INTERDEPARTMENTAL PROGRAMME OF POSTGRADUATE STUDIES IN MEDICAL PHYSICS

Assessment of errors and quantification of the required Planning Target Volume margins for Image Guided Radiation Therapy: a study of three major Greek hospitals

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ΣΠΟΥΔΩΝ ΣΤΗΝ ΙΑΤΡΙΚΗ ΦΥΣΙΚΗ

Εκτίμηση σφαλμάτων και ποσοτικοποίηση των απαιτούμενων
περιθωρίων ασφαλείας για τον όγκο-στόχο σχεδιασμού
θεραπείας στην απεικονιστικά καθοδηγούμενη ακτινοθεραπεία:
μελέτη σε τρία μεγάλα ελληνικά νοσοκομεία

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Abstract

The treatment process of external beam radiation therapy of tumors inevitably introduces geometrical uncertainties. These errors might be introduced during the preparation phase of the treatment (systematic errors), or during the execution of the treatment (random errors). Investigating the errors and assessing their magnitude is a prerequisite for the quantification of the required margin by which the Clinical Target Volume (CTV) must be expanded in order for the Planning Target Volume (PTV) to be acquired.

In this thesis, the required PTV margins were calculated for the radiotherapy departments of three major Greek hospitals: the University Hospital of Patras, the University Hospital of Larissa and the Theageneio Anticancer Hospital of Thessaloniki. Specifically, the protocols followed by each department were studied and reviewed, the sources of all geometrical uncertainties throughout the course of radiotherapy were investigated, the errors were calculated, the required PTV margins were quantified per anatomical site for each hospital and a comparison of the results between the departments was made.

In total, data from 278 patients and 2094 CBCT scans were recorded, studied and reviewed. Four different methods of statistical processing of the data were suggested for the computation of the setup error, with two of them being introduced by this thesis as the most representative for departments that follow a hybrid correction strategy protocol. Moreover, a simple and practical method for the assessment of organ motion was introduced and suggested, using the vendor image registration software available in our departments. Also, the delineation error of several anatomical sites was found, on the basis of a delineation experiment conducted in the departments of Patras and Larissa with the participation of the physicians. Finally, a comparison of the results between the three departments allowed for the extraction of useful conclusions regarding the operation of each department, as well as for the formulation of suggestions regarding protocol optimization in order to succeed the limitation of errors and the reduction of the required PTV margins.
Περίληψη

Η ακτινοθεραπεία με εξωτερική δέσμη φωτονίων αναπόφευκτα εισάγει σφάλματα στη διαδικασία της θεραπείας. Τα σφάλματα αυτά μπορεί να εισάγονται κατά τη διάρκεια της προετοιμασίας της θεραπείας (συστηματικά), ή κατά τη διάρκεια της εκτέλεσης της θεραπείας (τυχαία). Η διερεύνηση των σφαλμάτων και η εκτίμηση του μεγέθους τους αποτελεί απαραίτητη προϋπόθεση για την ποσοτικοποίηση του απαιτούμενου περιθωρίου κατά το οποίο πρέπει να επεκταθεί το Clinical Target Volume (CTV) ώστε να προκύψει το Planning Target Volume (PTV).

Στην παρούσα εργασία υπολογίστηκαν τα απαραίτητα PTV περιθώρια για τα ακτινοθεραπευτικά τμήματα τριών μεγάλων δημόσιων νοσοκομείων: του Πανεπιστημιακού Γενικού Νοσοκομείου Πάτρας, του Πανεπιστημιακό Γενικού Νοσοκομείου Λάρισας και του Θεαγένειου Αντικαρκινικού Νοσοκομείου Θεσσαλονίκης. Πιο συγκεκριμένα, μελετήθηκαν τα πρωτόκολλα που ακολουθούνταν, επιχειρήθηκε ο προσδιορισμός των πηγών σφαλμάτων, πραγματοποιήθηκε ο υπολογισμός τους, έγινε η ποσοτικοποίηση του απαιτούμενου PTV περιθωρίου για κάθε ανατομική περιοχή ανά νοσοκομείο και ακολούθησε η σύγκριση των αποτελεσμάτων μεταξύ των τμημάτων.

Συνολικά καταγράφηκαν, μελετήθηκαν και αξιολογήθηκαν δεδομένα από 278 ασθενείς και 2094 CBCT απεικονίσεις. Προτάθηκαν τέσσερις διαφορετικές μέθοδοι στατιστικής επεξεργασίας των δεδομένων για τον υπολογισμό του σφάλματος τοποθέτησης, με τις δύο από αυτές να εισάγονται για πρώτη φορά από την παρούσα εργασία ως οι πλέον αντιπροσωπευτικές για τιμήματα που ακολουθούν υβριδικές στρατηγικές διόρθωσης σφαλμάτων. Επιπρόσθετα, εισήχθη και προτάθηκε μια απλή και πρακτική μέθοδος εκτίμησης της εσωτερικής κίνησης του προς ακτινοβόληση στόχου με τη χρήση των επιλογών που παρέχει το εμπορικό πρόγραμμα που χρησιμοποιούν τα τμήματα (XVI). Επίσης, υπολογίστηκε το σφάλμα καθορισμού στόχου (delineation error) για διάφορες ανατομικές περιοχές για τα τμήματα της Πάτρας και της Λάρισας, στη βάση πειράματος που διεξήχθη με τη συμμετοχή των γιατρών των τμημάτων. Τέλος, η σύγκριση των αποτελεσμάτων μεταξύ των τμημάτων επέτρεψε την εξαγωγή χρήσιμων συμπερασμάτων για την λειτουργία κάθε τμήματος, καθώς και τη διατύπωση προτάσεων για τη βελτιστοποίηση των πρωτοκόλλων και των περιορισμών των σφαλμάτων και των απαιτούμενων περιθωρίων.
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Abbreviations

3DCRT Three Dimensional Conformal Radiation Therapy
4D-CBCT Four Dimensional Cone Beam Computed Tomography
4DCT Four Dimensional Computed Tomography
AP Anterior-Posterior
ART Adaptive Radiation Therapy
CBCT Cone Beam Computed Tomography
CT Computed Tomography
CTV Clinical Target Volume
DRR Digitally Reconstructed Radiograph
DVH Dose Volume Histogram
EBRT External Beam Radiation Therapy
eNAL extended No Action Level
EORTC European Organization for Research and Treatment of Cancer
ESTRO European Society for Radiotherapy and Oncology
FOV Field of View
FROGG Faculty of Radiation Oncology Genito-Urinary Group - Australian and New Zealand Radiation Oncology Genito-Urinary Group
GTV Gross Tumor Volume
ICRU International Commission on Radiation Units and Measurements
IGRT Image Guided Radiation Therapy
IM Internal Margin
IMRT Intensity Modulated Radiation Therapy
ITV Internal Target Volume
IV Irradiated Volume
kV kilovolt
LINAC Linear Accelerator
LR Left-Right
MLC Multi Leaf Collimator
MRI Magnetic Resonance Imaging
MV Megavolt
NAL No Action Level
OAR Organ At Risk
PET Positron Emission Technology
PSA Prostate Specific Antigen
PTV Planning Target Volume
QA Quality Assurance
R&V System Record and Verify System
RADICALS Radiotherapy and Androgen Deprivation In Combination After Local Surgery
RT Radiation Therapy

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<th>Description</th>
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<tbody>
<tr>
<td>RTOG</td>
<td>Radiation Therapy Oncology Group</td>
</tr>
<tr>
<td>RTT</td>
<td>Radiation Therapy Technologist</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SI</td>
<td>Superior-Inferior</td>
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<tr>
<td>SM</td>
<td>Setup Margin</td>
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<tr>
<td>T+R</td>
<td>Translations and Rotations</td>
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<tr>
<td>TCP</td>
<td>Tumor Control Probability</td>
</tr>
<tr>
<td>TPS</td>
<td>Treatment Planning System</td>
</tr>
<tr>
<td>TV</td>
<td>Treated Volume</td>
</tr>
<tr>
<td>VMAT</td>
<td>Volumetric Modulated Arc Therapy</td>
</tr>
<tr>
<td>Σ</td>
<td>systematic error</td>
</tr>
<tr>
<td>σ</td>
<td>random error</td>
</tr>
<tr>
<td>Σ_d</td>
<td>systematic delineation error</td>
</tr>
<tr>
<td>Σ_m</td>
<td>systematic organ motion</td>
</tr>
<tr>
<td>σ_m</td>
<td>random organ motion</td>
</tr>
<tr>
<td>σ_p</td>
<td>standard deviation of the Gaussian penumbra</td>
</tr>
<tr>
<td>Σ_s</td>
<td>systematic setup error</td>
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1 Introduction

1.1 External Beam Radiation Therapy (EBRT)

External beam radiation therapy (EBRT) delivers ionizing radiation to a target (the tumour) within a patient from an external radiation source. This external source of radiation is usually a linear accelerator, although some Cobalt-60 machines that produce gamma rays are still in use, mainly in the developing world. The term “dose” or “absorbed dose” refers to a physical quantity relating to the amount of energy imparted by ionizing radiation to a small mass of matter. The unit of dose is the Gray (Gy), where 1 Gy is the absorption of 1 Joule of energy per 1 kg mass of matter. The goal of EBRT is to deliver a high dose of radiation to kill the cancer cells by destroying their DNA while sparing the surrounding normal healthy tissues. Malignant tumour cells specifically have been shown to be very sensitive to the adverse effects of ionizing radiation and are therefore preferentially killed over normal cells in the process.

A radiotherapy treatment regime is administered over several weeks and consists of many daily treatments where a fraction of the total dose is delivered. The dose is fractionated to allow normal cells in the path of the radiation beam time to recover from any repairable radiation induced DNA damage. Repair mechanisms are impaired in tumour cells. Thus, fractionation permits for a higher dose to be delivered to the tumour than is possible if the total dose was delivered in one treatment. Radiation doses are chosen specifically to kill the malignant tissue without exceeding the dose tolerances of surrounding normal tissue that will cause severe complications. The prescribed radiation dose also depends on many patient-specific factors such as whether radiation is the primary modality used to treat the cancer, if it is delivered in conjunction with surgery or chemotherapy, the stage of the disease and the baseline health of the patient.¹
1.1.1 Three dimensional Conformal Radiation Therapy (3DCRT)

Within the past years, the technology behind radiation therapy instrumentation has advanced tremendously in a short amount of time, leading to significant improvements in the accurate localization and treatment of disease. The invention of the Multileaf Collimator (MLC) revolutionized conventional field shaping permitting the fast and easy production of complex and irregular field shapes. An MLC is an extra collimation system at the distal portion of the treatment head consisting of several narrow abutting tungsten leaves. Each MLC leaf is motorized and individually controlled allowing the treatment fields to be shaped around the target itself. MLCs can contain anywhere from 60-120 leaf pairs of widths ranging from 1mm to 1cm depending on the linac design.

The birth of multi-leaf collimation along with the use of Computed Tomography (CT) in treatment planning gave rise to one of the most common treatment planning techniques used today, Three Dimensional Conformal Radiation Therapy (3DCRT). Prior to the invention of 3DCRT, treatment field shapes were limited to squares and rectangles which produce dose distributions with box shaped high dose region around the target. However, with the introduction of the MLC into the treatment head, high dose regions are now able to be shaped to conform to the target. Treatment planners use the CT data acquired in the simulation to conform the high dose region to the target in all three planes, hence the term “Three Dimensional Conformal Radiation Therapy”. This technique can drastically reduce the volume of normal tissue irradiated in comparison to the two dimensional conventional radiation therapy treatment techniques used prior. This has been, for example, extremely significant in lung radiotherapy and has lead to a reduction in adverse side effects from treatment, dose escalation and in turn better local disease control.

1.1.2 Intensity Modulated Radiation Therapy (IMRT)

Following the birth of 3DCRT, a new type of radiation therapy treatment technique was invented termed Intensity Modulated Radiation Therapy (IMRT). IMRT differs from 3DCRT as it modulates the photon fluence of the linac during a treatment as opposed to keeping it constant which occurs in conventional treatments. Photon fluence is defined as the number of photons incident on a small sphere, divided by its cross-sectional area and integrated over
time. Thus, IMRT employs radiation beams with non-uniform intensities to produce dose distributions more conformal than 3DCRT techniques. IMRT plans can be delivered by two different techniques employing multi-leaf collimators. In “step and shoot” IMRT, each treatment field is divided into multiple segments which are delivered individually. In “dynamic” or “sliding window” IMRT, the intensity modulation is achieved by moving the MLC leaves independently in and out of the field at varying speeds while the beam is on. In the vast majority of the cases, IMRT requires the implementation of an inverse treatment planning method in contrast to conventional “forward” planning. Inverse treatment planning requires the treatment planner to input the goals of the treatment in terms of the desired dose to the target and surrounding organs into a treatment planning program. Using an optimization engine, the treatment planning program then finds the optimal radiation beam intensity distributions which satisfy the user specified goals.

1.1.3 Volumetric Modulated Arc Therapy (VMAT)

Volumetric modulated arc therapy (VMAT) is a novel radiation technique, which can achieve highly conformal dose distributions with improved target volume coverage and sparing of normal tissues compared with conventional radiotherapy techniques. VMAT achieves dose distributions comparable to those achieved by IMRT techniques and it offers additional advantages, such as reduced treatment delivery time.

1.2 Review of the ICRU 50 and ICRU 62 Target Volumes

In 1993, the International Commission on Radiation Units and Measurements (ICRU) issued report number 50 (ICRU-50), entitled “Prescribing, Recording, and Reporting Photon Beam Therapy”. This was followed by report number 62 (ICRU-62) as a supplement to ICRU-50 in 1999. The goal of these reports is to ensure consistency in specifying and reporting radiation doses in radiation therapy to provide meaningful data for assessing the results of treatments. Thus, the ICRU-50 and ICRU-62 reports instill a worldwide standard for radiation therapy treatments. They provide guidelines to promote the use of a common language for specifying and reporting the doses in radiation therapy, as well as the volumes in
which they are prescribed. The volumes which need to be identified prior to the construction of any radiotherapy treatment plan according to ICRU-50 are depicted in Figure 1.1. Those volumes are defined to ensure that the entire tumour receives a high and uniform dose while sparing dose to the surrounding normal tissue.

The first crucial target volume to be defined is the “Gross Tumour Volume” (GTV) which is described as “The gross palpable or visible/demonstrable extent and location of malignant growth”\(^6\). The GTV may consist of primary tumor, metastatic lymphadenopathy, or other metastases and corresponds usually to those parts of the malignant growth where the tumor cell density is largest. No GTV can be defined if the tumor has been removed, e.g., by previous surgery. In other words, the GTV is the visible primary tumour and any bulky disease that is observed. GTV volumes can be based on prior diagnostic and functional imaging such as CT, magnetic resonance imaging (MRI), positron emission tomography (PET) and ultrasound as well as pathology reports and clinical examination\(^1\).

The second target volume, termed the “Clinical Target Volume” (CTV), is defined as “the tissue volume that contains a demonstrable GTV and/or sub-clinical microscopic malignant disease, which has to be eliminated. This volume thus has to be treated adequately in order to achieve the aim of therapy, cure or palliation”\(^6\). The delineation of a CTV is based on purely anatomical-topographic and biological considerations without regard to movement of the tissues/patient or technical factors, and it should be described in anatomical-topographic terms. In practice, the delineation of a CTV will require consideration of factors such as the local invasive capacity of the tumor and its potential to spread to, e.g., regional lymph nodes. Consideration may also need to be given to the presence of any specially radiosensitive normal tissue as well as to other factors such as the general condition of the patient. Therefore, the CTV is created by adding a margin determined by the radiation oncologist to the GTV to account for any microscopic extension of the disease into the surrounding normal tissue. Thus, it is quite clear that the determination and delineation of the Clinical Target Volume is highly depended on the clinical view of the radiation therapist.

The final target volume for which the treatment plans are designed around is termed the “Planning Target Volume” (PTV). To ensure that all tissues included in the Clinical Target Volume receive the prescribed dose, one has, in principle, to plan to irradiate a geometrically larger volume than the CTV. Ideally, the position, shape, and size of the CTV and of the treatment beams should be related to a common fixed coordinate system in a reproducible way. However, in practice, this will not be possible to achieve, and intrafractional as well as
interfractional variations in this respect may be foreseen due to a number of factors such as movements of the tissues which contain the CTV (e.g., with respiration), as well as movements of the patient, variations in size and shape of the tissues that contain the CTV (e.g., different fillings of the bladder), variations in beam geometry characteristics (e.g., beam sizes, beam directions). Therefore, a margin has to be added to the CTV to account for such uncertainties. It is important to clarify that the Planning Target Volume is a geometrical concept, and it is defined to select appropriate beam sizes and beam arrangements, taking into consideration the net effect of all the possible geometrical variations, in order to ensure that the prescribed dose is actually absorbed in the CTV.

Furthermore, the ICRU requires every “Organ at Risk” (OAR) to be delineated and identified for every treatment plan. OARs are defined as surrounding organs that possess sensitivities to radiation that may significantly influence the prescribed dose and treatment planning. Specific organs have dose tolerances in which serious complications will occur if they are exceeded. These tolerances were initially based on the 1991 report by Emami et al. This report provides partial volume irradiation tolerances for several organs based on an extensive literature search and opinions of experienced clinicians.

In order to report doses in a way that is consistent amongst cancer centers, a clearly defined point within the patient must be established to specify where the dose is prescribed to. The dose at this point termed the “ICRU Reference Point” should always be reported as well as the maximum and minimum doses in the PTV. The ICRU Reference Point is recommended to be placed in the central part of the PTV at the intersection of the beams and must be representative of the dose distribution throughout the PTV. Its location should be in an area where accurate dose calculation is achievable therefore excluding the build-up region and areas of steep dose gradients.

Additional definitions in reporting dose include the Treated Volume (TV), Irradiated Volume (IR), maximum dose, minimum dose and hot spots. The Treated Volume refers to a volume of tissue surrounded by a specified isodose value pertinent to achieve the treatment goal whereas the Irradiated Volume refers to the volume of tissue receiving a dose significant compared to the normal tissue tolerance. The terms maximum dose and hot spots are often mistakenly used interchangeably as both require a minimum diameter of 15 mm to be clinically relevant according to the ICRU. However, the term maximum dose refers to the highest dose within the PTV and hot spots refer to areas outside the PTV. The ICRU definition of minimum dose has no volume restriction and refers to the lowest dose inside the
PTV volume. According to the ICRU, in order for a treatment plan to be acceptable, it must be reproducible, the highest dose must be located within the target volume, the lowest dose must be located outside the target volume and the dose to organs at risk must be kept to a minimum and below tolerance. The dose within the PTV must be uniform to within -5% to +7% of the dose prescribed at the ICRU reference point. Therefore, it is crucial that the PTV receive no less than 95% of the prescribed dose in order for the plan to be clinically acceptable.6

**Figure 1.1: Definition of volumes according to ICRU-50**

The supplementary report number 62 (ICRU-62) inserted three additional target volumes in order to better describe the Planning Target Volume: Internal Margin (IM), Internal Target Volume (ITV) and Setup Margin (SM).

Internal Margin (IM) represents a margin that must be added to the CTV to compensate for all movements and all variations in site, size, and shape of the organs and tissues contained in or adjacent to the CTV during therapy in relation to an Internal Reference Point and its corresponding Coordinate System. These internal variations are basically physiological ones (respiration, different fillings of the bladder, different fillings of the rectum, swallowing, heartbeat or movements of the bowel) and they result in changes in site, size, and shape of the
CTV. The combination of the CTV and the IM creates a sub-volume called the Internal Target Volume (ITV). The ITV accounts for the motion of the CTV within the patient and is related to the patient coordinate system, however it does not account for setup uncertainties. Finally a Setup Margin (SM) is added, which accounts for patient setup variations. These volumes are shown in Figure 1.2 illustrating three of the possible clinical scenarios (labeled A→C). The scenarios are explained briefly in the following text.

Scenario A describes the basic interaction between the volumes. The GTV is the gross, palpable tumour volume. The CTV is the GTV plus any suspected subclinical growth. An Internal Margin (IM) is added to compensate for potential changes in position and/or size and shape of the CTV relative to bony anatomy. A Setup Margin (SM) is added to compensate for potential variations/uncertainties in the patient position. The PTV equals CTV + IM + SM and should assure that the complete CTV always receives the prescription dose. Thus the PTV is defined in the Room Coordinate System and the CTV lie within this volume at all times during treatment.

Scenario B describes a slightly more complex situation, in which the Internal Margin (IM) varies with time, for example due to patient respiration, and sensitive normal tissue abutting (Organ At Risk illustrated as an inward-facing arrow). The presence of an OAR (e.g. spinal cord or rectal tissue) means that the conservative and linearly combined margins (IM and SM) in Scenario A may not be sufficient and smaller margins must be sought. In this case, the clinician would typically define a margin based on clinical experience.

Scenario C describes the situation where the OAR impinges to varying degrees on the PTV and CTV. Also, scenario C describes a circumstance where the internal and setup margins may be prescribed as a single “global” margin. In this case, recipes for defining the size of margin can be used.
To date, motion encompassing methods such as the use of ITVs is the most common form of respiratory motion management for lung cancer as they do not require extra resources and additional advanced equipment such as gating or tracking. However, it has also been shown that ITV margins are the largest and most conservative. Thus, they do not leave room for PTV margin reduction and dose escalation like some of the more labor intensive motion management options. An alternative approach to an ITV is to use a margin recipe which generates smaller but still effective PTV margins based on statistical models that limit how the dose distribution is affected by respiratory motion.

1.3 Errors and margins in radiotherapy

The treatment process of external beam radiotherapy of solid tumors inherently introduces geometrical uncertainties. The main sources of uncertainty are tumor delineation inaccuracies of the gross tumor volume (GTV) or the Clinical Target Volume (CTV), unknown extent of microscopic tumor, organ positional variation within the patient, and setup variations.
1.3.1 Errors in radiotherapy

High geometrical accuracy is a prerequisite for a safe clinical application of conformal radiotherapy. Several factors contribute to the overall treatment accuracy. In this thesis, the word “error” will be used to describe any deviation between planned and executed treatment, however small it is. Gross errors, which should be caught using quality assurance procedures, are outside the scope of this thesis. Usually, it is possible to reduce the magnitude of “small” errors at an increase of workload (e.g., by implementing online CBCT-guided radiotherapy). At present, one expands the CTV with a safety margin to obtain the planning target volume (PTV). The PTV is given a high dose to ensure that the CTV receives adequate dose despite “small” geometrical errors.

1.3.2 Classification of errors

Errors in radiation therapy can be classified according to the treatment phase during which they are introduced, but also according to their source of origin. Thus, they are fundamentally divided into systematic and random errors on the basis of the phase that they occur and into delineation errors, setup errors, organ motion, registration errors and other residual errors on the basis of the source that introduced them.

Random errors, also termed treatment execution errors are stochastic amongst patients and individual treatment fractions. Systematic errors, also termed treatment preparation errors, are stochastic amongst patients but are systematic for a single radiotherapy treatment regime for each patient. They can be due to imprecision in equipment or individual biases in the application of a procedure. Since these errors occur in the planning phase, they are propagated to the treatment phase and occur in an identical manner during each fraction for the entire duration of the treatment. Because they can affect the entire treatment course, systematic errors are the more important of the two types of geometrical uncertainties.

The effect of random and systematic errors on the dose is different. Random errors blur the dose distribution, whereas systematic errors cause a shift of the cumulative dose distribution relative to the target. The blurring can be described as a convolution of the dose distribution with the probability distribution function of the random error. This method is not completely correct but is quite accurate in practice. It was found that the error in convolution follows a Gaussian distribution with a width equal to the SD of the random
deviations divided by the square root of the number of fractions.\textsuperscript{13,19,20} The blurring effect of the random errors leads to small decrease of dose at the edge of the high-dose region that will moderately affect all patients. The systematic errors, on the other hand, lead to a shift of the dose that will strongly affect some patients (e.g., when the shift is such that the CTV moves outside the high-dose region).

\textit{Figure 1.3: Graphical presentation of systematic and random set-up errors of a group of five patients (by Korreman et al. 2010 )}

![Graphical presentation of systematic and random set-up errors](image)

\subsection{1.3.3 Delineation error}

Several geometrical uncertainties are involved in the delineation process of the GTV or the CTV (for postoperative treatments). First, the imaging modalities have a limited resolution, in particular perpendicular to the slice planes causing the partial volume effect.\textsuperscript{21} Then, there is observer “noise” (i.e., when the same observer is asked to delineate the target volume twice, the answer will not be the same - intraobserver variation).\textsuperscript{22,23} Interpretation differences between observers or image modalities are also important (interobserver variation).\textsuperscript{23-27} If different or unclear guidelines are used for target volume delineation, this will have a major impact on the consistency of delineated structures.\textsuperscript{28-30} Delineation uncertainty is a purely systematic error; it will influence all treatment fractions in an identical way through the treatment planning process. According to International Commission on Radiation Units and Measurements (ICRU) Report 50,\textsuperscript{6} the CTV is defined as the GTV plus the regions with suspected microscopic tumor. This CTV may be the GTV plus a margin or it may include nodal regions as well. For prostate cancer, a combination of clinical findings and other tumor
characteristics (like the prostate-specific antigen level and Gleason score) are used to estimate the probability of microscopic capsular invasion and involvement of the seminal vesicles.\textsuperscript{31-34} These estimations are based on pathology of resected prostates. A statistical atlas of tumor spread in the prostate was presented by Chen et al.\textsuperscript{35} Kestin and colleagues,\textsuperscript{36} among others, gathered statistics of tumor spread in the seminal vesicles. Also, for head and neck and non-small-cell lung cancer, surgical resection specimens have been analyzed to provide information on the probabilities of microscopic tumor deposits.\textsuperscript{37} Furthermore, for pathological high-risk prostate cancer adjuvant irradiation has shown a survival benefit,\textsuperscript{38} as well as in the salvage setting at prostate-specific antigen (PSA) relapse or when the PSA remains elevated after radical prostatectomy.\textsuperscript{39} However, for postoperative RT gross tumor volume (GTV) does not exist clearly in adjuvant setting and it can be hardly estimated, clinically or radiologically, for salvage purpose in condition of a rising PSA because it remains microscopic most of the time. Thus CTV definition is based on the pathological study of the prostate: size of the gland, seminal vesicle invasion, and location of positive margins.\textsuperscript{40} This volume corresponds to the prostate bed and the delineation of this “invisible target” remains a major challenge for radiation oncologists.\textsuperscript{41} The use of consensus guidelines, i.e. evidence-based contouring protocols that are based on phase III randomized studies, ensures less heterogeneity in contouring, thus leading to smaller interobserver delineation variations.\textsuperscript{42} Nowadays, in the literature exist numerous guidelines for postoperative external beam radiotherapy for prostate cancer focusing on CTV consensus guidelines using CT, such as the European Organization for Research and Treatment of Cancer (EORTC),\textsuperscript{43} the Australian and New Zealand Radiation Oncology Genito-Urinary Group [the Faculty of Radiation Oncology Genito-Urinary Group (FROGG- RANZCR)],\textsuperscript{44} the Princess Margaret Hospital (PMH),\textsuperscript{45} the Radiation Therapy Oncology Group (RTOG)\textsuperscript{46} and the Radiotherapy and Androgen Deprivation In Combination After Local Surgery (RADICALS) trial contouring protocol.\textsuperscript{47}

\section*{1.3.4 Setup error}

Numerous authors have presented data on setup accuracy.\textsuperscript{48-50} With careful immobilization or well-designed setup protocols,\textsuperscript{51-54} a setup accuracy for each axis of 2-mm SD or better can be achieved for prostate irradiation. For other treatment sites, such as the head and neck, smaller setup errors are achieved by routinely applying rigid immobilization.\textsuperscript{55} For the lung,
setup errors in the order of 2 to 4 mm have been reported.\textsuperscript{56} Setup error has both a random and a systematic component. The systematic component exists if a setup error occurs during the simulation process, which will offset the patient in the same manner during every fraction of treatment. In particular, motion of skin with respect to the internal anatomy limits the reproducibility of the patient setup on the computed tomography (CT) scanner, introducing a systematic setup error. Random variations in patient setup occur during treatment due to a variety of reasons that occur normally and are difficult to pin-point and remove. The patient position may not be reproduced exactly during each treatment due to co-morbidities or other situational differences.\textsuperscript{14}

Figure 1.4: Graphic representation of dose delivery on target
(a) Small systematic and small random errors; treatment both accurate and precise
(b) Large systematic and small random errors; treatment precise but not accurate
(c) Small systematic and large random errors; treatment accurate but not precise
(d) Large systematic and large random errors; treatment neither accurate nor precise

1.3.5 Organ motion
Another important source of uncertainty is organ motion.\textsuperscript{57-61} Organ motion causes both systematic and random errors. Respiratory and/or peristaltic motion introduces a systematic error because the treatment is planned with the target volume being in an arbitrary position. Also, the CTV position randomly varies due to respiratory and/or peristaltic motion. The motion of the prostate during treatment has been investigated by implanting markers and
measuring their position relative to the bony anatomy using portal imaging or under fluoroscopy. Alternatively, repeat CT scans have been used to study the movement of organs during the course of radiotherapy. van Herk et al. observed that a translation (mainly in the anterior-posterior direction) and a rotation (mainly around the left-right axis) could describe the combined motion of prostate and seminal vesicles. These results are in good agreement with findings of other authors. In the lung, in particular for lesions close to the diaphragm, tumor movement with 2- to 3-cm amplitude is possible. To precisely plan and treat lung tumors, it is therefore important to reduce this movement. Besides daily anatomical variation (interfraction organ motion), short-term motion also occurs during a single treatment fraction (intrafraction organ motion). This motion is notable, especially for long treatment sessions, and should be taken into account for the assessment of errors and the calculation of the required margins.

**1.3.6 Adding all the errors**

As seen from the tumor, there is almost no difference between organ motion, setup error and delineation error. All of these errors lead to a shift of the high dose region away from the CTV and these errors should therefore be treated equally. This means that for an individual patient, all these errors must be added linearly. In terms of SDs, this means that the SDs must be added in quadrature. There is, however, a marked difference between random and systematic errors if multiple fractions are delivered: All fractions are influenced the same by the systematic errors, whereas random errors will point in different directions for different fractions and this results, in general, in a much smaller dose effect of random errors than of systematic errors.

**1.3.7 Elimination of all errors**

One might consider that because of modern developments in image-guided radiotherapy, it is possible to eliminate all geometrical errors and it may become safe to reduce the margin to zero. However, it is probably impossible to completely eliminate all geometrical errors. For instance, even if the treatment is completely accurate, there will still be uncertainties in GTV and CTV definition. Then, online systems for image guided radiotherapy will not be perfectly accurate because of detection or observer errors in the imaging system. There will always be
registration errors in the software. In addition, there will always be some delay between imaging and treatment leading to uncertainties because of short-term organ movement. Furthermore, there will be limits on the accuracy of correction procedures. Finally, when using indirect methods for detection of the tumor position, there will still be the possibility of relative movement of the structure of reference and the tumor.

1.4 Incorporation of uncertainties into treatment planning: margins

According to ICRU Reports 50 and 62, setup and organ positional uncertainties should be incorporated into the treatment planning process by taking a margin around the CTV, thereby defining the PTV. How these margins should be defined as a function of the distribution of organ position and setup errors was not specified. In the Northern Association of Clinical Physics recommendation, separate margins were proposed for positioning uncertainty and for organ motion, called the setup margin and the internal margin, respectively. This concept of separate margins suggests that a linear separation of the internal errors (organ motion) and setup errors can be made. However, because external error sources and internal error sources are generally not correlated, a linear addition of their standard deviations is, in general, not correct.

Several margin recipes have been published, however, with little supporting data for the clinical impact of the given recipe and often ignoring preparation (systematic) errors. Austin-Seymour et al defined an anisotropic margin for setup and organ position errors by a cylindrical expansion of the CTV. By targeted interviews of physicians, it was found that recorded PTV margins corresponded to a nominal probability of 75%. Hunt et al showed that the required margin for random errors depends on treatment technique and field design. Bel et al showed, through simulation, that a margin for random deviations of 0.7 times their SD is adequate to keep a 95% dose coverage. This number of 0.7 depends on the particular beam arrangement. Aaltonen et al derived a margin for random errors of 0.5 to 0.7 times the SD based on biological modeling. The impact of preparation (systematic) errors was tested by computing DVHs for a few possible shifts, which confirmed that systematic errors are much more important than random errors. Extensive numerical simulations of prostate radiotherapy have been performed by Killoran et al. 
These authors introduced the concept of probability of prescription dose, which can be described for each part of the anatomy. The beam margin was iterated to ensure coverage up to a given dose for a given fraction of the patient population. Fontenla et al\cite{80} described a method to include the target shape into a quantitative optimization process to derive treatment margins explicitly accounting for uncertainties in the position of target and organs at risk. A number of groups\cite{73,81,82} explored the use of coverage probability matrices to derive margins. With this method, it is easy to include rotations and the CTV shape of individual patients. In addition, coverage probabilities can be used to take organs at risk into account.\cite{82} Stroom et al\cite{81} provide the following margin recipe based on coverage probability. A margin should be used that is 2 times the total SD of systematic errors plus 0.7 times the total SD of random errors ($2\Sigma + 0.7\sigma$) to ensure that, on average, 99% of the target volume receives 95% of the prescribed dose or more. A fundamental problem of coverage probabilities is that they tend to undervalue sharp tumor extensions, which are smeared out to very low probability levels and will not be included in the margin. Craig et al\cite{73} described the relation between the geometrical measure of CTV coverage and tumor control probability (TCP) for random errors and some systematic errors. van Herk et al\cite{14} used the minimum cumulative CTV dose as a “gauge” for geometrical misses. Based on the dose population histograms as shown in Figure 1.3,\cite{11} they derived a margin recipe to guarantee that 90% of patients in the population receive a minimum cumulative CTV dose of at least 95% of the prescribed dose. This margin is approximately 2.5 times the total SD of systematic plus 0.7 times the total SD of random errors. Löf et al\cite{83} accounted for both measured and non-measured (random) positioning uncertainties using a planning algorithm based on a combination of dynamic and stochastic optimization techniques. Their formulation explicitly describes the dependence of the treatment outcome on the incident fluence distribution, the patient geometry, the radiobiological properties of the patient, and the fractionation schedule. However, they consider that all systematic errors are measurable and correctable.
Figure 1.5: Example of dose-population histograms for different margins (0, 6, and 12 mm) for the minimum in the total dose delivered to the CTV.\textsuperscript{11}

1.4.1 Adding all the margins

Although the SD of different geometrical errors should be added in quadrature, random and systematic often result in different margins, and how these should be added may not always be clear. The simplest situation is when the margin is defined as a probability level of the minimum dose. In that case, the PTV margin is generated using a first margin for systematic errors that ensures a certain percentage coverage, followed by adding a margin for random errors that ensures coverage of the first margin up to a given dose. However, such a linear addition of margins is not valid for margins based on probabilities and/or biological effects. When margins are defined based on probability levels, they should be added in quadrature because the margins represent the width of probability distributions.\textsuperscript{11}

1.4.2 Effect of respiration

Respiration motion during imaging has 2 effects.\textsuperscript{84} First, the image is blurred over the time and space corresponding to a single slice. Second, the image is distorted because of the relative speed of motion and scanning. If the scanning time is very short with respect to the respiration cycle, the tumor is imaged in an arbitrary respiration phase, leading to a systematic organ motion error. In practice, the image is distorted due to the interference of the scanning process and the respiration. The SD of the distortion is just given by the SD of the respiration motion, which is typically about one third of the peak-peak amplitude.\textsuperscript{13} Respiration motion during treatment causes an asymmetric deviation in the shape of the total dose distribution. It is important to mention that irrespective of the shape of the probability
distributions, SDs will add in quadrature. With a random error SD of 3 mm and respiration amplitude of 1 cm or less (SD < 0.36 cm), the asymmetry is negligible. For respiration motion in excess of 1 cm in amplitude, isodose lines shift in a distinctly asymmetric fashion and asymmetric margins need to be used. Applying a common margin recipe (2.5 SD of systematic errors plus 0.7 SD of random errors) to respiration motion only, the total margin that is required is about the peak-peak amplitude. This finding is not surprising because such a margin ensures that the periodic motion is always covered. However, it is a nice illustration of the validity of this common margin recipe that was derived for normally distributed errors, even in the case of an explicit non-normal distribution because of respiration. Due to the fact that respiration movements and movement of the beam in dynamic treatments are on the same time scale, there may be some interference between both variations leading to hot and cold spots delivered in a single fraction (interplay effect). Respiration motion with clinical relevant amplitude has a small impact on the dose compared with other errors that may occur in clinical practice. Note that in a study by van Herk et al a zero systematic error is assumed. In practice that means that a representative CT scan has to be available showing the tumor exactly in the average position. Methods to obtain representative CT scans are slow scanning, respiration correlated CT, or fast 4-dimensional magnetic resonance imaging. In a slow scanning method, the CT scanner is run slowly and/or multiple CT scans are averaged such that multiple respiration phases are recorded per slice. A disadvantage of slow CT scan methods is the loss of the resolution because of motion. It has been suggested that PET, which inherently performs slow scanning, is also a good solution to estimate the motion path of a tumor. The most promising solution to obtain high quality CT data in presence of respiration motion is respiration correlated CT. Here 4-dimensional data are acquired that can be analyzed to determine the mean tumor position (4DCT).

### 1.4.3 Comparison of margin recipes

As mentioned above, most published margin recipes ignore systematic errors or fail to differentiate between random and systematic errors. The published margin recipes that do differentiate between random and systematic errors can often be written as a linear combination of the SD of the random and the SD of the systematic errors (Table 1.1).
Table 1.1: Summary of Published Margin Recipes for Target, Respiration (Target) and Organs of Risk

Abbreviations: $\Sigma$, SD of systematic errors; $\sigma$, SD of random errors; $\sigma_p$, describes width of beam penumbra fitted to a Gauss function; $A$, peak-peak amplitude of respiration; M, margin before adjustment for described effect.

<table>
<thead>
<tr>
<th>Author</th>
<th>Application</th>
<th>Recipe</th>
<th>Assumptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bel et al, 1996\textsuperscript{76}</td>
<td>Target</td>
<td>0.7 $\sigma$</td>
<td>Random errors only (linear approximation) Monte Carlo</td>
</tr>
<tr>
<td>Antolak and Rosen, 1999\textsuperscript{95}</td>
<td>Target</td>
<td>1.65 $\sigma$</td>
<td>Random errors only, block margin</td>
</tr>
<tr>
<td>Stroom et al, 1999\textsuperscript{81}</td>
<td>Target</td>
<td>$2\Sigma + 0.7\sigma$</td>
<td>95% dose to on average 99% of CTV tested in realistic plans</td>
</tr>
<tr>
<td>Van Herk et al, 2000\textsuperscript{14}</td>
<td>Target</td>
<td>$2.5\Sigma + 0.7\sigma$ or (more correct): $2.5\Sigma + 1.64(\sigma - \sigma_p)$</td>
<td>Minimum dose to CTV is 95% for 90% of patients. Analytical solution for perfect conformation</td>
</tr>
<tr>
<td>McKenzie et al, 2000\textsuperscript{77}</td>
<td>Target</td>
<td>$2.5\Sigma + \beta(\sigma - \sigma_p)$</td>
<td>Extension of van Herk et al for fringe dose due to limited number of beams</td>
</tr>
<tr>
<td>Parker et al, 2002\textsuperscript{96}</td>
<td>Target</td>
<td>$\Sigma + \sqrt{\sigma^2 + \Sigma^2}$</td>
<td>95% minimum dose and 100% dose for 95% of volume. Probability levels not specified</td>
</tr>
<tr>
<td>Van Herk et al, 2002\textsuperscript{97}</td>
<td>Target</td>
<td>$2.5\Sigma + 0.7\sigma - 3\text{mm}$ or (more correct): $\sqrt{2.7^2\Sigma^2 + 1.6^2\sigma^2} - 2.8\text{mm}$</td>
<td>Monte Carlo based test of 1% TCP loss due to geometrical errors for prostate patients</td>
</tr>
</tbody>
</table>
| Van Herk et al, 2003\textsuperscript{98} | Target      | $M - 2\text{ mm}$  
$M - 5\text{ mm}$ | Correction for nonuniform cell density                                                          |
| Ten Haken et al, 1997\textsuperscript{99} and Engelsman et al, 2001\textsuperscript{100} | Respiration (liver and lung) | 0$A$ | No margin for respiration but compensation by dose escalation to iso-NTCP, reducing target dose homogeneity constraints |
| McKenzie et al 2000\textsuperscript{101} | Respiration  | $A$ | Margin for respiration on top of other margins when respiration dominates other errors         |
| van Herk et al, 2003\textsuperscript{13} | Respiration (lung) | $0.25A$ (caudally) 
$0.45A$ (cranially) | Margin for (random) respiration combined with 3 mm random SD, when respiration dominates other errors ($A>1\text{ cm}$) |
| McKenzie et al, 2002\textsuperscript{102} | OAR         | $1.3\Sigma \pm 0.5\sigma$ | Margins for small and/or serial organs at risk in low (+) or high (-) dose region             |
1.5 Image Guided Radiation Therapy (IGRT)

Over the past years, Image Guided Radiation Therapy has revolutionized the way Radiation Therapy is conducted. Typically, generous safety margins are applied around the target and optionally for organs at risk (OARs) such that under- and overtreatment caused by geometric uncertainties can be avoided with an acceptable probability.\textsuperscript{14} However, the dose delivered to these margins affects surrounding tissues such that to spare these tissues the achievable dose for the tumor is often compromised. The tremendous evolution of apparatus, software and techniques has offered the possibility to quantify and correct geometric uncertainties, thus applying tighter margins and achieving higher dose-gradients as with conventional RT and has shown to benefit patient outcomes\textsuperscript{103,104} These techniques aim at maximizing the dose to the target while minimizing the dose to the OARs. IGRT has increased the precision of the dose delivery by frequently imaging the target and/or healthy tissues just before treatment and acting on these images to adapt the treatment. There are several image-guidance options available. Crucial components of any image-guidance system are an image-acquisition system that provides soft-tissue contrast and/or adequate imaging of the used surrogate. The imaging system should be in a calibrated position and have a high speed of acquisition and reconstruction. Then, a reference dataset should be available, such as the planning CT with the contours of the target volumes. The user should have the ability to define a region of interest so that the target localization software, which consists of fast automatic image registration, knows which part of the image to focus on. Finally, there should be a method for correction (e.g., online or offline).

1.5.1 IGRT systems

All major research vendors have developed IGRT Systems using volumetric imaging. Clinical experience has been reported with megavoltage\textsuperscript{105,106} and kilovoltage\textsuperscript{107,108,109} CBCT systems and diagnostic CT scanners on rails.\textsuperscript{110,111} These systems focus on the acquisition of images with sufficient image quality for the clinical task at hand. In addition, several image-registration techniques have been developed to localize specific organs. Ultrasound image guidance and electronic portal imaging are older developments in IGRT. However, the 2-dimensional nature of these systems limits the information that can be gathered. Portal imaging is generally limited to bony anatomy, and it has been observed that the accuracy of the CBCT for bone localization by far exceeds that of planar imaging, especially for lung
treatments. Also, ultrasound imaging has been hampered with large observer errors. However, with the implementation of 3-dimensional ultrasound sensors for soft-tissue localization purposes, these errors will probably decrease. Nowadays, most of the radiation therapy departments worldwide use commercial IGRT systems, which consist of linear accelerators with an on board CBCT acquisition device and dedicated software for image registration and error corrections. The acquisition of multiple projection images, coupled with tomographic reconstruction methods enables the creation of 3D volumetric images termed Cone Beam CT (CBCT). Due to the large longitudinal Field of View (FOV) of the kV source, the projections can be acquired in a single gantry rotation and yields a pre-treatment CT dataset that can be compared with the planning CT data (reference CT). The ability to acquire volumetric images in the treatment room combined with the admirable improvement of the image registration algorithms over the few past years allows for a full three dimensional assessment of the target position with both bony structure and soft tissue visualization to provide the highest degree of treatment accuracy yet.

1.5.2 Proper IGRT preparation

Preparation for a correct IGRT is extremely crucial. This means that an advisable use of IGRT begins with a correct treatment plan, where high-quality image data that are representative for the patient in treatment position are provided (i.e. reference CT, plus any complementary imaging such as MR or PET). If available, 4D-CT should be acquired for thoracic malignancies to account for respiration motion, since respiratory correlated CT offers highly accurate determination of the mean position, the trajectory and the shape of the moving anatomy. Slow CT acquisition has also been proposed for departments that do not possess 4D-CT scanners, as it can depict the trajectory of the tumour due to image overlapping, although it may result to a poorer image quality.

Despite the difficulties mentioned above, tumor motion in the lung is mostly predictable; in prostate cancer, however, this is not the case. So it is essential when using a single-planning CT is to avoid that this CT is an outlier. This means that the scan needs to be redone when the rectum is distended and maybe when there is extreme or minimal bladder filling. Other reasons for redoing the planning CT could be a awkward patient setup that would be hard to reproduce during treatment or patient or gas motion during scanning. For improved target volume delineation, the scan can be fused with magnetic resonance imaging. For
many tumor sites, it is beneficial to apply a moderate amount of contrast to help in distinguishing normal vessels from tumor even though this might have some impact on dose computation.\textsuperscript{119} The bottom line is that adequate image information should be available to accurately delineate target volumes and normal structures. Even in optimal conditions, one should realize that interobserver variation is not negligible and may exceed by far the uncertainties in the rest of the treatment chain (i.e., the largest part of the margin will have to deal with this uncertainty).\textsuperscript{120} Furthermore, clinicians must have population statistics of the uncertainties available and, if required, also data on predictable patient-specific motion (e.g., amplitude in 3 directions of breathing motion from 4-dimensional CT)\textsuperscript{121,122}. Next to the so-called “stationary” errors, there may be time trends in the position and shape of the tumors that should be investigated.\textsuperscript{123-125}

1.5.3 Immobilization

Proper patient immobilization provides limitation of patient’s movement, reduces the probability of a geometrical miss and ensures that the patient remains on the correct therapeutic position throughout the whole treatment. Furthermore, it guaranties reproducibility, which plays a key role in the radiotherapy procedure.\textsuperscript{51,54,126} Nowadays numerous immobilization devices are available, which specialize depending on the anatomical region that is being treated. With the advent of the relatively new IGRT Systems, index immobilization has become very common. Index immobilization has the advantage of rigid, steadier immobilization compared to a non-index device, and can be easily achieved and reproduced. Such immobilizers are very simple and versatile to use and often provide additional settings, such as slope and length definition. Some institutions use vacuum bags that can take the form of the patient. These immobilization devices provide a custom and effective immobilization for each patient, having although the disadvantages that they can’t account for any body changes of the patient (weight gain or weight loss), some patients find them inconvenient, they usually occupy a lot of space, thus making storage difficult, and in some cases they can’t be reused. For head and neck cases, thermoplastic masks are the norm, since they provide immobility, stability and reproducibility.
1.6 Correction strategies

The first-generation IGRT systems typically only allow corrections through table shifts. For offline protocols, one needs a relative couch readout, allowing a programmed ad hoc couch shift after setup to reference marks. It is also possible to have non-permanent marks during the initial fractions and draw the permanent tattoo marks after the couch shift is implemented, in order to use the couch move assistant only once, thus reducing the workload. Rotations in setup error had generally been ignored in the early years of IGRT, because of the difficulty to estimate out-of-plane rotations from 2-dimensional images. With the advent of in-room volumetric systems, accurate measurement of rotational errors is straightforward and their correction was clearly a next step to improve the precision. Deformations of prostate and seminal vesicles during the course of RT are small relative to organ motion. Therefore, it is a valid approximation in IGRT of prostate cancer, in first order, to correct only for translations and rotations. Based on these results, methods for automatic localization of the prostate for online or offline IGRT have been developed using local automatic or semi-automatic rigid grey-value registration of CT scans. Tables that can tilt and roll are now available. For the patients’ comfort and safety, these tables are limited to rotations of a few degrees. This is generally enough to correct for rotations of the bony anatomy, even though it is important to have rigid immobilization because the patient will react to and potentially compensate for the rotation with a translation. Because such systems are limited to a few degrees rotation, they cannot deal with prostate rotations that can easily exceed 10°. Tilt-and-roll couches remain interesting for some stereotactic applications, even though the impact of rotational errors up to 3° (i.e., 1° standard deviation [SD]) are very limited for most tumors. So, rotating the patient is generally not a useful option. Therefore, it may be more suitable to adapt parameters, such as gantry and collimator angle of the treatment machine, which allow corrections of larger and, therefore, more relevant rotations such as of the prostate. Next to rotations, deformations and changes of the anatomy are important. Large deformations in cervix cancer were found for which rotational corrections would certainly not be enough. Also, considerable lung tumor shrinkage occurs, maybe in up to 40% of the patients. Several groups have developed methods to include knowledge of organ deformations. A full replan based on the modified geometry probably provides the most versatile correction method, though it is feasible to replan using knowledge of the accumulated dose. Online planning for single-fraction treatment is also an option.
1.6.1 Correction procedures: how to correct setup error or organ motion

There are 3 types of correction strategies:

a. offline corrections— reacting to the image, data are delayed to a subsequent fraction;
b. online corrections— a reaction is made immediately following imaging;
c. intrafraction corrections— multiple images and corrections are made per fraction.

A mixture of these 3 is also possible.\textsuperscript{139}

1.6.2 Offline correction strategies

The rationale for offline correction strategies is that margin requirements are dominantly determined by systematic errors and much less by random errors. Offline protocols aim to correct for the mean error of a patient without correcting daily variation. They allow a large step in margin reduction with limited workload.\textsuperscript{140} Statistical procedures to drive offline corrections have been addressed extensively from the field of electronic portal imaging. Early correction strategies were aimed at correcting systematic errors with minimal workload.\textsuperscript{141,142} More recently, a no-action level protocol has been proposed that requires less workload but that is, in its base form, less fail-safe.\textsuperscript{143,144} It has therefore later been expanded with extra measurements to improve safety\textsuperscript{145} or to correct time trends.\textsuperscript{146} Corrections based on maximum likelihood have been proposed as further improvement of these protocols.\textsuperscript{114,147} Based on biological modeling and physical considerations, the optimal number of imaging days in offline correction protocols was considered to be \textasciitilde10\% of all fractions.\textsuperscript{148,149}

1.6.3 Adaptive radiotherapy

Yan and coworkers\textsuperscript{150} extended the idea of off-line corrections to include organ motion. By combining the information of multiple CT scans obtained in the first week of treatment, a better representation can be made of the average position of internal anatomy, and margins can be tailored to individual patients (adaptive RT).\textsuperscript{150} They found that a single-plan modification within the second week of treatment improves the efficacy of dose delivery and dose escalation for RT of prostate cancer. The construction of the adapted target volume can
be done in different ways. Yan applied patient specific statistics to determine the margin size; the convex hull of the prostate on 4 CT scans was used to replan, and this hull will be bigger when the prostate moves more. Adaptive RT based on kilovoltage CBCT images has been also implemented.\textsuperscript{109,128} van Herk et al suggest the use of population statistics instead of adapting for the margin for individual patients, by deriving the mean prostate position and using a reduced margin. Analysis showed that the convex hull approach with a 4-mm margin (similar to Yan) and the mean prostate with a 7-mm margin are equally efficient in terms of normal tissue sparing and coverage.\textsuperscript{151} This is probably because of the fact that too few measurements are available to make a definitive statement about an individual patient’s statistic.\textsuperscript{152} This means that a patient-specific PTV derived from a few scans will be a poor estimate of the required margin. Because of the large uncertainty in the estimate of the SD, it is better to use a Kalman or Bayesian style approach\textsuperscript{153}. The adaptive RT approach is also feasible for bladder cancer irradiation, resulting in 40% reduction of the mean boost treatment volume.\textsuperscript{154} Because adaptive RT is an offline correction, it can correct complex errors (e.g., rotation/deformation) by simply replanning.

\section*{1.6.4 Online correction strategies}

The rationale for online corrections is that the workload of measurement and correction is reducing; it becomes feasible to perform corrections directly after imaging. Ghilezan and coworkers\textsuperscript{155} analyzed the potential for daily online IGRT for prostate cancer and found that, on average, a 13% dose escalation (ranging from 5%-41%) was possible. However, such an application requires that efficient correction strategies are available that go beyond a simple couch shift. An obvious advantage of online corrections is that both systematic and random errors are corrected efficiently. A disadvantage is that analysis and corrections must be fast, simple, and unambiguous, whereas the time pressure could affect the accuracy of the procedure. In addition, because of remaining uncertainties, the gain of online procedures must not be overestimated. Careful analysis showed that in prostate cancer online correction based on kilovoltage CBCT imaging could allow margins of 5 mm.\textsuperscript{128} Even though surrogates for prostate motion can be localized with a much higher accuracy, uncertainties such as the initial target volume delineation and later deformations will probably limit the accuracy to similar levels.\textsuperscript{139} One should also realize that more and more accurate delivery might expose limitations in the accuracy of the CTV definition. Therefore, margins of less
than 5 mm are considered unrealistic for most applications. Online planning using volumetric imaging data have been explored, specifically for application in the context of “simulate and treat” cases. The arguments for this development include more accurate target definition compared with radiographic methods (e.g., conventional simulator), reduced time spent in the department by the patient, and more conformal treatment volumes for the increasing practice of retreats in the palliative context. The challenges are numerous. Image quality, accurate CT numbers, and rapid segmentation, planning, quality assurance, and delivery all need to be addressed for this process to be feasible. Letourneau and coworkers have shown that this process can be completed in less than 30 minutes with appropriate streamlining of existing imaging, planning, and quality assurance tools.

1.6.5 Correction of intrafraction motion

The rationale for intrafraction correction is to correct even the last bit of motion. The conventional solution to correct for respiratory motion is to expand the PTV. Consequently, high dose is also delivered to adjacent structures. For prostate cancer, with online correction of both translations and rotations, a 4-mm margin was sufficient for 15 of 19 patients, whereas the remaining four patients had an underdosed CTV volume <1%. Margin reduction combined with online corrections resulted in a similar or lower dose to the rectum and bladder. The more advanced the correction strategy, the better the planned and accumulated dose agreed. For lung cancer, if the time-averaged tumor position is accurately known (i.e. there are no systematic errors) the required margin for respiration is relatively small. Methods that lead to a further margin reduction are gated RT, breath-hold techniques, and tumor tracking. For unpredictable motion, such techniques add safety, whereas for predictable motion it removes the dose blurring effect of the motion. Also, changes in anatomy and respiratory pattern occur that need to be monitored and corrected. For this reason, CBCT-guided linear accelerators have been developed that acquire regular (3-dimensional) or respiratory correlated (4-dimensional) CBCT just before treatment. Especially for hypofractionation, online verification and correction of tumor position is extremely important and CBCT provides soft-tissue localization without implanting markers. However, 3-dimensional CBCT of lung has a poor quality when respiratory motion is large, therefore daily respiration correlated (4-dimensional) CBCT acquisition is necessary. With this IGRT technique typically margins in the order of 7
mm are required that account for delineation uncertainty and some intrafraction motion of the patient. Respiratory motion has a very limited impact on the margin requirement because of the shallow penumbra in lung tissue and because the dose prescription at 70 or 80% of the nominal dose.\textsuperscript{13,166}
2 Materials and methods

2.1 Radiation therapy treatment chain

Major hospitals as ours follow specific protocols to ensure the provision of qualitative health services and the safety of both patients and staff. The incorporation of the protocols into an effective workflow is crucial for each department’s proper operation. In radiation therapy the sequence of tasks that must be performed by the department’s staff is usually referred as the “Radiation Therapy Treatment Chain” and usually includes scientific medical and paramedical staff from many disciplines.

2.1.1 University Hospital of Patras

*Figure 2.1: Schematic representation of the Radiation Therapy Treatment Chain*

![Schematic representation of the Radiation Therapy Treatment Chain](image)

Target localization is performed by the physicians, with the aid of radiation physicists, in simulation room. Initially, index immobilization devices are set on SIMULIX table, just as they will be in the treatment room. Although there is a consensus between the physicians of the department regarding the immobilizers to be used for each anatomical region, radiation oncologists take the final call on which immobilization devices will be used for each particular patient, based on the clinical situation of the patient. Once the patient is placed on the table, it is of major importance to achieve and establish a clinically correct, yet
comfortable and repeatable position, which will be adopted throughout the whole therapy. The positioning of the patient is done in such a manner, that the anatomical region of interest is roughly inside the FOV of an approximately 20 x 20 cm field. Then, a planar image is captured to verify that this positioning is representative for the anatomical region of interest. Lasers are turned on and one mark is drawn with a black marker on each laser point. This results usually in 3 marks on the reference plane, one ventrally and two lateral – one on each side. Rarely, an extra mark is drawn along the sagittal laser to ensure the alignment of the patient.

Imaging is performed at the radiological unit, where a diagnostic CT-scanner has been equipped with an indexed flat couch in order to serve the purposes of the radiotherapy department. The scanner has been modified to simulate as best as possible the treatment table. After the positioning of the patient, with the immobilization devices being also set on the table, small ball bearing balls (BBs) are placed on top of the 3 marks on the reference plane. The scan is made with specific settings in order to meet the requirements of the MONACO Treatment Planning System (e.g., slice thickness) and there are already customized imaging protocols created by the medical physicists (i.e. lung, pelvis, brain etc). For example, for lung cases a “slow CT” acquisition protocol is being used. Finally, the images are sent to MONACO via the hospital PACS. This will be the reference-CT for treatment planning.

Treatment planning is performed in MONACO treatment planning system. One of the CT axial slices (reference plane) contains the three BBs. This is the scan reference point. A physicist outlines the external contour and as many organs as possible and a doctor draws the target volumes (GTV if there is one, CTV, PTV) and the OARs. Target delineation is performed on the basis of RTOG report guidelines and other international consensuses (e.g. RADICALS trial report, EORTC, ESTRO courses), depending on physician’s clinical judgment. Most often, the isocenter of the fields is set by the planner as the geometric center of the PTV and is the setup reference point and it also serves as a dose reference point for dosimetric purposes. MONACO calculates the 3D distance between these two points – scan reference point and setup reference point- and then derives a 3D vector to go from the first to the latter. This vector is translated into 3 distances, one along each axis, which is ultimately the shift that needs to be made later during the procedure of simulation in the SIMULIX Room or in the treatment room. When a boost field is prescribed, PTVboost shares the same reference point with the large PTV, so the beam isocenter remains the same, which means that the dose reference point is still the same. Thus, no further distances have to be calculated.
Simulation is performed in simulation room. The patient is once again placed on the SIMULIX table and positioned on the markers with the aid of in-room isocenter lasers, with the immobilization devices on place. The shift that was calculated by the TPS is being implemented. The patient is now positioned at the setup reference point. After that, a planar image is taken, in order for the doctor to have a visual confirmation regarding the proper positioning. This planar image can also be visually compared to the image (DRR) extracted by MONACO (reference-CT scan), since both images can be viewed with respect to the multi-leaf collimators (MLC) of the LINAC’s head. Red marks are drawn at the laser points, corresponding to the isocenter of the beams. The marks on the side help for proper positioning with respect to the longitudinal and vertical axes, while the mark on top mainly helps for proper lateral positioning as well as longitudinal.

Any errors introduced until this point are purely preparation (systematic) errors and will affect every session in identical way. Therefore, extreme care should be taken in order to minimize errors during this preparation phase. In general, it is considered wise to avoid perplexed protocols by limiting the preparation steps to the minimum amount necessary, because any errors introduced in each step will be carried out through the next phases of the preparation.

Treatment is performed in the linear accelerator room. In general it is the doctors’ intention that the treatment starts at the same day that the simulation is performed. If this is not feasible, patients are instructed to refrain from washing and rubbing the particular area that includes the non-permanent marks. All the relevant details regarding patient’s positioning and immobilization have been recorded into MOSAIQ. The RTTs perform the positioning of the patient. For the first fraction, a radiation oncologist and a radiation physicist are present to ensure that the patient is positioned properly. With the use of XVI-Elekta a CBCT is taken and the image is reviewed by a suitably trained RTT, although a doctor and a radiation physicist are also present during this process for the first 3 fractions. Image registration is performed and an offset derives between the reference-CT and the treatment scan (CBCT). Details on how image registration is performed for each department are listed later on, in “Image Registration” section. Finally, a correction is performed by shifting the couch via the remote controller (couch move assistant) and the dose is delivered.

Patient specific QA is performed using a Delta-4 cylindrical phantom from ScandiDos. For patients treated with 3D Conformal Radiotherapy techniques this is done following a sampling pattern. As much as possible patient specific QA is done before the first treatment
of the patient. However, machine availability and other department workflow limitations require that many patient cases are grouped together for QA. So in some cases patient specific QA may take place after the first treatment but, in any case, during the first week of treatment. For VMAT, IMRT or SRS treatments it is mandatory to perform the patient specific QA before the first treatment for every patient. Using the Delta-4 phantom allows the comparison of the Monaco calculated 3D dose distribution to the measured one which is actually delivered by the LINAC. For the evaluation of the delivered dose distribution compared to the calculated dose from the TPS, a gamma analysis is performed. A gamma evaluation of the dose distribution with a 3%/3mm criterion is used with a minimum pass rate of 90%. This "pass" criterion is in line with the recommendations of the Netherlands Commission on Radiation Dosimetry-Report 24 (Code of Practice for the Quality Assurance and Control for Volumetric Modulated Arc Therapy). Note that this is more stringent than the 5%/5mm criterion with a pass rate of 85% recommended by ICRU rept. 83 but clinical experience has shown that it is achievable.

Before the first treatment, a "Second Review" is performed by the RTTs. They verify that all treatment parameters are exported correctly to the linac and that all treatment parameters sent by the TPS are within operating limits of the linac as defined in the R&V system. During this step the CBCT acquisition protocol is also reviewed and the image registration parameters and methods are set.

### Table 2.1: Workflow overview of treatment preparation phase

<table>
<thead>
<tr>
<th>Patient Registration</th>
<th>Secretary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generate Quality Check List (QCL)</strong></td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td><strong>Introduce Clinical Data</strong></td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td><strong>Schedule &amp; Complete Localization and CT</strong></td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td><strong>Import and Prepare Images in Monaco</strong></td>
<td>Radiation Physicist</td>
</tr>
<tr>
<td><strong>Define Volumes/Organs at risk</strong></td>
<td>Radiation Oncologist/Radiation Physicist</td>
</tr>
<tr>
<td><strong>Complete Treatment Plan</strong></td>
<td>Radiation Physicist</td>
</tr>
<tr>
<td><strong>Approve Plan in Monaco</strong></td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td><strong>Export to Mosaig, Prepare and Approve</strong></td>
<td>Radiation Physicist</td>
</tr>
<tr>
<td><strong>Approve Plan PDF, Rad RX &amp; Inform Patient</strong></td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td><strong>Schedule and complete Simulation</strong></td>
<td>Radiation Oncologist</td>
</tr>
<tr>
<td><strong>Prepare RO Treatment Calendar</strong></td>
<td>Radiation Physicist</td>
</tr>
<tr>
<td><strong>Plan QA</strong></td>
<td>Radiation Physicist</td>
</tr>
<tr>
<td><strong>Treatment Schedule &amp; Second Review</strong></td>
<td>RTT</td>
</tr>
</tbody>
</table>
2.1.2 University Hospital of Larissa

Larissa has implemented a similar workflow. However, there are some differences that are mentioned below.

During the process of localization, permanent skin marks (tattoos) are drawn on the laser points in the simulator room at the beginning of the preparation phase. There is an established protocol based on which tattoos are drawn, depending on the anatomical region to be irradiated:

For brain tumors, regularly three markers are drawn on the thermoplastic mask; one mark is drawn on the glabella and two on the greater wings at the same height, one on each side. An extra tattoo is drawn on the xiphoid process to help with the alignment. For head and neck cases, one tattoo is drawn ventrally under the patient’s nose and two laterally on the same axial level, at the vertical height of each ear’s tragus. For lung malignancies, one tattoo is drawn on the center of the body of the sternum and one on each side at the same longitudinal height. An extra alignment tattoo is drawn on each side, on the iliac crest bone. For breast irradiation, if both of the breasts are intact, a ventral tattoo is drawn at the height of the nipples and two laterals on the same axial level. If the breasts cannot be aligned, the ventral tattoo is drawn at the height of the treated breast’s nipple. When there is a mastectomy, the ventral tattoo is drawn at the height of the existing breast. In every case, alignment tattoos are made laterally on the height of the iliac crest bone. For abdomen malignancies three tattoos are drawn on the axial height of T12 vertebra, one ventrally and two laterally; an alignment tattoo is made on the pubic symphysis. For pelvis, a tattoo is made on the upper limit of the pubic symphysis and two on the heads of the femurs, all at the same axial level. An additional alignment tattoo is drawn on xiphoid process. Finally, for rectum irradiation three tattoos are drawn at the axial height of the upper limit of the acetabulum, one ventrally and two laterally, and an alignment tattoo on the xiphoid process.

These anatomical sites have been chosen as permanent skin marks because skin movement relative to rigid bony anatomy is confined, thus limiting the setup error and providing better reproducibility.

During treatment planning, regularly two or three phases of treatment are prescribed to achieve dose escalation. This leads to smaller boost fields that do not share the same isocenter with the original larger fields. This means that the distance between the scan reference point
and the setup reference point differs throughout the different phases of the treatment and must to be separately calculated for each phase. The setup reference point is also set as the geometric center of the PTV and serves as a dose reference point as well.

Simulation phase is skipped and patients go directly to treatment. Patient positioning is performed by the RTTs on the tattoos representing the scan reference point with the help of in-room isocenter lasers. However, this position does not represent the beam’s isocenter and a couch shift, that was calculated during treatment planning, has to be made in order to go to the setup reference point. During the first treatment, a radiation oncologist is also present to ensure that the patient is positioned properly and to review the registration of the CBCT to the reference CT. Generally, if there is a significant difference in organ filling (e.g. bladder and/or rectum filling) between the treatment image and the reference CT, the dose is not delivered at that time and patients are instructed to fill their bladder and/or empty their bowel before going over the positioning and imaging process later. All treatment images are reviewed offline by the attending physicians, who can also make comments and remarks regarding patient positioning and organ filling.

Quality assurance involves standard daily equipment QA checks, but no patient-specific QA, since this department only performs 3DCRT radiotherapy technique.

### 2.1.3 Theageneio Anticancer Hospital of Thessaloniki

Theageneio has implemented a workflow that is similar to the one followed in University Hospital of Larissa. However, during treatment planning, it is generally pursued that the scan reference point will serve as a dose reference point as well. When this is not applicable, the offset between these two points is derived manually by the radiation physicist in the form of an integral shift. This dose reference point remains the same throughout the treatment regardless any dose escalation phases (boost). During treatment, suitably trained RTTs compare the volume of the bladder and the rectum between the treatment and the reference image, although the review protocol is not as strict as in Larissa. Regarding immobilization, fewer immobilization devices are used and they are not indexed to the treatment couch. Patient-specific QA is performed with the use of MAPphan-Mapcheck or IMF-Mapcheck 2D arrays, provided by Sun Nuclear Corporation.
2.2 Equipment

All three departments use an Infinity™ linear accelerator, XVI Release 5.0.3, iViewGT™ Release 3.4.1 and Monaco version 5.11.02, all provided by Elekta. Additionally, MOSAIQ version 2.64 by Elekta / IMPAC Medical Systems is used as an oncology management system.

In University Hospital of Patras a SIMULIX EVOLUTION CT simulator scanner by Nucletron, along with Oncentra Simulation version 2.5.0, is used for target localization and treatment simulation. Reference CT scans are performed by a GE LightSpeed16 scanner, while patient specific QA is performed with the use of Delta-4 Phantom provided by ScandiDos. For patient immobilization, index immobilization devices are used. For brain irradiation, thermoplastic masks, black pillow (B) and HeadSTEP; for lung and breast irradiation, blue pillow (A) and WingSTEP; for abdomen irradiation, a regular pillow, ProSTEP and/or KneeSTEP and for pelvis irradiation a regular pillow and proSTEP.

University Hospital of Larissa is using a mix of equipment that is very similar to the Patras equipment. The diagnostic CT is an Aquillon 16 from Toshiba. Regarding patient immobilization, a wider variety of devices is used and a stricter protocol is followed, with respect to each anatomical region. ProSTEP and KneeSTEP are used in all treatments performed in supine position, back wedges are used for breast irradiation if necessary and large head & shoulder thermoplastic masks, HeadSTEP, as well as shoulder retractors are used for head and neck treatments. For rectum irradiation, which is the only treatment performed in prone position, BellySTEP and inversed KneeSTEP are used. Black pillow (B) is used for brain and head & neck irradiation and blue pillow (A) is used for the irradiation of all other anatomical sites except of rectum, where no pillow is used.

Theageneio Anticancer Hospital of Thessaloniki uses a SOMATOM Emotion Duo/6/16 CT scanner by Siemens and Acuity System, provided by Varian Medical Systems. They also use MAPphan-Mapcheck or IMF-Mapcheck 2D arrays, provided by Sun Nuclear Corporation2D.
2.3 Correction strategies

As mentioned in the introduction, there are plenty of correction strategies in IGRT. Offline corrections usually demand a small amount of work that is done only once through the course of the treatment and aim to drastically reduce the systematic component of the errors. They also provide the possibility to replan (Adaptive Radiation Therapy – ART) and account for errors or tumor changes. The no-action-level (NAL) protocol demands a minimum amount of work and could reduce the systematic compound of setup error up to 1/3 of what it would be without the correction; this makes it extremely suitable for departments that face a heavy workload.\textsuperscript{143,144} With the advent of volumetric treatment imaging (CBCT) many departments prefer to use an online correction strategy, which is simply implemented with the push of a button right before the delivery of the dose and eliminates all setup errors; the disadvantages of this technique is that each treatment has a prolonged duration and that the imaging equipment might get overwhelmingly stressed. Hybrid strategies with elements of both online and offline correction strategies are very common in departments like ours, which have to deal with heavy workload while being understaffed.

2.3.1 University Hospital of Patras

A hybrid model of online and offline correction is used.

During the first three sessions, patient positioning is performed by the RTTs on non-permanent marks with the help of in-room isocenter lasers, index immobilization devices and the table vertical value that was calculated by the MONACO treatment planning system. The three marks (right, left and top) correspond to the machine isocenter, which is the center of the planned PTV.

For each of the three initial fractions of the treatment a CBCT is acquired. After each CBCT an online correction is being implemented to correct the offset that derived due to faulty patient positioning. This offset is recorded into the system. After the third session, the localization trend, i.e. the average offset of the three first sessions, is calculated in the form of one distance per axis. The opposites of these values give the vector of table movement that has to be implemented during the rest of the treatment sessions in order to account for systematic setup errors. This is a typical example of a no-action-level (NAL) offline correction.
Before the delivery of the 4\textsuperscript{th} fraction, the patient is positioned again on the marks. The offline correction is performed with the use of couch move assistant utility provided by Elekta Infinity and the table moves in order to account for the localization offset derived by the 3 first fractions. At this position, new markers are drawn; these will be the points where the permanent tattoos will be done. A CBCT is taken right after that, as an extra verification that the offline correction has actually limited the setup errors. Any residual setup errors are corrected online with the shift of the table. Once the fraction is delivered, the patient is moved to another room and gets the permanent tattoos. This means that the positioning of the patient will occur on these tattoos for the rest of the treatment.

One CBCT per week is scheduled for the rest of the treatment, as an extra verification that the positioning of the patient is still performed correctly. Each time a CBCT is implemented, an online correction of patient’s positioning is performed. The values of the offset are recorded. These extra data derived by the additional weekly CBCTs are not used for further statistical improvement of positioning accuracy at that time, but only as qualitative data. However, these data are extremely helpful as patient population data for the calculation of the customized CTV-to-PTV margins for the department.

During dose escalation phase (boost) the center of PTV remains the same, which means that the beam isocenter is also the same and the offline correction is still valid for this phase of the treatment as well.

2.3.2 University Hospital of Larissa

Similarly to Rio, a hybrid model combining a NAL offline and online corrections is used. Patient positioning is performed by the RTTs on permanent tattoos with the help of in-room isocenter lasers, index immobilization devices and the table vertical value that was calculated by the MONACO treatment planning system. The three marks (right, left and top) represent the scan reference point. This means that every time a patient is positioned, a couch shift that has been calculated by MONACO during treatment planning has to be performed in order to shift to the beam isocenter, which is often the center of PTV.

For the three initial treatment days a CBCT is acquired. After each CBCT an online correction is performed to correct the offset that derived due to faulty patient positioning. This offset is recorded into the system. After the third session, the average offset of the three
first sessions is calculated, in the form of one distance per axis. The opposites of these values give the vector of table movement that has to be implemented during the rest of the treatment sessions in order to account for systematic setup errors.

The fourth fraction is performed without treatment imaging. Before the delivery of the 5th fraction a CBCT is taken in order to verify that the offline correction has indeed reduced the systematic setup error. If this error exceeds the value of 5mm in any of the three planes, a new series of three consecutive imaging days is programmed by a suitably trained RTT, in order to correct more efficiently the setup error. The initial offline correction is discarded and the values that derive from this new series of imaging are used to calculate the offline correction vector. Once the offline correction is made, a weekly CBCT is scheduled to verify proper patient positioning. Every time a CBCT is performed, an online correction is made.

In general, two or three phases of treatment are programmed by the department’s radiation oncologists in order to achieve dose escalation (boost) to the treated organ. Because each phase of the treatment does not have the same center of PTV and a different beam isocenter occurs, the offline correction has to be redone. Therefore, before the 1st fraction of each new phase the whole procedure is repeated and any past offline corrections are discarded.

2.3.3 Theageneio Anticancer Hospital of Thessaloniki

In this department occasional online corrections are performed during the course of each patient’s treatment. Patient positioning is performed by the RTTs on permanent tattoos with the help of in-room isocenter lasers, basic non-index immobilization devices and the table vertical value that was calculated by the MONACO treatment planning system. The three marks (right, left and top) represent the scan reference point, which is usually set as the dose reference point as well, for simplicity purposes. This means that the patients are generally positioned directly at the beams isocenter. Sometimes though, the scan reference point and the dose reference point do not coincide and a couch shift that has been calculated in MONACO during treatment planning has to be performed in order to shift to the beam isocenter, which is often the dose reference point and the center of PTV.

For the first three days a CBCT is scheduled. The resulting offsets are not used for an offline correction but are simply treated as a gauge for the positioning of the patient. A weekly CBCT is usually scheduled and the offsets are utilized for qualitative evaluation of setup
errors. After each CBCT an online correction is performed. All offsets are recorded into the system.

2.4 Data acquisition and classification

In total, 278 patients were studied and data from 2094 CBCT scans were reviewed. The main goal of this study was primarily to quantify the setup error in every anatomical region that was treated in our departments and then derive the CTV-to-PTV margin. On a second level, the purpose of this study was to find a way to assess the interfraction organ motion of the prostate and the prostate bed, as well as the delineation error of several anatomical sites and then calculate the department-specific CTV-to-PTV margins. Because this margin aspires to be indicative for everyday clinical practice, not every patient and/or CBCT scan was deemed fit for statistical analysis. Possible outliers caused by out-of-date techniques and human errors that should be easily spotted and corrected were excluded from this study. Furthermore, extreme patient cases regarding positioning that were characterized out of the ordinary, such as excessively obese, non-compliant or patients with chronic pain which caused inability to maintain a reproducible setup were excluded as well.

Setup offsets that derive after the performance of image registration and “convert to correction” are recorded into XVI. XVI and MOSAIQ are interconnected and this data is easily accessible through MOSAIQ, by opening each patient’s log. The values of the offsets are displayed with a precision of a tenth of a millimeter before the couch shift. However, they are rounded to the millimeter after performing the correction and thus are saved into the system. This makes sense, since the therapeutic table cannot account for translations smaller than 1 mm. All the data acquired are expressed in centimeters and with a precision of a millimeter.

The classification of the data for each department was primarily performed with respect to the anatomical region treated. This resulted in grouping the data in 9 different categories: Brain, Head & Neck, Lung, Breast, Abdomen, Prostate, Bladder, Gynaecological and Rectum.

Because organ motion for prostate and prostate bed differs significantly compared to uterus, cervical and endometrial organ motion, prostate cases were grouped separately and all the gynaecological malignancies were grouped together. Also, bladder cases were grouped
separately, as well as rectum cases, because of the particularity that each of these sites presents in terms of organ motion and organ volume.\textsuperscript{169}

Lung includes non-small cell lung cancer and mediastinum tumors, as well as non-Hodgkin lymphomas. All these malignancies were grouped together due to their anatomical proximity and the similarity they display in terms of organ motion and delineation deviation. No further separation between intact tumors and postoperative cases was made.

2.4.1 Specification and computation of errors

As it was previously mentioned in the overview of errors in radiotherapy, errors are classified as random and systematic. Suppose that we have measured an error on a daily basis for a number of patients and fractions. Figure 2.2 shows how these data are analyzed to determine the SD of the random error, $\sigma$, the SD of the systematic error, $\Sigma$, and the overall mean (or group systematic) error, $M$. Mean and SD of the daily measurements are first obtained per patient. The group systematic error is just the mean of all means. One expects this error to be small. However, $M$ often deviates significantly from zero because of imprecision in the equipment (lasers) and procedure. The SD of the means per patient is an estimator for the SD of the systematic error, $\Sigma$. It described how reproducible the treatment preparation is performed. The individual SDs give the SD of the random error for each patient. When the number of measurements per patient is limited, differences between individual patients are difficult to prove. Therefore, in general, group means of the SD of the random error, $\sigma$, are presented. The correct way to determine this group mean is to determine the root mean square of the SD’s of all patients.

As mentioned before, besides errors that vary from patient to patient or from fraction to fraction (interfraction), there are also movements that occur within a single fraction (intrafraction). In particular, respiration motion and peristaltic motion have a time scale that is shorter than the delivery time of a single fraction. In general, uncertainties that are introduced during treatment preparation (i.e., once) are larger than day-to-day variation during treatment execution. The magnitude of all uncertainties is similar. This means that all uncertainties should be addressed to significantly reduce the overall uncertainty. Rotational errors are significant in some cases.\textsuperscript{66,67,131}
2.4.2 Quantification of setup errors

In order to fully quantify the setup error, offsets of each and every fraction are required. However, this data is not available for many departments such as ours, where IGRT sessions are normally limited to once a week per patient. Furthermore, when a CBCT is performed, patient positioning is corrected and setup error is considered to be zero for that fraction. So it is clear that a method has to be developed in order to make use of this data, but at the same time account for the corrections made throughout the course of the treatment.

In this thesis, four methods of statistical analysis of these data were used for the quantification of the setup error, with respect to the correction strategies that they account for:

a. A plain method that includes all the setup offsets that derive after the performance of image registration. This method does not account for any offline or online correction strategies and thus will be referred as the “no corrections” method.

b. A method that accounts for the NAL offline correction applied after the third fraction, by excluding from the calculations the data that derived from the three initial fractions. This method will be referred as the “offline correction” method.

c. A method that includes the scaling of the errors per anatomical site, with respect to the imaging ratio of each anatomical site. This method accounts for the online corrections...
performed throughout the course of the treatment and will be referred as the “scaling” method.

d. A more sophisticated method that will take account for both offline and online corrections, by simulating the course of each treatment and will be referred as the “hybrid” method.

The first method of data utilization includes all the translations recorded into the system for each patient and the quantification of the setup error is performed on the basis of Figure 2.2. This method is most representative for departments that perform treatment imaging but do not correct the positioning of the patient by a couch move on site, neither by an offline correction.

The second method takes into account the offline correction which is performed after the three initial fractions. This is achieved by excluding the translations occurred during these three initial fractions, because they are no longer representative for patient positioning after the offline correction has been applied. In other words, large translations that are usually observed during the first three treatments and are later partly corrected by the performance of the offline correction should not be included in data analysis and setup error quantification. This method is most representative for departments that only apply a NAL offline correction protocol. However, it is important to note that the offline correction is performed anyway in the departments of Patras and Larissa. The differentiation between the first and the second method is that the latter excludes the offsets derived by the three initial fractions that would “blur” the results, since they should not have a contribution on the final setup error per anatomical site. In a way, the comparison between these two methods illustrates the impact that the initial offsets have on the resulting setup errors.

The third method performs a scaling on the value of setup errors that derived for each anatomical site. Each patient’s treatment can be divided into IGRT and non-IGRT fractions. When an IGRT fraction is performed, that is when a CBCT is acquired, an online correction on the basis of image registration is performed by moving the couch and setup errors are considered to be eliminated. In particular, every anatomical site had a different imaging ratio, which is defined as the ratio of the number of IGRT fractions over the number of all fractions delivered to this particular site. In order to account for these online corrections per anatomical site, one has to scale the derived setup error of each site (as calculated in Figure 2.2) on the basis of this imaging ratio. For example, if the prostate imaging ratio was 30%, then the non-
IGRT fractions made the 70% of the treatment. This 70% has to be multiplied with the derived setup error from “no corrections method” in order to represent the clinical reality. The other 30% corresponds to the online corrections, where setup errors were zero.

The fourth method simulates the course of every treatment in a more patient-specific manner. The rationale of the proposed method is that for every IGRT fraction setup error will be set to zero and the offsets acquired will be used as a gauge for the forthcoming non-IGRT fractions, for which no data is available. The average imaging ratio, i.e. the number of IGRT fractions over all fractions, for the three departments was roughly 27%. However, if the total number of fractions of a treatment is replaced solely by the number of its IGRT fractions, an overestimation of setup error will occur, because any corrections made throughout the treatment will not be taken into account. This will not lead to CTV coverage loss, but it will result in larger margins that will affect healthy surrounding tissue and that are not representative of the department’s clinical routine. In other words, a correct method should also account for the nullification of the setup error during IGRT fractions, as well as the offline correction. This is achieved by simulating the course of the entire treatment, thus keeping the same number of fractions that was actually delivered. As described in “Correction Strategies”, the three first fractions of every treatment are IGRT fractions and a mean offset is calculated and performed once and for all the remaining fraction as an offline correction. The data from these initial fractions should be discarded in order to account for the offline correction that is also applied, as described above. Fraction number four is also an IGRT fraction, which serves as a verification of the offline correction; the setup error for this fraction is also set to zero. However, the offset that occurred during this fraction will be used as a gauge to fill in the next non-IGRT fractions until the next imaging day. After the first four fractions, the patient would be imaged once a week. After each imaging, a mean shift is calculated from all the previous corrections and used as an offset to subsequent fractions. This method was used for the quantification of the setup errors for selected anatomical regions in each department.

2.5 The van Herk margin formula

Van Herk et al\textsuperscript{43} used the minimum cumulative CTV dose as a “gauge” for geometrical misses. Based on the dose population histograms, they derived a margin recipe to guarantee
that 90% of patients in the population receive a minimum cumulative CTV dose of at least 95% of the prescribed dose. This margin is approximately 2.5 times the total SD of systematic plus 0.7 times the total SD of random errors

\[ M = 2.5\Sigma + 0.7\sigma \]  

(2.1)

It is important to realize that Eq. 1 is a linear approximation of a general nonlinear recipe given by

\[ M = a\Sigma + \beta(\sigma - \sigma_p) \]  

(2.2)

where \( M \) is the prescribed PTV margin, \( a \) is given by a Gaussian probability density function, \( \Sigma \) is the standard deviation (SD) of all the systematic errors, \( \beta \) is the value of the inverse cumulative standard normal distribution at the prescribed PTV minimum dose level, \( \sigma_p \) the width of the penumbra modeled by a cumulative Gaussian and \( \sigma \) the quadratic sum of the SD of all random errors including the SD describing the penumbra, \( \sigma_p \).

For a confidence level of 90% and a dose level of 95% (i.e. 90% of patient population receives a minimum cumulative CTV dose of at least 95% of the prescribed dose), equation (2.2) becomes

\[ M = 2.5\Sigma + 1.64(\sigma - \sigma_p) \]  

(2.3)

The margin derivation relies on a model which provides an analytical description of the influence of random and systematic geometrical deviations on the dose distribution. The first step of the derivation is to create a model of the planned dose distribution (\( D_{\text{planned}} \)) by convolving a top hat function (A) spanning the CTV with a Gaussian distribution (B) in order to produce a clinically realistic dose profile (Figure 2.4). A convolution is the integral of the product of two functions after one is reversed and shifted to produce a third function that is a blurred representation of the original function. In this case is, the Gaussian is flipped (even though it is a symmetrical function) and shifted across the top hat function to create the planned dose profile. The mathematical definition of convolution is:

\[ A(y) \otimes B(y) = \int A(z) B(y - z) \, dz \]  

(2.4)

The Gaussian distribution convolved with the top hat function is centred on the tumour and a SD describes the width of the beam penumbra (\( \sigma_p \)). The value of \( \sigma_p \) was assumed to be 3.2 mm by van Herk, approximating the width of the penumbra in soft tissue and has shown to be 6.4 mm for lung tissue due to the wider penumbra in low density media\textsuperscript{38, 39}.
Next, it is assumed that the impact of random errors on the dose distribution can be modeled by blurring the planned dose profile, yielding the blurred dose profile ($D_{\text{blurred}}$) depicted in Figure 2.4. Assuming that the dose distribution does not change as it is shifted, blurring of the dose can be modeled by convolution. $D_{\text{blurred}}$ is constructed by convolving $D_{\text{planned}}$ with a Gaussian distribution that has a mean of 0 and a SD of $\sigma_{\text{random}}$. $\sigma_{\text{random}}$ can be divided into its individual components of random organ motion ($\sigma_m$), setup error ($\sigma_s$) and the SD of the Gaussian penumbra ($\sigma_p$). $D_{\text{blurred}}$ can be obtained directly by convolving a top hat function with a Gaussian function with a SD of $\sigma$, where:

$$\sigma = \sqrt{\sigma_m^2 + \sigma_s^2 + \sigma_p^2} \quad (2.5)$$

According to van Herk, the PTV margin required for adequate CTV coverage in the presence of random error is equivalent to the distance between the planned and blurred dose distributions at the 95% dose level as indicated in Figure 2.5 by the black arrows. It should also be noticed that the 50% level of blurred dose coincides with the width of the original top hat function. The slope of the edge of the blurred dose profile is fitted to a linear function from which the distance between the 50% dose level and the 95% dose level is derived to be $1.64\sigma$. Thus, the 95% level of blurred dose is situated 1.64 standard deviations ($\sigma$) from the beam edge. Since the distance between the 50% and 95% dose levels of the planned dose profile is $1.64\sigma_p$, the distance between the 50% and the 95% dose levels of the blurred dose profile is $1.64\sigma$ and the 50% dose level is invariant to blurring, the distance between the blurred and planned dose profiles at the 95% level is $1.64\sigma_p - 1.64\sigma$ which reduces to equation...
Therefore, the van Herk PTV margin accounting for random geometrical uncertainties only, can be calculated by applying the reduced equation:

\[
M_{\text{random}} = 1.64(\sigma - \sigma_p)
\] (2.6)

**Figure 2.4:** Profiles of planned and blurred dose. The hatched red profile indicates \(D_{\text{blurred}}\) which was constructed by convolving the blue \(D_{\text{planned}}\) profile with a Gaussian of SD = \(\sigma_{\text{random}}\). The black arrows indicate the distance between the two profiles at the 95% dose level which is the PTV margin required for random error.

As mentioned previously, the dosimetric effect of systematic errors is a shift of the dose distribution. Therefore, the margin to account for systematic uncertainties is calculated based on the probability that a systematic error results in the displacement of the CTV outside the region bounded by the 95% dose level in the blurred dose profile \(D_{\text{blurred}}\). The component of the PTV margin for systematic errors is chosen based on an objective set by the physician which is most commonly that 90% of the patient population receives a minimum CTV dose of 95% of the prescribed dose. Assuming that systematic errors are normally distributed, the 3D volume that encompasses 90% of all positions is given by \(2.5\Sigma\), where \(\Sigma\) is the SD of the Gaussian distribution describing systematic errors. It should be noted that the PTV margin for systematic errors is an entirely geometrical concept that does not depend on the shape of the CTV or dose distribution. \(\Sigma\) can be divided into its individual components of systematic organ motion (\(\Sigma_m\)), setup error (\(\Sigma_s\)) and the delineation error (\(\Sigma_d\)) where:

\[
\Sigma = \sqrt{\Sigma_m^2 + \Sigma_s^2 + \Sigma_d^2}
\] (2.7)
The combination of the separate random and systematic components of margin leads to equation (2.3):

\[ M = 2.5 \Sigma + 1.64 (\sigma - \sigma_p) \]

or simply to its linear approximation that excludes the SD of the penumbra, which is equation (2.1):

\[ M = 2.5 \Sigma + 0.7 \sigma \]

According to this formula, the contribution of systematic errors is roughly one and a half times greater than random errors and therefore contributes to a larger portion of the PTV margin. Therefore, more emphasis is placed on minimizing systematic errors because reducing the \( \Sigma \) value has a much greater shrinking effect on the PTV. It is also much more clinically practical to reduce systematic errors with the use of motion management techniques as well imaging during treatment and IGRT. Reducing random errors is less of a clinical focus as they account for a much smaller portion of the PTV margin, are much harder to predict and therefore account for. However, the dosimetric effects of random errors are still important to characterize for accurate PTV construction.

*Table 2.3* gives the margin for preparation (systematic) errors at a number of confidence levels (corresponding to a percentage of the patient population). In this table, perfect conformation in 1D, 2D, or 3D is assumed. Because, in reality, the conformation might not always be perfect, a smaller margin may sometimes be used. For example, for an irradiation with opposed-blocked fields, the conformation is perfect in 2D instead of 3D. In such a case, the column for 2D errors is most suitable. Note that it is impossible to reach a 100% confidence level, because this would require an infinite margin (i.e., as in total body irradiation). *Table 2.4* lists the dosimetric part of the margin, i.e., the part of the margin between the CTV and the PTV that accounts for penumbra and treatment execution (random) variations. In the third column, the magnitude of the PTV margin was linearly approximated for a penumbra SD of 3.2 mm. Note that a minimum CTV dose of 100% of the nominal dose cannot be achieved since that would require an infinite margin. Combining tables 2.3 and 2.4 allows for the definition of many margin recipes, at different confidence levels and dose levels.

For example, inside the lung, where the medium is less dense, a broader Gaussian penumbra is observed and its standard deviation, \( \sigma_p \), is considered to be 6.4 mm, compared to the 3.2 mm value that is used for soft tissue calculations. Thus, it is usually pursued that inside the
lung 90% of patient population will receive at least 80% of the prescribed CTV dose and the expression used for the margin calculation is

\[ M = 2.5\Sigma + 0.84(\sigma - \sigma_p) \] (2.8).

or its linear approximation, which is

\[ M = 2.5\Sigma + 0.4\sigma' \] (2.9)

**Table 2.2:** Margins for preparation (systematic) errors at different confidence levels

<table>
<thead>
<tr>
<th>Confidence level (% of patients)</th>
<th>Errors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1D</td>
</tr>
<tr>
<td>80</td>
<td>1.28\Sigma</td>
</tr>
<tr>
<td>85</td>
<td>1.44\Sigma</td>
</tr>
<tr>
<td>90</td>
<td>1.64\Sigma</td>
</tr>
<tr>
<td>95</td>
<td>1.96\Sigma</td>
</tr>
<tr>
<td>99</td>
<td>2.60\Sigma</td>
</tr>
</tbody>
</table>

**Table 2.3:** Additional PTV margin required for execution (random) variations.

*\(\sigma\) is the quadratic sum of the SD of all random errors including the SD describing the penumbra, \(\sigma_p\). The SD describing the penumbra term is next subtracted linearly.

**These approximated values are valid for \(\sigma_p = 3.2\) mm over a range of \(\sigma\) from 0 to 5 mm. Here, \(\sigma'\) is the combined SD of random variations excluding the penumbra. The numerical values of in the second column give the value of \(\beta\) that must be used in Equation (2.2), while numerical values in the third column give the simplified version of the formula (Equation 2.1).

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Additional margin*</th>
<th>Linear approximation**</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>0.84((\sigma-\sigma_p))</td>
<td>0.4(\sigma')</td>
</tr>
<tr>
<td>85%</td>
<td>1.03((\sigma-\sigma_p))</td>
<td>0.5(\sigma')</td>
</tr>
<tr>
<td>90%</td>
<td>1.28((\sigma-\sigma_p))</td>
<td>0.6(\sigma')</td>
</tr>
<tr>
<td>95%</td>
<td>1.64((\sigma-\sigma_p))</td>
<td>0.7(\sigma')</td>
</tr>
<tr>
<td>99%</td>
<td>2.34((\sigma-\sigma_p))</td>
<td>0.95(\sigma')</td>
</tr>
</tbody>
</table>
2.6 Image registration

2.6.1 Measurement of setup error and organ motion in an IGRT system

Methods for measurement of setup error and organ motion in an IGRT system are based on image registration. The simplest systems are based on rigid registration of the entire scanned portion of the patient. However, this has a disadvantage because anatomical deformation will invariably lead to poor registration. It is better to have a rigid registration method using a box-shaped or arbitrarily shaped region of interest; this accelerates registration, provides a stable solution even in the presence of deformations, and provides a visual aid when validating the registration results. Sophisticated soft tissue matching algorithms have already found their way to commercial products and provide a credible image registration method, especially for lung cancer. Additional utilities such as creating a mask from an existent contour, or performing dual registration with a combination of methods (i.e. bone and soft tissue registration) are also available by most of the vendors.

In all cases, automatic image-registration techniques can fail so a fallback mechanism must be available based on user interaction. In general, the process of registration has more degrees of freedom than the applied correction. This is acceptable as long as one realizes that the registered images do not show a setup that is clinically achievable (e.g., a couch shift after deformable registration can only correct a few out of the hundreds parameters determined). This means that there is a need to convert registration results into a correctable error. The great progress regarding algorithm development over the past years has resulted in more sophisticated methods to discard rotations from a rigid body registration (translation and rotation) and to obtain an optimal couch shift based on a correction reference point that acts as a virtual rotation point (see Figure 2.6). In all cases, it is extremely important to define protocols in which algorithm setting, regions of interest, visual tools to be used, and other settings are defined. In an optimal image-guidance system, such options should be preset once and reused for all fractions. However, one should realize that visual verification (and manual registration tools as fallback) remains essential because automatic algorithms will fail occasionally. The screen layout and image fusion methods of the image guidance application should be such that misregistration can be quickly detected.
2.6.2 Image registration in XVI

There is an option within the XVI system to display structures in the viewers. The structures are sent from the treatment planning system and can be selected in Volume Reference. By default GTV, CTV and PTV are displayed. These structures are helpful to evaluate target coverage in the presence of changes and/or rotations during registration.

Two images can be accurately registered with 6 degrees of freedom (3 translations and 3 rotations). A table shift however can only correct the translations (and a robotic couch can only correct up to 3° of the rotations). For this, the strategy “smart ignoring of rotations” is used, by properly selecting the correction reference point. When using a correction reference point, the point of rotation is redefined. In all our departments the center of PTV is set as the correction reference point. Therefore the residual errors due to ignoring the rotations will be zero in the correction reference point. It is important to choose this point wisely, when the correction reference point is too far away from the PTV, the PTV could move away from the target area.

![Figure 2.5: Correction reference point](image)

(a): Correction reference point away from the PTV (red ellipse) may result in large rotational errors
(b): Correction reference point at the center of PTV (red ellipse) results in smaller rotational errors

The Bone (T+R) mode of automatic registration uses a chamfer matching algorithm that calculates the translations and rotations with densities that are the same as bone densities. The chamfer matching algorithm is not very sensitive to image noise and XVI can calculate it
quickly. If the chamfer matching algorithm cannot find a solution, the message “Match stopped close to search limits – possibly incorrect answer” appears. It is possible for the chamfer matching algorithm to give an incorrect registration solution and not give an error. This can occur when XVI does a registration of spinal vertebrae, as the algorithm can do an incorrect registration by one vertebra, when XVI tries to do a registration of mobile anatomy (e.g. neck), when XVI tries to do a registration of image artifacts, or when XVI tries to do a registration of the treatment table top.

The Grey Value (T+R) registration algorithm uses all the gray value pixels in the registration volume (Clipbox or Mask) to calculate the translations and rotations. It performs a registration on the gray scale intensity values of the voxels in the registration volume. The algorithm used is a gray level “correlation ratio” procedure. More time is necessary for XVI to calculate this algorithm than the chamfer matching algorithm.

### 2.6.3 Registration options

There are different registration options: clipbox, mask, and first clipbox then mask (dual registration). All options are designed to register only a part of the CBCT scan, to be able to register and correct what is considered to be representative for a treatment. A clipbox is placed around a representative region of interest for a match. A mask is a region of interest that can be designed in all shapes and sizes, but is usually generated from a GTV, CTV or PTV structure. The dual registration (first clipbox then mask) is designed to compare the outcome of the two registrations and can be used for a critical structure avoidance strategy, as well as a gauge for the assessment of interfraction organ motion (see next chapter). The mask is created from the target volumes usually with a margin, and without removing air or high densities. Any high densities inside the mask that should not be included, e.g. bony anatomy, should be removed.

The chamfer match algorithm (Bone T+R) is the first choice when registering bony anatomy because it is fast and robust. When this fails on visual inspection, Grey Value (T+R) registration is used. Manual registration is only used, if the automatic registrations have failed. It will sometimes help the Bone or Grey Value match to manually match the two scans and then try one of the automatic registration algorithm. If even this fails, manual registration is performed by specially trained RTTs or physicists. This is best visualized in the green-
purple display mode and by using the arrows next to the translation. To evaluate any registration, first the green-purple display is checked for gross errors before using any other display options like cut-view. Cut-view display provides the capability to compare the CT reference image with the treatment CBCT image. This is extremely useful in order to qualitatively evaluate any organ displacement due to different bladder and rectal volumes. After the evaluation of the registration the staff checks whether the target volume is within the PTV structure.

In general, Bone (T+R) registration method is used in the anatomical sites of pelvis, brain, head and neck and breast. For lung malignancies that are located ventrally or in the upper lobe, bone registration is preferred as well. For cancers located on the lower region of the lung, Grey Value (T+R) is usually preferred.

The restrictions that are set in all three departments are similar. For translations in any plane the limit is set to 1 cm and for rotations in any plane the limit is set to $10^6$. If these limits are exceeded, realigning the patient might be considered, especially if great rotations are noticed. If translations limit is just slightly exceeded, a manual override is performed. In general these restrictions are used to flag differences in patient setup that are not expected to happen and can have an impact on dose distribution. If the rotations are a result of anatomical variation and cannot be optimized by re-aligning the patient it is important to check after ‘convert to correction’ whether this has any negative impact on target volume coverage. It is noteworthy to mention that after the evaluation of the registration, the correction derived after “convert to correction” is also checked, because rotations of the registration are recalculated to translations as the rotations cannot be corrected by a simple table displacement (see Correction Reference Point). This final inspection focuses on target coverage, i.e. if the CTV is still within PTV. After “convert to correction” XVI will give a warning if the restrictions are exceeded. These may be accepted if the match is correct or patients can be realigned (a physicist or physicians will be consulted in these cases).

2.6.4 Assessing the interfraction organ motion with the use of dual registration method

For Rio University Hospital, a method to assess prostate motion between the fractions of a treatment was employed. Eighteen out of twenty patients treated for prostate cancer in our
department so far received postoperative adjuvant radiotherapy. Therefore, they did not have an intact organ, but instead a tumor bed was irradiated. However, there is no evidence of great deviation between the interfraction motion of the intact prostate and the prostate bed in the literature.\textsuperscript{11,66,171-175} Thus, data from all patients were included as well in this method of organ motion quantification and thus the results represent the interfraction motion of both the prostate and the prostate bed.

The notion behind dual registration is that the relative motion of the soft tissue with respect to the bony anatomy could be used as a gauge for the quantification of the interfraction organ motion. Because many departments lack the means to track organ motion with the use of surrogates, such as intraprostatic fiducial markers, it is difficult to collect patient population data regarding this source of errors; this fact discourages many departments from extracting a customized CTV-to-PTV margin, since this data is essential for such calculations. Very often departments use margins given by literature and sometimes they use the setup data they have combined with organ motion data taken from literature. Nevertheless, as mentioned before, it is always preferable for each department to have its own population data in order to assess the errors and calculate a customized CTV-to-PTV margin for each anatomical site. The process described below enables the acquisition of patient population data with minimum means and effort, just by using the utilities provided by the XVI software.

The reference CT is acquired with the target in an arbitrary position. This introduces an error in the radiotherapy process, i.e. interfraction organ motion. Each time a treatment scan (CBCT) is performed, the target is also in an arbitrary position that might deviate significantly compared to the one in the reference CT (reference organ motion). Since none of our three departments use fiducial markers as surrogates to track the motion of the prostate bed and image registration is performed on the basis of bony anatomy (Bone T+R), the corrections implemented only account for setup errors, which normally after the correction are set to zero (even though there might be some residual registration errors due to image registration algorithms, which are considered negligible in this thesis). An easy way to assess the magnitude of this motion is to use the dual registration method that is available within XVI.

XVI is linked with the Elekta Infinity LINAC, as well as with MOSAIQ. The software itself provides classification per patient, providing the ability for the user to choose from a list of patients that have been treated. A list of treatment images (CBCT) is also available for each
patient. An offline review as well as an offline registration between these images and the reference CT image can be made.

Initially, for a specific patient and a specific treatment image, dual registration is selected as the registration method. Then, a mask is created from the CTV contour without any added margin. The selection of a zero margin is crucial, because the mask must not include any high densities, e.g. bones, as this would affect the efficacy of the algorithm. The first registration occurs with a Bone (T+R) registration method and the region where the algorithm focuses on is a Clipbox. This clipbox is placed around the rigid bony anatomy of the pelvic region, excluding the femoral head and trochanter minor as much as possible and containing the target and the pubic symphysis.

![Figure 2.6: Example of dual registration method for prostate](image)

This registration will result to an offset that represents the distance, expressed in the form of three translations (i.e. one per axis), between the reference CT and the CBCT of that day, as derived by the bony anatomy match.

The second registration occurs with a Grey Value (T+R) method and the mask that was created from the CTV acts as the source for the registration. This registration will result to an
offset that represents the distance between the mask’s center of mass in the CBCT and in the reference CT (without taking into account any possible deformations), again in the form of three translations, one per axis. With the selection of “convert to correction” a scrollbar is available that enables the user to adjust between the two methods of correction, i.e. the clipbox and the mask. Clipbox registration is used as the reference method and the residual difference between the two methods is displayed in the overview tab, expressed in the form of three translations. These values indicate, for each plane, the relative position of the CTV’s center of mass with respect to the bony anatomy, which is considered to be rigid.

These values were recorded into an in-house sheet for each patient and for each fraction, resulting in the creation of specific patient population data. Clipbox registrations with a rotation that exceeded 5° in any of the three planes were deemed invalid for experimental exploitation, due to the limitation that registration algorithms set and have thus been ignored. For mask registration, 10° of rotation was set as a limit.

### 2.7 Patient instructions and organ filling protocols

Appropriate patient instructions play a crucial role in radiation therapy and can have an impact on the outcome of the treatment. These instructions mainly concern rectum and bladder filling for pelvic malignancies, such as prostate and gynaecological cancer, and calm and steady breathing for cancers located in thorax. Especially for prostate cancer, which is one of the most common type of cancer being treated in our departments, proper organ filling instructions may significantly reduce interfraction variation of the organ’s position (interfraction organ motion), as well as reduce the potential peristaltic organ motion during the irradiation (intrafraction motion).

Marker based corrections have shown in numerous studies that the uncertainties caused by the prostate movement might be significant, requiring safety margins greater than 1cm. These errors are severe obstacles to further escalate the dose and should be reduced; therefore, most investigators recommend the use of intraprostatic markers used as surrogates to track the prostate in order to reduce safety margins. However, under clinical conditions marker implantation is not only an additional invasive procedure (with some additional risk), but also time-consuming and expensive. On the contrary, organ filling protocols are risk-free, inexpensive and require a minimum amount of effort from the staff. These protocols might include the use of some medication, such as mild laxatives and
enemas, or may be only limited to specific instructions provided by the physicians or the nurses.

To account for any organ motion, a good level of reproducibility is requested. It is of paramount importance to achieve this reproducibility not only for all the treatment fractions, but on for the planning CT as well, because this will be the reference image where the dose will be calculated. An outlier CT could introduce major systematic organ motion errors that will affect all the fractions of the treatment. Therefore, the conditions prevailing during the acquisition of the planning CT are considered to be reference conditions and it is pursued that they are reproduced during each fraction. Nevertheless, it is presumed impossible to precisely reproduce reference conditions even with the use of strict organ filling protocols, since bladder and rectum movements are often unpredictable, especially for gas pockets in rectum.

2.7.1 University Hospital of Patras

During the interview with the patients, physicians usually give advice regarding bladder and rectum filling. Particularly for prostate and gynaecological malignancies located on the pelvic area, patients are advised to empty their bowel and bladder and drink a glass of water before coming to the department either for their reference CT or for any of the treatment fractions. While being at the department, they are instructed to drink a small bottle of water (1/2 liter). For bladder cancer, patients are advised to empty their bladder before treatment. These instructions may vary from patient to patient depending on their bladder capacity.

However, there is no supervision mechanism established for the time being on behalf of the department to ensure that these instructions are actually followed by all patients, because there is a lack of nursing stuff.

2.7.2 University Hospital of Larissa

Patients are given specific instructions regarding rectum and bladder filling for prostate and gynaecological malignancies. They are advised to empty their bowel and bladder and then drink a bottle containing ½ liter of water all at once 30 minutes before reference CT scan, as well as before each treatment fraction. RTTs are responsible to supervise that this protocol is
followed by each patient and treatment appointments are scheduled in a way that ensures that patients have the demanded time and attention in order to follow the instructions.

For bladder irradiation, patients are instructed to empty their bladder just before treatment.

### 2.7.3 Theageneio Anticancer Hospital of Thessaloniki

Similarly to Larissa University Hospital, patients with pelvic malignancies are instructed to empty their bowel and bladder and then drink a bottle of water all at once. The time interval between the consumption of the water and the conduction of the reference CT scan is noted by the RTTs in each patient’s file. This time interval is characteristic for each patient and it is followed throughout the treatment fractions. RTTs are responsible to assure that these instructions are followed by all patients and may even modify the schedule in order to reproduce reference conditions.

### 2.8 Assessment of the Delineation Error

Delineation error has a great impact on the CTV-to-PTV margin, since it is a systematic (preparation) error that effects the treatment throughout its whole course, from the first fraction until the last. The margins required in order to compensate for this error are significant, thus its contribution to the final margin is noteworthy. Especially with the new IGRT techniques that allow for setup and organ motion corrections, this type of uncertainty becomes the predominant one. Therefore, it is crucial to acquire a reliable assessment of its magnitude. Adequate imaging, training and use of contouring recommendations are the main strategies to minimize delineation uncertainties. Establishing and using consensus and guidelines have shown to reduce heterogeneity in contouring. Delineation error depends strongly on imaging modalities (MRI, CT, ultrasound, PET), physicians’ clinical judgment and the adaptation of particular evidence-based protocols such as RTOG, EORTC and RADICALS. It is then important to note that delineation errors could significantly vary between different radiation therapy centers and should be investigated specifically for each radiation therapy department.

In our departments, we tried to assess the inter-observer variation for the delineation of the GTV for various anatomical sites. This means that there was no “golden standard” rule, so
there is no comparison between a specialist’s contour and the contours of the rest. Instead, our goal was to quantify the overall observer variation between the doctors.

In MONACO Planning System environment, the doctors were appointed to delineate the organs – which in our case are considered to be the target volumes, thus the GTV. A treatment planning specialist (medical physicist) helped them adjust the contrast and the window level of the CT image in order to succeed a satisfactory result according to their judgment. When an MR image was available, a fusion of the two imaging modalities was made. It is noteworthy to mention that despite the existence of some presets provided by the software (lung, brain etc.) there are no custom contrast/window level presets on our departments yet.

Each doctor was tasked to draw a contour of the GTV, without being able to see the contours of the rest of their colleagues. After all doctors had delineated the target volume, the encompassing volume and its geometric center (or center of mass) were found using the MONACO’s utilities and then the distance between this point and the edge of each contour along each cardinal axis and each direction was measured, i.e. in X axis Left and Right, in Y axis Inferior and Superior and in Z axis Posterior and Posterior. This lead to six distances being measured for each contour, namely six distances for each doctor’s contour over each patient.

The Overall Observer Variation for the prostate delineation is given by

\[ S = \sqrt{\frac{\sum_{o=1}^{n_o} S_p^2}{n_o}} \]  

(2.10)

, where

\[ S_p = \frac{\sum_{o=1}^{n_o} (x_{po} - \bar{x}_p)^2}{n_o - 1} \]  

(2.11)

is the SD of the distances per axis and per direction (i.e. one distance per observer) for a specific patient (p= patient, o=observer), \( n_o \) is the number of observers, \( x_{po} \) is the distance between the center of mass of the encompassing volume and the edge of the contour and

\[ \bar{x}_p = \frac{\sum_{o=1}^{n_o} x_{po}}{n_o} \]  

(2.12)

is the average of the distances per axis and per direction for a specific patient.
The selection of the GTV, instead of the CTV, was made in order to limit the physicians’ clinical judgment as much as possible, since it was not feasible for the doctors to study the history file of every particular patient, due to heavy workload. Therefore, what is mostly tested is the interobserver variation regarding the physicians’ preferences on the quality of the image and subsequently their judgment on the visual edges of the organs. The experiment aimed to reproduce as much as possible the actual procedure of delineation as it is performed in our departments. As mentioned before, the quantification of the delineation error was calculated separately for each department.

2.8.1 University Hospital of Patras

Delineation of the target volumes is performed by the physicians. Although, some Organs At Risk (OARs) are delineated by the radiation physicists, who are also responsible for the treatment planning.

Normally, the doctors study the file of each patient and at a certain point of the Radiotherapy Chain Workflow (MOSAIQ) they delineate the target volumes. When there is an intact organ, i.e. the RT is not post-operative, they delineate the GTV. If the RT is post-operative and there is no organ, they draw the CTV, creating the tumour bed. The delineation of the tumour bed is performed based on the RTOG and RADICALS protocols.

Six patient cases were chosen in total: two with a prostate malignancy, two with a lung malignancy and two with a brain malignancy. As mentioned before, all of the patients had an intact organ in order for the GTV to be contoured. The CT images for all patients were acquired in our hospital with the use of a dedicated CT scanner (GE LightSpeed 16), thus having the same quality specifications.

Three doctors and one treatment planning expert participated in this experiment. Each participant was tasked to draw a contour of the GTV, without being able to see the contours of the rest of their colleagues. A medical physicist was present throughout the whole procedure to assist with the use of the MONACO treatment planning system, i.e. achieving a satisfactory visual result in terms of window level, image contrast and image fusion of the CT and the MR images, in the cases that the latter were available.

Regarding prostate, it has to be noted that the majority of the patients that are treated in the new Infinity linear accelerator in our department are undergoing postoperative adjuvant...
radiation therapy. Nevertheless, a small number of patients during these 9 months underwent radical 3D conformal Radiation Therapy having an intact prostate. From these patients, only two were ultimately selected for this experiment. The main reason for this is the heavy workload of the doctors, which set an objective limit to the number of cases they could delineate during their daily clinical routine. Additionally, those two cases were chosen for being representative of a common type of prostate malignancy being treated in our department.

The participants were asked to delineate the prostate gland alone and not the seminal vesicles. This choice was made in order to minimize the uncertainty, since the apex of the prostate and the seminal vesicles tend to generate the greatest deviations in contouring.

As described before, the encompassing volume of all four contours was found and the distance between its center of mass and the edge of each contour was measured.

*Figure 2.7: Delineation of the prostate by the participants*
Regarding lung, our goal was to assess the delineation variation for well defined lung malignancies that can be delineated with a high confidence in a CT image. So any small-cell cancers or lymphomas, as well as any malignancies that included multiple cancerous outbreaks had to be excluded. Similarly to the prostate case, most of the patients underwent postoperative Radiation Therapy. Among those patients that underwent a radical 3D radiation therapy having a GTV, only a few fulfilled the requirements mentioned above. Due to heavy workload, only two of those cases were ultimately chosen. Participants were asked to delineate the GTV, which in this case is not considered to be the whole organ. Like before, a medical physicist was present to assist with the imaging parameters.
Regarding brain, patients undergoing EBRT were only a few during this 9 month period. Most of the cases were treated in the old linear accelerator, while some of those that were treated in the INFINITY LINAC were treated with the use of hypofractionated radiotherapy. Like before, two typical and representative cases of brain malignancies were selected. Both of the patients had MR images as well, which were fused with the CT images using the utilities provided by the MONACO treatment planning system. All four participants found the MR images more helpful and chose to delineate the targets taking advantage of its superior visual result in brain imaging. So, yet again, all doctors drew using the same modality.
2.8.2 University Hospital of Larissa

Within the Radiation Therapy treatment chain, delineation of the target volumes is performed by the physicians. However, some OARs are delineated by the radiation physicists, who are also responsible for the treatment planning.

Normally, the doctors of the department study the file of each patient and then delineate the target volumes. When the RT is not post-operative, they usually delineate the GTV, although sometimes, based on their clinical judgment, they might delineate the CTV directly. If the RT is postoperative and there is no GTV, they draw the CTV, creating the tumour bed. The delineation of the tumour bed is performed on the basis of the RTOG protocol.

Due to heavy workload, only the prostate delineation error could be assessed. In the case of a lung tumour, radiation therapists always consult a PET scan for the delineation of the target volumes, using a second PC monitor. Unfortunately, this type of imaging could not be imported to the MONACO Treatment Planning System yet, due to lack of expertise. Therefore, it would be not representative of the day-to-day clinical routine to delineate any lung malignancies just by looking at the CT images.

Three patients with a malignant neoplasm of the prostate, who were treated at the department, were selected for the experiment. All three patients had a well defined GTV and their CT images were acquired within the Hospital, using the same CT scanner. Three doctors agreed to participate in this experiment. In order to reproduce the exact conditions under which they normally work, the doctors chose for themselves the parameters of the CT images, such as window width and contrast. Similarly to the University Hospital of Patras, each doctor performed the task alone and without looking at the contours of the rest. Also, they were asked to delineate the prostate gland alone and not the seminal vesicles.

2.8.3 Theageneio Anticancer Hospital of Thessaloniki

No data could be retrieved regarding the delineation process of this department, due to the heavy workload of the staff.
3 Results

3.1 University Hospital of Patras, Rio

In total, data from 43 patients and 357 CBCTs were recorded, categorized, studied and statistically analyzed. The imaging ratio of the department was found to be 27%. Assessment of all errors across the radiotherapy treatment chain was essential in order to quantify the PTV margin needed for each anatomical site.

3.1.1 Assessment interfraction organ motion (prostate and lung cases)

Data from 20 patients that received prostate radiation therapy and from 12 patients that received lung radiotherapy were analyzed. Interfraction organ motion was calculated according to the method described in Figure 2.1, using the specific patient population data that derived after dual registration correction. In total, 184 and 95 CBCTs were registered to the reference CTs for the prostate and lung cancer patients respectively. The results of these registrations were recorded and statistically analyzed. The imaging ratio was found to be 28% for prostate cases and 33% for lung cases. Both systematic ($\Sigma_m$) and random ($\sigma_m$) components of the interfraction organ motion are listed in Table 3.1, with respect to the anatomical site. The largest values were observed in the vertical direction for both types of errors and for both sites, while the smallest were observed in the lateral direction.

| Table 3.1: Systematic and random translational errors attributed to interfraction motion of the prostate bed |
|---|---|---|
| | LR (mm) | SI (mm) | AP (mm) |
| | $\Sigma_m$ | $\sigma_m$ | $\Sigma_m$ | $\sigma_m$ | $\Sigma_m$ | $\sigma_m$ |
| Prostate | 0.5 | 1.0 | 1.4 | 1.7 | 2.4 | 2.4 |
| Lung | 1.6 | 1.9 | 1.9 | 1.9 | 2.2 | 2.7 |
For the anatomical site of the prostate, these values are in good agreement with other results from the literature, as seen in Table 3.2.

**Table 3.2:** Comparison of systematic and random translational errors attributed to interfraction prostate or prostate motion for a selection of studies

<table>
<thead>
<tr>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( \Sigma_m )</td>
<td>( \sigma_m )</td>
<td>( \Sigma_m )</td>
</tr>
<tr>
<td>Current thesis interfraction motion</td>
<td>0.6</td>
<td>1</td>
<td>1.4</td>
</tr>
<tr>
<td>van Herk 2004(^{14})</td>
<td>0.9</td>
<td>0.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Stroom et al. 1999(^{15})</td>
<td>0.5</td>
<td>0.6</td>
<td>2.7</td>
</tr>
<tr>
<td>Huang et al. 2011(^{16})</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Soete et al. 2007(^{17})</td>
<td>1.3</td>
<td>1.6</td>
<td>4.2</td>
</tr>
<tr>
<td>Tanyi et al. 2010(^{17})</td>
<td>0.5</td>
<td>0.4</td>
<td>2.9</td>
</tr>
<tr>
<td>Ost et al. 2011(^{18})</td>
<td>0.4</td>
<td>1.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Graf et al. 2012(^{19})</td>
<td>0.5</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Glowacki et al. 2015(^{20})</td>
<td>1.1</td>
<td>1.2</td>
<td>3.1</td>
</tr>
</tbody>
</table>
For lung, the values found are comparable with other results from the literature as well, as seen in Table 3.3.
Table 3.3: Comparison of systematic and random organ motion of lung for a selection of studies

* Referred as interfraction baseline variation, i.e. day-to-day variation in the mean time-weighted tumor position

<table>
<thead>
<tr>
<th>Site</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current thesis</td>
<td>1.7</td>
<td>2.1</td>
<td>2.1</td>
<td>lung</td>
</tr>
<tr>
<td>Wolthaus et al. 2008*</td>
<td>1.6</td>
<td>1.2</td>
<td>3.9</td>
<td>lung</td>
</tr>
<tr>
<td>Sonke et al. 2009*</td>
<td>1.8</td>
<td>1.1</td>
<td>2.9</td>
<td>lung</td>
</tr>
</tbody>
</table>

Figure 3.3: Systematic organ motion for a selection of studies
The values that derived by dual registration were used for the calculation of the CTV-to-PTV margin for Rio Radiation Therapy department as well as for the other two departments, since they were considered to be representative of the interfraction organ motion of these anatomical sites.

3.1.2 Delineation Error

Delineation error was calculated for the anatomical sites of prostate, lung and brain using the methodology and the formulas that are described in subchapter 2.X. The results are listed in Table 3.3. For prostate delineation, the largest overall observer deviation is spotted along the longitudinal axis and the smallest in the vertical axis, while a significant deviation is also present in the lateral direction. For lung delineation, the predominant error can be spotted in the vertical axis, while large deviations are also seen in both lateral and longitudinal axes. For brain delineation, interobserver deviation exceeds the 3 mm along the posterior direction and shows a significant value along the longitudinal axis as well, while it is clearly confined in the lateral axis.
**3.1.3 Setup error**

Quantification of the setup error was performed according to the methodology described in subchapters 2.4.1, 2.4.2 and *Figure 2.1* with the use of the translations recorded into the system after the registration of each treatment’s CBCT with the reference CT. All patients were treated in supine position. For each anatomical region, same immobilization devices were used among patients.

Initially, the setup error without any offline or online corrections was calculated; that is, the data of every IGRT fraction was used for the calculation. This is the “no corrections” method for calculating the setup error and was performed for every anatomical site. On a second level, a calculation of the setup error occurred with the “offline correction” method, where translations of the three first fractions were excluded. Then, according to the “scaling” method, a scaling was performed to both systematic and random setup errors that derived using the “no corrections” method. Finally, for prostate, lung and brain cancer cases, setup error was calculated by taking into account both offline and online corrections, according to the “hybrid” method. Systematic and random setup errors with respect to the method followed for their quantification can be seen in *Table 3.5* and *Figures 3.5 & 3.6*.

For prostate, execution (random) errors are predominant along all axes when no correction is applied as well as when an offline NAL correction is applied, but dramatically decrease when the scaling method and the hybrid method of online and offline corrections are used. Preparation (systematic) errors appear to increase along the lateral and longitudinal axes after

<table>
<thead>
<tr>
<th></th>
<th>Lateral (mm)</th>
<th>Longitudinal (mm)</th>
<th>Vertical (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
<td>Superior</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>1.1</td>
<td>1.8</td>
<td>1.7</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>1.7</td>
<td>1.4</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td>0.7</td>
<td>1.2</td>
<td>1.5</td>
</tr>
</tbody>
</table>
the implementation of the offline correction, which is in total contradiction of what was anticipated, but significantly decrease when the scaling and hybrid methods are applied. The reasons that led to the increase of the systematic setup error after the application of the offline correction will be thoroughly discussed in the next chapter. Quantification of the setup errors according to the scaling and hybrid methods resulted in significantly lower values.

For lung, random errors predominate along each axis when no correction strategy is applied, but slightly decrease when the offline correction is taken into account. The values of the random setup errors reduce even further when the scaling method is applied and are drastically limited when the hybrid correction model is taken into account. Systematic setup errors are slightly reduced along the vertical axis after the offline correction is performed, but increase significantly along the lateral axis and the longitudinal axis, against expectations. Finally, they are notably limited when the scaling and hybrid methods are used for the calculations.

For brain, setup errors are confined, but remain significant. Positioning after the offline correction seems to get worse in terms of systematic error along the lateral and vertical axes, while it is reduced in half along the longitudinal axis. However, setup errors are significantly lower when offline and/or online corrections are taken into account.

For abdomen, random setup errors appear to be significant before the online correction, but are limited after the three initial fractions, while systematic errors increase significantly along all the axes.

Finally, for gynaecological malignancies random setup errors are larger than systematic when no correction is applied, but when the three first fractions are excluded from the calculation systematic errors become larger while random errors are limited. The scaling method results in the smallest errors.
Table 3.5: Quantification of setup errors for the positioning of patients on several anatomical sites with respect to the different methodologies of calculation

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
<th>Number of patients</th>
<th>Imaging ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Σs</td>
<td>σs</td>
<td>Σs</td>
<td>σs</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
<td>2.4</td>
<td>3.6</td>
<td>2.0</td>
<td>3.6</td>
<td>1.8</td>
</tr>
<tr>
<td>offline correction</td>
<td>3.3</td>
<td>3.1</td>
<td>2.7</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>scaling</td>
<td>1.7</td>
<td>2.6</td>
<td>1.4</td>
<td>2.6</td>
<td>1.3</td>
</tr>
<tr>
<td>hybrid</td>
<td>2.4</td>
<td>1.9</td>
<td>1.5</td>
<td>1.6</td>
<td>1.2</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
<td>3.9</td>
<td>4.7</td>
<td>3.0</td>
<td>3.2</td>
<td>2.1</td>
</tr>
<tr>
<td>offline correction</td>
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<td>3.3</td>
<td>3.6</td>
<td>2.3</td>
<td>1.9</td>
</tr>
<tr>
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<td>1.4</td>
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<td>2.7</td>
<td>2.0</td>
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<td>Brain</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
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<td>1.3</td>
<td>1.2</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
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<td>1.4</td>
<td>0.6</td>
<td>1.6</td>
<td>2.0</td>
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<td>1.0</td>
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</tr>
</tbody>
</table>
Figure 3.5: Systematic setup error, $\Sigma_s$, for every anatomical site
Figure 3.6: Random setup error, $\sigma_s$, for every anatomical site
3.1.4 Calculation of the required PTV margins

The margin that needs to be added to the CTV in order to obtain the PTV for the various anatomical sites, while making sure that 90% of patient population will get at least 95% of the prescribed CTV dose, was calculated with the use of the van Herk formula, as it is expressed in equation (2.3):

\[ M = 2.5\Sigma + 1.64(\sigma - \sigma_p) \]

For lung, CTV-to-PTV margins are calculated using equation (2.8):

\[ M = 2.5\Sigma + 0.84(\sigma - \sigma_p) \]

To obtain the total systematic error, \( \Sigma \), the systematic errors that originate from different sources of errors have to be added in quadrature, as expressed in equation (2.7). The same applies for the total random error, \( \sigma \), which is derived when all of its components are be added in quadrature, as seen in equation (2.5).

For this thesis, the procedures of target delineation and patient setup, as well as the interfraction and intrafraction organ motion were considered to be sources of errors. Excluding delineation error that only has a systematic component and Gaussian penumbra that only has a random component, every other source of errors has both a systematic and a random component. Therefore, for the calculation of the total systematic error, \( \Sigma \), systematic setup error \( \Sigma_s \), systematic interfraction organ motion \( \Sigma_m \), systematic intrafraction motion \( \Sigma_{\text{intra}} \) and systematic delineation error \( \Sigma_d \) were considered. Likewise, for the calculation of the total random error, \( \sigma \), random setup error \( \sigma_s \), random interfraction organ motion \( \sigma_m \), random intrafraction organ motion \( \sigma_{\text{intra}} \) and the standard deviation of the Gaussian penumbra \( \sigma_p \) were considered. On the contrary, any errors that may occur during image registration between the treatment CBCT and the reference CT images or any other residuals were not taken into account.

All results can be seen in Table 3.6.
3.1.5 Assessment of the PTV margins for prostate irradiation

Quantification of the required CTV-to-PTV margin for the anatomical site of the prostate was performed by using the interfraction organ motion, delineation error and setup error as they were derived in subchapters 3.1.1, 3.1.2 and 3.1.3 respectively and can be seen in Table 3.6 and Figure 3.10. Four different calculations were performed, with respect to the different methods that were used for the assessment of the setup error. Data about intrafraction organ motion were retrieved by the work of Tanyi et al.173 The magnitude of the margin follows the trend created by the different values of setup error depending on the calculation method used. All other values, i.e. delineation error, interfraction and intrafraction organ motion remain the same. The exclusion of the initial three fractions of every treatment, that is the offline correction, only seems to work along the vertical axis, thus following the trend of the setup error. Along the lateral and longitudinal axes results are not what it was expected, since larger margins are required after the offline correction was applied. However, PTV margins significantly reduce when the online corrections are taken into account, according to the scaling method. The hybrid method results in even further reduction of the required PTV margins along longitudinal and vertical axes.

Figure 3.7: CTV-to-PTV margins for the prostate depending on the correction method

![Graph showing CTV-to-PTV margins for the prostate depending on the correction method]

- no corrections
- offline correction
- scaling
- hybrid
3.1.6 Assessment of the PTV margins for lung irradiation

Target delineation and setup errors were assessed in subchapters 3.1.2 and 3.1.3 respectively. For the time being there is a lack of proper equipment and dedicated software that could provide the possibility of 4DCT and 4D-CBCT acquisition, so no data regarding organ motion is available. This means that treatment planning cannot be performed at the time-weighted average target position and thus a systematic organ motion component is introduced. An attempt to assess interfraction organ motion with the use of the dual registration method was made. Intrafraction organ motion data was retrieved by the work of Sonke et al. 2009.9

Generous margins are required along the lateral axis, mainly due to large setup errors observed in this direction. Excluding the first three fractions results to greater margins; this means that the offline correction did not deliver the anticipated result for this anatomical site either. Reduced values for PTV margins derived by the scaling and hybrid methods.

Figure 3.8: CTV-to-PTV margins for lung depending on the correction method

3.1.7 Assessment of the PTV margins for brain irradiation

The values of delineation and setup errors were found previously and are used for the assessment of the PTV margin. Organ motion is absent inside the brain, so all of its
components are considered to be zero. The required PTV margin is small compared to other anatomical sites and offline correction seems to have little effect on it. Greater values are observed along the vertical axis, while lower deviations are present along the lateral axis.

3.1.8 Assessment of the PTV margins for abdomen irradiation

No department-specific values of delineation deviation and organ motion are available for this anatomical region. However, a value of 2.5 mm was chosen to represent the delineation error, based on the methodology that is usually followed for margin calculation during educational courses in radiation therapy. On the other hand, organ motion has not been taken into account for margin calculation for abdomen malignancies in this thesis.

3.1.9 Assessment of the PTV margins for gynaecological malignancies

Department-specific values of delineation error and organ motion were not available for this particular anatomical size. Again, a broad value of 2.5 mm was considered to be
representative to express delineation deviation and organ motion was not taken into consideration for margin calculation.

### 3.1.10 Synopsis of margins

All the required PTV margins that were calculated for each anatomical site with respect to the calculation method can be seen in Table 3.11 and Figure 3.11. Note that for the categories of abdomen and gynaecological malignancies organ motion was not considered for margin calculation and thus an extra margin should be added by the physicians, according to the specific organ being irradiated and based on their clinical opinion.

**Table 3.6: Inclusion of the required PTV margins for the radiotherapy department of University Hospital of Patras**

*Organ motion not included*

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
<td>10.5</td>
<td>11.4</td>
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<td>offline correction</td>
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<td>scaling</td>
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<td>9.2</td>
<td>7.4</td>
</tr>
</tbody>
</table>
Figure 3.10: PTV margins for every anatomical site with respect to the method of calculation

*Organ motion not included for abdomen and gynaecological
3.2 University Hospital of Larissa

In total, data from 67 patients and 777 CBCT scans over 2035 fractions were recorded, categorized, studied and statistically analyzed. The imaging ratio of the department was found to be 38%.

3.2.1 Assessment of prostate delineation variation

Three radiation oncologists participated in the process of quantifying the prostate delineation error. Based on their contours, an overall delineation variation was derived, as seen in Table 3.9.

![Table 3.7: Inter-observer variation of prostate delineation](image)

<table>
<thead>
<tr>
<th>Lateral (mm)</th>
<th>Longitudinal (mm)</th>
<th>Vertical (mm)</th>
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<td>Right</td>
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3.2.2 Setup errors

The methodology followed for the quantification of setup error is similar to the one that was used for General University Hospital of Rio. The calculation method which accounts for hybrid correction strategies that include both offline and online corrections was used for the anatomical sites of prostate, lung and breast, because malignancies of these sites make up the majority of cases treated in the new Elekta Infinity linear accelerator during its first year of operation. In general, excluding the translations that occurred during the three initial fractions from setup errors calculations, and therefore accounting for the offline correction performed, results in reduced errors. When offline and/or online corrections are taken into account, setup errors are limited even more.
Table 3.8: Quantification of setup errors for the positioning of patients on several anatomical sites with respect to the different methodologies of calculation

<table>
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<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
<th>Number of Patients</th>
<th>Imaging Ratio</th>
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<tr>
<td></td>
<td>( \Sigma )</td>
<td>( \sigma )</td>
<td>( \Sigma )</td>
<td>( \sigma )</td>
<td>( \Sigma )</td>
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<tr>
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<td>2.4</td>
<td>1.0</td>
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<tr>
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<td>1.6</td>
<td>0.7</td>
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3.2.3 Calculation of the required PTV margins

Required PTV margins for each anatomical site can be seen in Table 3.10.

For the quantification of the PTV margin in the anatomical site of the prostate, the department-specific values of delineation deviation and setup errors were used. Since there was no data available regarding organ motion, the values of interfraction prostate motion that were found for Rio’s Hospital are used; intrafraction prostate motion data were retrieved by the work of Tanyi et al.\textsuperscript{173} Margins along the vertical axis are larger, but decrease remarkably when correction strategies are accounted for. Margins also decline along both lateral and longitudinal axes when the correction protocols are simulated.

\textit{Figure 3.11: PTV margins for prostate irradiation depending on the correction method}

![Figure 3.11: PTV margins for prostate irradiation depending on the correction method](image)

Setup error for patient positioning in lung was retrieved by Table 3.13. For interfraction organ motion and delineation error, data from Rio’s corresponding department was used, while data regarding intrafraction motion was retrieved by the work of Sonke et al.\textsuperscript{9} Remarkable reduction of the required margin can be observed along the vertical axis after correction strategies are applied. Significant margin reduction is also achieved in the craniocaudal direction.
For an irradiation with opposed fields, which is usually the case for breast irradiation, the conformation is better in 2D instead of 3D. In such a case, the column for 2D errors from Table 2.2 is most suitable. Therefore, margins for breast irradiation were calculated based on the formula

\[
M = 2.15\Sigma + 1.64\left(\sigma - \sigma_p\right)
\]  

(3.1)

Delineation error is assumed to be small along all axes and is given a value of 2 mm. Organ motion could not be assessed, but added margins of 5 mm are considered acceptable to account for it, as most inter- and intrafraction motion is less than 5 mm. PTV margins with an incorporated margin of 5 mm to account for breast motion can be seen in Table 3.10. Accounting for the offline correction (offline correction method) results in great reduction of the required margins along longitudinal and vertical axes, while the scaling method and the hybrid method both result to even smaller values.

| Table 3.9: margins for breast irradiation without taking account for organ motion |
|---------------------------------|-----------------|-----------------|-----------------|
|                                 | LR (mm)         | SI (mm)         | AP (mm)         |
| no correction                  | 7.9             | 9.6             | 11.3            |
| offline correction             | 8.4             | 7.0             | 8.9             |
| scaling                        | 5.4             | 6.0             | 6.6             |
| hybrid                         | 5.8             | 5.6             | 5.6             |

The required PTV margins for head and neck cases were calculated with respect to setup and delineation errors. Delineation error was given a representative value of 2 mm. On the contrary, organ motion could not be assessed and has not been taken into account.

Assessment of the required PTV margin for gynaecological malignancies was performed with respect to the in-house data regarding setup errors and a selected value of 2.5 mm for delineation deviation, which was considered to be both realistic and representative for the department. Because motion of the various organs being treated in gynaecological malignancies tend to differ significantly between each other (i.e. uterine motion, uterine canal
motion, uterine fundus motion, endometrial motion, cervical motion, cervical os motion, vaginal motion, lymph nodes motion etc.), it is hard to assess a general value that will be representative for each of these particular sites. Generally, generous margins are applied for gynaecological malignancies, due to the large magnitude of motion that most of these sites display. Therefore, margins to account for both interfraction and intrafraction organ motion have to be carefully selected according to each case by the physicians and then be added to the margins derived by this thesis.

For rectum cancer, all patients were treated with the same positioning, that is feet first and in prone position, and with the use of the same immobilization devices. Geometrical uncertainties of setup and delineation errors have been taken into consideration for margin calculation; an indicative value of 2.5 mm was chosen as the delineation variation along all three axes. On the other hand, organ motion has not been addressed for this particular anatomical site and proper margins should be added in order to account for it. For abdomen irradiation, required PTV margins derived by accounting for setup and delineation errors. Because many organs fall into this category, it would be wrong to adopt a sole value of organ motion. Having the proper PTV margin for setup and delineation errors, physicians should choose an extra safety margin to account for geometrical uncertainties attributed to the specific organ being treated each time. Delineation error was assumed to be 2.5 mm.

3.2.4 Synopsis of margins

The required margins for each anatomical site with respect to the calculation method used for their derivation can be seen in Figure 3.12 and Table 3.10. For breast irradiation, a suggested extra margin of 5 mm to account for organ motion is included in the given value. For head & neck, abdomen and gynaecological malignancies organ motion was not considered for the derivation of the required PTV margins and an appropriate margin has to be added each time by the physicians.
Table 3.10: Inclusion of PTV margins for various anatomical sites with respect to the method of calculation used for their derivation

* An added margin to account for organ motion is included
** Organ motion was not included in calculations

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
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<tr>
<td>no corrections</td>
<td>8.3</td>
<td>9.7</td>
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<td>8.0</td>
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<tr>
<td>scaling</td>
<td>7.1</td>
<td>7.8</td>
<td>8.4</td>
</tr>
<tr>
<td>Abdomen**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
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<td>11.0</td>
</tr>
<tr>
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<tr>
<td>scaling</td>
<td>8.0</td>
<td>9.7</td>
<td>8.9</td>
</tr>
</tbody>
</table>
Figure 3.12: Inclusion of PTV margins for various anatomic sites, with respect to the method of calculation used for their derivation

* An added margin to account for breast organ motion is included

** Organ motion was not included for head & neck, gynaecological, rectum and abdomen
3.3 Theageneio Anticancer Hospital, Thessaloniki

In total, data from 147 patients and 821 CBCT scans over 4129 fractions were recorded, categorized, studied and statistically analyzed. The imaging ratio of the department was found to be 20%.

3.3.1 Setup error

No offline correction is performed in this department. Generally, a treatment scan is performed during the three initial fractions of each patient and then, for most of the cases, weekly CBCT scans are programmed for the rest of the treatment. Every time a CBCT was performed, an online correction of the couch position was made. Using the hybrid method, an extra calculation of the PTV margins for the sites of prostate and lung was made, accounting for these online corrections. In general, significant setup errors were observed. Systematic and random components of the setup error can be seen in Table 3.23.

3.3.2 Assessment of PTV margins for several anatomical sites

For prostate, a median of the values of delineation deviation from the other two departments was set as the delineation error. For lung and brain, delineation errors were retrieved from UGHP, as well as the prostate and lung organ motion. For the rest of the anatomical sites, the same arbitrary delineation error values as in the other two departments were used. Organ motion has not been taken into account for margin calculation for head and neck, gynaecological, abdomen, rectum and bladder malignancies. For breast irradiation, an extra margin of 5mm is incorporated into the PTV margin value. All calculated margins can be seen in Table 3.12 and Figure 3.13.
Table 3.11: Systematic and random setup errors for various anatomical sites with respect to the method used for their calculation

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
<th>Number of Patients</th>
<th>Imaging Ratio</th>
</tr>
</thead>
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<tr>
<td></td>
<td>Σs</td>
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<td>σs</td>
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<td>2.9</td>
<td>2.6</td>
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</tr>
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<td>2.4</td>
<td>2.1</td>
<td>2.3</td>
<td>2.7</td>
</tr>
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<td>2.3</td>
<td>1.2</td>
<td>2.4</td>
<td>1.3</td>
<td>2.7</td>
</tr>
<tr>
<td>Lung</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3.0</td>
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<td>3.1</td>
<td>3.1</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>hybrid</td>
<td>2.9</td>
<td>1.8</td>
<td>2.9</td>
<td>1.7</td>
<td>2.3</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
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<td>1.8</td>
<td>2.6</td>
<td>2.4</td>
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<td>2.0</td>
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<td></td>
<td></td>
<td></td>
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<tr>
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<td>2.8</td>
<td>2.8</td>
<td>2.9</td>
<td>2.9</td>
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<tr>
<td>Head &amp; Neck</td>
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<td></td>
<td></td>
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<td></td>
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<td>1.9</td>
<td>2.0</td>
</tr>
<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3.1</td>
<td>3.4</td>
<td>3.1</td>
</tr>
<tr>
<td>Rectum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
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<td>3.1</td>
<td>3.2</td>
<td>2.8</td>
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</tr>
<tr>
<td>scaling</td>
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<td>2.5</td>
<td>2.6</td>
<td>2.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Abdomen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
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<td>3.8</td>
<td>3.4</td>
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</tr>
<tr>
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<td>3.1</td>
<td>2.8</td>
<td>2.7</td>
<td>2.2</td>
</tr>
<tr>
<td>Bladder</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>no corrections</td>
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<td>3.7</td>
<td>1.4</td>
<td>2.5</td>
<td>3.6</td>
</tr>
</tbody>
</table>
Table 3.12: Inclusion of PTV margins per anatomical site with respect to the method of calculation used

* A margin of 5 mm to account for organ motion is included
** Organ motion not included

<table>
<thead>
<tr>
<th>Method</th>
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<th>SI (mm)</th>
<th>AP (mm)</th>
</tr>
</thead>
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<td></td>
</tr>
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<td>11.5</td>
<td>14.0</td>
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<td>8.9</td>
<td>10.2</td>
<td>12.4</td>
</tr>
<tr>
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<td>10.0</td>
<td>11.8</td>
</tr>
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<td>Lung</td>
<td></td>
<td></td>
<td></td>
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<tr>
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<tr>
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<td>9.5</td>
<td>10.7</td>
</tr>
<tr>
<td>scaling</td>
<td>7.4</td>
<td>8.3</td>
<td>9.6</td>
</tr>
<tr>
<td>Breast*</td>
<td></td>
<td></td>
<td></td>
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<td>18.8</td>
</tr>
<tr>
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<td>13.2</td>
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<td>Head &amp; Neck**</td>
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<td></td>
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<td>8.8</td>
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<td>7.9</td>
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<tr>
<td>Gynaecological**</td>
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<td>15.2</td>
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</tr>
<tr>
<td>Rectum**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no correction</td>
<td>12.7</td>
<td>11.9</td>
<td>13.6</td>
</tr>
<tr>
<td>scaling</td>
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<td>10.1</td>
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</tr>
<tr>
<td>Abdomen**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no correction</td>
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<td>12.9</td>
<td>11.0</td>
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<td>Bladder**</td>
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<td></td>
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<tr>
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<tr>
<td>scaling</td>
<td>10.0</td>
<td>7.5</td>
<td>11.9</td>
</tr>
</tbody>
</table>
Figure 3.13: Inclusion of PTV margins for various anatomic sites, with respect to the method of calculation used for their derivation

* 5mm margin included to account for breast organ motion

** Organ motion not included for head & neck, gynaecological, rectum, abdomen and bladder
4 Discussion

4.1 Comparisons between the departments

4.1.1 Delineation errors

Delineation variation among the participants was found to be similar in both departments. A comparison of the values can be seen in Figure 4.1. The only significant difference can be seen in the superior direction, where the participants in Larissa showed a particularly small variation in the delineation of the prostate gland apex. However, this difference between the participants of the two departments might have occurred due to the image quality and the anatomical characteristics of the patients studied. It is of great importance to remind that this experiment was performed separately in the two departments and participants in each department were asked to delineate targets belonging to patients that had been previously treated in their own department. Thus different parameters, such as patients, equipment and acquisition protocols might alone lead in different values of delineation error for each department. Besides, this was the rationale behind the assessment of the department-specific delineation deviation.

Despite the small values, the contribution of the delineation error to the final PTV margin should not be underestimated; even without any offset corrections, it remains comparable to both setup error and organ motion. Moreover, it becomes the predominant source of errors when daily setup corrections are performed, or even when a successful offline NAL correction strategy is performed. Additionally, this experiment was performed under some idealized conditions, such as the exclusion of the seminal vesicles for the prostate delineation, the selection of well defined tumors in both lung and brain cases, the underestimation of clinical judgment and the adjuvant presence of a treatment planning expert. It is noteworthy to mention that “perfect” delineation cannot exist and uncertainties will always be present, due to technical or medical reasons. So, since there is no “golden standard”, the adoption of evidence-based contouring protocols that are based on phase III randomized studies is crucial, ensuring less heterogeneity in contouring among the physicians of the department and thus leading to smaller interobserver delineation variations.42
Delineation error can be a useful measure of intra-department deviation regarding target delineation when everyone involved in this process is drawing on the basis of proper guidelines. On the other hand, it might not be appropriate for margin calculations when the physicians draw excessively large contours in order to avoid target miss. This tactic was prevalent during past years, when no scientific approach regarding errors and margins was available and population based data could not be recorded. However, some doctors still delineate the targets conservatively and wish to account for any geometrical misses by this contour alone. Despite the good intentions though, this approach usually results in large margins and it is not suitable for dose escalation and modern radiotherapy techniques, such as IGRT. It is, therefore, strongly recommended to adopt and follow contouring protocols, as mentioned before.

In conclusion, there were certain limitations in the process of evaluating the delineation deviation. The specimen of both the participants as well as the patients was relatively small. The clinical data regarding each patient’s file were not available to the participants and this might have resulted in greater deviations. Additionally, due to the lack of this information, the delineation procedure of each department cannot be assessed in terms of clinical judgment. Finally, acquisition and statistical analysis of the data was performed in Cartesian coordinates, while similar experiments have used polar coordinates,\textsuperscript{27} and this particular technique of evaluating the delineation error is just one of the many used in literature.\textsuperscript{181}

\textit{Figure 4.1: Comparison of prostate delineation deviation between University Hospitals of Patras and Larissa}
4.1.2 Setup errors and correction strategies

Positioning variations introduce a considerable error in the radiation therapy treatment chain, therefore assessing the setup errors was a crucial part for determining the PTV margin for each anatomical site. In general, the scaling method is the most representative for the quantification of the setup errors in our departments. It accounts for the online corrections performed throughout the treatment and the inclusion of the three initial offsets in the calculations has a minor effect on the results. Note that this scaling should be applied to the standard deviation of the averages of all patients (i.e. to the systematic setup error) and to the root mean square of the standard deviations of all patients (i.e. to the random setup error) and not to each patient separately. This is because the imaging ratio, on the basis of which the scaling occurs, is derived by population data, thus the whole method is a patient-population approach.

Table 4.1: Comparison of the imaging ratio among the departments

<table>
<thead>
<tr>
<th></th>
<th>prostate</th>
<th>lung</th>
<th>brain</th>
<th>breast</th>
<th>head &amp; neck</th>
<th>gynaec/col</th>
<th>abdomen</th>
<th>rectum</th>
<th>bladder</th>
<th>AVERAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patras</td>
<td>28</td>
<td>33</td>
<td>26</td>
<td>n/a</td>
<td>n/a</td>
<td>27</td>
<td>31</td>
<td>n/a</td>
<td>n/a</td>
<td>29</td>
</tr>
<tr>
<td>Larissa</td>
<td>38</td>
<td>32</td>
<td>n/a</td>
<td>43</td>
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<td>37</td>
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<td>21</td>
<td>18</td>
<td>20</td>
<td>19</td>
<td>20</td>
</tr>
</tbody>
</table>

On the other hand, including the results of the initial fractions when only an offline correction is performed would have a blurring effect on the derived results. In order to outline the different approach that is needed when an offline correction is performed, two methods of setup errors calculation have been investigated in this thesis, despite the fact that none of our departments perform an offline correction protocol alone.

Setup errors have both a systematic and a random component, with the systematic component representing the preparation phase of the treatment and the random component representing the execution phase. Because systematic errors have a greater impact in required margins, it should be one’s intention to limit them as much as possible. In order to achieve that, offline correction strategies are usually applied, since they require a minimum effort and usually give a good result.140

A NAL offline correction strategy is followed in the University Hospitals of Patras and of Larissa. This thesis proposed a method of statistical analysis of the data in order to account for this type of correction during the quantification of the setup errors, by discarding from the
calculations the offsets that derived during the three initial fractions, because they are not representative of the positioning of the patient for the rest of the fractions to be delivered. It is essential to clarify that this offline correction is applied anyway and the rejection of the three first fractions is a method to avoid mixing the data that derived before the implementation of the offline correction with the data that derived after the application of the correction. The mixture of these data would somehow “blur” the results, with respect to the derived setup errors. However, a calculation including all the IGRT fractions is also made. Despite the fact that this calculation method is frequently referred as “no corrections” for simplicity reasons, it has to be clear that the offline correction was applied anyway for every patient and this method was used in order to represent the difference between accounting and not accounting for the offline correction and to present an example of setup error calculations for departments that do not follow any correction strategies. Also, this method comprised the basis for the application of the scaling, in the scaling statistical analysis method.

In general, it was expected that rejecting the three first fractions from setup errors calculation would result in a decrease of setup error values. However, this only applied for the department of Larissa, while in Patras the values of the setup error increased. In other words, instead of achieving smaller offsets during the rest of the treatment after the three initial fractions, larger values were observed. In order to quantify the relation between the setup errors derived during the three first fractions (i.e. before the offline correction was applied) and those derived during the rest of the treatment, an extra calculation was made and can be seen in Table 4.1. It is reported that systematic error may decrease up to 50% when an offline correction is applied.\(^{149}\) This is actually the case for University Hospital of Larissa, where the offline correction seems to work well, by reducing the values of the systematic error by 47% on average. On the other hand, for the department of Patras an unexpected increase by 63% on average was observed. The reasons for this increase should be sought mainly in the preparation phase of the treatment.

Patras applies a complicated, multi-step preparation protocol that may introduce significant geometrical uncertainties. The use of the simulation phase, despite giving to the physicians the advantage of visually verifying the isocenter location using radiographic images, inevitably introduces some systematic errors due to the use of separate equipment (machine, treatment couch, isocenter lasers). Moreover, drawing in total 3 different sets of non-permanent marks throughout the course of the treatment (i.e. one set during localization, one set during simulation and one set after the application of the offline correction, where the
final permanent tattoos are drawn later) results in larger errors. Additionally, drawing the permanent marks in the isocenter may give an extra visual confirmation to the RTTs, but jeopardizes reproducibility, because these spots may display great interfractional differences due to skin movement. More importantly, the data extracted from this department corresponded to a period when the staff was on a learning curve. The notion of an offline correction was not completely clear at the time, resulting in intuitive interventions and corrections on behalf of the staff during the positioning of the patient during the first treatments. Despite these corrections may have temporarily fixed the offsets for these particular fractions, on the long run they resulted in inaccurate localization trends and thus in large offsets throughout the treatment. Also, lack of ventral alignment marks results in great errors along the lateral axis. Finally, positioning error would be better evaluated if a standard tattoo protocol per anatomical site was followed. Therefore, skipping the simulation phase and adopting a standard tattoo-drawing and immobilization protocol for each anatomical site would be preferable when a modern linear accelerator with IGRT capabilities is available.

Table 4.2: Comparison of the systematic component of setup error, Σ, before and after the application of the offline correction for the department of Patras.

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
</tr>
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<tr>
<td>Prostate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>2.1</td>
<td>2.8</td>
<td>3.2</td>
</tr>
<tr>
<td>after</td>
<td>3.3</td>
<td>2.8</td>
<td>1.7</td>
</tr>
<tr>
<td>difference</td>
<td>+57%</td>
<td>0%</td>
<td>-48%</td>
</tr>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>6.2</td>
<td>4.3</td>
<td>3.6</td>
</tr>
<tr>
<td>after</td>
<td>4.6</td>
<td>3.6</td>
<td>1.9</td>
</tr>
<tr>
<td>difference</td>
<td>-26%</td>
<td>-15%</td>
<td>-46%</td>
</tr>
<tr>
<td>Brain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>before</td>
<td>1.0</td>
<td>2.4</td>
<td>1.3</td>
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<tr>
<td>after</td>
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<td>2.4</td>
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<tr>
<td>difference</td>
<td>+72%</td>
<td>-72%</td>
<td>+79%</td>
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<td>before</td>
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<td>3.2</td>
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<tr>
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<td>+26%</td>
<td>+60%</td>
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<tr>
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<tr>
<td>difference</td>
<td>+397%</td>
<td>+36%</td>
<td>+447%</td>
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</tbody>
</table>

Larissa’s radiotherapy department makes a proper use of the NAL offline correction strategy. Although the department-established constrains allow offsets up to 20 mm, it is the staff’s
intention to consider realignment when 10mm of translations are exceeded. It is also usual to
go over a new triplet of IGRT fractions when application of the initial offline correction
results in translations larger than 7 mm. When a new IGRT triplet is applied, results of the
initial three fractions must be discarded from the calculation of the new mean offset. Because
dose escalation fields do not share the same isocenter with the originals, the procedure of the
offline correction is repeated from the scratch when a new phase of treatment begins and a
new mean offset is calculated out of a triplet of IGRT fractions. This could be avoided if the
original mean offset was incorporated into the new localization trend derived by the treatment
planning system, but this would be a manual procedure and thus error prone. A much simpler
solution would be for the new fields to share the same isocenter with the originals; this
capability is provided by modern linear accelerators that have Multi-Leaf Collimators
(MLCs) which can shape the new field while maintaining the same isocenter.

Table 4.3: Comparison of the systematic component of setup error, $\Sigma_s$, before and after the application of
the offline correction for the department of Larissa.

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate before</td>
<td>2.0</td>
<td>1.7</td>
<td>3.3</td>
</tr>
<tr>
<td>after</td>
<td>1.2</td>
<td>1.0</td>
<td>1.3</td>
</tr>
<tr>
<td>difference</td>
<td>-39%</td>
<td>-38%</td>
<td>-59%</td>
</tr>
<tr>
<td>Lung before</td>
<td>3.4</td>
<td>6.6</td>
<td>8.6</td>
</tr>
<tr>
<td>after</td>
<td>1.2</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>difference</td>
<td>-65%</td>
<td>-78%</td>
<td>-82%</td>
</tr>
<tr>
<td>Breast before</td>
<td>2.7</td>
<td>4.2</td>
<td>6.1</td>
</tr>
<tr>
<td>after</td>
<td>2.6</td>
<td>1.9</td>
<td>2.6</td>
</tr>
<tr>
<td>difference</td>
<td>-5%</td>
<td>-55%</td>
<td>-57%</td>
</tr>
<tr>
<td>Abdomen before</td>
<td>1.1</td>
<td>6.7</td>
<td>6.4</td>
</tr>
<tr>
<td>after</td>
<td>2.7</td>
<td>1.3</td>
<td>1.4</td>
</tr>
<tr>
<td>difference</td>
<td>+52%</td>
<td>-81%</td>
<td>-78%</td>
</tr>
<tr>
<td>Gynaecological before</td>
<td>2.5</td>
<td>2.8</td>
<td>3.3</td>
</tr>
<tr>
<td>after</td>
<td>2.2</td>
<td>2.1</td>
<td>1.1</td>
</tr>
<tr>
<td>difference</td>
<td>-14%</td>
<td>-26%</td>
<td>-66%</td>
</tr>
<tr>
<td>Head &amp; Neck before</td>
<td>3.2</td>
<td>3.7</td>
<td>1.7</td>
</tr>
<tr>
<td>after</td>
<td>0.8</td>
<td>0.7</td>
<td>1.4</td>
</tr>
<tr>
<td>difference</td>
<td>-74%</td>
<td>-82%</td>
<td>-16%</td>
</tr>
<tr>
<td>Rectum before</td>
<td>2.0</td>
<td>2.5</td>
<td>4.1</td>
</tr>
<tr>
<td>after</td>
<td>1.0</td>
<td>1.4</td>
<td>2.6</td>
</tr>
<tr>
<td>difference</td>
<td>-48%</td>
<td>-46%</td>
<td>-37%</td>
</tr>
<tr>
<td>average difference</td>
<td>-28%</td>
<td>-58%</td>
<td>-56%</td>
</tr>
</tbody>
</table>
Theageneio Anticancer Hospital of Thessaloniki has not adopted an offline correction strategy yet, although it would be very effective in reducing the setup errors. Because the preparation protocol of the treatment was found to be solid and reproducible, a single NAL offline correction would benefit the decrease of systematic setup errors. Further on, the establishment of an immobilization protocol per anatomical site with the use of carefully selected index immobilization devices is advisable.

The rationale of the hybrid correction calculation method was extensively explicated in subchapter 2.4.2. The methodology of filling the non-IGRT fractions with the average of the past IGRT offsets resulted in relatively small random errors. This is because these values are very close to each other and thus their standard deviation for each patient is small. Consequently, the root mean square of all patients’ standard deviations per anatomical site, namely the random setup error of each site, is also small. However, the values derived by this method are similar with those that derived by the scaling method and thus it is believed that it is a reliable alternative method for data analysis and setup errors calculation.

4.1.3 PTV margins

Required PTV margins were calculated according to the four different methods of statistical analysis used for the quantification of the setup errors. In general, smaller PTV margins are required in the University Hospital of Larissa, as it was expected, due to the prudent use of the offline correction strategy and the large imaging ratio, as well as the adoption of a correct preparation protocol, which subsequently resulted in small setup errors. The department of Patras struggled with the offline correction at first, but improved significantly over time. Theageneio Anticancer Hospital of Thessaloniki demonstrates the largest margins, but would be considerably benefited by the adoption of a simple offline correction, such as NAL.

For simplicity and comparison reasons, the same values of delineation errors have been used per anatomical site for all the departments. Sole exception to this was the delineation error of the prostate, where a separate experiment occurred in Patras and Larissa and the average of these values was set as delineation error for Thessaloniki, where the experiment could not be performed. As mentioned in the previous chapter, the results derived after dual registration of prostate and lung cases were in good agreement with other studies in the literature and therefore were deemed as valid for use during the calculation of the margins. Although organ motion values should derive by department-specific patient population data, the values found
for Patras’ department were used for the evaluation of the prostate and lung PTV margins in the other two departments as well. The reason this procedure (i.e. dual registration) could not be repeated in Larissa and Thessaloniki is of practical nature, that is due to the heavy workload of these departments.

In general, no distinction and no separate grouping of the data was made between patients that underwent postoperative radiotherapy and patients that had an intact organ. Specifically for prostate patients, postoperative radiotherapy is quite common in Greece due to the large percentage of patients having a prostatectomy and despite the fact that high-dose IMRT is well tolerated and is associated with excellent long-term tumor-control outcomes in patients with localized prostate cancer. The absence of an intact prostate has no impact on setup errors and has been reported that interfraction and intrafraction motion of the prostate bed is comparable to the corresponding one of the intact prostate (see Table 3.2). Anyway, interfraction organ motion in prostate or prostate bed displays larger magnitudes than intrafraction and thus has a greater impact on margins. On the other hand, delineation error might present a notable deviation between intact prostate and prostate bed. However, for reasons that have been extensively outlined before, delineating patients with a tumor bed would be impractical. Therefore the use of the delineation error that derived by delineating intact prostates might not be representative for prostate bed cases and it may have lead to an underestimation of the required margins. The same applies to lung delineation as well.

<table>
<thead>
<tr>
<th>(Σ) Systematic errors (mm)</th>
<th>(σ) Random errors (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
<td>SI</td>
</tr>
<tr>
<td>Delineation error</td>
<td>1.8</td>
</tr>
<tr>
<td>Setup error</td>
<td>2.4</td>
</tr>
<tr>
<td>Organ motion (interfraction)</td>
<td>0.5</td>
</tr>
<tr>
<td>Organ motion (intrafraction)</td>
<td>0.3</td>
</tr>
<tr>
<td>Total error *</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* Summation of the values for each column was made in quadrature
Table 4.5: Non-isotropic PTV margins for prostate irradiation. Margins were calculated according to the simplified form of the van Herk margin formula, $M = 2.5 \Sigma + 0.7 \sigma$. Margins for systematic errors are equal to 2.5$\Sigma$ along each axis, where margins for random errors are equal to 0.7$\sigma$ along each axis. The sum of the margins for systematic and random errors along each axis is the total margin needed. For the analytical form, $M = 2.5 \Sigma + 1.64 (\sigma - \sigma_p)$, the standard deviation of the Gaussian penumbra ($\sigma_p$) has to be added in random errors as well, with a value of 3.2 mm for soft tissue and 6.4 mm for lung. For breast irradiation with opposed fields the formula becomes $M = 2.15 \Sigma + 0.7 \sigma$.

<table>
<thead>
<tr>
<th>PTV margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
</tr>
<tr>
<td>Systematic ($\Sigma$)</td>
</tr>
<tr>
<td>Random ($\sigma$)</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Figure 4.2: Comparison of required CTV-to-PTV margins between the three departments for various anatomical sites with respect to the no-corrections method

*An extra margin of 5 mm is included in breast PTV margin to account for organ motion

** For the anatomical sites of Head & Neck, Gynaecological, Abdomen and Rectum organ motion was not included in calculations
Figure 4.3: Comparison of the required PTV margins among the three departments according to the scaling method.
Figure 4.4: Comparison of required PTV margins between the two departments according to the offline correction method.

*An extra margin of 5 mm is included in breast PTV margin to account for organ motion

** For the anatomical sites of Head & Neck, Gynaecological, Abdomen and Rectum organ motion was not included in calculations

Figure 4.5: Comparison of the required PTV margins for the anatomical sites of prostate and lung between the three departments with respect to the hybrid method

* Note that the department of Thessaloniki does not apply an offline correction and these results represent the calculations when the online corrections are accounted for.
4.2 Limitations of the van Herk margin formula

Despite the logic behind the derivation of the van Herk margin formula, certain assumptions were made that may limit its application to all treatment sites and situations. For example, it is assumed that the planned dose distribution, $D_{\text{planned}}$, conforms exactly to the CTV, representing a perfectly conformal dose distribution in a homogeneous medium.\textsuperscript{14,166} The term “homogeneous” refers to the assumption that all tissues in the body are water equivalent. However, in reality tissues such as bone and lung have significantly different radiobiological properties compared to water and the dose distribution will be altered if these tissues are present in the path of the treatment beam.

Also, for the derivation of the dose-population histograms, the patient population was assumed to be homogeneous, i.e., the same SDs were applied for each patient. In order to include differences in statistics for individual patients or patient groups the dose-population histograms for a range of SDs have to be calculated and the weighted average of the resulting curves should be computed.

Additionally, it was assumed that there are many fractions, i.e., that the average treatment execution error is zero. If the number of fractions is small, this assumption is not valid and the average of the execution (random) errors may differ from zero. In practice, the residual average of treatment execution (random) variation may be ignored for high-dose fractionated radiotherapy except in those situations where exceptionally large treatment execution (random) variation occurs, or when there are only a few fractions.

Moreover, spherical symmetry was assumed in the closed form derivations, which questions the applicability of the model for non-spherical target shapes. However, the resulting curves and margin recipe are independent of the CTV size. This means that, as long as the structure of the CTV is large compared with $\sigma$, the results are independent of the shape of the CTV. Those CTV regions that are narrow compared with $\sigma$ receive a lower cumulative dose due to the blurring of the dose distribution. However, in a realistic treatment planning procedure, the conformation of narrow CTV regions is poor and the curvature of the dose distribution remains low.

The perfectly conformal nature of the van Herk dose model is also unrealistic as is not physically achievable in radiation therapy due to the dose fall off at the target periphery. Although with the advancement of IMRT highly conformal treatments are available, a perfect conformation can never be reached. For a realistic treatment planning scenario the ICRU
specifies that the 95% dose volume must encompass the entire PTV which results in the volume of the 95% isodose being slightly larger than the PTV.

Finally, the use of convolution to model the planned dose distributions assumes that the CTV is large in comparison to the width of the beam penumbra. However, for small lesion sizes, the isodose surfaces can become sharply curved and therefore may alter the assumed penumbra shape so that they cannot be modeled by convolution with a Gaussian. Therefore, PTV margins derived from the van Herk formula may not be reasonable for small targets.

4.3 Limitations of the organ motion assessment method

A simple and practical method was proposed in order to evaluate interfraction organ motion with the use of the dual registration utility, provided by XVI. Although the results were in good agreement with other studies in the literature, there are certain limitations of the method.

First, there was no separation between intact organs and tumor beds. The results of the dual registration were used according to the method described in Figure 2.2. A mix of data from patients that have intact organs and postoperative cases may have led to errors, despite the differences of interfraction organ motion for postoperative and non-extracted being relatively small.

Then, the selection of the CTV with zero margins as the source of the applied mask for grey-value registration may not be correct for every patient case, especially when this mask corresponds to a large volume that includes voxels of higher density (i.e. bones). The residual differences that derive between the two registration methods correspond to the distance between the rigid bony anatomy and the center of mass of the mask that was created by the CTV. Despite the use of the center of PTV – and thus the center of CTV, since the PTV margins used by the department are isotropic- as the correction reference point, rotations of the structures are still an issue that has not been fully taken into account. The value of 10° of rotations that has been set as an upper limit in order to accept the result of the mask registration does not guarantee that rotations were insignificant during the registration process, especially for the prostate. The 5° limit of clipbox bony anatomy registration
might be stricter, but still introduces uncertainties that have not been taken into consideration. Deformations were also impossible to assess, although they are small relative to organ motion for prostate and seminal vesicles during the course of RT.\textsuperscript{127}

More importantly, the precision of the grey-value algorithm itself cannot be assessed, since it is part of a vendor program and not in-house developed software. This aspect is very crucial for the outcome of this proposed method, since all the data derived were based on the computations of this algorithm. Especially for structures less definite than intact organs or tumors, such as the tumor beds, there cannot be absolute confidence in the efficacy of the algorithm.

\section*{4.4 Suggestions}

The clinical implementation of IGRT has improved treatment accuracy and allows for substantial margin reduction in cancer radiotherapy, leading to healthy tissue sparing and avoidance of target miss. Although no level 1 evidence is available to date on whether the dosimetric and geometric gains can actually lead to improved clinical outcomes, several studies have found supporting data in favor of IGRT.\textsuperscript{183} Further, as the majority of the dose-escalation trials that showed improved outcomes relied on portal imaging of bony anatomy for localization, it has been argued that the benefit of dose-escalation may relate to better coverage of the prostate rather than the higher dose.

The clinical benefit of daily over weekly imaging has also been assessed. It was found that daily IGRT control in prostate cancer significantly improves biochemical progression-free interval (BPI), clinical progression-free interval (CPFI), as well as rectal toxicity.\textsuperscript{184} Furthermore, daily kV-CBCT has negligible influence on plan quality and is commendable for the clinical routine.\textsuperscript{185}

Despite all three of our departments having both the necessary equipment as well as the required expertise to perform daily CBCT imaging, none has applied such an imaging protocol so far. The main reason for that is that it is believed that daily imaging of every patient’s fraction is impracticable, due to the already heavy workload and the tight program of the radiotherapy departments. However, there are fast-scan protocols that demand less than a minute to perform a scan of the region of interest, without any considerable costs in image quality. Additionally, the use of daily imaging would inspire confidence in the RTTs
regarding patient positioning and would compensate the time of the scan with the less time for patient positioning. Also, proficiency of the staff on this protocol will grow with time and the whole procedure would become even faster.

4.4.1 University Hospital of Patras

For University Hospital of Patras in particular, a daily CBCT imaging protocol would result in significant margin reduction, as can be seen in Table 4.1 and Figure 4.1. It is clear that the larger the setup errors, the greater the benefit from margin reduction, due to the nullification of the setup errors. These results would be similar for the departments of Larissa and Thessaloniki.

In the case that the daily IGRT protocol will not be immediately adopted, an alternative step to the right direction for University Hospital of Patras would be to adopt a different preparation protocol, similar to the one followed in Larissa. This would limit the uncertainties during the preparation phase of the treatment and would result in the reduction of setup errors. Also, it is important for the staff to have confidence in the offline correction strategy followed by the department and refrain from intuitive interventions, which might have a long-term cost regarding positioning reproducibility, during the initial fractions of the treatment. Additionally, because the imaging data are available, offline adaptive radiation therapy should be considered. Data of positioning offsets would find a good use in the extension of the current NAL offline correction to an eNAL protocol.146

Furthermore, a stricter organ filling protocol would be advisable. It is important that these directions regarding bladder and rectum filling are given by the physicians before the reference CT as well, because its proper acquisition will affect the whole treatment. The RTTs should familiarize themselves with this stricter protocol and put an effort in organizing the treatment schedule on its basis. When a considerable difference in the volumes of the organs is observed between the planning CT and the treatment CBCT, it would be recommendable to defer the delivery of the dose and give the patient further instructions.

Finally, 4DCT and 4D-CBCT acquisition would be extremely beneficial for lung cancer cases. Planning at the target’s mid-position in combination with daily 4D-CBCT would minimize systematic respiratory motion, resulting to considerable margin reduction.
Table 4.6: Comparison of required PTV margins between the current correction strategy used and an everyday online correction strategy for the department of Patras
* Organ motion has not been taken into account for margin calculations; a value of 2.5 mm is selected to represent the delineation error

<table>
<thead>
<tr>
<th>Method</th>
<th>LR (mm)</th>
<th>SI (mm)</th>
<th>AP (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate hybrid correction</td>
<td>8.7</td>
<td>8.9</td>
<td>9.7</td>
</tr>
<tr>
<td>everyday IGRT</td>
<td>5.0</td>
<td>7.2</td>
<td>8.7</td>
</tr>
<tr>
<td>margin reduction</td>
<td>43%</td>
<td>19%</td>
<td>10%</td>
</tr>
<tr>
<td>Lung hybrid correction</td>
<td>11.6</td>
<td>11.3</td>
<td>11.8</td>
</tr>
<tr>
<td>everyday IGRT</td>
<td>7.5</td>
<td>8.2</td>
<td>11.3</td>
</tr>
<tr>
<td>margin reduction</td>
<td>35%</td>
<td>27%</td>
<td>4%</td>
</tr>
<tr>
<td>Brain hybrid correction</td>
<td>5.6</td>
<td>5.7</td>
<td>7.0</td>
</tr>
<tr>
<td>everyday IGRT</td>
<td>3.0</td>
<td>5.0</td>
<td>6.3</td>
</tr>
<tr>
<td>margin reduction</td>
<td>46%</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Abdomen* offline correction</td>
<td>12.7</td>
<td>13.5</td>
<td>15.6</td>
</tr>
<tr>
<td>everyday IGRT</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>margin reduction</td>
<td>50%</td>
<td>53%</td>
<td>60%</td>
</tr>
<tr>
<td>Gynaecological* offline correction</td>
<td>10.6</td>
<td>11.8</td>
<td>9.2</td>
</tr>
<tr>
<td>everyday IGRT</td>
<td>6.3</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>margin reduction</td>
<td>41%</td>
<td>47%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Figure 4.6: Comparison of required PTV margins between the current correction strategy used and an everyday online correction strategy for the department of Patras
* Organ motion has not been taken into account for margin calculations; a value of 2.5 mm is selected to represent the delineation error
4.4.2 University Hospital of Larissa

For the department of Larissa it would be easier to follow a daily imaging protocol, since they already image roughly the 40% of the fractions. The benefit would be considerable, while the workload would be just slightly burdened. If they choose to proceed with their current imaging protocol, they should consider keeping the same isocenter throughout all the phases of the treatment, so they will not have to correct all over again for each phase. Extended offline protocols and adaptive radiotherapy is a feasible option for this department as well.

4.4.3Theageneio Anticancer Hospital of Thessaloniki

The department of Theageneio Anticancer Hospital would benefit the most from a daily CBCT protocol. Also, a simple NAL offline correction would immediately benefit the department in terms of limiting the setup errors and reducing the required PTV margins. However, because the particular department is the only one that casually uses VMAT and dynamic IMRT techniques, which require the highest amount of accuracy and precision due to the high dose gradient they demonstrate, a daily IGRT correction strategy is strongly recommended. Finally, using the index immobilization devices on their full potential would result in increased patient positioning reproducibility.

4.5 Future work

In order to fully assess the PTV margins for each department, proper evaluation of all errors is essential. In this thesis an effort has been made in order to investigate as many error sources as possible and various methods have been proposed in order to evaluate the errors that are introduced during external beam radiation therapy with the minimum resources available. However, it was practically impossible to fully assess all types of errors and there is a vast field of future work that could either improve the accuracy and validity of the methods used here, or even go to the next level and look into more specialized and novel methods and techniques.

A large-scale, department-tailored delineation experiment that would provide all the relevant clinical data to the participants is necessary for quantifying the delineation error with higher
precision. An investigation of the differences that might arise within a department by delineating on the basis of a specific protocol versus delineating on the basis of a mixture of protocols and guidelines would be of great interest, since this is a tactic widely followed among the radiation oncologists in our departments. A comparison between the tumor bed delineation variations and the tumor/organ delineation variations for various anatomical sites would be enlightening. Assessing the intra-observer error would also be the next step for the delineation experiment. Finally, because there is no consistent or widely accepted method of systematic contour comparison and numerous contouring metrics exist, further investigation is needed to assess the advantages and disadvantages of each delineation metric in various situations.

The development of an in-house image registration algorithm that would allow modifications and constant improvements would be very helpful for image registration. It would also allow enhanced tracking of the organ’s translations, rotations and deformations. This work is essential for the assessment of organ motion and the establishment of a precise adaptive radiotherapy protocol as well. Also, development of a sophisticated algorithm that would allow the calculation of the time-weighted average position of the target during treatment imaging for lung radiotherapy is a prerequisite for the reduction of lung PTV margins.

In the case that our departments follow the suggestions made for each of them, a follow-up study would allow for a useful comparison of the results between the new methods and the old. The department of Patras, in particular, has already adopted the proposed preparation protocol since nearly one month. Quantification of the setup errors would indicate the impact of the new methodology on treatment margins. A comparison of the impact that index immobilization devices and non-index immobilization devices have on setup errors would also be enlightening. Also, it would be interesting to investigate whether the establishment of an immobilization protocol with a wide variety of index immobilization devices has actually a positive impact on patient positioning.

Finally, further research is needed in investigating the optimization of the margin formulas for IMRT and VMAT techniques, which demonstrate better conformity than 3DCRT. Also, probabilistic treatment planning, which incorporates the mathematical models of geometric uncertainties into the plan optimization framework with goal of creating a plan that is robust or tolerant to such geometric uncertainties, comprises an expansion of this work.
References


Appendix: The hybrid method of statistical analysis of the data

Suppose that we have a patient that is scheduled to receive the prescribed dose in 18 fractions. The simulation of this treatment will be performed as follows:

<table>
<thead>
<tr>
<th># fraction</th>
<th>type</th>
<th>offset</th>
<th>setup error</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>IGRT</td>
<td>5.0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>IGRT</td>
<td>-2.0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>IGRT</td>
<td>7.0</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>IGRT</td>
<td>5.0</td>
<td>0</td>
</tr>
</tbody>
</table>

initial offset = $O_4 = 5.0$

<table>
<thead>
<tr>
<th># fraction</th>
<th>type</th>
<th>offset</th>
<th>setup error</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>5.0</td>
</tr>
<tr>
<td>6</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>5.0</td>
</tr>
<tr>
<td>7</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>5.0</td>
</tr>
<tr>
<td>8</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>5.0</td>
</tr>
<tr>
<td>9</td>
<td>IGRT</td>
<td>3.0</td>
<td>0</td>
</tr>
</tbody>
</table>

mean offset $\Rightarrow M_1 = (O_4 + O_9) / 2 = 4.0$

<table>
<thead>
<tr>
<th># fraction</th>
<th>type</th>
<th>offset</th>
<th>setup error</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>4.0</td>
</tr>
<tr>
<td>11</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>4.0</td>
</tr>
<tr>
<td>12</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>4.0</td>
</tr>
<tr>
<td>13</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>4.0</td>
</tr>
<tr>
<td>14</td>
<td>IGRT</td>
<td>6.0</td>
<td>0</td>
</tr>
</tbody>
</table>

mean offset $\Rightarrow M_2 = (O_4 + O_9 + O_{14}) / 3 = 4.7$

<table>
<thead>
<tr>
<th># fraction</th>
<th>type</th>
<th>offset</th>
<th>setup error</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>4.7</td>
</tr>
<tr>
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<td>non-IGRT</td>
<td>unknown</td>
<td>4.7</td>
</tr>
<tr>
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<td>non-IGRT</td>
<td>unknown</td>
<td>4.7</td>
</tr>
<tr>
<td>18</td>
<td>non-IGRT</td>
<td>unknown</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Simulation of a treatment: Offsets derived by IGRT fractions are used as gauge for the setup errors on forthcoming fractions ($O_4$: offset of the 4th fraction, $O_9$: offset of the 9th fraction, etc)