



## Verification and correction of geometrical uncertainties in conformal radiotherapy

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### ABSTRACT

*Geometrical errors are presented as deviation between intended geometry of radiotherapy plan and real geometry of radiotherapy treatment. Total geometrical error is build up of smaller errors, which can be generally classified as set-up, organ motion, organ delineation, and technical condition related errors. The clear distinction must be made between systematic and random component of these errors and its amount should be encountered in treatment planning process. Errors' measuring for specific patient group with electronic portal imaging device and proper correction strategy enables to predict, minimize, and keep under control the amount for most of geometrical errors; it also improves the preciseness of treatment and consequent results. Nature and characteristics of most frequent geometrical errors are discussed and clinically applicable methods for their proper managing are described in this paper.*

**KEY WORDS:** Radiotherapy, Conformal; Radiotherapy, Planning, Computer-Assisted; Image Processing, Computer-Assisted; Numerical Analysis, Computer-Assisted

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### INTRODUCTION

The goal of three-dimensional conformal radiotherapy (3D-CRT) is to increase the likelihood of tumour control while minimizing irradiation of normal surrounding tissues by precise conforming the dose distribution to the target volume shape. Quality assurance (QA) is an essential component of CRT, as only tight conformity will allow one to escalate the dose to the levels needed for improved local control, without increasing normal tissue toxicity.

Although most of them are image guided, each of CRT numerous procedures can be related with corresponding geometric uncertainties or errors (Table1).

**Table 1.** Geometrical errors in radiotherapy treatment chain

#### SOURCES OF TREATMENT PREPARATION AND EXECUTION ERRORS RELATED TO THE TECHNICAL CONDITIONS

- Lasers alignment in CT room
- Lasers beams quality/preciseness in CT room
- Dimension/position/alignment of skin marks
- CT imaging parameters
- Lasers alignment in RT treatment room
- Laser beams quality/preciseness in RT treatment room
- RT beams geometry stability
- Treatment unit geometry stability

#### SOURCES OF TREATMENT PREPARATION ERRORS RELATED TO THE PATIENT

- Patient positioning in the moment of CT image acquisition (Skin marks-bone structures relation affects on referent geometry – DRR)
- Tumor and risk organs position in the moment of CT image acquisition
- Target volume and risk organs delineation (proper GTV< CTV<PTV margin)

#### SOURCES OF TREATMENT EXECUTION ERRORS RELATED TO THE PATIENT ("INTERFRACTION / INTRAFRACTION ERRORS")

- Organ shape changes between each fraction (bladder, rectum, stomach)
- Physiology movements during each fraction of treatment (breathing, swallowing...)

These errors are usually small but, regarding the number of procedures, it is expectable that larger geometrical uncertainties can occur in some cases. The magnitude of technical conditions related errors is substantially reduced by using the modern and sophisticated equip-

ment; in this text, the set-up, organ motion, and organ delineation errors are discussed, and clinically applicable methods to measure and improve the preciseness of treatment delivery in radiotherapy are described.

### SYSTEMATIC AND RANDOM GEOMETRICAL ERRORS

Geometrical errors are represented as deviations between radiotherapy plan (intended) and radiotherapy treatment (real) geometry.

If the technical conditions of radiotherapy treatment are controlled with adequate quality assurance procedures, the geometrical errors mainly consist of external set-up and internal organ movement deviations. Both deviations consist of systematic and random component (Figure 1a).

Systematic errors occur if the mean irradiation geometry in fractionated treatment differs from the geometry in the treatment plan. The mean deviations are then called systematic errors, denoted by  $\Sigma$ . It represents the recurring difference between intended and actual geometry.

As the deviation from the referent geometry is more or less different during each fraction, the total deviation in a given fraction is presented by the sum of the recurring systematic error and an additional, fraction specific error. These fraction-to-fraction variations are called random errors and they represent the fluctuating component of the total error. Random errors are often characterized by standard deviations (SD) of their frequency distribution, usually denoted by  $\sigma$  (Figure 1b).

The total error consists of many small errors so it is reasonable to assume that, following the rules for sum of many variables with arbitrary distributions; the total error tends to have a normal distribution.

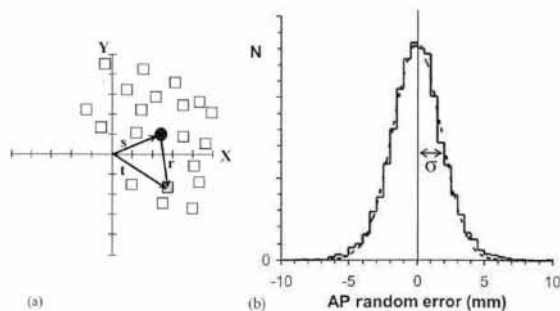
A systematic error may be introduced into an individual patient's treatment at any point, starting from the initial patient positioning and immobilization through the final treatment

delivery. Once introduced, this error is fixed, and if not corrected, will lead to a consistent discrepancy between intended and actual target coverage (1).

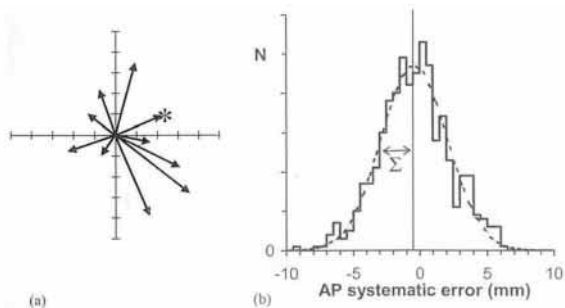
Random errors are mainly introduced during the treatment execution process and will therefore vary between fractions.

Both components of total geometrical error (external - set-up deviations and internal - organ movement) should be accounted in the treatment planning, but for individual patient they are not predictable.

Measured for an individual patient, both systematic and random errors can be fully assessed after completion of all treatment fractions (Figure 1a,b). By their measuring before the end of the treatment by means of electronic portal imaging device (EPID), it is possible to partially correct systematic error by applying the off-line or the on-line correction protocol and to correct random error by using the on-line protocol.



**Figure 1.** Figure 1. Set-up error measured for individual patient during the fractionated RT treatment 1a. Measured set-up errors for 20 fractions of specific patient, in two directions (x, y). Each square represent the set-up error of particular fraction. The solid circle indicates the mean of these errors and the corresponding displacement (arrow 's') is the systematic set-up error of this patient. The total set-up error of any fraction (the greyed square and corresponding arrow 't') is the sum of the systematic error and the random set-up error (arrow 'r') of that fraction. b. Random set-up errors (c) described by standard deviation (SD) of their frequency distribution.



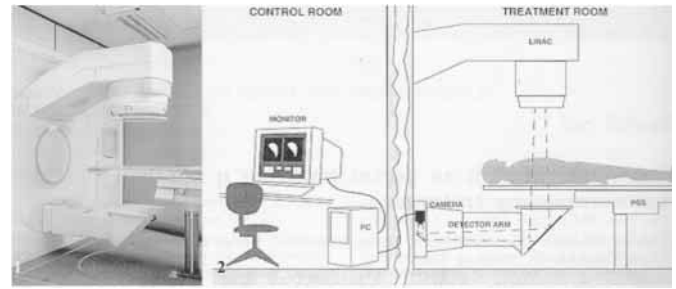
**Figure 2.** Set-up systematic errors measured for patient specific group 2a. Systematic set-up errors for 10 patients, represented by arrows (an asterisk marks the systematic error of the patient in Fig. 1a). b. Frequency distribution of systematic set-up errors (solid line), measured in the patient specific group of Fig. 1b. The mean of this distribution is indicated by the vertical line, which is displaced by some amount from 0, the SD equals  $\Sigma$ .

However, geometrical errors components can be measured in a group of previously treated similar patients, and described using standard deviations (Figure 2 a, b). Once the typical values for specific group of patient are known they can be used to establish institutional correction protocols and included in the treatment planning in order to define planning target volume (PTV) (2).

### ELECTRONIC PORTAL IMAGING DEVICE (EPID)

In recent years, EPIDs have a wide clinical use for detection and management of geometrical errors during radiotherapy treatment. The EPID is attached to the LINAC gantry and it may intercept the exiting photon beams at all gantry angles. EPID uses a fluorescent screen to convert the high-energy photons of the treatment beam into visible light. The light is captured by a CCD camera or amorphous silicon flat panel detector and the ensuing images are

processed and analysed by dedicated software (Figure 3).



**Figure 3.** External beam radiotherapy configuration with EPID

The first generation of camera-based EPIDs had a number of limitations mostly related to image quality while the current commercially available take advantage of flat panel display technology, providing faster acquisition and superior image quality. In combination with a modern digital accelerator fitted with multileaf collimator, field set-up and image acquisition can be done remotely and displayed in seconds, obviating the need to re-enter the treatment room each time. This allows more frequent treatment verification, or to acquire a series of images during a single treatment for patient movement estimation. Another powerful feature is that the images are in digital form, which allows application of software tools for processing to extract information relevant to treatment verification and their managing by picture archiving and communication systems (PACS) specially designed for radiotherapy.

EPID is a primary tool for quality assurance in radiation delivery. To verify patient positioning the portal image of the first treatment is compared with the corresponding reference image which can be digitised simulator image, but the digitally reconstructed radiography (DRR), image generated by treatment planning system from the CT data set is most often used for this purpose. Various algorithms have been developed to enable computerized comparison of images for detection of field placement errors. This is usually accomplished in several steps:

1. Information about the position of the patient anatomy (bony structures) and radiation field is extracted from both portal and reference images.
2. A common reference frame for both images is established by registration of the radiation fields.
3. Set-up error is determined by registering the patient anatomy in both images, then measuring the resulting displacement between the portal and reference radiation field edges.

Three most common methods of interactive, or manual, image registrations are:

1. The drawing curves technique ("template technique"): by tracking the outlines of bony landmarks on DRR, same pattern automatically appears on portal image. If the referent and portal curves are misaligned in relation to the same bony landmarks, it indicates the patient set-up misalignment, which can be corrected according to calculation of deviation.
2. Point pair registration: by digitising the point over the recognizable bony landmark in the reference image and identifying the relations between corresponding point position and bony landmark in portal image - if necessary, deviation calculation and set up correction are possible.
3. Automatic (software) reference and portal image matching: reference and port image are automatically overlapped and in case of any apparent shift in the images position, the patient misalignment is indicated.

To define the positioning (and set up error) in all three planes it is necessary to provide two sets of reference-portal images. Images with  $0^\circ$  or  $180^\circ$  gantry angle provide positioning information in the lateral and longitudinal axes, while these with  $90^\circ$  or  $270^\circ$  gantry angle provide positioning information in the longitudinal and vertical axes.

Portal images are part of the overall quality assurance program for ongoing verification of treatment accuracy. They can reveal errors in the patient set-up position, field size and orientation or placement and shaping of MLC (or shielding blocks). Portal images should be estimated; discrepancies should be investigated and corrected according to clinical criteria and established protocols and finally approved and signed (electronically via radiotherapy PACS).

In recent years, a number of patient position monitoring systems have been developed. Some of them use one or more image detectors together in combination with diagnostic x-ray sources in the treatment room. Diagnostic quality radiographs facilitate automatic image registration and beam alignment just before treatment or in real time during treatment (3). By the newest systems, it is also possible to obtain kilovoltage or megavoltage quality 3D treatment image set through cone beam image reconstruction. The source-detector pair moves around the patient to collect a set of 2D projection images, which are then processed with a cone-beam reconstruction algorithm to obtain a 3-D image set. After software matching with the 3D plan corresponding volumes, it is possible to apply fully 3D set-off calculation and on-line set-up correction.

Except to set-up verification and correction procedures, EPIs can be used in transit dosimetry. This application requires that the intensities measured in the EPI can be translated to the radiation dose impinging on the detector with a high accuracy. The resultant "portal dose images" can be used to verify the dose delivered to the patient (4).

EPI thus combine information on geometry and dosimetry during the actual treatment and therefore yield an ideal tool for quality assurance and improvement of treatment delivery, particularly in conformal radiotherapy, where the demands on the set-up accuracy are high and technique of dose delivery may involve complex dynamic processes.

#### **Correction of set-up errors - off line and on line correction protocols**

Total set-up error consists of systematic ( $\Sigma$  set-up) and random component ( $\sigma$  set-up).

Systematic set-up error is affected by two groups of sub errors -  $\Sigma$  prescription parameters transfer (combines many systematic errors at around the 1 mm level, which have been subdivided into imaging geometry, treatment planning system and treatment machine geometry errors) and  $\Sigma$  set-up (related for some differences regarding couch and immobilization device sag which may cause deformation of internal organs).

All parts of systematic error can be corrected by altering the patient set-up for an amount based upon portal images measurements. This enables these systematic errors to be controlled within defined tolerances. QA checks of all equipment involved in the treatment process should be made regularly to ensure  $\Sigma$  transfer is maintained within acceptable limits. Couch and immobilization equipment compatibility between simulation and treatment machines is also very important.

Random set-up error gives information about the variation for patient set-up on a day-to-day basis. It is therefore a good indicator for the ability of an individual technique to immobilize the patient in a reliably reproducible position. It will also be affected by treatment technique, staff experience, subjective interpretation of set-up instructions and reference marks. Random set-up deviations may be estimated by comparing portal images against a DRR reference image. Unless immediate (on-line) correction of daily set-up error is performed, the best way to reduce  $\sigma$  set-up is by improving immobilization and set-up reproducibility. EPI can be used as effective technique to measure and reduce set-up errors relative to the intended set-up geometry. There are two different approaches to calculate and correct set-up errors i.e., off-line and on-line.

In the on-line approach, an EPI is obtained using a small part of the fraction dose at the beginning of each fraction, the total amount of daily fraction set-up deviation is measured

and corrected immediately by adjusting the couch position (while the patient remains on the treatment couch), after which the remaining daily dose is delivered. In this way, the patient position is verified at each fraction so both, systematic and random set-up deviations can be reduced to negligible values (5-7). However, on-line correction procedures are too time-consuming to be routinely used in clinical practice.

In the off-line approach, measured deviations are not used to correct the set-up immediately but instead the systematic error is calculated from EPI-s of various fractions and the mean systematic error level is used for correction in subsequent fraction according to the criteria of department/technique correction protocol (5-7).

The most effective way to reduce large systematic set-up errors for individual patients is to take portal images and compare them, between fractions, with the DRR as a reference image, during the first few fractions. Using off-line approach significant systematic error may then be corrected for subsequent irradiations by couch resetting (7-10). Apparently, the off-line corrections reduce only systematic deviations while random deviations remain unchanged as correction procedure is applied after examined fraction, so they cannot affect to daily variation designated by random error ( $\sigma$ ).

By imaging several patients of a specific patient group regularly, the typical size of the systematic and the random positioning deviations for that group can be determined, which may be the base for establishing the specific correction protocol in order to improve specific set-up techniques by using a suitable correction strategy (11,12). As a result of this measuring, a suitable "action level" can be defined. Set-up errors exceeding this action level may then be regarded as not occurring by chance and so regarded as systematic. Ideally, all departments should perform an analysis of set-up geometrical uncertainties in order to establish baselines and determine if any significant systematic set-up error exist. If it is not possible to apply correction procedure on the protocol base then the data from the literature could be used as a guide and a strategy for reducing set-up errors. As it is difficult to correct a total set-up error precisely when a random set-up component is dominant, the effectiveness of off-line strategies decreases as the ratio  $\sigma$  set-up /  $\Sigma$  set-up increases.

Example of possible correction protocol for radiation of abdominal tumours:

- Acceptable initial deviation = 10 mm.
- Apply correction after first fraction if set-up error exceeds 10 mm.
- Apply correction after second fraction if average error of first and second fraction exceeds 8 mm.
- Restart procedure after correction.
- Weekly imaging after second uncorrected fraction.

#### **Correction of organ movement related errors**

According to International Commission for Radiation Units and Measurements (ICRU) Report-50 and ICRU Report-62 recommendations, tumour volume is defined as gross tumour volume (GTV) - visible tumour on available images, and clinical tumour volume (CTV) - tumour microextension volume. Around CTV additional margin should be added for PTV delineation, which accounts for geometrical uncertainties related to treatment preparing and execution procedures and guarantee adequate dose coverage of CTV during treatment (13, 14). It should therefore be based on knowledge of interfraction and intrafraction target movement within the patient and with respect to treatment fields, and machine geometry.

These movements cannot be predicted and assessed directly by portal imaging since the tumour is generally not visible. By implantation of radio-opaque markers in or near CTV the internal organ motion can be visualized, which enables estimation of movement (15,16) and on-line positioning correction. Also, repeated CT scans could be acquired to get information of internal organ motion (17).

ICRU-62 recommendations divide CTV - PTV margin in two parts, i.e. internal margin (IM - covers the magnitude of internal organ motion) and set-up margin (SM - covers the magnitude of set-up variations) (14). However, the ICRU reports do not give a clear recommendation how the CTV-PTV margin should be chosen. These reports do not recommend to "adding all uncertainties linearly" but a root sum of squares of external (set-up) and internal (organ motion) errors is suggested. Therefore, the effect of these two errors (of similar size and direction) to CTV should be equal. Even the need for compromising the CTV- PTV margin according the estimated risk of local control failure and unacceptable level of side effects is emphasized.

Strom et al. (18) have derived a general calculation method based on the dose coverage probability of CTV to derive a 3D margin from known set-up errors and errors related to internal organ movements. They found that a clear distinction should be made between systematic and random component of these errors. If we exclude the technical condition related errors, the total geometrical error is influenced by total internal movement error (sum of  $\Sigma$  int. move. and  $\sigma$  int. move.) and total set-up (external) error (sum of  $\Sigma$  ext. and  $\sigma$  ext). For a Gaussian error distributions, with a standard deviation (SD)  $\Sigma$  for the systematic errors and  $\sigma$  for the random errors, a CTV-to PTV margin of  $2 \Sigma_{tot.} + 0.7 \sigma_{tot.}$  seems appropriate to guarantee that, on average, 99% of the CTV receives at least 95% of the prescribed dose (if the 95% isodose contour encompasses the PTV in the treatment planning). These results confirm that systematic deviations are more important than random deviations in establishing planning margins and that planning margins can predominantly be reduced through reduction of systematic errors.

Results of applying described mathematical model for three tumour localization show that the delineated CTV contour for lung carcinoma should be expanded with a 6-9 mm margin to cover internal and external systematic deviation while the random deviations require an additional 3-5 mm margin for the final PTV and the total margin becomes 10-13 mm. For prostate carcinoma the random deviations add only an extra 1-2 mm and total CTV - PTV margin should be anisotropic, varying from minimally 6 mm in the caudal to maximally 13 mm in the cranial region due to significant rotation around the apex of prostate.

Comparing with prostate cancer patients, external set-up deviations play a major role in the group of cervix cancer patients. Also, the internal organ movements are relatively small considering the involved anatomy. CTV - PTV margin due to systematic deviations varies from 6-9 mm (mainly caused by the external deviations) and taking account for random deviations, final PTV margin should be about 1 cm width (18).

As part of CTV - PTV margin depends of set-up deviations; its width is not unique for all institutions regarding the differences of positioning methods, applied treatment techniques and QA standards. Specific group set-up errors and used margins reported in the literature are only an indication but cannot be simply translated into daily practice for one's own practice. It is therefore advisable to use the data from institutional protocol for reduction of set-up deviations, combine them with specific organ movement examination data from literature (or to do own examination) and make own propositions to defining CTV-PTV margin and its possible reduction (19,20).

The reducing of both set-up and organ motion errors, on an individual basis is possible only if concerned organ is visible (fiducial marks implantation) applying on line portal imaging correction strategy. By taking an image at the start of each treatment, stopping and analysing the image, and correcting for any measured error, it is possible to reduce both random and systematic set-up and interfraction organ motion error. This process could be useful for sophisticated radiotherapy technique, like IMRT but for standard conformal techniques it is too much time consuming procedure.

Due to breathing and cardiac motion, a tumour in thorax and abdomen can vary significantly in position over a short time so intra-fraction movement of the tumour should be added to the random movement deviation. By good CT imaging protocol it is possible to reduce the influence of organ motion to some degree.

Complex techniques like real-time couch movement, respiration gated irradiation or breathing control might limit the consequences of this variation (21).

Relatively simple way to affect to some organs movement is control of physiology habits and adjusting them to the treatment timing (urine and stool passing).

### **Reduction of organs delineation errors**

In the preparing procedures for RT treatment (positioning and immobilisation, imaging, 3D-planning) the most critical steps are the precise delineation of the clinical target volume (CTV) from available imaging data and definition of the planning target volume (PTV) by adding the margin around CTV.

ICRU-50 and ICRU-62 Reports provide guidelines for the consistent defining of target and normal tissue volumes and a framework for the incorporation of geometric uncertainties into planning process (13,14). ICRU-62 refined the definitions of these original concepts to take into account the consequences of the advances made in 3D planning, and the fact that modern imaging procedures provide even more information on the location, shape and limits of the tumour/target volumes, as well as the normal tissue.

Delineation of CTV is based on physician clinical experience because current imaging techniques cannot be used to detect subclinical tumour involvement directly. Although CT is the principal source of imaging data for 3D planning there is a growing demand to incorporate the complementary information available from multimodality imaging (CT, MRI, PET) in structure contouring and treatment planning process.

GTV and CTV are anatomic-clinical concepts that should be defined before a choice of treatment modality and technique is made.

Contouring CTV, the physician must consider not only the microextensions around the GTV, but the natural paths of tumour spread including lymph nodes, perivascular and perineural extension.

Error in target volume delineation occurs only once and may be the biggest one in the whole radiotherapy procedures chain. It describes the systematic error introduced between the defined and "true" CTV ( $\Sigma$  doctor). Once defined this error is fixed throughout the treatment and cannot be corrected unless the CTV is redefined (22). This potential error must therefore be incorporated into CTV-PTV margin.

Organ delineation error may be measured by multi-observer studies and reduced by clear protocols, multimodality imaging, training and multidisciplinary consultations (23, 24).

Image based cross-sectional anatomy training should become an essential component in radiation oncology training programs as the radiation oncologist needs to become much more familiar with image reconstruction of normal tissue anatomy and paths of tumour spread to be accurately define GTV and CTV.

One of the important ways for minimizing these errors could be the standardization of nomenclature and methodology for defining the volume of known tumour, suspected microscopic spread, and marginal volumes, all of which should be taken into account for set-up variations and organ and patient motion, as published in the ICRU reports.

### **CONCLUSION**

- The maintenance of technical condition related errors within known and acceptable limits must be ensured by regular applying of QA procedures for all equipment involved in the radiotherapy procedures chain.

- Total geometrical error is built up of many smaller errors, which are presented by sys-

tematic and random component (deviation). Measured for specific patient group the typical size of the systematic and the random deviations can be predicted and used for correction strategy.

- Systematic errors introduced by target volume delineation, organ motion, and set-up errors should be reduced by clear delineation protocols, multimodality imaging, correct CT scan procedures, and by the application of electronic portal imaging with decision rules (protocols).

- It is difficult to correct the total set-up error when its random component is dominant. Proper immobilization technique and staff experience can substantially affect to reduce this error.

- CTV-PTV margin can be reduced predominantly through reduction of systematic errors magnitude, as it is more important than random component.

- Reduction of organ motion is possible to some degree by proper CT scan protocols, applying movements reducing and gated treatment and adjusting the some physiology activities to treatment timing.

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