissue becomes higher, the therapeutic ratio decreases accordingly. The purpose of IGRT is to make the PTV-margin as small as possible by improving the accuracy of positioning. The concrete workflow of IGRT is as follows. Data on the target position and bony structure is obtained using an X-ray fluoroscopy device

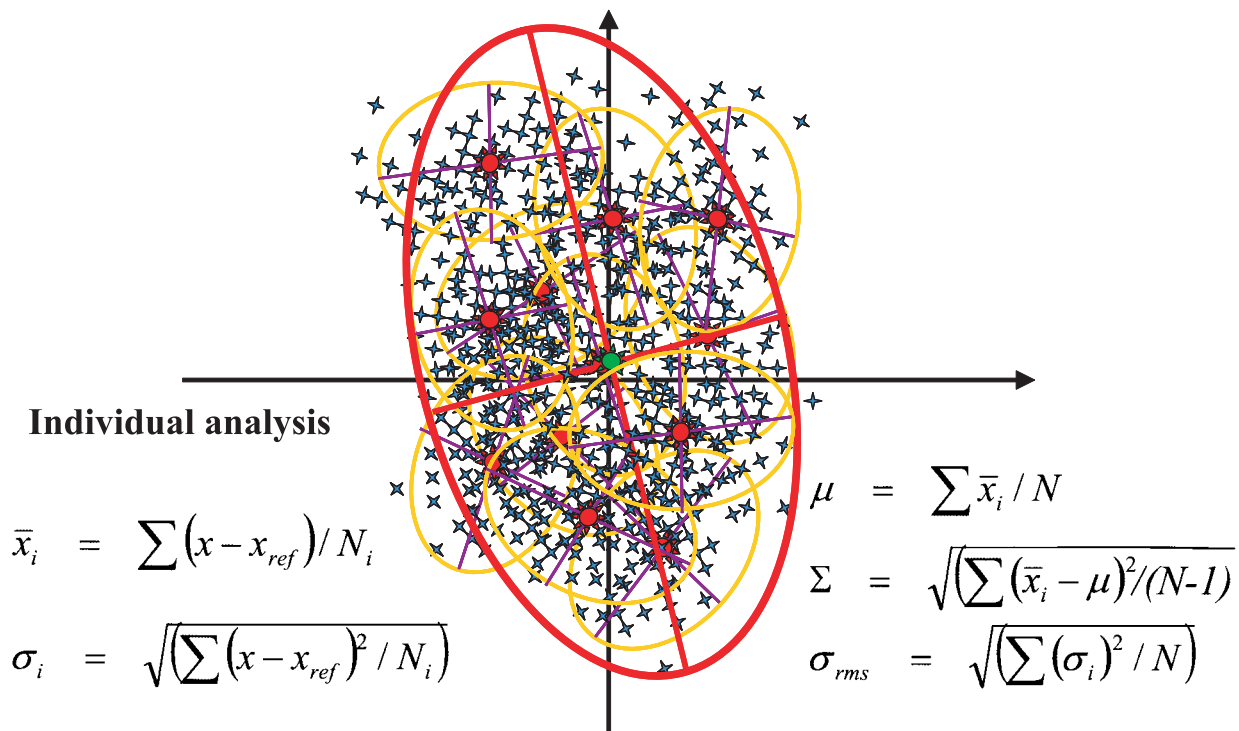


Figure 7. Analyses of target position errors
 \bar{x}_i : mean value of target position errors in a case of i=systematic error (red point), x : target position at the time of start of radiation therapy, x_{ref} : target position at the time of radiation therapy planning, N_i : fraction number of radiation therapy in a case of i, σ_i : variation of target position error in a case of i (standard deviation)=random error (yellow ellipse), μ : mean value of systematic error (green point), N : number of cases, Σ : standard deviation of systematic error (red ellipse), σ_{rms} : square root of square mean of random error

or CT scanner set up in the RT room just prior to patient irradiation. The difference from the anatomical position derived from the RTPS is then calculated simultaneously so that the patient position can be adjusted. The term 'IGRT' means not only a technology used for the reduction of positioning errors at irradiation, but also includes the accurate diagnosis of the area of tumor invasion for CTV delineation and evaluation of the treatment effect using various kind of imaging modalities. IGRT is a concept that means improvement in the precision of RT by the use of imaging technology through all the steps of RT. There is a new concept of RT technology using IGRT called adaptive RT (ART). In general, RT requires several weeks to complete, and changes in the position, size and shape of the target and OAR during the treatment period influence the dose distribution and treatment accuracy. As shown in Figure 8, the concept of ART involves endeavoring to perform more accurate and elaborate RT. This is achieved by altering the irradiation according to the anatomical changes that occur during the treatment period, using IGRT technology and new software that enables deformable registration. If ART makes it possible to avoid a dose deficiency in the target or dose excess of OAR caused by anatomical changes during treatment, a decrease in late radiation morbidity and an improvement in the tumor control rate will be achieved.

Remote controlled after-loading system

The history of brachytherapy began in 1898 when Mr. and Mrs. Curie discovered radium. A large body of RT science was created and matured into the field of radiation medicine, during the half century between the 1910s and the 1950s, and formed the basis of current brachytherapy. However, radium disappeared completely from the clinical scene in the 1990s, because of its long physical half-life of 1602 years, and the risk of a radon gas leak caused by exposure of the radium to air due to breakage of its protective platinum covering and seal. A remote controlled after-loading system (RALS) using cesium, cobalt or iridium was developed as an alternative to radium brachytherapy, and has been popularized since first reported by Walstam (8) in 1960. The application of brachytherapy has expanded into many organs due to downsizing of the source used in RALS and the development of applicators that enable precise delivery of the source to the tumor. This has resulted in a shortening of the treatment time, thus relieving the physical burden of treatment on patients. The advantage of negligible radiation exposure to the medical staff, due to the replacement of radium sources with RALS is significant. When RALS first started to be used in brachytherapy, a potential increase in the incidence of radiation morbidity was a concern, due to

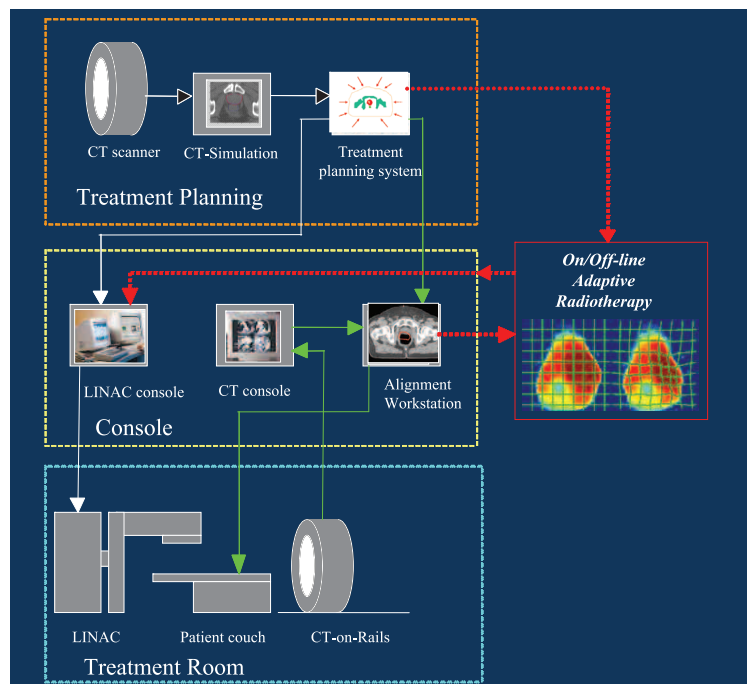


Figure 8. Work flow diagram of CT-guided adaptive radiation therapy
CT : computed tomography, LINAC : linear accelerator

the significant increase in the dose-rate relative to radium therapy. However, such apprehension has been almost swept away due to the progressive accumulation of positive clinical data. If the insertion technique of the interstitial applicator is improved, or the optimization of dose distribution is realized through IGRT, the future clinical significance of brachytherapy will be maintained.

ROLE OF RADIATION THERAPY AS A STANDARD TREATMENT METHOD

RT is a first treatment option in various kinds of head and neck cancer. Glottis cancer in Clinical Stage (CS) I or II is one of representatives of disease treated with definitive RT, and 80 to 90% of glottis cancer in CS I is cured by RT alone (9). Standard treatment method for epipharyngeal cancer is chemoradiation therapy, because most of them have undifferentiated carcinoma sensitive for RT. Patients with early stage epipharyngeal cancer treated with RT showed 80 to 90% of overall survival (10). Also, RT became one of standard treatment options for uterine cervical cancer in CS I-IVA, non-small cell lung cancer (NSCLC) in CS IIIB, esophageal cancer in CS III, prostate cancer in CS I-III, and malignant lymphoma in CS I or II (11). Since 2008 insurance policies have started to cover IMRT for brain tumor, head and neck tumor, and prostate cancer in Japan. In the next few years, IMRT will spread in treatment for cancer, and it will result in decrease of risk of late radiation morbidity such as rectal bleeding after RT for prostate cancer and xerostomia after RT for head and neck tumor. It is expected that dose escalation achieved by risk reduction of radiation morbidity brings improvement of tumor control.

High level evidences to demonstrate efficacy of concurrent chemotherapy to RT for various kinds of cancer were reported in this decade. For example, all of five randomized controlled trials of chemoradiation therapy for uterine cervical cancer reported 30 to 50% of survival improvement by performing concurrent chemotherapy to RT at the annual meeting of American Society of Clinical Oncology in 1999 (12-16). There are some difficulties in applying the same regimen to Japanese women because patients' characteristics and RT methods in those trials were different from those in Japan (17). However, chemoradiation therapy has a potential to improve treatment results of uterine cervical cancer, if suitable regimen

of concurrent chemotherapy for Japanese women will be established. Chemoradiation therapy has also become standard treatment option for locally advanced esophageal cancer of medically operable patients after Cooper et al. (18) reported its efficacy in 1999.

Radiation therapy as an alternative to surgery

STI initiated by Leksell (19) in 1951 spreads rapidly after insurance policies started to cover in Japan, and it became a standard treatment method for metastatic brain tumor less than 4 and less than 3 cm in maximum diameter instead of surgery. Local control rate of STI for metastatic brain tumor is over than 85% (20) regardless of radiation sensitivity of primary lesion. Coverage by insurance policies for STI was expanded to lung and liver tumor in 2004. Local control rate of 257 patients with NSCLC in Stage I reported by Japanese institutes was 86% (21) at a median follow-up period of 38 months, and no serious radiation morbidity developed in those patients. There are video-assisted thoracic surgery and radiofrequency wave ablation as treatment methods conflict with STI, but STI is superior to the others at a point of view of low invasiveness. STI can become an alternative treatment method to surgery even if for medically operable NSCLC in Stage I, depending on the clinical results from now.

Iodine-125 permanent implant therapy began in 2003 as a new treatment method of brachytherapy for low risk prostate cancer instead of surgery. Number of patients treated with Iodine-125 permanent implant increases rapidly, because it shows high tumor control rate same as the radical prostatectomy and lower invasiveness.

Radiation therapy in palliative care

RT plays an important role in palliative care for cancer with consistently high efficacy in the relief and control of bone pain, neurological symptom, obstructive symptoms, and tumor hemorrhage. Over than 80% of patients who developed bone metastasis and superior vena cava syndrome obtained symptom relief by RT (22, 23). Low irradiation dose and short treatment period of palliative RT can minimize somatic burden of the patients resulting from treatment, and palliative RT is applicable to the patient even in poor general condition.

Malignant spinal cord compression syndrome occurring in 5% (24) of cancer patients causes spinal paraplegia. A prompt and appropriate treatment strategy decision is required for this disorder

deteriorating quality of life of the patient with limited prognosis. The most important factor predicting functional prognosis is the level of neurological deficits at the time of start of RT, and RT must be delivered before patient becomes non-ambulant. If the patient falls into paraplegia, walk function recovery rate becomes only 0 to 30% (25-32). RT is indispensable treatment for these cancer-related clinical disorders described as oncologic emergency.

CONCLUSIONS

The field of RT has entered a period of significant change. A rapid increase in the number of patients undergoing RT and an improvement in the social recognition of RT are supported by a fundamental anti-cancer law announced in 2004, by RT restructuring and by the basic postural establishment of evidence-based medicine. However, the proportion of patients who undergo RT in Japan is limited to approximately 25% of all cancer cases, as compared with 60% of all cancer cases in Europe and America. We cannot say that the appropriate decision on the application of RT is always made in medical care for cancer patients in Japan. The new high-precision RT techniques reported in the present paper are enabling the expansion of RT applications to more diseases. However, achieving a high technical level based on the quality assurance of machines is indispensable to fully utilize the power of these high technology devices. Unfortunately, in Japan, there is a shortage of medical staff who are specialized in and can maintain a satisfactory technical level in RT. Indeed, increasing the numbers of highly specialized RT medical staff, including radiation oncologists, radiation therapists, RT nurses and medical physicists is essential to Japanese RT as it enters this new era.

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